

**THE EFFECT OF SPECIFIC INTERVENTIONS ON CARDIAC
POWER OUTPUT AND SELECTED CARDIO-RESPIRATORY
VARIABLES IN PATIENTS WITH MILD TO SEVERE HEART
FAILURE**

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ABSTRACT

Cardiac power output is a central haemodynamic measure which describes pumping capability and performance of the heart. This is a unique measure as it accounts for both, flow- and pressure-generating capacities of the heart. Cardiac power output (CPO) is calculated from mean arterial pressure and cardiac output. Popular non-invasive methods for cardiac output measurement today include rebreathing methods. From the practical and clinical perspective it is important to know which of the commonly measured cardio-respiratory variables, obtained from a cardiopulmonary exercise test, are good predictors of peak CPO in healthy but also in heart failure populations. Until now there has been no measurement of cardiac power output in patients implanted with a left ventricular assist device (LVAD) and those explanted (recovered) patients. In a comparison study design it has been shown that peak cardiac power output differentiates well during cardiac restoration using LVADs and emphasizes the benefits of this therapy. It seems that CPO has the potential to be a key physiological marker of heart failure severity and can guide the management of LVAD patients. Furthermore as a consequence of acute reduction of LVAD support, there is a decrease in cardiac pumping capability and exercise performance. A decrease at rest and at peak exercise, expressed in percentages, was higher in central haemodynamics, particularly in CPO, than in the conventionally measured peak oxygen consumption. This suggests that CPO is more sensitive to acute reduction of LVAD support than oxygen consumption. In patients with severe heart failure and those implanted with an LVAD, the relationship between peak CPO and peak oxygen consumption is only modest. In healthy adults and LVAD explanted patients this relationship was high. No strong relationship was found between peak CPO and anaerobic threshold, circulatory power, oxygen pulse or ventilatory efficiency in LVAD implanted and patients with severe heart failure. Finally, regarding different modalities of exercise training, in contrast with resistance training, aerobic exercise training may increase both maximal flow-generating capacity of the heart and peak oxygen consumption and also delays anaerobic metabolism in patients with stable chronic heart failure. Improved peak oxygen consumption, following aerobic exercise training, is closely associated with an exercise-induced increase in cardiac output.

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LIST OF ABBREVIATIONS

AT	Anaerobic threshold
$a-\bar{v} O_2$ diff.	Arterial-venous oxygen difference
BMI	Body mass index
BSA	Body surface area
CaO_2	Arterial blood oxygen concentration
CI	Cardiac index
CP	Circulatory power
CPO	Cardiac power output
$C\bar{v} O_2$	Venous blood oxygen concentration
DBP	Diastolic blood pressure
$F_E CO_2$	Fraction of expired carbon dioxide
$F_E O_2$	Fraction of expired oxygen
HR	Heart Rate
LVAD	Left ventricular assist device
LVEDV	Left ventricular end-diastolic volume
LVEF	Left ventricular ejection fraction
LVESV	Left ventricular end-systolic volume
MAP	Mean arterial blood pressure
OP	Oxygen pulse
\dot{Q}_T	Cardiac output
$P_{ET} CO_2$	End tidal carbon dioxide concentration
$P\bar{v} CO_2$	Partial pressure of mixed venous carbon dioxide
RER	Respiratory exchange ration
SBP	Systolic blood pressure
SV	Stroke volume
$\dot{V}C_2$	Carbon dioxide production
\dot{V}_E^O	Minute ventilation
$\dot{V}O_2$	Oxygen consumption

GLOSSARY OF TERMS

Apoptosis: A form of programmed cell death in multicellular organisms.

Anaerobic threshold: Exercise oxygen consumption that marks the transition between no change or little change in arterial lactate concentration and the sustained increase in concentration of lactate (also known as the lactate threshold). Postulated by some authors to be the oxygen consumption above which anaerobic energy production substantially supplements aerobic energy production.

Bio-reactance method: A novel, non-invasive, easy to perform method for continuous measurement of cardiac output based on the discovery that changes in aortic blood volume induce small changes in the frequency of electrical signals propagating across the thorax.

Body surface area: The total surface area of the human body. It is the product of the weight in kg times the height in cm divided by 3600.

Borg scale: A scale which is used for individual to rate their perceived level of exertion during exercise.

Bruce protocol: Treadmill exercise test which is conducted in three minute stages. Each 3 minutes the workload is increased by a combination of increasing the speed and the grade of the treadmill.

Cardiac index: A cardiodynamic measure ($l \cdot \text{min}^{-1} \cdot \text{m}^2$) which is obtained dividing cardiac output by the body surface area.

Cardiac output: The volume of blood ($l \cdot \text{min}^{-1}$) pumped from the heart each minute and expressed in units of liters per minute. It is the product of the average stroke volume per beat and the heart rate.

Cardiac pumping capability: The maximum performance of the heart that can be achieved during stimulation.

Cardiac pumping reserve: The difference in cardiac power output between resting and maximally stimulated states.

Cardiac power output: Is a descriptor of overall cardiac function, calculated from the product of cardiac output and mean arterial pressure expressed in watts.

Circulatory power: Is the product of systolic arterial pressure and oxygen uptake, expresses in $\text{mmHg} \cdot \text{lO}_2 \cdot \text{min}^{-1}$.

Cardiac resynchronisation therapy: Cardiac resynchronization therapy (CRT) is a proven treatment for selected patients with heart failure-induced conduction disturbances and ventricular dyssynchrony. When used in combination with stable, optimal medical therapy, CRT is designed to reduce symptoms and improve cardiac function by restoring the mechanical sequence of ventricular activation and contraction. CRT uses a specialized pacemaker to re-coordinate the action of the right and left ventricles in patients with heart failure. CRT re-coordinates the beating of the two ventricles by pacing both ventricles simultaneously.

Desensitization: Is a method to reduce or eliminate an organism's negative reaction to a substance or stimulus.

Dobutamine: Dobutamine is a direct-acting inotropic agent whose primary activity results from stimulation of the β -receptors of the heart while producing less marked chronotropic, hypertensive, arrhythmogenic or vasodilatory effects.

Ejection fraction: Stroke volume divided by end-diastolic volume.

End-diastolic volume: Is the volume of blood in a ventricle at the end of filling (diastole).

Fat-free mass: The mass (weight) of the body that is not fat, including muscles, bone, skin and organs.

Fibrosis: Is the formation or development of excess fibrous connective tissue in an organ or tissue as a reparative or reactive process, as opposed to a formation of fibrous tissue as a normal constituent of an organ or tissue.

Functional residual capacity: Volume of gas in lungs after maximal expiration.

Heart failure: Is a condition that can result from any structural and functional cardiac disorder that impairs the ability of the heart to fill with blood or pump a sufficient amount of blood through body.

Heteroscedasticity: When the amount of error increases as the measurement value increases (individuals who score the highest values on a particular test also show the

greatest amount of measurement error).

Homoscedasticity: When there is no relation between the error and the size of the measured value.

Hydraulic power output: Is a description of the heart's capability to act as pump and maintain circulation.

Inflammation: Complex biological response of vascular tissues to harmful stimuli, such as pathogens, damaged cells, or irritants. It is a protective attempt by the organism to remove the injurious stimuli as well as initiate the healing process for the tissue.

Lean body mass: The sum of the body's fat-free mass and essential fat.

Likert scale: A rating scale measuring the strength of agreement towards a set of clear statements.

Oedema: Is observable swelling from fluid accumulation in body tissues. Oedema most commonly occurs in the feet and legs, where it is referred to as peripheral oedema.

Oxygen consumption: The amount of oxygen utilized by the body's metabolic processes in a given time, expressed in millilitres or litres per minute, STDP.

Oxygen pulse: Oxygen uptake ($\text{ml}\cdot\text{min}^{-1}$) divided by heart rate ($\text{b}\cdot\text{min}^{-1}$) i.e. the volume of oxygen consumed per given stroke volume.

Oxygen uptake: The amount of oxygen extracted from the inspired air in a given period of time, expressed in millilitres or litres per minute. This can be differed from oxygen consumption under conditions in which oxygen is flowing into or being utilized from the body's stores. In the steady-state, oxygen uptake equals oxygen consumption.

Mass spectrometry: Measurement of fractional concentrations of the components of a gaseous mixture on the basis of their mass : charge ratio alone.

Mean arterial pressure: Is a pressure estimated by the auscultation of the systolic and diastolic blood pressure over the brachial artery. It is equal $\text{DBP} + 0.412(\text{SBP} - \text{DBP})$, where DBP is diastolic blood pressure, and SBP is systolic blood pressure.

Minute ventilation: The volume of the air taken into or exhaled from the body in one minute. This is conventionally expressed in litres per minute.

Mitral regurgitation: A valvular heart disease also known as mitral insufficiency, is the abnormal leaking of blood through the mitral valve, from the left ventricle into the left atrium of the heart.

Modified Bruce Protocol: Treadmill exercise test which contains two preliminary three minute stages of 2.7 kph at 0% incline and 2.7 kph at 5% incline. It is then followed by the standard Bruce protocol.

Myocytolysis: Degenerative change (often reversible) that occurs to myocytes upon myocardial strain. This phenomenon tends to occur when neighboring cardiac muscle loses its ability to contract (i.e. in ischemia or infarction). The remaining viable muscles, as the result, strain to compensate for the loss of other muscles in order to deliver the necessary cardiac output. During the process, myocardial cells are stretched and stressed to produce new contractile elements.

Necrosis: A form of traumatic cell death that results from acute cellular injury, apoptosis, in general, confers advantages during an organism's life cycle.

Parameter: A statistical quantity, such as a mean or standard deviation of a total population, that is calculated from data and describes a characteristic of the population as opposed to a sample from the population. It is a measurement or value on which something else depends.

Peak cardiac power output: The highest cardiac power output achieved during a maximum work rate test.

Peak oxygen consumption: The highest oxygen consumption achieved during a maximum work rate test.

Postcardiotomy (postpericardiotomy) syndrome: Medical condition which indicate a complication that occur after open-heart surgery. The condition is possibly caused by and autoimmune process triggered by a virus.

Power or work rate: This reflects the rate at which work is performed, e. g., work per unit of time. It is measured in watts ($\text{kg m}^2/\text{sec}^3$ or joule/sec) or in kilopond meters per minute kpm/min); 1W is equivalent to 6.12 kpm/min.

Pulmonary blood flow: Is the blood flow that perfuses the ventilated part of the alveoli.

Residual volume: Volume of gas in the lungs after maximal inspiration.

Respiratory exchange ratio: The ratio of carbon dioxide output to oxygen uptake per unit of time.

Stroke volume: The volume of blood ejected from a ventricular in a single beat.

Stroke work index: A measure of the work by the heart with each contraction, adjusted for body surface area; equal to the stroke volume of the heart multiplied by the arterial pressure and divided by body surface area.

Tidal volume: The amount of air inspired or expired during a normal breathing cycle.

Ultrasonography (sonography): Is an ultrasound-based diagnostic imaging technique used to visualize muscles and internal organs, their size, structures and possible pathologies or lesions.

Ultrasound: Is a sound with a frequency greater the upper limit of human hearing, this limit being approximately 20 kilohertz (20,000 hertz).

V slope method: A technique that allows detection of the onset of lactic acidosis during an incremental exercise test when one notes an accelerated rate of carbon dioxide output compared to oxygen uptake.

Variable: A variable is a quantity whose value may vary over the course of an experiment (including simulations), across samples, or during the operation of a system. Variables are generally distinct from parameters, although what is a variable in one context may be a parameter in another.

Ventricular compliance: As the ventricle fills with blood, the pressure and volume that result from the filling are determined by the compliance of the ventricle. Compliance curve is plotted as the change in volume over the change in pressure. The slope of the relationship is the reciprocal of the compliance, which is sometimes referred as ventricular “stiffness”.

Ventricular filling pressure: The pressure in the ventricle as it fills with blood.

Ventricular remodelling: Changes in size, shape, and function of the heart after

injury to the left ventricle.

Vital capacity: The maximal volume of air expelled from the lungs after maximal inhalation.

EXTERNAL PUBLICATIONS FROM THIS THESIS

Published papers

- **Jakovljevic DG**, Nunan D, Donovan G, Hodges L, Sandercock GRH, Brodie DA. (2008) Lack of agreement between gas exchange variables measured by two metabolic systems. *Journal of Sport Science and Medicine*, 7(1): 15-22. (Chapter 2)
- **Jakovljevic DG**, Nunan D, Donovan G, Hodges L, Sandercock GRH, Brodie DA. (2008) Comparison of cardiac output determined by different rebreathing methods at rest and at peak exercise. *European Journal of Applied Physiology*, 102(5):593-599. (Chapter 3)

Manuscripts in preparation:

- **Jakovljevic DG**, Donovan G, Nunan D, Hodges L, Sandercock GRH, Brodie DA. Relationship between peak cardiac power output and selected cardio-respiratory variables in healthy adults. (Chapter 5)
- **Jakovljevic DG**, Donovan G, Nunan D, George RS, Bougard RS, Birks EJ, Yacoub MH, Brodie DA. Comparison of cardiac power output and exercise performance in patients with left ventricular assist devices, explanted (recovered) patients and those with severe heart failure. (Chapter 6)

Conference proceedings

1. **Jakovljevic DG**, Nunan D, Donovan G, George R, Bougard R, Birks E, Yacoub M, Brodie DA. Relationship between peak cardiac power output and selected cardio-pulmonary variables in patients on left ventricular assist devices, explanted (recovered) patients and those with severe heart failure. In *Proceedings of the Heart Failure Congress – Heart Failure Association (European Society of Cardiology), Milan, Italy, 14 – 17 June 2008* – *European Journal of Heart Failure*, 7, suppl. 1, 73(287). (Chapter 8)
2. **Jakovljevic DG**, Nunan D, Donovan G, George R, Bougard R, Birks E, Yacoub M, Brodie DA. Cardiac power output measurements in patients on left ventricular assist devices, explanted (recovered) patients and those with severe heart failure. In *Proceedings of the Europrevent Meeting – European Association for Cardiovascular Prevention and Rehabilitation (European Society of Cardiology)*,

Paris, France, 1 – 3 May 2008 - European Journal of Cardiovascular Prevention and Rehabilitation, 15, suppl. 1, 111(487). (Chapter 6)

3. **Jakovljevic DG**, Nunan D, Donovan G, George R, Bougard R, Birks E, Yacoub M, Brodie DA. Current tendencies in cardiopulmonary exercise testing in heart failure – role of cardiac power output. In *Proceedings of the International Scientific Conference “Physical Activity and Health”, Faculty of Sport, Belgrade University, Serbia, 10 – 11 December 2007. (Chapters 4 and 8)*
4. **Jakovljevic DG**, Nunan D, Donovan G, Hodges L, Sandercock GRH, Brodie DA. Three different rebreathing methods for measuring cardiac output at rest. In *Proceedings of the 12th annual congress of the European College of Sport Science, Jyväskylä, Finland, 11 - 14 July 2007. (Chapter 3)*
5. **Jakovljevic DG**, Nunan D, Donovan G, Hodges L, Sandercock GRH, Brodie DA. Direct comparison of two automated metabolic gas analysis systems during exercise. In *Proceedings of the 12th annual congress of the European College of Sport Science, Jyväskylä, Finland, 11 - 14 July 2007. (Chapter 2)*

Abstract submitted

- **Jakovljevic DG**, Donovan G, Nunan D, McDonagh S, Grocott-Mason R, Brodie DA. The effect of aerobic versus resistance exercise training on cardiac power output and selected cardio-respiratory variables in patients with stable chronic heart failure. *Heart Failure Congress – Heart Failure Association (European Society of Cardiology), Nice, France, 29 May – 02 June 2009. (Chapter 10)*

Invited presentation

- **Jakovljevic DG**, Nunan D, Donovan G, George R, Bougard R, Birks E, Yacoub M, Brodie DA. Cardiac power output in patients with severe heart failure, to include those with implanted and explanted left ventricular assist devices. *Thematic Meeting on Clinical Consequences of Hemodynamic Measurements under Exercise Testing (Innovision, Denmark), Copenhagen, 24 – 25 September 2007. (Chapter 6).*

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AUTHORS DECLARATION

I take responsibility for all the material contained within this thesis and confirm this thesis is my own work.

D. Jakovljevic

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CHAPTER 1: INTRODUCTION

1.1 Context

This thesis focuses on metabolic, ventilatory and haemodynamic measurements, obtained from a cardiopulmonary exercise test, in healthy adults and patients with moderate to severe heart failure. A number of measurements obtained from a cardiopulmonary exercise test have been used to assess functional capacity in a healthy population, but also to evaluate responses to medical treatment and exercise therapy, to assess progression of disease process, and to determine prognosis in heart failure patients (Ingle et al., 2008). Most commonly reported and routinely measured cardio-respiratory variables include peak oxygen consumption, peak carbon dioxide production, oxygen consumption at anaerobic threshold, minute ventilation, ventilatory efficiency, oxygen pulse, heart rate, and arterial blood pressure. Compared with these variables, central haemodynamic measurements such as cardiac output and cardiac power output have been less frequently reported within the literature. Nonetheless, the importance of the measurement of power- and flow-generating capacities of the heart (e.g. cardiac power output and cardiac output) is essential to evaluate overall cardiac function and cardiac performance, particularly in heart failure patients.

Currently, it seems that of all the haemodynamic variables in use, cardiac power output has the potential to represent the best overall cardiac function and performance of the cardiac pump. According to Dr Tan, the main function of the heart is to provide hydraulic energy to maintain circulation (Tan, 1986, 1987, 1991). Hydraulic power output or cardiac power output is a measure of the heart's capability to act as a mechanical pump (Cotter et al., 2003). The rate of hydraulic energy output is calculated from the multiplication of flow- and pressure-generating capacities of the heart (e.g. cardiac output and mean arterial blood pressure). Therefore, the maximum performance of the cardiac pump, its pumping capability, can be represented by its power output during maximal stimulation (Tan, 1986). When the mechanical function of the heart deteriorates (e.g. heart failure), the pumping capability of the heart is also reduced. A number of studies have shown that cardiac power output is a powerful and major determinant of prognosis in heart failure patients (Tan, 1986; Tan and Littler,

1990; Roul et al., 1995; Williams et al., 2001; Fincke et al., 2004; Mendoza et al., 2007; Lim et al., 2008), and therefore may play an important role in risk stratification in heart failure.

A recent review by Mezzani et al. (2008) suggests that central haemodynamic measurements (e.g. cardiac output) under exercise in heart failure patients as an invasive procedure, has possible risks for the patients. Nonetheless, measurement of central haemodynamics is not unimportant, as in the genesis of the heart failure “an initial cardiac abnormality is essential” (Clark et al., 1996). With the availability of several non-invasive methods today (e.g. CO₂ or inert gas or rebreathing, bio-reactance method, etc.), measurement of cardiac output and cardiac power output responses to exercise could become a standard clinical tool for evaluation and management of heart failure patients.

The definition of advanced heart failure, (also called severe, end-stage, refractory heart failure) includes symptoms which limit daily activities (New York Heart Association III and IV) despite the inclusion of strong pharmacological therapy with angiotensin-converting enzyme inhibitors, β -blockers, digoxin and diuretics (Adams and Zannad, 1998). Despite advances in the medical management of heart failure the only really effective form of therapy for patients with advanced heart failure is cardiac transplantation (Yacoub, 2001). Transplantation offers an effective alternative for many patients with advanced heart failure, yet the lack of donors still currently limits the number of transplantations performed annually nationwide. The success and limitations of transplantation have stimulated alternative therapies for patients with advanced heart failure.

Mechanical circulatory support in the form of a left ventricular assist device (LVAD) is a viable therapy for severe end-stage heart failure (Frazier, 2002). To date a number of clinical trials have shown clear benefits of LVAD in terms of survival and improved quality of life. The LVAD is not therefore considered as bridge to cardiac transplantation only, but also as destination therapy (Lietz et al., 2007; Rose et al., 2001) and bridge to recovery (Birks et al., 2006).

The supine cycle and upright treadmill exercises are safe during chronic support with

LVAD (Jaski et. 1997). Cardio-pulmonary exercise testing and evaluation of exercise capacity is a standardized procedure for heart failure evaluation in most world heart transplantation centres. To date, several studies investigated functional capacity using a cardiopulmonary exercise test in patients implanted with an LVAD (Murali et al., 1991; Jaski et al., 1993; Levin et al., 1994; Foray et al., 1996; Mancini et al., 1998; Jaski et al., 1999; De Jonge et al., 2001; Maybaum et al., 2007). Surprisingly, cardiac power output has not yet been reported in patients implanted with an LVAD and those who have had the device explanted following sufficient myocardial recovery.

Prior to the late 1980s, bed rest and restricted physical activity were recommended for all stages and forms of heart failure (Working Group Report, 2001). Research, however, over the past 20 years has expanded the understanding and knowledge of the role of exercise training in patients with left ventricular dysfunction and heart failure. Over time it has become clear that patients with CHF may benefit from exercise training so much that it has been recommended by a number of international scientific organizations such as the American Heart Association and the European Society of Cardiology (Pina et al., 2003; Working Group Report, 2001). It has been shown that exercise training is firstly safe in CHF patients (Smart and Marwick, 2004) and can improve peak oxygen consumption (Duscha, 2008; Pina et al, 2003; Working Group Report, 2001), muscle strength and mass (Braith and Beck, 2008), New York Heart Association Class (Hambrecht et al., 2000), quality of life (Belardinelli et al., 1999), and also reduces hospital admission and mortality rate (Piepoli et al., 2004). Clinical evidence suggests that both aerobic and resistance exercise training may improve exercise tolerance in patients with chronic heart failure (CHF). Whether the two modalities of exercise training (aerobic and resistance) have a similar effect on cardiac power output and other cardio-respiratory variables remains unclear.

1.2 Aims and Objectives for the Thesis

Over the years, peak oxygen consumption has been used as a “gold” standard among other cardiopulmonary exercise measures in heart failure evaluation and prognosis. It has, however, several key limitations in the assessment of cardiac function. In chronic heart failure, peak oxygen consumption can be influenced by comorbidities and non-cardiac factors such as muscle conditioning, motivation for performing exercise,

anaemia, abnormal reflex response, and obesity (Fleg and Lakata, 1988; Wilson et al., 1995). Therefore, peak oxygen consumption should be considered as an indirect indicator of cardiac function/dysfunction, particularly in patients with severe heart failure and heart transplant candidates.

By introducing a novel, central haemodynamic measure such as cardiac power output in cardiopulmonary exercise testing procedure at the Harefield Heart Science Centre, the present thesis firstly aimed to enable better selection for cardiac transplantation and LVAD implantation, potential risk stratification and improvement in clinical practice. Currently, there is a lack of evidence to show that cardiac power output has been evaluated in patients implanted with a LVAD. Secondly, the current work aimed to answer the question whether aerobic or resistance exercise intervention have similar effect on overall cardiac function represented by cardiac power output in patients with stable chronic heart failure.

The objectives of this thesis were:

1. To assess the agreement between gas exchange variables measured by the two metabolic systems;
2. To compare CO₂ and inert gas rebreathing methods for cardiac output measurement at rest and at peak exercise;
3. To review the existing literature regarding cardiac power output and determine future research directions;
4. To assess the relationship between peak cardiac power output and a number of cardio-respiratory variables obtained from cardiopulmonary exercise testing in healthy adults;
5. To evaluate cardiac power output in LVAD-implanted and explanted (recovered) patients and severe heart failure patients;
6. To assess resting and peak exercise haemodynamic and metabolic responses to

acute reduction of LVAD support;

7. To determine the relationship between peak cardiac power output and selected cardio-respiratory variables in LVAD implanted and explanted (recovered) patients and those with severe heart failure patients;

8. To investigate reproducibility of cardiac power output and selected cardio-respiratory variables in patients with stable chronic heart failure;

9. To assess the effect of aerobic and resistance exercise training on cardiac power output and selected cardio-respiratory variables in patients with stable chronic heart failure.

1.3 Structure of the Thesis

This thesis conforms to the modern style where each chapter represents a self-contained study which contributes in a coherent manner to the overall aim of the thesis (Figure 1.1). Each chapter will take the style of a conventional paper. The final chapter is a brief summary written according to the style of the British Medical Journal. This includes two sections: 1) what is already known of the topic; and 2) what this study adds for each chapter of the thesis.

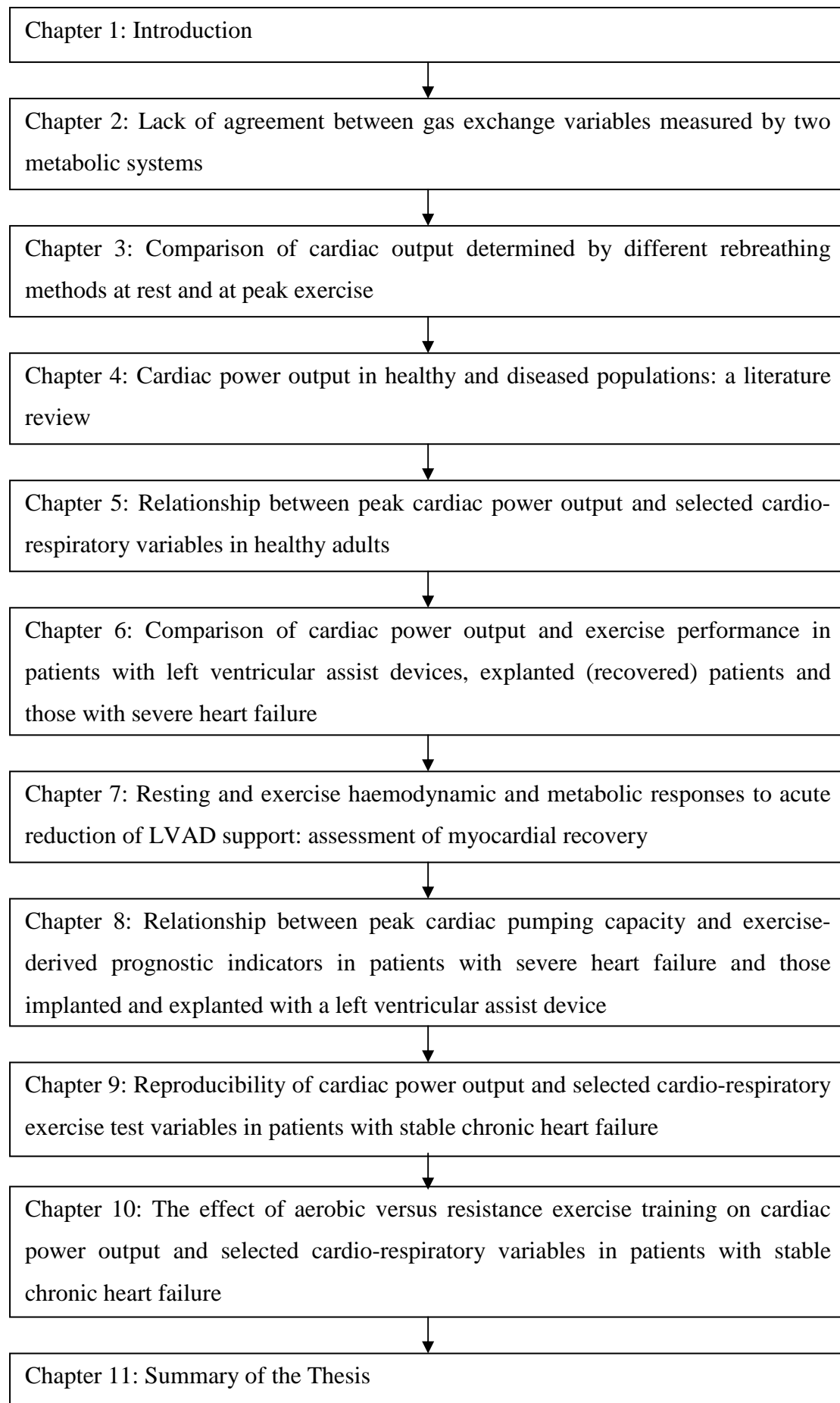


Figure 1-1 Outline of PhD

Chapters two and three were undertaken before starting the main research on the topic of cardiac power output. These chapters describe new technological advances in regards to gas exchange and haemodynamic measurements during a cardiopulmonary exercise test. Specifically, **Chapter two** reports the findings on the agreement between gas exchange variables measured by two metabolic systems, one of which has recently appeared on the market and does not have published data on its performance. **Chapter three** demonstrates results on non-invasive cardiac output measurements by different rebreathing methods at rest but also at peak exercise. Well-established carbon-dioxide rebreathing methods were compared with a newly-developed inert gas rebreathing method. **Chapter four** is a review of available literature which is related to cardiac power output measured in both healthy and diseased populations. The final sections of **Chapter four** outlines recommendations for future work, most of which will be undertaken in the following chapters. **Chapter five** shows the relationship between peak cardiac power output and a number of gas exchange variables, routinely measured during cardiopulmonary exercise tests, in a cohort of healthy adults. **Chapter six** compares cardiac power output and exercise performance in patients implanted and explanted with an LVAD, and those with severe heart failure. For the first time cardiac power output has been evaluated in this unique category of patients. **Chapter seven** demonstrates haemodynamic and metabolic responses to acute reduction of LVAD support in patients implanted with an LVAD.

Chapter eight reports the findings of the relationship between peak cardiac power output and selected exercise-derived prognostic indicators in heart failure patients in patients with severe heart failure and those implanted and explanted with an LVAD. **Chapter nine** illustrates reproducibility of cardiac power output and selected cardio-respiratory variables in patients with stable chronic heart failure, whereas **Chapter ten** investigates whether different modalities of a 12-week exercise programme (e.g. aerobic and resistance) have similar effect on cardiac power output and selected cardiorespiratory variables. Finally, **Chapter eleven** provides a brief, integrated summary of the whole thesis.

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CHAPTER 2: LACK OF AGREEMENT BETWEEN GAS EXCHANGE VARIABLES MEASURED BY TWO METABOLIC SYSTEMS

Abstract

Introduction: Technological advances have contributed to the development of portable metabolic systems. A recently-introduced online metabolic measuring system (Innocor, Innovision, Denmark) has only limited data available on the reliability and validity of metabolic measurements. The purpose of this study was to assess the consistency and agreement between gas exchange variables measured by the Innocor and an alternative online metabolic system (CardiO₂, Medical Graphics Corp., St Paul, MN, USA) during an incremental exercise test. **Methods:** After obtaining local ethical approval and informed consent, 15 healthy subjects (34±11 years) performed an incremental exercise test to volitional fatigue using the Bruce protocol. The Innocor and CardiO₂ systems were placed in series, with the Innocor mouthpiece attached into the pneumotach of the CardiO₂. Metabolic data were analysed during the last 30 seconds of each stage and at peak exercise. **Results:** There were non-significant differences ($p>0.05$) between the two systems in estimation of oxygen consumption ($\dot{V}O_2$) and in minute ventilation (\dot{V}_E). Mean Cronbach's alpha for $\dot{V}O_2$ and \dot{V}_E was 0.94 and 0.92. The Bland-Altman analysis revealed that limits of agreement were -7.17 to 7.18 ml·kg⁻¹·min⁻¹ and -0.52 to 0.55 l·min⁻¹ for $\dot{V}O_2$, and -8.74 to 10.66 l·min⁻¹ for \dot{V}_E . Carbon dioxide production ($\dot{V}C_{O_2}$) and consequently respiratory exchange ratio (RER) measured by the Innocor were significantly lower ($p<0.05$) through all stages. At peak exercise the $\dot{V}C_{O_2}$ difference of 7.5% was not statistically different ($p>0.05$), while the RER value remained significantly different ($p<0.05$). The CardiO₂ measured fraction of expired carbon dioxide (FeCO₂) significantly higher ($p<0.05$) through all exercise stages. **Conclusion:** The differences in estimated $\dot{V}C_{O_2}$ are due to a systematic overestimation in FeCO₂. Although there were non significant differences in estimated $\dot{V}O_2$ and measured \dot{V}_E between the Innocor and the CardiO₂, the limits of agreement appear to be wide and unacceptable in exercise testing. Therefore, the Innocor and the CardiO₂ metabolic systems cannot

be used interchangeably, as to do so could affect the diagnosis of an individual patient.

2.1 Introduction

2.1.1 Historical Perspective

Exercise testing provides a global assessment of the integrative exercise responses involving the pulmonary, cardiovascular, neuropsychological, and skeletal muscle systems, none of which are adequately reflected by measuring individual system functions (Weisman et al., 2003). For over two centuries physiologists have been interested in monitoring the respiratory gas exchange of oxygen and carbon dioxide during different types of exercise (Macfarlane, 2001). Historically, the first technique with considerable advances was made in 1911 in the Oxford School of Respiratory Physiology by Douglas. The Douglas bag method today is still considered as a criterion method and serves as the “gold standard” for gas exchange measurements (Basset et al., 2001). The Douglas bag method is based on open circuit spirometry and involves the collection of exhaled air in large, impermeable canvas bags (Consolazio et al., 1963). The subsequent measurement of gas fractions of oxygen ($F_{E}O_2$) and carbon dioxide ($F_{E}CO_2$) is then performed using chemical methods described by Scholander (1947) or Haldane and Priestly (1935). Apart from its accuracy, reproducibility and simplicity, the Douglas bag method has several disadvantages and its own sources of error (Carter and Jeukendrup, 2002). Firstly, the measurement on a breath-by-breath basis is not possible and therefore rapid changes in ventilation (\dot{V}_E) or oxygen consumption ($\dot{V}O_2$) cannot be studied. Secondly, the method is time consuming due to requirements for gas collection and its analysis. Also, the bags are usually made of a PVC material, which might be slightly permeable to the external air (Carter & Jeukendrup, 2002). These factors have little consequence on the gas measurement and do not invalidate the Douglas bag method (Hodges, 2005).

During the 1960s and 1970s, a number of new electronic devices were introduced such as rapidly responding gas analysers and a variety of flow-sensing devices. These devices influenced the development of semiportable computer systems, which

produced a dedicated metabolic analysis method with online data recording (Macfarlane, 2001). Beaver et al. (1973) were the first to develop an online computer system for breath-by-breath measurement of alveolar gas exchange. Since that time a considerable number of automated systems have been developed, with over a dozen manufacturers.

2.1.2 Recent Metabolic Systems

Today, the use of automated metabolic gas analysis systems, also called metabolic measurement carts, has become common in cardiopulmonary exercise testing throughout the world. They have become essential tools for diagnosing cardiorespiratory performance, not only in healthy and sporting populations, but also in those with different cardiovascular and ventilatory pathophysiological abnormalities. Metabolic gas analyser systems have permitted the automated breath-by-breath measurement of both oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}C_{O_2}$) measurements (Macfarlane, 2001). Also, some of these systems provide noninvasive measurement of the anaerobic threshold (Beaver et al., 1985), cardiac output (Vanhess et al., 2000) and respiratory gas exchange kinetics (Whipp and Ward, 1990).

As a new online metabolic analysis system becomes available, information on its performance, particularly of its validity and reliability is essential. Based on these data scientists and clinicians should make decisions about the suitability of the system against their own requirements (Hodges, 2004). Automated systems for measuring metabolic function during exercise should increase the accuracy, reliability and objectivity of such tests (Yeh et al., 1987). However, limited knowledge is available about the validity and reliability of the measurements produced by a number of these commercially available systems (Carter and Jeukendrup, 2002).

A few studies have focused on making direct comparisons of new automated systems over the past decade (Babineau et al., 1999; Brent and Papadopoulos, 2005; Jackson et al., 1983; Jacobs et al., 1999; Maiolo et al., 2003; Melanson et al., 1996; Miles et al. 1994; Miodownik et al., 2000; Wideman et al., 1996). Simultaneous measurements

eliminate diurnal and day-to-day variations reported by Armstrong and Costill (1985). On the other hand, several studies made comparisons between the new automated systems and the Douglas bag procedure as a criterion method (Basset et al., 2001; Carter and Jukendrup, 2002; Engebretson, 1998; Hodges, 2004; La Mere et al., 1993; McLaughlin et al., 2001; Miodownik et al., 2000; Porszasz et al., 1994; Prieur et al., 1997; Unnithan et al., 1994).

A recently-introduced online metabolic measuring system (Innocor, Innovision, Denmark) has no current published data available on the reliability and validity of metabolic measurements during both submaximal and maximal exercise. Reliability is an integral part of validity which pertains to the consistency of a measure (Thomas and Nelson, 2001). According to Safrit et al. (1989) reliability is defined as the consistency of measurements, or of an individual's performance on a test or the absence of measurement error. It has also been suggested that other terms such as 'agreement', 'concordance', 'consistency', 'reproducibility', 'repeatability' and 'stability' have been used in the literature interchangeably with 'reliability' (Atkinson and Nevill, 1998). The purpose of this study was to assess the reliability (consistency and agreement) between gas exchange variables measured by the Innocor and an alternative online metabolic system (CardiO₂, Medical Graphics Corp., St Paul, MN, USA) during a standard incremental exercise test. This study examined whether the Innocor metabolic system can be used interchangeably with the CardiO₂ system without affecting the diagnosis of an individual patient.

2.2 Validity and Reliability of Metabolic Measurement Systems

According to Macfarlane (2001) a great number of researchers feel that many fully automated systems have become a "black box" which can generate high densities of data without the user having sufficient understanding of how the breath-by-breath data were generated. This suggests that considerable care is needed when comparing metabolic data obtained from different or even identical automated metabolic systems. It is well known that errors in calculation of $\dot{V}O_2$ can be caused by errors in measurements of ventilation, the fractions of oxygen and carbon dioxide, as well as ambient temperature and pressure, with ventilation being the key variable (Howley et

al., 1995). Gore et al. (1997) stated that the validity and reliability of metabolic systems using an integrated or biological approach involving humans is problematic as humans are not reliable standards and may not be able to generate sufficiently high flow rates (up to 220 l·min⁻¹).

The reliability of an automated gas analysis system will be influenced by the variability of each physiological measure. The total obtained variability is the summary of the biological and technical differences (Macfarlane, 2001). Biological variability accounts for about 90% of the total variability, with only 10% or less of the variability coming from technical problems. Armstrong and Costil (1985) reported day-to-day variability of $\dot{V}O_2$ and \dot{V}_E measurements may alter by 4% and 3.6%, respectively.

An electronic literature search was used to identify the validity and reliability studies which compared two or more laboratory-based automated metabolic systems. It is important to record that the results of the search showed that several papers exist (Jacobs et al., 1999; Koh et al., 2005; Maiolo et al., 2003; McLaughlin et al., 2001; Melanson et al., 1996; Twaddle et al., 2005; Wideman et al., 1996; Wong and Duncan, 2005) which aimed to determine the validity and/or reliability of portable telemetric systems. However, the literature review of these systems was beyond the scope of this review.

2.2.1 Validity Studies – Automated Metabolic Analyser System vs. “Gold Standard”

2.2.1.1 Medical Graphics CPX/D system validity studies

Hodges (2004) assessed the validity and reliability of the CardiO₂ (Medical Graphics Corp., St Paul, MN, USA) metabolic analyser system compared with a criterion method (Douglas bag) using 20 subjects aged 33±11 years. They performed an incremental exercise test to volitional fatigue described by Bruce et al. (1973). Respiratory gas exchange data were analysed during the last 30 seconds of each stage and at peak exercise. T-test and Bland-Altman plots were used to examine differences

between the Cardio₂ and Douglas bag method. Peak $\dot{V}O_2$ and $\dot{V}C_2$ values measured by the two systems differed by 6%. These differences were significant ($p < 0.05$). Peak \dot{V}_E , $\dot{V}O_2$ and $\dot{V}CO_2$ values recorded by the two systems were not significantly different ($p < 0.05$). Stage by stage analysis revealed a range of differences in each of measured variables during the exercise test. The highest differences were for $\dot{V}O_2$ (14%) occurring at stage two, $\dot{V}C_2$ (14%) at stage one, \dot{V}_E (10%) at stages one and four, and $\dot{V}CO_2$ (6%) during peak exercise. $\dot{V}O_2$ was constant through all stages of the exercise test with a maximum difference of 1%. The author concluded that the Cardio₂ system is valid and reliable in assessment of $\dot{V}O_2$ and $\dot{V}CO_2$ across a range of exercise intensities. However, significant error exists in the system's measurement of expiratory flow. The measurement error in the Cardio₂ system may result from software application of the system. Although during peak exercise the data for $\dot{V}O_2$, $\dot{V}C_2$ and \dot{V}_E were both valid and reliable.

A study by Engebretson (1998), using 30 subjects aged between 17 to 53 years, compared Medical Graphics CPX/D system over a wide range of work rates, including maximum values, whilst in series with a conventional Douglas bag system. The steady-state values at the end of three minutes exercise showed no significant differences between the systems in \dot{V}_E and $\dot{V}O_2$, but there were significant differences (<3.6%) in $\dot{V}C_2$ variation, respiratory exchange ratio (RER), $\dot{V}O_2$, and $\dot{V}CO_2$, which the author noted were within the 4% standard range of most metabolic systems. Porszasz et al. (1994) focused not only on validating the Pitot tube flowmeter from the Medical Graphics system, but also evaluated the system's validity and reproducibility. They performed 23 tests on four participants at rest and during exercise. The Medical Graphics CPX/D system produced values for $\dot{V}O_2$ that were within 5.9%, whereas $\dot{V}C_2$ was within 3% of the Douglas bag values at rest. During exercise, computer $\dot{V}O_2$ averaged of 101.8% and $\dot{V}C_2$ averaged of 100.6% of the bag values. However, \dot{V}_E produced absolute differences ranging from +1.1 $l \cdot min^{-1}$ at low flow rates to -2.6 $l \cdot min^{-1}$ at higher flow rates, and were generally within the $\pm 2\%$ target range. The authors concluded that the symmetrically disposed Pitot tube flowmeter is a sensitive and accurate device, and the Medical Graphics system is

valid and reliable.

Prieur et al. (1998) compared Douglas bag measurements of $\dot{V}O_2$ to those obtained with a Medical Graphic CPX/D system (n = 7) during exercise under both normoxic and hyperoxic conditions. Using two-way ANOVA and Student's t-test, these authors reported non-significant differences (p>0.05) between two systems either in $\dot{V}O_2$, $\dot{V}C_{O_2}$ or \dot{V}_E . The authors concluded that the CPX/D system is stable and valid for assessing $\dot{V}O_2$ at a moderate hypoxia. However, the tests were from submaximal exercise only and did not include maximal efforts.

Walschlager and colleagues (1996) determined the validity of assessing $\dot{V}O_2$, $\dot{V}C_{O_2}$, and \dot{V}_E using two Medical Graphics systems (CPX/D and CPX Express) against the Douglas bag method. Fifteen well-trained male runners and cyclists with moderate to high exercise capacities, aged from 23 to 40 years, were recruited. Subjects performed an incremental exercise test either running or cycling. Differences in $\dot{V}O_2$, $\dot{V}C_{O_2}$, and \dot{V}_E between the traditional and the CPX/D and the CPX Express were determined using paired t-tests. Differences between the Douglas bag and CPX/D and the CPX Express were for \dot{V}_E 5.2% and 5.9%, for $\dot{V}O_2$ 3.9% and 2.2%, and for $\dot{V}C_{O_2}$ 2.6% and 4.9%, respectively. These authors concluded that the Medical Graphics systems were valid when compared to the Douglas bag method.

From the above it can be concluded that the Medical Graphics automated metabolic system provides a valid equipment for measurement of gas exchange and ventilation measures.

2.2.1.2 Validity and repeatability of other metabolic systems

Carter and Jeukendrup (2002) compared the validity and reliability of three online metabolic systems (Oxycon Alpha, Jaeger, Wuerzburg, Germany; Oxycon Pro, Jaeger, Wuerzburg, Germany; and Pulmolab EX670, Morgan Medical, Kent, UK) with that of the Douglas bag method. The results showed that during exercise all

systems produced higher mean values for \dot{V}_E compared to the Douglas bag. The Pulmolab produced significantly lower mean values for $\dot{V}O_2$ when compared to the Douglas bag. No differences for $\dot{V}O_2$ were reported between other systems. Also, no differences were reported between any of the systems for total mean $\dot{V}C_2$ and RER at lower intensity of exercise (100 W), whilst at higher intensity (150 W) the Pulmolab produced significantly higher mean values for $\dot{V}C_2$ and RER. Carter and Jeukendrup (2002) concluded that the Oxycon Alpha and Oxycon Pro are valid systems for generating accurate respiratory data for $\dot{V}O_2$, $\dot{V}C_2$ and RER during steady state exercise up to 150 W. These findings are supported by Rietjens et al. (2001), who found no differences for respiratory variables throughout an incremental cycle test between the Oxycon Pro and Douglas bag system. Further, Basset et al. (2001) assessed the accuracy of a computerized metabolic system using inspiratory and expiratory methods of measuring ventilation (TrueMax 2400, ParvoMedics, Salt Lake City, UT) in eight male subjects aged 27.5 ± 5.6 years. The criterion Douglas bag method assessed \dot{V}_E and fractions of O_2 and CO_2 in expired gas (FeO_2 and $FeCO_2$) for subsequent calculation of $\dot{V}O_2$, $\dot{V}C_2$ and RER. The results of this study showed that the close agreement exists between ParvoMedics system and Douglas bag method for all of the gas exchange variables. Also, Unnithan et al. (1994) assessed the validity of the Sormedics S2900Z automated metabolic system against values recorded from a Douglas bag method in ten active, healthy children aged 11.6 ± 2.3 years. The validity was assessed using two different exercise intensities either walking or running on a treadmill during physiological steady state. Significant differences were found in measurements of $\dot{V}C_2$ (3.6%) and $FeCO_2$ (6.5%) at high ventilatory flow. The authors noticed that possible reasons of differences in $\dot{V}C_2$ are water vapour and mixing capacity of the mixing chamber. The inability of the infrared sensors to cope with the water vapour could have contributed to the greater variability in $\dot{V}C_2$. Unnithan et al. (1994) concluded that the Sormedics system is valid instrument for gas exchange measurement. However, it is important to add that the authors did not state how many measurements fell within 95% limits of agreement. Also, the results showed that positive bias lay marginally outside of the acceptable 3% error recommended by Jones and Kane (1979).

The study by Miles et al. (1994) evaluated the reproducibility of four metabolic systems (Q-PLEX I/Corival ergometer, Quinton Instrument Co., Seattle, WA; SensorMedics 2900/Ergometrics ergometer, SensorMedics Corp., Yorba Linda, CA; MGC 2001 Mijnhardt ergometer, Medical Graphics Corp., St. Paul, MN; and MGC CPX/Medifit ergometer, Medical Graphics Corp.). Results of this study showed that all four system demonstrated excellent reproducibility (<5%) for values obtained during either submaximal or maximal exercise. While \dot{V}_E and $\dot{V}O_2$ were similar for all the systems during light intensity of exercise, the CPX system measured a higher $\dot{V}C_2$ compared with other systems. Surprisingly, this study reported that the average $\dot{V}O_2$ peak varied by 22% among the systems. The authors concluded that this might be due to differences in the hardware and software used to acquire and process the information. Miles et al. (1994) argued that substantial differences in data were due to gas analyser transport delay, different individual analyser times (dynamic response) and inherent noise in the respiratory signals. It was suggested that each manufacturer should describe clearly the way in which the basis measurements of oxygen and carbon dioxide concentration as well as ventilation are calculated to produce $\dot{V}O_2$, $\dot{V}C_2$ and \dot{V}_E . Also, La Mere at al. (1993) examined the reproducibility of a single maximal test on three metabolic systems (Quinton QPLEX I, Quinton Instrument Co., Seattle, WA, USA; Sensor Medics 2900, Sensor Medics, Yorba Linda, CA, USA; and the Medical Graphics 2001, Medical Graphics Co., St. Paul, MN, USA). Each of three metabolic analyser system was independently compared with the Douglas Bag method. This study reported small but significant mean differences in peak $\dot{V}O_2$ between systems, with the QPLEX and the Medical Graphics systems tending to overestimate $\dot{V}O_2$ peak compared to the Douglas bag method. The Sensor Medics system tended to underestimate \dot{V}_E by 2.8 l·min⁻¹ while the Medical Graphics system overestimated \dot{V}_E by 3.1 l·min⁻¹. There was significant difference between the Sensor Medics and Medical Graphics systems and a non-significant difference between the QPLEX and the Medical Graphics systems. Despite the statistical significance of the differing measurements the authors considered their practical significance small enough to be acceptable. Further, Jackson and colleagues (1983) evaluated the reliability of the Gould 9000IV computerized pulmonary

exercise system. This system was compared to an established component refereed system (Applied Electrochemistry O₂ analyser, Beckman LB-2 CO₂ analyser, and Parkinson-Cowab CD-4 gasometer) during simultaneous measurements of oxygen consumption. Two systems were placed in series. The results showed that the reliability estimated from both systems were extremely high, exceeding 0.981. The authors concluded that $\dot{V}O_2$ measured by the Gould system was highly reliable and reproduced the measurements obtained by the refereed system. Additionally, Miodownik et al. (2000) developed a semi-automated gas exchange measurement system based on a Douglas bag design. This system was validated using a modified version of the quantitative funnel burner lung model and standard water volume displacement. The validated system was further compared to the SensorMedics Deltatrac (mixing chamber Yorba Linda, California, USA) and Medical Graphics CPX (breath-by-breath) systems (Medical Graphics Corp., St. Paul, MN, USA). The Sensor Medics Deltatrac average $\dot{V}O_2$ and $\dot{V}C_{2O}$ error was 11.4% and 2.1%. The Med Graphics CPX average $\dot{V}O_2$ and $\dot{V}C_{2O}$ error was 2.6% and 1.7%, respectively. The Deltatrac and CPX systems both tended to increase $\dot{V}O_2$ errors as F_{IO_2} was increased. There was no significant difference in $\dot{V}C_{2O}$ measurements for all devices. Miodownik et al. (2000) further suggested that the increasing inaccuracy of the automated systems was traced to the limitations of their flow measuring devices. A study by Babineau et al. (1999) reported differences from 5 to 10 ml·kg⁻¹·min⁻¹ (10-17%) between three metabolic systems in the absolute and relative values of $\dot{V}O_{2max}$ and in the volume of expired gas for submaximal and maximal work, respectively. Furthermore, Hodges (2004) cited the study by Hiilloskorpi et al. (2000) which reported a significant difference between 6% and 22% in $\dot{V}O_{2max}$ between three metabolic analyser systems.

From previous cited studies it is clear that the results from different brands of automated metabolic systems can vary by surprisingly significant amounts. These variations have commonly been explained in the literature with following reasons (Miles et al., 1994): 1) differences in hardware and software used to acquire and process the information; 2) presence of the water vapour in the analyser which can lead to errors of up to 25% in the measurements of F_{EO_2} and therefore have an

important influence on the accurate calculation of $\dot{V}O_2$ (Beaver et al., 1973; and Cole, 1954); 3) substantial differences in data reduction which will occur due to correction for the varying alveolar oxygen concentration retained in the lung between breaths of different length and gas analyser transport delay; 4) temporal alignment of gas flow; 5) accuracy and reproducibility of flow and gas fraction measurements (Noguchi et al., 1982) 6) different individual analyser rise times (dynamic response), inherent noise in the respiratory signals, interpolating data between known points, and smoothing the record, such as with a five point moving average (Beaver et al., 1973).

Hodges (2004) suggested that probably the greatest problem in metabolic gas analysis systems today is the exact temporal alignment of gas flow with gas analysis. According to Proctor et al. (1996) the delay time between gas flow and gas analysis can cause an error in $\dot{V}O_2$ measurements of up to 30% at high breathing frequencies. Furthermore, Hodges (2004) suggested standardisation of the procedure when comparing two or more systems in the following aspects: 1) type of exercise protocol (e.g. step vs. ramp); 2) type of exercise (e.g. treadmill vs. cycle); 3) manner in which systems are compared (e.g. in series, in parallel or repeated measures); 4) timing of measurements (e.g. mid-stage, last minute of each stage, etc.); 5) acceptable limits for gas exchange measurements; and 6) the way in which data are treated for statistical analysis.

2.2.2 Acceptable Level of Accuracy

It has been suggested that respiratory volumes should be accurate within $\pm 2\%$ or within ± 50 ml (Macfarlane et al., 2001). For the overall measurement of $\dot{V}O_2$, an early suggestion was that repeated Douglas bag measures should be within $\pm 4\%$ (Wagner et al., 1973). Davies et al. (1974) considered a much higher level of agreement of $\pm 10\%$ to be acceptable. Thoden (1991) suggested a precision of less than ± 1 ml \cdot kg $^{-1}$ \cdot min $^{-1}$ over repeated tests, but acknowledged that ± 2 ml \cdot kg $^{-1}$ \cdot min $^{-1}$ was a more realistic day-to-day variation, and that over a period of a week the same individual should be within ± 3 ml \cdot kg $^{-1}$ \cdot min $^{-1}$. Skinner et al. (1999) recommended that the CV using an automated system should be within 4-9%. Further, Babineau et al. (1999) argued that most certifying organizations tolerate a maximal error of 4% in

$\dot{V}O_2$ determination or $2-3 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. Differences varying from 3% to 10% can be found in the literature (Hodges, 2005).

Thus for the purposes of this study, a value of 4% will be considered to lie within the acceptable range. The limits of agreement of $\pm 1.2 \text{ l}\cdot\text{min}^{-1}$ for minute ventilation and $\pm 0.15 \text{ l}\cdot\text{min}^{-1}$ for oxygen consumption will be acceptable, as suggested by Basset et al. (2001).

2.2.3 Rationale and Purposes of the Study

The Innocor (Innovision, Denmark) is a new commercial automated metabolic system which has been primarily developed to measure non-invasively cardiac output at rest and during exercise. However, the manufacturer has also produced a breath-by-breath module which allows measurements of $\dot{V}O_2$, $\dot{V}C_{O_2}$, and \dot{V}_E interactively with haemodynamic data. Before purchasing the Innocor automated metabolic system, it was considered prudent to evaluate its agreement with existing metabolic system. Currently, there is no published information concerning both the validity and reliability of the Innocor metabolic measurements. There are, however, such data on the CardiO₂ (Medical Graphics Corp., St Paul, MN, USA). Thus, the purpose of this study was to assess consistency and agreement between gas exchange variables measured by the Innocor and the CardiO₂ during an incremental exercise test.

The Innocor system should be used in later studies for testing people with heart failure. It was reasonable to establish its consistency and agreement by comparing with the CardiO₂ system before proceeding to the following stage. This study examined whether the Innocor metabolic system can be used interchangeably with the CardiO₂ system without affecting the diagnosis of an individual patient.

2.2.4 Research Hypotheses

H_1 – There will be a non-significant difference between gas exchange variables measured by the two metabolic systems.

H_2 – There will be a high consistency between gas exchange variables measured by

the two metabolic systems.

H_3 – There will be acceptable levels of agreement between gas exchange variables measured by the two metabolic systems.

2.3 Methods

2.3.1 Subjects

Fifteen healthy adults (ten males and five females), staff and students of a South East UK University gave their signed informed consent to participate in this investigation. Subjects were recruited by personal contact. None of the subjects were taking any medications that might interfere with physiological responses and none had any limitations to strenuous exercise as determined by a standard physical activity readiness questionnaire (PAR-Q) adapted from Thomas and Nelson (2001). Subjects reported that they were active (e.g. walking, running, swimming, cycling, and weight lifting approximately 2-3 times per week). However, none were engaged in regular structured training programme. All subjects were familiar with graded exercise testing. Subjects were asked to refrain from eating for a minimum of 2 h prior to the test and from vigorous exercise on the day of and the day before the test. All procedures were in accord with the local research guidelines as approved by the Faculty ethics committee and the declaration of Helsinki.

2.3.2 Equipment

2.3.2.1 Innocor system design

The Innocor (Innovision, Odense, Denmark) is a compact device intended to be used for non-invasive measurement of cardiac output using an inert gas (N_2O) rebreathing methodology. It incorporates a breath-by-breath module to measure gas exchange variables (e.g. fractions of expired O_2 and CO_2 (F_{EO_2} and F_{ECO_2}), minute ventilation (\dot{V}_E)) and to calculate a number of derived variables (e.g oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}C_{O_2}$)). Despite the significant increase in

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functionality with the breath-by-breath option, the Innocor is still a compact device. The total weight of the instrument is less than 10 kg (Figure 2.1).



Figure 2-1 Innocor metabolic gas analyser.

Subjects are connected to the Innocor by a disposable rubber mouthpiece, attached directly to the respiratory valve unit (RVU). The RVU is connected to the Innocor via a 6 tube connector for controlling the pneumatic valves, bag filling and evacuation, and a tube for measuring the mouth piece pressure. The gas sample line and airflow umbilical are also connected to the RVU. Gas data analysis is performed and results presented by the Innocor software (version 5.05). Monitoring and presentation of the data is via the Innocor integrated computer with a Pentium MMX and Windows NT / XP embedded operating system. Measurement of airflow is performed by a pressure difference pneumotach. CO₂ gas analysis is performed by the photo acoustic gas analyser which uses the principle of Photo Acoustic Spectroscopy (PAS). Oxygen is analysed using an oxygen sensor (Oxigraf Inc., USA) based on the principle of laser diode absorption spectroscopy. Only the oxygen sensor needs 1-point calibration on a regular basis by the user while both oxygen sensor and photoacoustic gas analyser require multi-point calibration performed by manufacturer periodically (6-12 months). The manufacturer reported accuracy for measurements of ventilation $\pm 1\%$, while for O₂ and CO₂ concentrations $\pm 0.01\%$.

Measurement of airflow, gas sampling, carbon dioxide and oxygen detection is

provided in detail in Appendix II.1.

2.3.2.2 Medical Graphics CardiO₂ system design

The CardiO₂ (Medical Graphics Corp., St Paul, MN, USA) is an automated breath-by-breath respiratory gas analysis system with integrated 12-lead stress ECG diagnostic exercise testing system (Cardio Perfect ST 2001, Cardio Control, Delft, Netherlands). Together with other computerised metabolic systems, the CardiO₂ measures volume, flow and gas fractions. It provides the advantage of a single, light weight, sample line and pressure transducer umbilical. Subjects performed the exercise test using a motor driven treadmill. Subjects are connected to the metabolic cart by means of a disposable rubber mouthpiece, attached directly to the flowmeter, to which the gas sample line and airflow umbilical were connected. Gas analysis is performed and results presented by the BreezeSuite (version 5.0) gas exchange testing software (Medical Graphics Corporation, St. Paul, Minnesota, USA). The software presents respiratory data as 30-second means. Monitoring and presentation of the data is via a personal computer (Dell Precision 340 Pentium 4, Dell Computer Corporation, Texas, USA). Gas analysis is performed by means of Zirconia electrochemical (O₂) and infrared (CO₂) analysers. Airflow is measured by means of a pitot tube flowmeter. This operates by incorporating prevent bi-directional differential pressure. The manufacturer of the CardiO₂ reported accuracy for measurement of ventilation $\pm 3\%$ or 50 ml, while for O₂ and CO₂ concentrations $\pm 0.03\%$.

Characteristics of CardiO₂ measurement of airflow, gas sampling, carbon dioxide and oxygen detection is provided in detail in Appendix II.2.

2.3.3 Procedure

2.3.3.1 Calibration

Both systems were calibrated before each exercise test according to manufacturer recommendations. The gas mixtures used for the CardiO₂ calibration were 5% CO₂ , 12% O₂ in balanced N₂ (calibration gas) and 21% O₂ in balanced N₂ (references gas). The Innocor system only requires gas delay determination (specific breathing pattern

performed by user) and O₂ adjustment to the ambient air prior to the test. In order to obtain simultaneous measurements the two systems were placed in series and subsequently calibrated according to the manufacturers' recommendations before the exercise test. The volume calibration was performed using a certified volume syringe (MedGraphics, St Paul, Minn) of 3 litres following the two systems were placed in series. The Innocor respiratory valve unit, with bacterial filter, was attached into the pneumotach of the CardiO₂ system using a five cm flexible tube. Both systems were attached to the subject's face mask, where the pneumotach of the CardiO₂ system was closer to the subject's mouth and the Innocor respiratory valve unit was 10 cm from the subject's mouth (see Figure 2.2). Such configuration increased dead space and the distance between the subject's mouth and the Innocor gas sensors.

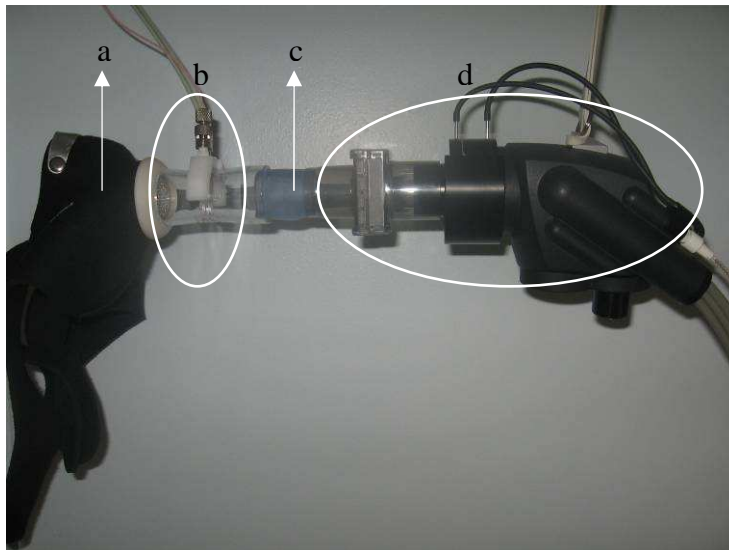


Figure 2-2 Pictorial description of the installation of the two systems

a) face mask, b) CardiO₂ pneumotach with flow sensor and gas sample line, c) flexible tube, d) Innocor respiratory valve unit with bacterial filter, flow sensor and gas sample line.

2.3.3.2 Pre-test procedure

Following calibration the Innocor respiratory valve unit together with the CardiO₂ pneumotachometer were attached to the Innocor support arm above the front side of the treadmill. Age, height and weight were obtained before exercise testing. Weight was measured using a Secca scale and height was measured on a wall-mounted stadiometer. All subjects were instructed on the use of Borg 6-20 Rating of Perceived Exertion (RPE) scale to ascertain their perception of effort during each test.

2.3.3.3 Testing procedure

All tests were performed by an incremental exercise test to volitional fatigue on a motor driven treadmill (Cardio Control, Delft, Netherlands) using the protocol described by Bruce and colleagues (1973). The Bruce protocol begins with 3-minute stages of walking at 1.7 mph and 10% gradient. Thereafter, the grade is incremented 2% every 3 minutes, and the speed is incremented 0.8 mph every 3 minutes until the treadmill reaches 18% grade and 5 mph. After this, the speed is increased by 0.5 mph every 3 minutes. During the test, expiratory gas was analysed repeatedly using both the Innocor and CardiO₂ systems, sampled on a breath by breath basis. Metabolic data were analysed during the last 30 seconds of each stage and at peak exercise.

2.3.4 *Statistical Analysis*

All statistical analysis was performed using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA). Prior to the statistical analyses all data were screened for univariate and multivariate outliers using Z-scores and Mahanobis distance test. In order to determine differences between the Innocor and CardiO₂ system, a t-test for paired samples or Wilcoxon signed rank test were used. Statistical significance was indicated if $p < 0.05$. Bland-Altman plots (Bland and Altman, 1986) were constructed to assess agreement between gas exchange variables measured by the Innocor and CardiO₂ system. Cronbach's alpha (Cronbach, 1951) was calculated to demonstrate consistency in individual measure between the two systems. Values are expressed as means \pm SD unless otherwise indicated.

2.4 Results

Subjects were aged 34 ± 11 years; height, 173 ± 11.2 cm; weight, 70.7 ± 12.7 kg. All 15 subjects completed the first three stages of the Bruce protocol. Twelve subjects completed stage four and finished the test during stage five, while only three subjects completed the stage five and entered stage six before terminating the test. The three sets of results from the end of the stage five were not included for comparison due to the small sample size. Table 2.1 illustrates the peak values measured by the Innocor and the CardiO₂ metabolic systems.

Table 2.1 Differences in Measured Gas Exchange Variables at Peak Exercise of Bruce Protocol between Innocor and CardiO₂ (N=15) – Paired samples t-test (t) and Wilcoxon signed rank test (z)

Gas exchange variables	Innocor mean±SD	CardiO ₂ mean±SD	t	z	p	Cronbach's Alpha
FeO ₂ (%)	17.29±0.54	17.31±0.52	-0.16	-	0.87	0.78
FeCO ₂ (%)	3.69±0.59	3.97±0.39	-1.71	-	0.11	0.35
$\dot{V}O_2$ (ml·kg ⁻¹ ·min ⁻¹)	39.63±10.34	39.69±8.33	-0.04	-	0.97	0.89
$\dot{V}O_2$ (l·min ⁻¹)	2.88±1.02	2.83±0.80	0.49	-	0.63	0.95
\dot{V}_E (l·min ⁻¹)	79.62±28.72	81.31±32.76	-0.61	-	0.56	0.97
$\dot{V}C_2$ (l·min ⁻¹)	2.95±1.14	3.19±1.21	-1.40	-	0.19	0.91
RER	1.02±0.13	1.11±0.14*	-	2.07	0.04	0.53

FeO₂ - fraction of expired oxygen; FeCO₂ - fraction of expired carbon dioxide; $\dot{V}O_2$ - oxygen uptake; \dot{V}_E - minute ventilation; $\dot{V}C_2$ - carbon dioxide production; RER - respiratory exchange ratio; * = Indicates the Innocor result is significantly different from the CardiO₂ system (p<0.05).

At peak exercise the Innocor measured FeO₂ equivalent to the CardiO₂ system, with non significant difference. Mean peak $\dot{V}O_2$ in both relative (ml·kg⁻¹·min⁻¹) and absolute (l·min⁻¹) values, recorded by the two systems were different by 0.15% and

2%, respectively. \dot{V}_E at peak exercise measured by the Innocor was slightly underestimated (by 2%) compared with the CardiO₂ system. FeCO₂ measured by the Innocor at peak exercise was lower by 7% compared with the CardiO₂ system, while $\dot{V}C_2$ and RER were lower by 7.5% and 8%. RER difference was the only significant (p<0.05) measure. Cronbach's alpha showed that at peak exercise all variables except FeCO₂ and RER have acceptable or high consistency.

Stage by stage analysis revealed a range of differences in measured variables (Appendix I). Figures 2.3 to 2.9 show the results for respiratory variables measured by the Innocor and CardiO₂ systems through all exercise stages.

For FeO₂ and $\dot{V}O_2$ the differences between the two systems ranged from 2% - 7%, dependant on the stage. The difference of 5% in measured FeO₂ was significant at stage one (p<0.05) (Figure 2.3). Estimated $\dot{V}O_2$ in relative and absolute units was not significantly different (Figures 2.5 and 2.6). Cronbach's alpha ranged from 0.80 to 0.99, with an average of 0.88 for relative $\dot{V}O_2$, and from 0.93 to 0.95 with an average of 0.94 while for absolute $\dot{V}O_2$ (Appendix I).

FeCO₂, $\dot{V}C_2$ and RER measured by the Innocor were significantly lower compared with CardiO₂ (Figures 2.4, 2.7 and 2.9). The differences for FeCO₂ ranged from 12% - 20%, while for $\dot{V}C_2$ and RER from 9% - 22% and 8% - 15%. Cronbach's alpha ranged from 0.20 to 0.77 for FeCO₂, 0.84 to 0.94 for $\dot{V}C_2$ and 0.22 to 0.61 for RER.

\dot{V}_E measurements recorded by the Innocor were higher compared with CardiO₂ throughout all exercise stages, but these differences were not significant (Figure 2.8) and ranged from 2% - 7%. Cronbach's alpha for measured \dot{V}_E ranged from 0.84 to 0.98, with an average of 0.92.

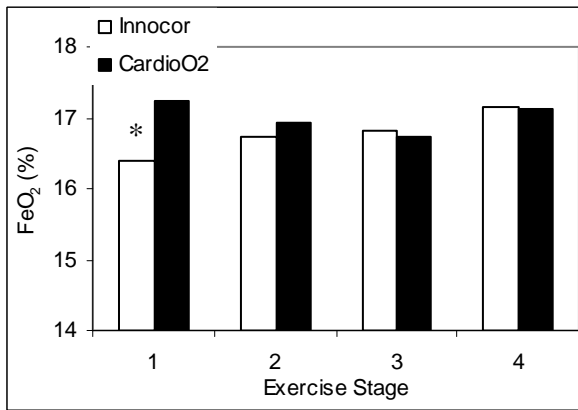


Figure 2-3

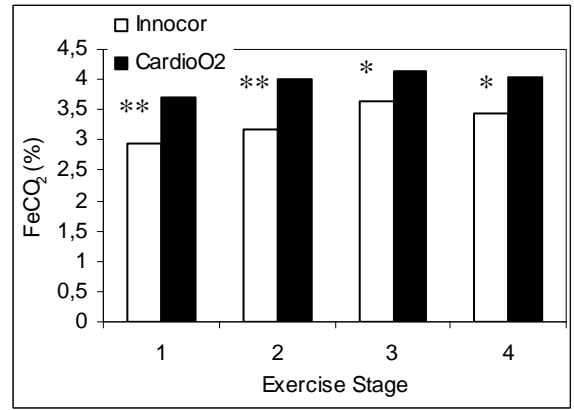


Figure 2-4

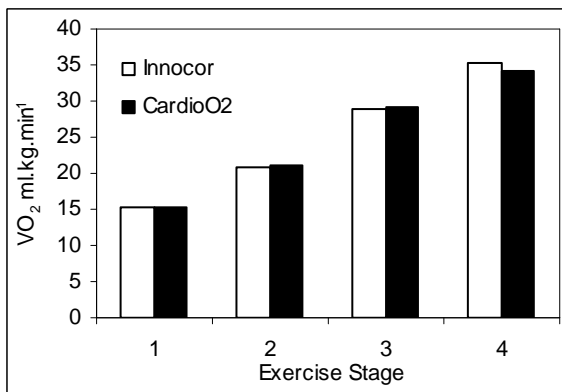


Figure 2-5

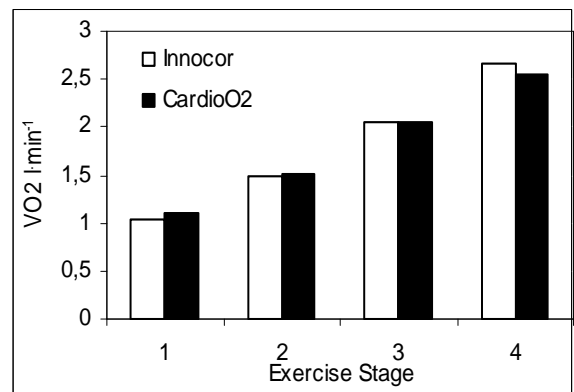


Figure 2-6

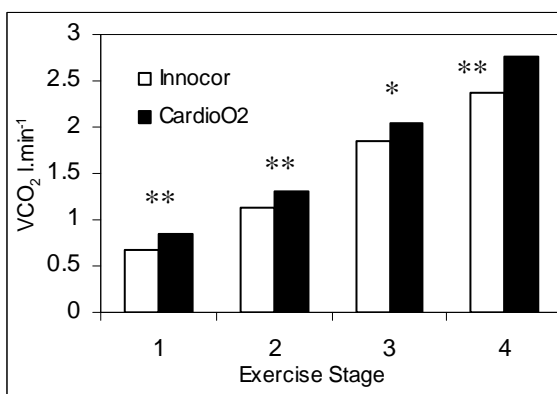


Figure 2-7

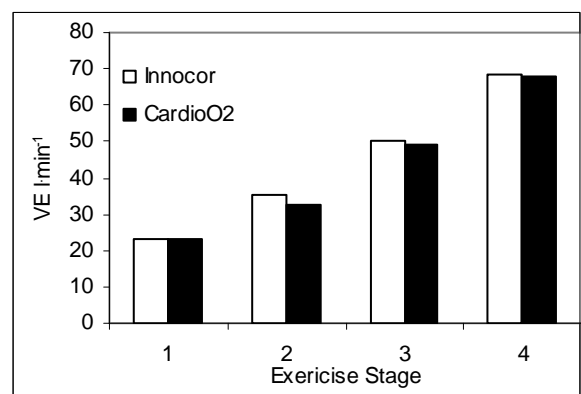


Figure 2-8

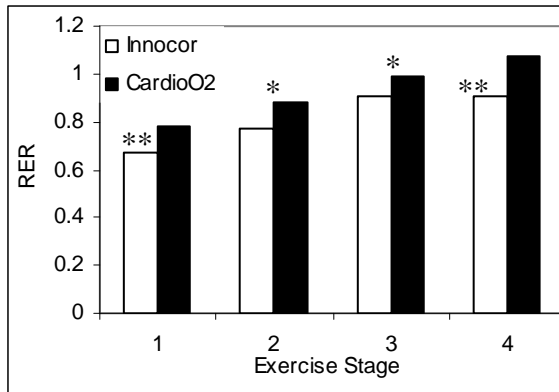


Figure 2-9

Figures 2.3 – 2.9 Differences in means of gas exchange variables between the Innocor and CardioO₂ systems through four exercise stages of Bruce protocol.

*indicates significant difference (p<0.05); **indicates significant difference (p<0.01).

Bland-Altman analysis which included data from the end of each exercise stage and from peak exercise showed that the Innocor reported higher V_E values by a mean value of 0.96 l·min⁻¹ compared with the CardioO₂ and the limits of agreement of -8.74 and 10.66 l·min⁻¹ (Figure 2.10).

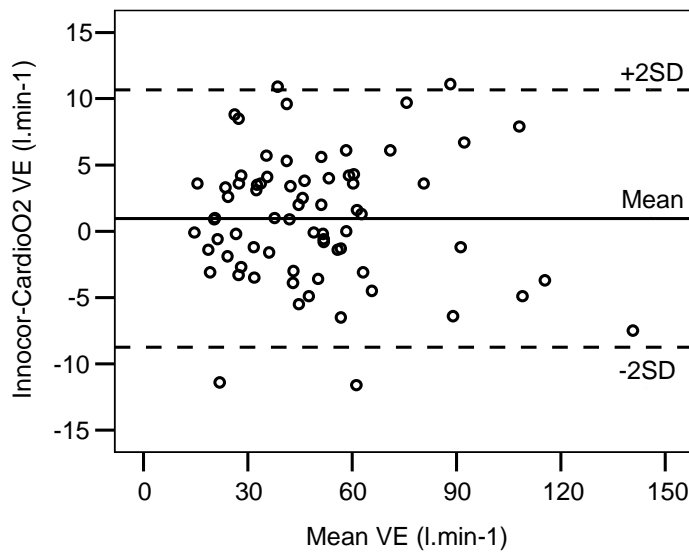


Figure 2-10 Bland-Altman plot to demonstrate limits of agreement shown by the two metabolic systems in measuring \dot{V}_E . The solid line is at the bias (mean of the difference) and the dashed lines represent lower and upper limits of agreement ($\pm 2SD$ of the mean difference).

Mean difference between the two systems in estimated $\dot{V}O_2$ in relative and absolute units were 0.02 ml·kg⁻¹·min⁻¹ and 0.04 l·min⁻¹ and the limits of agreement were -7.15 to 7.18 ml·kg⁻¹·min⁻¹ and -0.52 to 0.55 l·min⁻¹ (Figures 2.11 and 2.12).

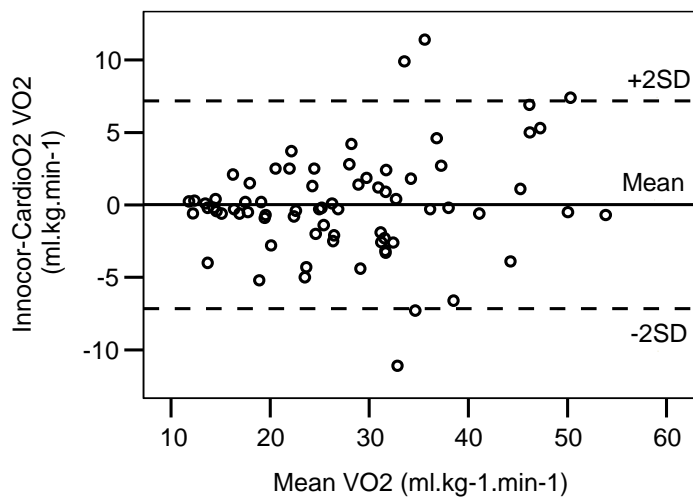


Figure 2-11 Bland-Altman plot to demonstrate limits of agreement shown by the two metabolic systems in measuring relative $\dot{V}O_2$. The solid line is at the bias and the dashed lines represent lower and upper limits of agreement.

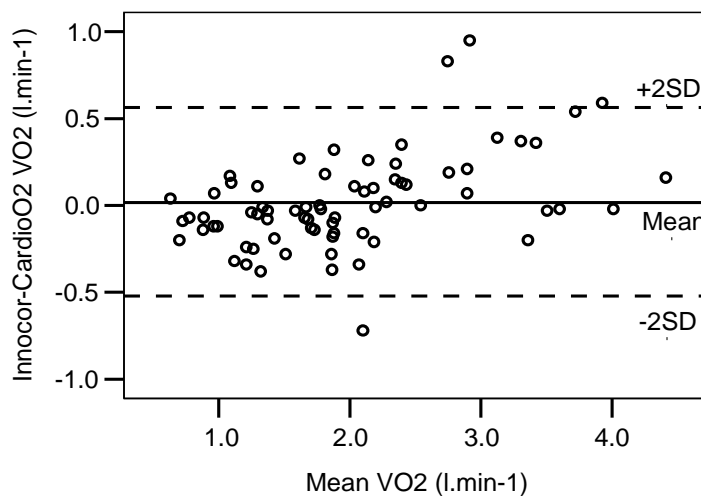


Figure 2-12 Bland-Altman plot to demonstrate limits of agreement shown by the two metabolic systems in measuring absolute $\dot{V}O_2$. The solid line is at the bias and the dashed lines represent lower and upper limits of agreement.

Figure 2.13 shows that systematic bias exists between the two systems in estimation of $\dot{V}C_2$ through different stages of exercise. $\dot{V}C_2$ was underestimated by a mean value of $-0.23 \text{ l}\cdot\text{min}^{-1}$, and the limits of agreement were -1.01 to $0.56 \text{ l}\cdot\text{min}^{-1}$.

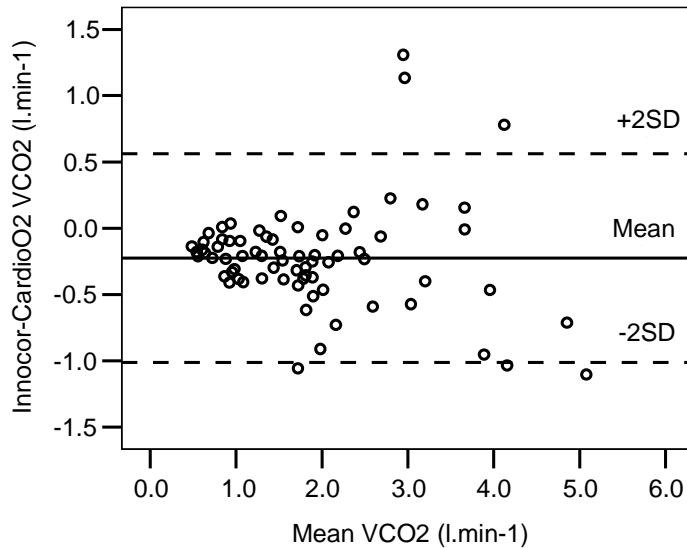


Figure 2-13 Bland-Altman plot to demonstrate limits of agreement shown by the two metabolic systems in measuring $\dot{V}C_{O_2}$. The solid line is at the bias and the dashed lines represent lower and upper limits of agreement.

Bland-Altman analysis also revealed that a mean difference in measured $\dot{V}O_2$ between the two systems was -0.19 % and the limits of agreement were -1.77 to 1.38 %. For $\dot{V}CO_2$ mean difference between the two systems was -0.59 % with upper and lower limits of agreement of -1.87 and 0.70 %.

2.5 Discussion

The purpose of this study was to assess the reliability (consistency and agreement) between gas exchange variables measured by the InnocoR and the Cardio O_2 during an incremental exercise test.

The results of this study demonstrated that the InnocoR metabolic system yielded mean $\dot{V}O_2$, in both absolute and relative values, that were close to those obtained by the Cardio O_2 system, with non significant differences. Apart from stage one, measured $\dot{V}O_2$ was also non significant between the two systems.

As suggested, the Cronbach's alpha coefficient should be used to indicate a degree of consistency between measurements (Cronbach, 1951). Bland and Altman (1997)

recommended that the Cronbach's alpha should be a minimum of 0.90, and 0.95 to be desirable for clinical application. Based on this assumption it may be suggested that the Innocor and the Cardio₂ showed high consistency in measured \dot{V}_E and derived $\dot{V}O_2$.

The present $\dot{V}O_2$ values compare favourable with finding by Engebretson (1998) who reported difference less than 3.6% in measured $\dot{V}O_2$ between the Medical Graphics CPX/D system and the Douglas bag. Furthermore Porszasz et al. (1994) found that Medical Graphics CPX/D produced values of $\dot{V}O_2$ that were within 5.9% compared to the Douglas bag, while Walschlager et al. (1996) demonstrated differences of 3.9% and 2.2% in measured $\dot{V}O_2$ between the CPX/D and the CPX Express compared with the gold standard. In contrast Hodges (2004) reported that $\dot{V}O_2$ in both absolute and relative values was significantly ($p < 0.05$) underestimated (up to 14%) by the Cardio₂ compared with the Douglas bag during all exercise stages as well as at peak exercise. However, following recommendation of the manufacturer and installation of the drying cartridge, Hodges (2004) suggested that difference would decrease by 5%. The author concluded that the Cardio₂ is a valid system for measuring respiratory variables.

Bland-Altman plots also revealed that there was no systematic bias in reported $\dot{V}O_2$ in both absolute and relative units between the Innocor and Cardio₂. This can be recognised by the mean of the difference being centred closely to zero. However, the limits of agreement for $\dot{V}O_2$ were large and seem to be unacceptable in exercise testing. Furthermore this study demonstrates that even a high Cronbach's alpha coefficient must be taken with caution when examining consistency between two measurements. Hence when reporting statistical results, it is important to consider practical and clinical implications of the results before making conclusions and further recommendations.

It may be noticed that the Innocor measured \dot{V}_E slightly, but not significantly higher than the Cardio₂ through all exercise stages except at peak exercise. Cronbach's

alpha indicated high consistency in measured \dot{V}_E between the two systems, whilst the Bland-Altman analysis revealed no systematic bias. However, the limits of agreement were wide (-8.74 to 10.66 l·min⁻¹) and this is also unacceptable in exercise testing.

A study by Miles et al. (1994) demonstrated that the Medical Graphics CPX automated system produced the lowest \dot{V}_E measurement among four different metabolic systems. Furthermore, Hodges (2004) reported that \dot{V}_E measured by CardiO₂ system was significantly ($p < 0.05$) underestimated through all exercise stages compared with the Douglas bag (up to 10%). Also, Walschlager et al. (1996) found that the Medical Graphics CPX Express and CPX/D underestimated \dot{V}_E by 5.9 and 5.2 % compared with the Douglas bag, while Engebretson (1998) showed no significant differences between the Medical Graphics CPX/D and the gold standard in \dot{V}_E measurements. Only one study by La Mere et al. (1993) illustrated that the Medical Graphics 2001 system overestimated \dot{V}_E by 3.1 l·min⁻¹ compared with the gold standard.

Although both the Innocor and CardiO₂ systems use the principle of differential pressure for measurement of airflow, one of the potential sources of error is the method and equation used to estimate the BTPS factor (Hodges, 2004). When a subject exhales during a cardiopulmonary exercise test, the air leaves the lungs and enters the spirometer at 33-35°C (Cole, 1954) and is saturated with water vapour (Beaver et al., 1973). Most volume type spirometers assume instantaneous cooling of the air as it enters the spirometer, although errors can occur due to incorrect assumptions of instantaneous cooling of the air (Hodges, 2004). Depending on the environmental temperature, the BTPS correction factor could be as large as 10% (Crapo, 1994). Further, the distance between the flow sensor and the mouth may be another potential source of error (Hodges, 2004). As stated earlier, the two systems were placed in series where the CardiO₂ pneumotach was inserted into the face mask. Then the Innocor respiratory valve unit with a bacterial filter was attached into the CardiO₂ pneumotach using a flexible tube. This made the distance between the Innocor respiratory valve unit and subject's mouth of 10 cm. However, it is important to note that reversing the order of the systems, and subsequent measurement, was not

possible due to equipment design. Additionally, slight overestimation of \dot{V}_E may be due to the presence of water vapour in the analysers, temporal alignment of a gas flow or analyser rise time (dynamic response) as suggested by Beaver et al. (1973).

$\dot{V}C_{O_2}$ values reported by the Innocor were significantly lower than those by the CardiO₂. These differences were due to a systematic underestimation of FeCO₂. Although the Innocor measured \dot{V}_E slightly higher during all exercise stages, this was not enough to compensate for a significantly lower FeCO₂ in the determination of $\dot{V}C_{O_2}$.

Miodownik et al. (2000), when comparing a newly developed semi-automated metabolic system based on a Douglas bag design and the Med Graphics CPX, reported a non significant difference of 1.5% in $\dot{V}C_{O_2}$. Unnithan et al. (1994) assessed the validity of the Sensormedics automated metabolic system against the Douglas bag method and found out that measured $\dot{V}C_{O_2}$ was significantly different by 3.6% at high ventilatory flow. $\dot{V}C_{O_2}$ measured by the Truemax 2400 metabolic system was in close agreement with values obtained by the Douglas bag method (Basset et al., 2001). When compared with the Douglas bag method, the Med Graphics CPX Express and CPX/D systems underestimated $\dot{V}C_{O_2}$ by 4.9% and 2.9% (Walschlager et al., 1996). In agreement with this finding Hodges, (2004) reported that the CardiO₂ system produced a lower $\dot{V}C_{O_2}$ in range of 6% to 14%, while Engebretson (1998) also noted significant differences in $\dot{V}C_{O_2}$ and RER measured by the Medical Graphics system. By contrast, few studies reported no significant differences in measured $\dot{V}C_{O_2}$ between the Medical Graphics systems and the Douglas bag method (Porszasz et al., 1994; Prieur et al., 1998). Miles et al. (1994) reported that the Medical Graphics CPX system measured a higher $\dot{V}C_{O_2}$ compared with three other metabolic systems.

Apart from increased dead space and the distance between the Innocor sensors and the subject's mouth, differences in measured FeCO₂ may be explained by the technological differences between the two systems. The Innocor uses a newly

developed portable multigas analyser which uses the principle of photoacoustic spectroscopy with an infrared spectrum. In contrast, the CardiO₂ uses a standard infrared carbon dioxide analyser. Furthermore reported differences may be due to differences in the software used to acquire and process the information. These technological differences may contribute to the poor consistency in measured FeCO₂ and derived $\dot{V}C_{O_2}$ and RER between the two systems. An additional problem is that of correcting water vapour pressure in the expired air, as this pressure may be quite different to that in the calibration gas (Davies et al., 1974). Although mass spectrometers can be adjusted automatically to ignore the contribution of water vapour (effectively measuring dry air), most CO₂ analysers are sensitive to the presence of water vapour (Macfarlane, 2001). Ignoring the effects of water vapour pressure can lead to errors of up to 25% (Beaver et al., 1973). The inability of the infrared sensors to cope with the water vapour could have contributed to the greater differences in FeCO₂. Furthermore, as the dead space was increased, this could potentially enhance higher water condensation, and possibly affect CO₂ analyser and measurement of FeCO₂.

In summary, although the Innocor yielded similar mean values of $\dot{V}O_2$ and \dot{V}_E to those obtained by the CardiO₂ system, it has been shown that they were not within acceptable levels of agreement. Furthermore $\dot{V}C_{O_2}$ and RER were systematically underestimated over a wide range of exercise intensities due to lower FeCO₂ measurements. From this study it is difficult to say which metabolic systems measures more precisely. However, it may be suggested that these two systems cannot be used interchangeably on the same patient without affecting the diagnosis of an individual patient.

2.5.1 Study limitations

The same order of equipment was followed during all performed tests, where the Innocor's sample points were 10 cm far from subject's mouth. Increased the distance and possibly increased water condensation could effect CO₂ sensors and lead to the systematic error. However reversing the order of systems was not possible due to the equipment design.

Furthermore the Innocor respiratory valve unit, with a bacterial filter, was attached into the flow meter of the CardiO₂ system using a five centimetres long flexible tube. This bacterial filter could increase the resistance to airflow during exercise and consequently increase the subject's discomfort with an effect of terminating the exercise test earlier.

2.6 Conclusion

The proper interpretation of exercise test data depends on accurate data collection and correct calculations. The use of automated metabolic gas analysis systems has become common in cardiorespiratory exercise testing today. As a new online metabolic analysis system becomes available, information on its performance is essential. Therefore scientists and clinicians can make decision about suitability of the systems for their own requirements.

The design of this study allowed direct comparison between a recently introduced automated metabolic gas analysis system (Innocor, Innovision, Denmark) and the CardiO₂ (Medical Graphics Corp., St Paul, MN, USA) during exercise . The results of this study revealed that the Innocor produces very similar mean values of $\dot{V}O_2$ and \dot{V}_E to those obtained from the CardiO₂ system. However, the Bland-Altman analysis revealed that limits of agreement for $\dot{V}O_2$ and \dot{V}_E were wide, and therefore not acceptable in cardio-pulmonary exercise testing.

The data from the present study suggest that significant difference exists in the systems' estimation of $\dot{V}C_{O_2}$ and RER. This discrepancy is due to $\dot{V}C_{O_2}$ which was measured systematically higher by the CardiO₂.

It may be concluded that that the Innocor and the CardiO₂ metabolic systems cannot be used interchangeably, as to do so could affect the diagnosis of an individual patient. Results from the present study support previous suggestion that considerable care is needed when comparing metabolic data obtained from different automated metabolic systems.

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CHAPTER 3: COMPARISON OF CARDIAC OUTPUT DETERMINED BY DIFFERENT REBREATHING METHODS AT REST AND AT PEAK EXERCISE

Abstract

Introduction: The non-invasive determination of cardiac output (\dot{Q}_T) is of value in human physiology, especially clinical cardiology. Popular rebreathing methods today are the carbon dioxide (CO₂) rebreathing method (or indirect Fick) and the inert gas (nitrous oxide and sulphur hexafluoride) rebreathing method. The indirect measurement of mixed venous partial pressure of carbon dioxide using the CO₂ rebreathing technique can be estimated by the exponential method described by Defares (1958) or by the equilibrium method described by Collier (1956). The purposes of this study were: 1) to examine any differences between the equilibrium, exponential and inert gas rebreathing methods for measuring \dot{Q}_T at rest, 2) to evaluate reproducibility of these three methods at rest, and 3) to assess agreement between the exponential and inert gas rebreathing methods at peak exercise.

Methods: Following local ethics committee approval and informed consent, 17 healthy adults (10 males and 7 females) visited the exercise laboratory on separate days. Resting \dot{Q}_T was measured in a sitting position. The two measurements were separated by a five minutes rest. Twelve subjects performed a series of three incremental exercise tests to volitional fatigue using the Bruce protocol. The first test was used to determine the subjects' peak oxygen consumption. The other two exercise tests were used to measure \dot{Q}_T at peak exercise using the exponential and inert gas rebreathing methods. **Results:** The exponential method produced significantly higher ($p < 0.01$) estimates at rest (averaging 10.9 l·min⁻¹) compared with the equilibrium method (averaging 6.6 l·min⁻¹) and the inert gas rebreathing method (averaging 5.1 l·min⁻¹). There were non-significant differences ($p > 0.05$) in repeated measures for either method at rest. The exponential method had a larger variability (5.3%) than inert gas rebreathing method (4.8%), with the equilibrium method having the least variability (4.1%). At peak exercise there were non-significant differences between the exponential and inert gas rebreathing methods ($p = 0.14$). The mean difference between the exponential and inert gas rebreathing methods at peak exercise was 0.15

$\text{l}\cdot\text{min}^{-1}$ and the limits of agreement were -0.49 to $0.79 \text{ l}\cdot\text{min}^{-1}$. **Conclusion:** Based on a previous study that the resting \dot{Q}_T for healthy adults is $5 \text{ l}\cdot\text{min}^{-1}$, it is reasonable to suggest from this study that the inert gas rebreathing method seems to be more valid than the exponential and equilibrium methods for measuring \dot{Q}_T at rest. At peak exercise the exponential and inert gas rebreathing methods produced similar results and showed acceptable limits of agreement. Therefore the two methods may be used interchangeable at peak exercise.

3.1 Introduction

Knowledge of cardiac output is essential in many clinical situations and also of great value in human physiology, especially clinical cardiology. The measurement of cardiac output is useful in examining a patient's initial cardiovascular status and the cardiovascular response to various therapeutic interventions. Wasserman et al. (1999) suggested that cardiac output measurement is useful when trying to assess whether the patient's reduced O_2 uptake is due to reduced O_2 transport or failure of the muscles to extract O_2 .

Cardiac output is defined as the quantity of blood pumped into the aorta each minute by the heart (Guyton and Hall, 1996) and is usually expressed as litres per minute. This is also the volume of blood that circulates throughout the body and is responsible for transporting substances to and out from the tissues. Cardiac output is the product of the volume of blood ejected in each heart beat (stroke volume) and the frequency of heart beating per minute (heart rate) as below

$$\dot{Q}_T = SV \times f_C \dots\dots\dots(1)$$

where \dot{Q}_T is cardiac output, SV is stroke volume and f_C is heart rate.

For young, healthy men, the resting cardiac output averages about $5.6 \text{ l}\cdot\text{min}^{-1}$, while for adults it is often stated to be $5 \text{ l}\cdot\text{min}^{-1}$ (Guyton and Hall, 1996).

Over the past century, physiologists have applied much ingenuity to enhance both

invasive and non-invasive techniques for measuring cardiac output.

In 1870 Fick developed the original method and set out the equation for the measurement of cardiac output in steady state (Laszlo, 2004). This method is based on the principle of conservation of mass and is known as the Fick principle. Using oxygen as the test gas, it is the reference method or “gold standard” for cardiac output measurements to which all other methods are referred (Sun et al., 2000). According to the Fick principle “the output of fluid from a pump in a closed circuit system, can be determined from any change in concentration of a substance between the output and the input of the pump, and from the quantity of substance taken up by the fluid during a given time period” (McArdle, 2000). Fick states that the amount of a substance removed from or taken up by an organ per unit of time is equal to the arterial concentration minus the venous concentration of that substance multiplied by the blood flow through the organ (Wilmore and Costill, 2004). If the organ is represented by the total human body, the relationship between oxygen consumption ($\dot{V}O_2$), the $a-\bar{v}O_2$ difference (arterial and venous concentration of oxygen), and cardiac output (\dot{Q}_T , blood flow through the body) is expressed as the Fick equation:

$$\dot{V}O_2 = \dot{Q}_T \times a - \bar{v}O_2 \text{ diff} \dots\dots\dots(2)$$

$$\dot{Q}_T = \dot{V}O_2 / CaO_2 - C\bar{v}O_2 \dots\dots\dots(3)$$

According to the direct Fick technique the measurement of these variables involves venous cannulation and heart catheterization. This procedure is however, not without risks for the patient and therefore is not justifiable in many situations, especially during exercise (Ohlsson and Wranne, 1986). In the group of invasive techniques are also thermodilution and dye dilution methods (further description of these techniques is out of the scope of this chapter). However, apart from their complicated procedures, it has been suggested that invasive techniques are the most accurate for measuring cardiac output (Nugent et al., 1994).

During the 20th century, many non-invasive techniques for measuring cardiac output have been developed, such as electrical bioimpedance cardiography (Kubicek et al.,

1966), doppler ultrasound (Rawles and Haites, 1984), radionuclide angiography (Jeremy et al., 1985) and different gas rebreathing methods.

Rebreathing methods are based on the principle that the rate of uptake or excretion of physiological or non-physiological gases is determined from analysis of alveolar gas exchange. Based on this assumption it is possible to calculate pulmonary capillary blood flow which constitutes cardiac power output (Sackner, 1987).

This chapter describes differences between carbon dioxide and inert gas (nitrous oxide, sulphur hexafluoride) rebreathing methods.

3.1.1 Carbon Dioxide Rebreathing Method (Indirect Fick)

One of the several non-invasive techniques, the CO₂ rebreathing technique or indirect Fick method, estimates cardiac output from expired air measurements, using the following equation:

$$\dot{Q}_T = \dot{V}C_{O_2} / C(\bar{v} - a)CO_2 \dots\dots\dots(4)$$

Where \dot{Q}_T is cardiac output, $\dot{V}C_{O_2}$ is the volume of carbon dioxide produced, and $C(\bar{v} - a)CO_2$ is the difference in carbon dioxide concentration in arterial and mixed venous blood.

Carbon dioxide is virtually absent from inspired air, has high solubility, is relatively unaffected by non-uniformity of alveolar C₂ in the lung, and has a virtually linear slope to its dissociation curve over the physiologic range (Butler, 1965). Many gases are highly diffusible through the pulmonary membrane. Gas pressure in pulmonary capillary blood comes into equilibrium with that of the alveoli during the brief interval in which blood takes up oxygen from the lungs. If one knows the gas concentration in the alveoli, the gas concentration in the systemic arterial blood can be estimated (McHardy et al., 1967). To determine the blood flow through the capillaries the subject is required to breathe a foreign gas. The average concentration of the gas in the alveoli over a fixed period of time and the average rate of absorption during the

same period of time is used to calculate cardiac output (Hodges, 2004).

Carbon dioxide production is measured using breath-by-breath analysis by an online metabolic analyser. Pressure/concentration of venous carbon dioxide ($P/\bar{C}_v\text{CO}_2$) and pressure/concentration of arterial carbon dioxide (P/CaCO_2) are predicted by using rapid CO_2 analysers. Mixed venous CO_2 can be estimated by the exponential method described by Defares (1958) or by equilibrium method described by Collier (1956). Partial pressure of mixed venous CO_2 ($P\bar{v}\text{CO}_2$) is derived from the rebreathing method.

The exponential method involves analysing the exponential rise in end tidal carbon dioxide ($P_{\text{ET}}\text{CO}_2$) as the subject rebreathes from a bag containing 4% CO_2 , 35% O_2 , and the balance N_2 . The method requires that the subject rebreathes an initial gas mixture of 4% CO_2 . The bag is filled with approximately 1.5 to 2 times the subject's tidal volume. As the subject rebreathes, the $P_{\text{ET}}\text{CO}_2$ gradually increases and approaches $P\bar{v}\text{CO}_2$. End tidal CO_2 is measured using a capnograph. During rebreathing the CO_2 tension in the bag gradually increases with the number of respiration towards a limiting value. This limit is the CO_2 tension of the mixed venous blood (Defares, 1958). Using the technique described by Heigenhauser and Jones (1979) and later refined by Da Silva et al. (1985), a best fit line is plotted through the end tidal carbon dioxide points (Figure 3.1).

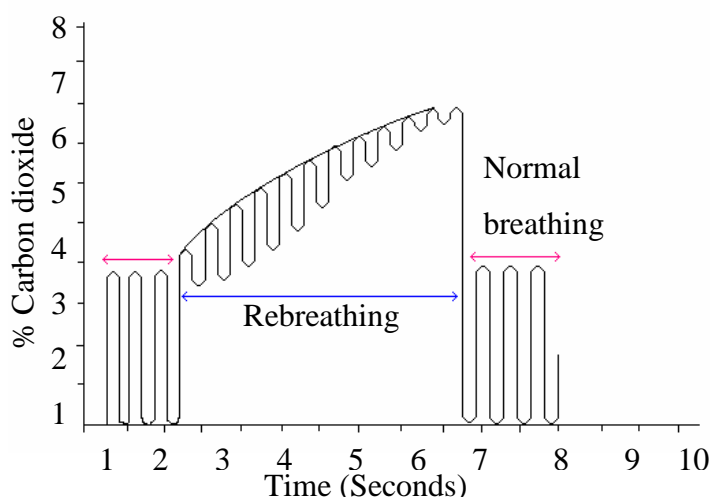


Figure 3-1 Exponential rebreathing capnograph tracing adapted from Medical Graphics Corporation (1993).

The blood leaving the lungs contains a high concentration of CO_2 . The blood is circulated through the body and more CO_2 is added. Recirculation occurs at approximately 15 seconds at rest and 10 seconds during exercise (Da Silva et al., 1985), when the exponential rise in CO_2 from rebreathing reaches the venous CO_2 level. A line of best fit is plotted through the end tidal CO_2 points.

The method is dependant on the initial CO_2 value and a uniform breathing pattern. A respiratory rate of 40 breathes per minute has been recommended during rest and exercise (Da Silva et al., 1985).

The equilibrium method requires the subject to rebreathe a high concentration of CO_2 until equilibrium is reached. This causes the lung to contain much more CO_2 than the venous blood, reversing the natural concentration gradient. The CO_2 will be moving from the lung in the arterial blood, and more CO_2 is added to the body, causing the rise on venous CO_2 . The CO_2 gradient that has been reversed comes into equilibrium on passing through the lungs. Therefore, the CO_2 concentration at the lungs is in equilibrium with CO_2 in mixed venous blood. The arterial CO_2 concentration is estimated from end tidal CO_2 levels using a capnograph (Figure 3.2). According to Da Silva (1985) recirculation takes approximately 10 to 15 seconds, which means that the

rebreathing manoeuvre should be completed within 10 to 15 seconds. A respiratory rate of greater than 40 breathes per minute speeds up the equilibrium (Da Silva, 1985). The equilibrium method for determining $P\bar{V}C_2$ and P_aC_2 is based on the assumption that P_2 equilibrium is reached across alveolar membranes (Klausen, 1965). A plateau is considered satisfactory when an inspired-expired CO_2 difference is less than 0.1% in two successive breathes and plateau occurred within 15 sec (Cambell and Howell, 1960).

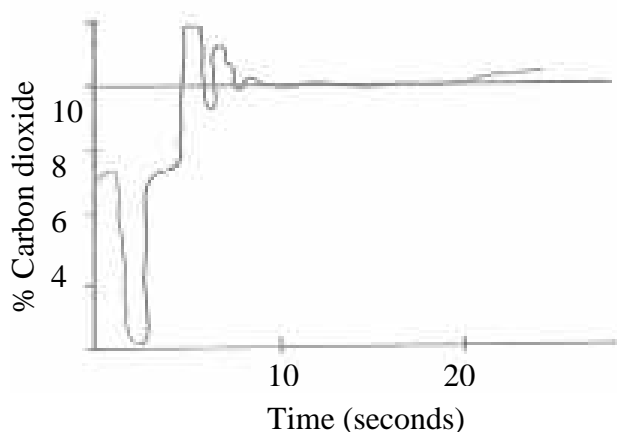


Figure 3-2 Equilibrium rebreathing capnograph tracing.

3.1.1.1 Validity and reliability of carbon dioxide rebreathing methods

A number of studies have been investigated to evaluate the validity and reliability of carbon dioxide rebreathing methods for measuring cardiac output at rest and during exercise. It has been compared with the direct Fick and other invasive and non-invasive methods, as shown below.

Muiesan et al. (1968) compared the equilibrium CO_2 rebreathing technique and the direct Fick method at rest in 17 healthy adults. They found a correlation coefficient of 0.94 ($p < 0.001$). Cardiac output values measured by the direct Fick were slightly higher (7.52%) than those obtained using the CO_2 rebreathing method. All values lay within 13% of the line of identity (the distance of each measured value squared from the line of best fit). In a separate experiment, Muiesan et al. (1968) found a high correlation ($r = 0.97$) between $P\bar{V}C_2$ as measured by the exponential and the

equilibrium method. Furthermore, Reybrouck et al. (1978) compared the exponential CO₂ rebreathing technique with the direct Fick method for measuring cardiac output at rest and during exercise in 16 healthy subjects. They found a moderate correlation at rest ($r=0.646$, $p<0.001$), and a high correlation was reported during exercise ($r=0.958$, $p<0.001$) between the two methods. During exercise it was found that 12% of the direct Fick and 10% of the exponential CO₂ rebreathing measurements were found to fall outside of the line of identity compared with 48% of the rebreathing measurements at rest. A study by Ferguson et al. (1968) reported a very low coefficient of correlation ($r=0.22$, $p<0.05$) between the dye dilution method and the exponential CO₂ rebreathing method at rest. During exercise, a high correlation of 0.87 ($p<0.05$) was reported. These results suggest that the exponential CO₂ rebreathing method is a poor indicator of cardiac output at rest. Ohlsson and Wranne (1986) compared the exponential CO₂ rebreathing method with the direct Fick during recumbent exercise in 13 patients. Results demonstrated that high relationship between the two methods exists ($r=0.91$, $p<0.001$). However, they noticed that cardiac output measured by the exponential CO₂ rebreathing method was significantly higher ($p<0.001$) than values obtained with the direct Fick method. These differences decreased gradually as intensity of exercise increased. Ohlsson and Wranne (1986) also reported no significant difference in cardiac output measured by CO₂ rebreathing method on separate days. Furthermore, Franciosa (1976) evaluated the equilibrium CO₂ rebreathing method in seriously ill patients. He found that the equilibrium method underestimates cardiac output compared to dye dilution and direct Fick method.

Nugent et al. (1994) compared cardiac output as measured by the equilibrium CO₂ rebreathing method with direct Fick and thermodilution method at rest in 11 patients undergoing routine cardiac catheterization. The equilibrium method gave significantly lower results compared with the direct Fick (4.80 vs. 5.53 l·min⁻¹). This also applied when comparing the equilibrium method with the thermodilution (4.96 vs. 5.69 l·min⁻¹). Also, Nugent and colleagues (1994) assessed reproducibility of the equilibrium CO₂ rebreathing technique in 10 healthy subjects at rest and during exercise. Measurements were made in triplicate on 3 separate days. The equilibrium method gave reproducible results between replicates at rest (coefficient of variation 9.1%) and

became more reproducible on exercise (5.6% and 5.4%).

Correlation coefficient used for method comparison in this context must be viewed with caution (Bland and Altman, 1986). That is highly dependent on the range of values within the given sample and it cannot assess systematic bias (Bland, 2002). The Pearson correlation coefficient does not indicate the extent to which the new measurements agree with an existing measurement, therefore this cannot be used to enable the direct method to be replaced with the indirect method. This can only be distinguished through the use of a method of assessing the limits of agreement between the methods, such as suggested by Bland and Altman (1986). The Bland-Altman method involves plotting the sum of the differences between the two methods against the average difference between the two methods. It is unlikely that the two measurements will agree exactly but it is an advantage to know how much the new measurement agrees with the old. The two methods of measurement agree if the difference is small enough to use the methods interchangeable. The differences are quantified by estimating the bias, which is the mean difference between the two methods and the limits of agreement. The limits of agreement are calculated from the mean and standard deviation of the difference. If the mean is close to zero there is a lack of systematic bias, the two measurements (methods) agree and the direct method could be substituted for the indirect method.

According to Nugent et al. (1994) the equilibrium method was found to underestimate cardiac output by mean value of $0.73 \text{ l}\cdot\text{min}^{-1}$ compared with the direct Fick. Nugent et al. indicated acceptable validity and limits of agreement (-0.09 to $-1.37 \text{ l}\cdot\text{min}^{-1}$) for the equilibrium method. A study by Cowley et al. (1986) compared the thermodilution technique with the equilibrium method. Using the Bland-Altman analysis they reported that limits of agreement were ranged from -0.37 to $0.47 \text{ l}\cdot\text{min}^{-1}$. Russel et al. (1990) reported wider limits of agreement (-1.80 to $1.24 \text{ l}\cdot\text{min}^{-1}$) when comparing the equilibrium method with the dye dilution technique.

It has been suggested that the coefficient of variation (CV) is a statistical measure which should be used in reproducibility studies (Bland, 2002). The CV assumes that the largest test retest variation occurs in the individuals scoring the highest values on the test. Acceptable levels of coefficient of variation are under 10% (Atkinson and

Nevill, 1998). Holmgren (1960) and Clausen et al. (1970) reported that the direct Fick method had a CV of 5.5-7.5%, whereas the CO₂ rebreathing method is more variable with CV of 8.2% (Clausen et al. 1970). Godfrey and Wolf (1972) supported the notion that the CV for cardiac output derived from the equilibrium method is smaller, being as accurate and reproducible as any of other direct methods. Zeidifard et al. (1972) investigated the reproducibility of the equilibrium method at rest and during exercise. They reported that the CV was high at rest but fell during exercise (up to 5.7%). Nugent et al. (1994) also found the equilibrium technique had a higher CV at rest (9.1%), and became more reproducible during exercise (5.6% and 5.4%). Rogers et al. (1997) determined the reproducibility of the exponential method measuring $\overline{P\dot{V}C}_2$ during exercise in four healthy subjects. The CV for $\overline{P\dot{V}C}_2$, determined by the CO₂ rebreathing technique, was 3.3% which compares favourable with 3.2% found by Clausen et al. (1970) for the direct measurement of pulmonary P_{aC}_2 . Smith et al. (1988) compared cardiac output measurements taken by electrical bioimpedance with the equilibrium carbon dioxide rebreathing techniques, both at rest and during exercise. No significant difference was found between the two methods at rest, while during exercise the equilibrium method overestimated cardiac output compared with electrical bioimpedance technique ($p < 0.005$). However, Smith and colleagues (1988) thought that the impedance signals may become distorted during exercise, and this may cause inaccurate measurements.

Vanhees et al. (2000) investigated the reproducibility of the exponential CO₂ rebreathing method. They subsequently compared both the equilibrium and exponential method at rest and during exercise in order to determine which method is superior in terms of reproducibility and clinical practicability. Twelve healthy men performed five graded exercise tests with a one-week interval. The equilibrium method was performed rebreathing from a bag containing high concentration of CO₂ (8.5%), O₂ (21%) with the balance nitrogen; the exponential method was performed using lower concentrations of CO₂ (4%). Estimated cardiac output was not significantly different between duplicate measurements at rest nor at any level of exercise with either method. At rest the mean difference ($l \cdot \text{min}^{-1}$) between duplicates and the coefficient of repeatability were 0.58 and 5.12, respectively for the exponential method and -0.25 and 3.25, respectively for the equilibrium method. At

rest, the exponential method showed a tendency toward larger variability than the equilibrium method. The exponential method produced significantly higher ($p < 0.001$) estimates at rest ($9.8 \text{ l} \cdot \text{min}^{-1}$) compared with the equilibrium method ($6.5 \text{ l} \cdot \text{min}^{-1}$). A second measurement at rest seemed to be more valid than the first. Reproducibility improved for both methods with increasing workloads. During exercise, both methods produced comparable values for cardiac output. Because of higher CO_2 concentration, the equilibrium method produced unpleasant side effects (e.g. dizziness, headache and dyspnoea) compared to the exponential method and led more subjects to premature interruption of the exercise test (Vanhees et al., 2000).

From previous cited studies it may be concluded that the exponential method is more appropriate and valid for use during high intensity exercise. The equilibrium method, however, has been suggested to be more valid for measuring cardiac output at rest.

3.1.2 Inert Gas Rebreathing Method

The inert gas rebreathing method, also known as the foreign gas rebreathing method, is an old technique first proposed by Bornstein (1910) and developed by Krogh and Linhard (1912). The Bornstein modification of the Fick principle states that if a physiologically inert gas is inhaled, its partial pressure in the pulmonary capillary blood equals that in the lungs. The change in the amount of the gas in the lungs, in an interval before recirculation occurs, equals its alveolar concentration times its solubility in blood and the amount of blood to which the gas is exposed during the interval (Rigatto et al., 1961).

Butler (1965) noted that the ideal gas for the measurement of pulmonary blood flow, which constitutes cardiac output in the absence of intrapulmonary shunt flow (Sackner, 1987), should be soluble in blood, relatively insoluble in lung tissue, easily analysed, and completely removed in the body. These aspects should eliminate the problem of recirculation. It should be an inert gas, its solubility in blood should not be influenced by the concentration of haemoglobin and it should not itself influence the pulmonary blood flow (Butler, 1965). Foreign gases usually used in the inert gas rebreathing method are physiologically inert, blood soluble gases such as acetylene, nitrous oxide and ethylene (Laszlo, 2004).

The principle of the inert gas rebreathing method is to let the subject breath a gas mixture containing a non-physiological soluble gas in a closed rebreathing assembly, which concentration in blood before rebreathing can be assumed to be zero (Hoeper et al., 1999). When the gas is inhaled it is rapidly taken up in the pulmonary capillary blood stream at a rate proportional to the effective pulmonary capillary blood flow. When the gas comes into contact with the blood in the lung capillaries, it is dissolved and is thus washed out by the blood perfusing the lungs (Liang et al., 2005). The pulmonary blood flow is therefore proportional to the rate of washout of blood soluble compound, which is measured continuously by a gas analyser (Liang et al., 2005). The rate of soluble gas disappearance allows the calculation of the pulmonary blood flow (Hoeper et al., 1999). Additionally, some systems today use gas mixture, which apart from an inert soluble gas (nitrous oxide, N₂O) also contains small amount of insoluble gas (sulphur hexafluoride, SF₆). This blood insoluble compound is used to determine the lung volume, which is required in the equation used to calculate cardiac output for the measured washout curve of the blood soluble compound (Liang et al., 2005). During the rebreathing period the concentration of insoluble gas (SF₆) decreases from the initial value in the bag to final equilibration value obtained after a few breaths. Since the volume of the rebreathing bag is known, the total systematic volume can be determined simply from dilution of the insoluble gas.

Calculations of the cardiopulmonary parameters are based on single-alveolar lung model and assumptions included in the model are (Innovision, 2005): 1) complete and instantaneous mixing in the volume consisting of alveolar and dead space air and bag volume, 2) instantaneous equilibration of the soluble gas between the alveoli and blood, and between alveoli and tissue, 3) constant pulmonary blood flow and constant volume of lung tissue, 4) negligible mixed venous concentration of soluble gas throughout the rebreathing period.

In the past, measurements of pulmonary blood flow and cardiac output by an inert gas rebreathing method have been performed using mass spectrometers (Liu et al., 1997; Hoeper et al., 1999; Darren et al., 1998; and Rosenthal and Bush, 1997). However, mass spectrometers are bulky, difficult to operate and require frequent calibration and maintenance (Gabrielsen et al., 2002). These factors have significantly limited the clinical application of cardiac output measurements using the inert gas rebreathing

method.

More recently, an accurate infrared photoacoustic gas analyser has been introduced for the continuous analysis of ventilatory gas concentrations (Clemensen et al., 1994). Compared with conventional mass spectrometers, this analyser weighs less, is stable, less expensive, less complicated for use and therefore facilitates clinical use markedly.

3.1.2.1 Validity and reliability of inert gas rebreathing method

Liang et al. (2005) examined a new device (Innocor, Innovision, Denmark) for non-invasive measurement of cardiac output at rest using an inert gas (N_2O , SF_6) rebreathing method. It was compared with conventional techniques such as thermodilution, echocardiography and left ventricular radiography in 34 patients with heart failure. Using linear regression and Bland Altman analysis, they reported that strong positive correlations ($r=0.94$) exists between cardiac output measured by the inert gas rebreathing method and thermodilution. However, the Bland-Altman plot showed that the inert gas rebreathing method produced systematically lower values for cardiac output (by mean of $0.66 \text{ l}\cdot\text{min}^{-1}$, $p<0.001$) than those obtained by the thermodilution. The inert gas rebreathing method did not correlate with the other two non-invasive methods used in this study. The authors concluded that the inert gas (N_2O , SF_6) rebreathing method is an easy, safe and well established method for non-invasive measurement of cardiac output with good prospects for clinical application in heart disease patients. Further, Gabrielsen and colleagues (2002) compared an inert gas rebreathing method, which uses an infrared photoacoustic gas analyser system, with the direct Fick and thermodilution method at rest in 11 patients with heart failure or pulmonary hypertension. Using the Bland-Altman analysis, they reported the means difference (bias) and limits of agreement ($\pm 2 \text{ SD}$) to be $0.6\pm 1.2 \text{ l}\cdot\text{min}^{-1}$ when comparing the direct Fick and inert gas rebreathing method. The same values were $-0.8\pm 1.3 \text{ l}\cdot\text{min}^{-1}$ when comparing the direct Fick and thermodilution methods. In conclusion they argued that the inert gas rebreathing method, with a new photoacoustic gas analyser, provides at least as reliable a measure of cardiac output as did thermodilution. Agostoni et al. (2005) examined the validity and repeatability of cardiac output measured at rest and during exercise by the inert gas rebreathing

method. They compared cardiac output measurements by the inert gas (N₂O, SF₆) rebreathing method with cardiac output obtained by the direct Fick and thermodilution method. Twenty chronic heart failure patients in stable condition participated in the study. Results (mean ± SD) showed that cardiac output measured at rest by inert gas rebreathing method was 5.1±1.3 l·min⁻¹, direct Fick 5.0±1.3, and thermodilution method 4.5±1.2 l·min⁻¹. At peak exercise, the inert gas rebreathing method and direct Fick also produced similar cardiac outputs (11.3±3.2 l·min⁻¹ vs. 11.2±3.2 l·min⁻¹), while the thermodilution method overestimated peak cardiac output compared to the other two methods (11.7±3.7). Agostoni et al. (2005) also reported that the coefficient of variation was 10.8% for the inert gas rebreathing method. They concluded that cardiac output in heart failure patients measured at rest and during exercise by the inert gas rebreathing method is repeatable and agrees closely with those obtained by direct Fick and thermodilution method. Christensen et al. (2000) investigated measurements of cardiac output by the inert gas rebreathing method and the thermodilution technique in 14 critically ill patients. Results demonstrated that mean difference between paired estimates was 0.01 l·min⁻¹, and the standard deviation for differences was 1.19 l·min⁻¹. Also, 95% limits of agreement were calculated and the interval for this bias was 0.47 to -0.45, respectively. Coefficients of variation for cardiac output measures were 8% for rebreathing method and 12% for thermodilution method.

Additionally, a number of articles have examined validity and reliability of inert gas rebreathing method using acetylene as a testing gas (Barker et al., 1999; Darren et al., 1998; Hoepfer et al., 1999; Johnson et al., 2000; Liu et al., 1997). Findings of these studies suggest that this method for measuring cardiac output is in good agreement and correlates highly with invasive techniques. Further review of this topic is out of the scope of this chapter.

3.1.3 Rationale and Purposes of the Study

Currently, there are limited number of studies which compared two or more different rebreathing methods for measuring cardiac output at rest and at peak exercise. Before discussing cardiac output further, it was considered sensible to evaluate which of the existing available non-invasive methods in the laboratory is more valid for measuring

cardiac output at rest. Based on previous suggestion (Vanhees et al., 2000) that the exponential, rather than the equilibrium method should be used at high intensity exercise, this study evaluated the exponential and inert gas rebreathing methods at peak exercise.

The purposes of this study were: 1) to examine any differences between the equilibrium, exponential and inert gas rebreathing methods for measuring \dot{Q}_T at rest, 2) to assess reproducibility of these three methods at rest, and 3) to evaluate agreement between the exponential and inert gas rebreathing methods at peak exercise.

3.1.4 Research Hypotheses

H_1 – There will be a significant difference between the exponential, equilibrium and inert gas rebreathing methods for measuring cardiac output at rest.

H_2 – There will be a non-significant difference between duplicated measures of cardiac output measured with these three methods.

H_3 – There will be acceptable levels of agreement between the exponential and inert gas rebreathing methods at peak exercise.

3.2 Methods

3.2.1 Subjects

After obtaining ethical approval and informed consent, 17 healthy adults (ten males and seven females) from a South East UK University volunteered to participate in the study. Subjects were recruited by personal contact. They visited the exercise laboratory on three occasions on separate days. Subjects reported that they were physically active, but none were engaged in regular structured programme. They were asked to refrain from eating for a minimum of 2 h prior to the test and from vigorous exercise on the day of and the day before the test. All procedures were in accord with the local research guidelines as approved by the Faculty ethics committee and the

Declaration of Helsinki.

3.2.2 *Equipment*

3.2.2.1 Innocor – Inert gas rebreathing method

The Innocor (Innovision, Odense, Denmark) recently introduced a compact device, primarily developed to measure cardiac output non-invasively at rest and during exercise. The Innocor is the first device on the market which uses an inert gas rebreathing method. For the inert gas rebreathing method, the Innocor uses nitrous oxide (N₂O) and sulphur hexafluoride (SF₆). The gas distribution system controls the pneumatics for the respiratory valve unit and the filling/evacuating of the rebreathing bag (Innovision, 2005). The gas bolus is stored in a pressurized gas bottle which is connected to a respiratory valve unit under pneumatic control. The pressure of 0.4 bar is sufficient to activate the balloons in the respiratory valve unit. Before the rebreathing test, the port to the bag is closed by inflating the balloon. When the rebreathing starts, the port to the rebreathing rubber bag is opened by releasing the pressure of the balloon, simultaneously closing the port to ambient air. The rebreathing bag is filled prior to a test with an oxygen enriched mixture containing typically 0.5% N₂O and 0.1% SF₆. The filling of the bag is achieved in two steps. Firstly, a bolus part is filled from the gas containing 94% O₂, 5% N₂O and 1% SF₆. Secondly, the rest comes from ambient air via an air pump. Under normal resting conditions it is recommended to use 10% bolus and 90% air, which gives a mixture of 28.3% O₂, 0.5% N₂O and 0.1% SF₆ (Innovision, 2005). During exercise it can be necessary to increase the bolus due to high oxygen uptake to avoid a low oxygen concentration at the end of the test.

The Innocor uses the principle of photoacoustic spectroscopy as described in Chapter 2. This principle operates by pulsatile exposure of the measured gases to filtered light, the absorption of which creates pressure oscillations. The amplitude of the oscillation, which is measured by a microphone, is proportional to the gas concentration.

3.2.2.2 CardiO₂ - Carbon dioxide rebreathing methods

The equilibrium or exponential carbon dioxide rebreathing methods were performed using the CardiO₂ (Medical Graphics Corp., St. Paul, Minnesota, USA) system. The CardiO₂ system is equipped with an integrated module for the measurement of cardiac output. This is a mobile free-standing unit. It consists of mouthpiece assembly connected to a rotary valve which has two movements to allow a three-way operation. The first movement exposes inspire and expire ports with one way valves for the measurement of $\dot{V}O_2$. The second movement connects the subject to a rebreathing anaesthetic 6 l black rubber bag. The bag is filled manually with a mixture of higher (equilibrium method) or lower (exponential method) CO₂ concentration from gas cylinders located at the base of the unit. The module is connected to gas analysers to measure O₂ and CO₂. Subjects are connected to the metabolic cart by means of a disposable rubber mouthpiece, attached directly to the flowmeter, to which the gas sample line and airflow umbilical are connected.

3.2.3 *Procedure*

3.2.3.1 Pre test procedure

Both systems were calibrated before each test according to manufacturers' recommendations. On arrival at the laboratory, subjects were asked for their completed physical activity readiness questionnaire forms and questioned about their medical health. Subjects were then required to complete the informed consent form in front of the researcher who countersigned it as a witness. Subjects had their mass recorded using floor scale (Seca model 761, Vogel ad Halke, Germany) and height recorded using a freestanding stadiometer (Leicester Height Measure, Invicta Plastics, Oadby, Leicester, UK) prior to test. Subjects received instructions about breathing pattern and fitting the mouthpiece and nose clip.

3.2.3.2 Testing procedure

Subjects were randomly allocated to three groups. In a third of the subjects, the exponential method was used at the first visit, with the equilibrium and inert gas

rebreathing method on the second and third visits. With the other two groups, the order was changed. After a resting period of 5 min in the sitting position on a chair, the rebreathing manoeuvre was performed in duplicate with an interval of 5 min between the measurements to allow elimination of CO₂ or N₂O. The second measurement at rest was required to ensure the reproducibility of the technique.

Twelve subjects performed a series of three incremental exercise tests to volitional fatigue using the Bruce protocol on separate days. The first test was used to determine subjects' peak oxygen consumption. The other two exercise tests were used to measure \dot{Q}_T at peak exercise using the exponential and inert gas rebreathing methods.

The exponential method was performed using a gas mixture of 4% CO₂, 34% O₂ and balance N₂, while in the equilibrium method subjects rebreathed a gas mixture of 10% CO₂, 35% O₂ and balance N₂. A 6 l anaesthetic rubber bag was filled with approximately 1.5 to 2 times the subject's tidal volume. For either CO₂ rebreathing method, a breathing frequency higher than 40 breaths per minute was used. This was ensured by the researcher saying "in" and "out" whilst looking at the stopwatch. The other researcher pushed the plunger at the end of expiration to switch the subject to rebreathe the gas mixture from the bag. This was rebreathed for a maximum of 15 seconds and then the plunger was pulled out and the subject rebreathed room air. A capnograph trace was produced on the screen whilst the subject rebreathed the gas mixture.

In the inert gas rebreathing method the bag volume was calculated automatically (40% of the predicted vital capacity at rest) and the bag was evacuated and filled automatically. Before each measurement, the subject put on a nose clip. A constant ventilation rate was ensured by having the subject breathe in synchrony with a graphical tachymeter on the computer screen set at 20 breaths per minute. A constant ventilation volume was ensured by having the subject completely empty the rebreathing bag with each breath. The rebreathing system software calculated cardiac output from the rate of uptake of N₂O into the blood. This was based on the slope of the regression line through logarithmically transformed expiratory (i.e. alveolar) N₂O concentrations plotted against time after correction for system volume changes using

the SF₆ concentration. The first two or three breaths were excluded from the analysis due to initial incomplete gas mixing.

3.2.4 Data Analysis

All statistical analysis was performed using SPSS version 13 (SPSS Inc., Chicago, IL, USA). Prior the statistical analysis all data were screened for univariate (Z-scores) and multivariate (Mahalanobis distance test) outliers. Descriptive statistics was performed in order to check data for parametric assumptions (normal distribution and homogeneity of variance). To test difference between three different methods for measuring cardiac output at rest, one-way analysis of variance (ANOVA) was used. To identify the groups that differed significantly from one another, a *post hoc* Tukey's test was performed. T-tests for paired samples were used to assess differences in repeated measures at rest, as well as to examine differences in \dot{Q}_T at peak exercise measured by the exponential and inert gas rebreathing methods. Statistical significance was indicated if $p < 0.05$. Bland-Altman plots were constructed to evaluate agreement between different methods (Bland and Altman, 1986). Coefficient of variation (CV) was used to assess reproducibility of each method at rest.

3.3 Results

Subjects were aged 37 ± 11 years, weight 74 ± 17 kg, height of 172 ± 8 cm with the mean maximal oxygen uptake of 46.6 ± 7.2 ml·kg⁻¹·min⁻¹, respectively. Analysis of variance revealed that there was a significant difference between the three methods ($F=43.03$). The Tukey *post hoc* test demonstrated that mean cardiac output measured by the exponential method was significantly higher ($p < 0.01$), respectively, than those measured by the equilibrium or inert gas rebreathing method (Figure 3.3). The difference in measured cardiac output of 1.4 l·min⁻¹ between the equilibrium and inert gas rebreathing method was not significant ($p=0.08$). Individual and mean values of cardiac output (l·min⁻¹) determined by exponential, equilibrium and inert gas rebreathing method are presented in table III.1 (Appendix III). Mean cardiac output measured by the exponential method was higher by 4.5 l·min⁻¹ and 5.8 l·min⁻¹ compared with equilibrium and inert gas rebreathing method, respectively.

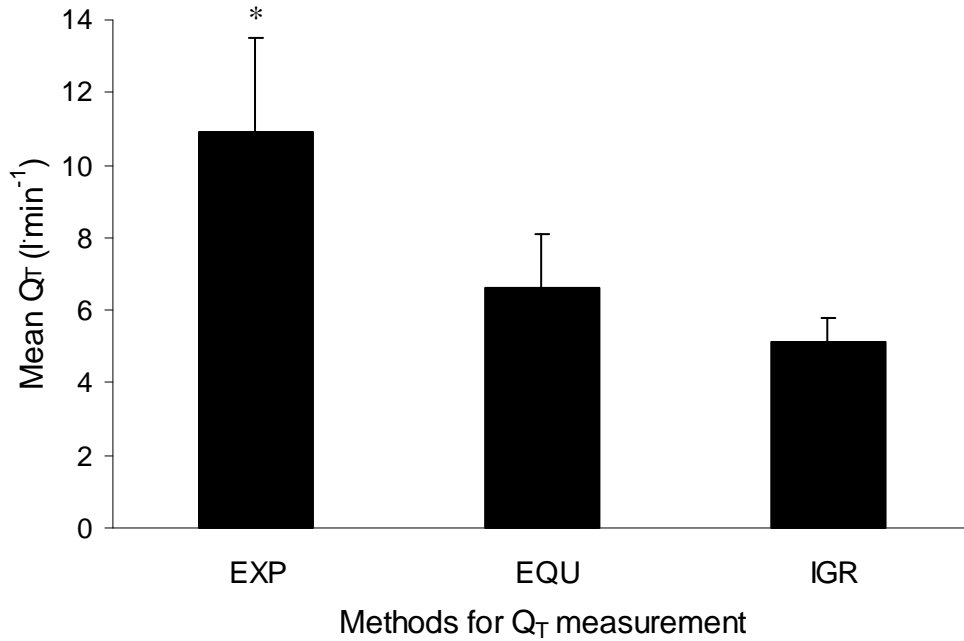


Figure 3-3 Mean values of cardiac output measured at rest by the exponential (EXP), equilibrium (EQU) and inert gas (IGR) rebreathing methods

* = indicates that cardiac output measured by the EXP was significantly higher than those measured by EQU and IGR methods ($p < 0.01$).

Bland-Altman analysis revealed that the mean difference between duplicate measures and limits of agreement were -0.13 (-2.71 to 2.45) l.min⁻¹ for the exponential method, 0.19 (-0.57 to 0.96) l.min⁻¹ for the equilibrium method and -0.15 (-1.18 to 0.87) l.min⁻¹ for the inert gas rebreathing method (Figures 3.4 to 3.6).

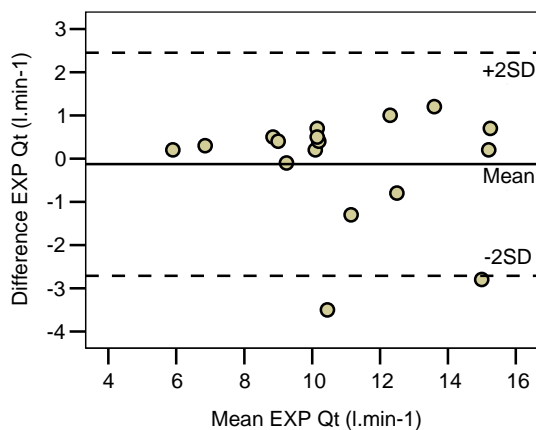


Figure 3-4

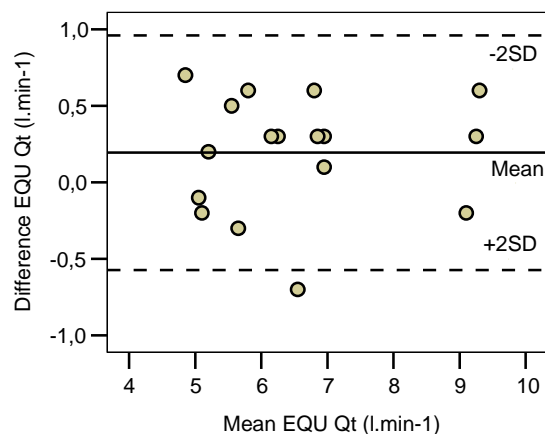
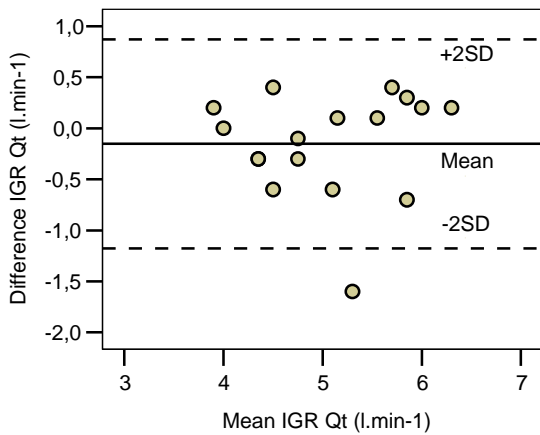


Figure 3-5



Figures 3.4-3.6 Bland-Altman plots to demonstrate limits of agreement between duplicate measures of cardiac output determined by the exponential (EXP) equilibrium (EQU) and inert gas rebreathing methods (IGR). The solid line is at the bias (mean of the difference)

Figure 3-6

There was no statistically significant difference in duplicate cardiac output values measured by any of the three rebreathing methods at rest (Table 3.1). The CV demonstrated that the exponential method showed a tendency toward larger variation than the equilibrium and inert gas rebreathing methods.

Table 3.1 Differences in Cardiac Output Values at Rest Measured by the Three Rebreathing Methods (N = 17) – Paired samples test (t).

Method	Test (mean±SD)	Retest (mean±SD)	p - Value	CV (%)
EXP	10.9±2.7	11±2.9	0.68	5.3
EQU	6.7±1.5	6.5±1.5	0.06	4.1
IGR	5±0.8	5.1±0.9	0.24	4.8

EXP – exponential CO₂ rebreathing method; EQU – equilibrium CO₂ rebreathing method; IGR – inert gas rebreathing method.

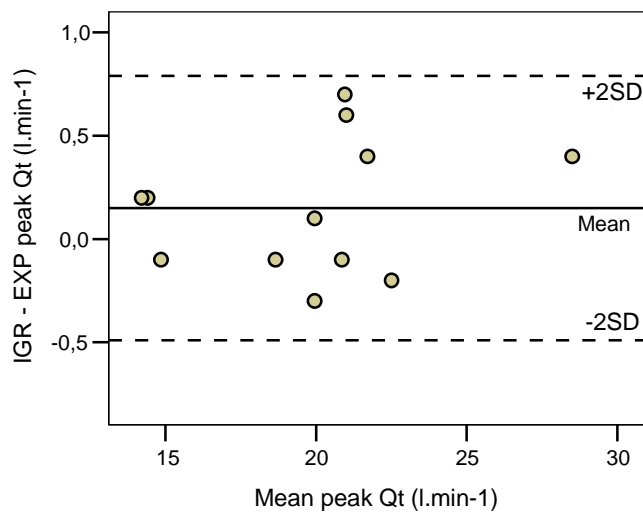


Figure 3-7 Bland-Altman plot to demonstrate limits of agreement between the exponential and inert gas rebreathing methods at peak exercise. The solid line is at the bias and the dashed lines represent lower and upper limits of agreement ($\pm 2SD$ of the mean difference).

There was a non-significant difference between the exponential and inert gas rebreathing methods at peak exercise ($p=0.14$). The mean \dot{Q}_T values were 19.7 ± 4.0 $\text{l}\cdot\text{min}^{-1}$ and 19.9 ± 4.1 $\text{l}\cdot\text{min}^{-1}$ measured by the exponential and the inert gas rebreathing methods, respectively. Bland-Altman analysis showed that the mean difference and the limits of agreement were 0.15 (-0.49 to 0.79) $\text{l}\cdot\text{min}^{-1}$ as shown in the Figure 3.7. Individual and mean peak \dot{Q}_T values measured by the exponential and inert gas rebreathing methods are presented in table III.2 (Appendix III).

3.4 Discussion

3.4.1 Validity of the Three Rebreathing Methods at Rest

The purposes of this study were: 1) to examine any differences between the equilibrium, exponential and inert gas rebreathing methods for measuring \dot{Q}_T at rest, 2) to assess reproducibility of these three methods at rest, and 3) to evaluate agreement between the exponential and inert gas rebreathing methods at peak exercise.

Validity of the cardiac output has previously been established by comparing invasive methods with the equilibrium (Cowley et al., 1986; Franciosa, 1976; Muiesan et al., 1968; Nugent et al., 1994; Smith et al., 1988) and the exponential method (Ferguson et al., 1968; Ohlsson and Wranne, 1986; Reybrouck et al., 1978). Ferguson et al. (1968) reported a very low coefficient of correlation between the exponential and dye dilutions methods at rest. Reybrouck et al. (1978) found moderate correlation between the exponential and direct Fick methods at rest.

In the present study the estimates of resting cardiac output obtained with the exponential method were higher than one would expect in healthy subjects and were significantly higher than those obtained by the equilibrium and inert gas rebreathing methods. Resting cardiac output values obtained in this study compare favourably to those reported by Vanhees et al. (2000). They reported that cardiac output measured by the equilibrium and exponential method were $6.3 \text{ l}\cdot\text{min}^{-1}$ and $9.1 \text{ l}\cdot\text{min}^{-1}$ respectively compared with $6.6 \text{ l}\cdot\text{min}^{-1}$ and $10.9 \text{ l}\cdot\text{min}^{-1}$ found in this study. Previous studies have also reported that exponential method tends to overestimate cardiac output at rest when compared with direct Fick, dye dilution and equilibrium CO_2 rebreathing method (Ferguson et al., 1968; Ohlsson and Wranne, 1986; Reybrouck et al., 1978). On the other hand, it has been reported that the equilibrium method rather underestimates cardiac output at rest compared with the direct Fick or dye dilution method (Franciosa, 1976; Muiesan et al., 1968; Nugent et al., 1994). Cowley et al. (1986) using the Bland-Altman analysis demonstrated good narrow limits of agreement (ranged from -0.37 to $0.47 \text{ l}\cdot\text{min}^{-1}$) between the equilibrium method and thermodilution, whereas Russel et al. (1990) reported wider limits of agreement (-1.80

to $1.24 \text{ l}\cdot\text{min}^{-1}$) when comparing the equilibrium with dye dilution. However, it has been frequently suggested that the equilibrium method is more valid than the exponential method for measuring cardiac output at rest, while during high intensity exercise the exponential method is preferred (Muiesan et al., 1968; Vanhees et al., 2000).

Butler (1965) has questioned the validity of both CO_2 rebreathing methods used to obtain $\bar{P}\bar{V}\text{C}_2$ for cardiac output measurement. Hamilton (1962) also pointed out several objections to the rebreathing method and argued that using the lungs as a tonometer for determining $\bar{P}\bar{V}\text{C}_2$ can be inaccurate. Firstly, he suggested that there is an appreciable quantity of residual arterialized blood (or other fluids) in the lungs which can absorb CO_2 from the inspired mixture. Secondly, this CO_2 can combine with fluids other than intravascular. Thirdly, there is a constant increase in values obtained for $\bar{P}\bar{V}\text{C}_2$ as rebreathing time is prolonged what may cause slow mixing, diffusion, and the equilibrium of arterialized pulmonary blood. However, the last objection is not applicable in this study because the rebreathing time was controlled automatically and never exceeded 20 sec and 15 sec for the exponential and equilibrium method. McHardy (1967) pointed out that since neither the haemoglobin concentration nor the pH of arterial and mixed venous blood is usually available when cardiac output is estimated by a CO_2 rebreathing method, a standard CO_2 dissociation curve is often used to derive blood CO_2 content from P_{CO_2} . Nevertheless the position and slope of the CO_2 dissociation curve may vary from subject to subject and both are affected by changes in oxygen saturation, haemoglobin and pH of the blood (McHardy, 1967).

The inert gas rebreathing method, performed using the Innocor system, has been validated against other invasive and non-invasive methods. Liang et al. (2005) compared inert gas rebreathing method with thermodilution, echocardiography and left ventricular radiography. This study reported high correlation between the thermodilution and inert gas rebreathing method, but also suggested that the inert gas rebreathing method systematically underestimated cardiac output compared with thermodilution, by a mean of $0.66 \text{ l}\cdot\text{min}^{-1}$. Further Gabrielsen et al. (2002) found the means difference and limits of agreement ($\pm 2\text{SD}$) were $0.6 \pm 1.2 \text{ l}\cdot\text{min}^{-1}$ when

compared with the direct Fick and inert gas rebreathing method. A study by Agostoni et al. (2005) assessed chronic heart failure patients who were in a stable condition. They reported cardiac output at rest measured by inert gas rebreathing method of 5.1 l min^{-1} , compared with the direct Fick and thermodilution of 5.1 l min^{-1} and 4.5 l min^{-1} . Finally, Christensen et al. (2000) demonstrated very good narrow limits of agreement of -0.45 to 0.47 between the inert gas rebreathing method and thermodilution at rest.

The finding of the present study suggests that the mean cardiac output measured at rest by the equilibrium method was higher by 1.4 l min^{-1} compared with the inert gas rebreathing method. Analysis of variance revealed that no statistically significant difference exists between the two methods. However, the magnitude of the difference in measured cardiac output between these two methods may have practical and clinical implications. There are several reasons why this difference may occur. It has been suggested that rebreathing manoeuvre performed at rest may require a certain effort by the subject, and therefore increase cardiac output (Ohlsson and Wranne, 1986). The breathing pattern required a frequency of 40 breaths per minute during the equilibrium method compared with 20 breaths per minute required by the inert gas rebreathing method. A high breathing frequency may influence higher O_2 demands of particularly respiratory muscles and consequently increase cardiac output. Secondly, during the inert gas rebreathing method, the rebreathing volume was controlled by asking the subject to empty the bag at each inspiration. Consequently subjects used the same tidal volume during each rebreathing manoeuvre. Also, the rebreathing bag was evacuated and then refilled with appropriate air volume automatically before the inert gas rebreathing manoeuvre. On the other hand, for the equilibrium as well as for the exponential method, the rebreathing bag was filled with approximately 1.5 to 2 times the subject's tidal volume. During the rebreathing manoeuvre it was not possible to control the subject's tidal volume as with inert gas rebreathing method. Damgaard and Norsk (2005) showed that reducing and changing the rebreathing volume during the test may influence the cardiac output result. Furthermore, higher estimates of cardiac output produced by the equilibrium method may occur due to high measurement of end-tidal carbon dioxide levels (Nugent et al., 1994). This may be caused by inaccurate estimates of arterial CO_2 levels which can be due to non-uniformity of ventilation and perfusion in the lungs (Nugent et al., 1994).

As suggested earlier, resting cardiac output for young healthy men averages about $5.6 \text{ l}\cdot\text{min}^{-1}$, while for adults it is often stated to be $5 \text{ l}\cdot\text{min}^{-1}$ (Guyton and Hall, 1996). The age of subjects participated in this study ranged from 26 to 58 years with an average of 37 years. It is reasonable to suggest from the results of this study that the inert gas rebreathing method seems to be more valid than the exponential and equilibrium method for measuring \dot{Q}_T at rest.

3.4.2 Reproducibility of the Three Rebreathing Methods at Rest

“If cardiac output is measured under standardized conditions on one day, these values are assumed to be valid on the next day, as long as the circulatory situation is stable” (Ohlsson et al., 1983; page 9).

This study reported good reproducibility and low coefficient of variation of all three rebreathing methods for measuring cardiac output at rest. Also, there was no significant difference between repeated measures with either method. The Bland-Altman analysis revealed that the limits of agreement between repeated measures were a little broader for the inert gas rebreathing method compared with the equilibrium method. However, they are not as wide as the limits of agreement obtained by the exponential method. Furthermore, the coefficient of variation (CV) was also higher for the exponential method (5.3%) compared with the equilibrium (4.1) and inert gas rebreathing method (4.8%).

Holmgren (1960) and Calusen et al. (1970) reported that direct Fick method had a CV of 5.5 and 7.5%, respectively. The results of the present study on reproducibility of either CO_2 rebreathing method for measuring cardiac output at rest are also in close agreement with those obtained by Vanhees et al. (2000). They reported the mean difference between duplicates and the coefficient of repeatability (twice the SD of difference) of 0.58 and 5.12 for the exponential method and -0.25 and 3.25 for the equilibrium method. Nugent et al. (1994) found that the equilibrium method gave reproducible results between replicates at rest with a CV of 9.1% and became more reproducible on exercise (5.6% and 5.4%). Also, Zeidifard et al. (1972) reported that CV was higher at rest and fell during exercise (5.7%) for the equilibrium method. On the other hand, results of Rogers et al. (1997) demonstrated a CV of 3.3% for the

exponential method during exercise which compares favourable with 3.2% found by Clausen et al. (1970). A study by Christensen et al. (2000) was the only one which has been investigated to assess the reproducibility of the inert gas rebreathing method using the Innocor system. They reported a CV of 8%.

Due to poor reproducibility of the CO₂ rebreathing method at rest, Ferguson et al. (1968) have recommended performing repeated measurements to achieve a reliable estimate of cardiac output at rest. The positive learning effect of the rebreathing manoeuvre has been reported by Vanhees et al. (2000). Vanhees et al. also recommended repeated measurements at rest where the first measurement is used for familiarization and should not be used in interpretation. In the present study all subjects were very familiar with rebreathing manoeuvre having taken part in an earlier study to assess cardiac output using the CO₂ rebreathing technique. This is likely to have contributed substantially to the high level of reproducibility in all three rebreathing methods.

3.4.3 Agreement between the Exponential and Inert Gas Rebreathing Methods at Peak Exercise

It has been suggested that the exponential, rather than the equilibrium method should be used during high intensity exercise (Muiesan et al., 1968; Vanhees et al., 2000). A high coefficient of correlations was reported when compared the exponential with the direct Fick and dye dilution methods during exercise (Ferguson et al., 1968; Ohlsson and Wranne, 1986; Reybrouck et al., 1978). On the other hand, Agostoni et al. (2005) evaluated inert gas rebreathing method against the direct Fick and thermodilution methods during exercise in heart failure. They concluded that cardiac output measured during exercise by the inert gas rebreathing is repeatable and agrees closely with those obtained by the direct Fick and thermodilution methods.

In the present study, the exponential and inert gas rebreathing methods produced non-significantly different \dot{Q}_T values at peak exercise. Bland-Altman analysis revealed good narrow limits of agreement between the two methods, with the mean difference of 0.15 lmin⁻¹ only. Reported limits of agreement in the present study compare

favourably with those reported earlier (Agostoni et al., 2005; Christensen et al., 2000; Cowley et al., 1986; Gabrielsen et al., 2002; Nugent et al., 1994). It is important, however, to outline an advantage of the inert gas rebreathing method.

In order to determine \dot{Q}_T both methods use blood soluble gases, CO₂ or N₂O. However, the inert gas rebreathing method in addition uses the insoluble gas (SF₆) which concentration curve provides direct information in regards of complete mixing of gases within alveoli (Gabrielsen et al., 2002). Thus compared to the exponential, the inert gas rebreathing method contains an inherent evaluation of the degree of gas mixing. This is very important assumption of rebreathing methods. Therefore, it is reasonable to suggest that the inert gas rebreathing method may measure \dot{Q}_T more precisely compared with the exponential CO₂ rebreathing method.

3.5 Conclusion

Availability of a valid, reliable, easily applied, non-invasive method for measuring cardiac output is of great value in clinical and scientific environment. The present study evaluated different rebreathing methods for measuring cardiac output at rest and at peak exercise. Resting Q_T values produced by the inert gas rebreathing method agreed well with previously suggested values in healthy adults, more so than those obtained by either the equilibrium or the exponential method. The equilibrium and particularly the exponential CO₂ rebreathing method tended to overestimated cardiac output at rest compared with the inert gas rebreathing method. The difference in measured cardiac output by the inert gas rebreathing method and the equilibrium method is likely to be due to differences in uniformity of breathing pattern. The inert gas rebreathing method has a lower required breathing frequency. It also has the capability to control lung volumes during rebreathing, and to estimate degree of gas mixing. On this basis it is believed that the inert gas rebreathing method has the potential to measure Q_T more precisely than both CO₂ rebreathing methods used in this study. All three methods produced very similar values of resting cardiac output between duplicated measures, demonstrating good reliability. At peak exercise the exponential and inert gas rebreathing methods produced non-significantly different \dot{Q}_T values at peak exercise. Bland-Altman analysis revealed good narrow limits of

agreement between the two methods. Therefore the exponential and inert gas rebreathing methods may be used interchangeable for measuring \dot{Q}_T at peak exercise.

The inert gas rebreathing method used in this study is totally non-invasive, easily performed, valid and reliable method for measuring cardiac output. It is a useful tool for monitoring cardiac output not only in healthy population, but also in patients with heart failure as suggested earlier.

3.6 References

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CHAPTER 4: CARDIAC POWER OUTPUT IN HEALTHY AND DISEASED POPULATIONS – A LITERATURE REVIEW

Abstract

The aim of this chapter was to review existing literature which has evaluated different aspects of cardiac power output. It has been shown that cardiac power output is a direct indicator of overall cardiac function. Cardiac power output represents the heart's ability to act as a mechanical pump and produce hydraulic energy which is used to maintain circulation. It takes account of both pressure and flow and is equal to the product of cardiac output and mean arterial pressure, expressed in watts. It has been demonstrated that cardiac power output plays a major role in risk stratification and prognosis in heart failure patients. Also it has been suggested that peak cardiac power output is a more powerful indicator of heart failure prognosis than commonly used peak oxygen consumption. Firstly, this review describes the concept of cardiac power output and its definition. Secondly it concentrates on the analysis of cardiac power output in healthy adults. Furthermore the chapter evaluates cardiac power output and its role in heart failure patients and in peripheral vascular disease. Also this review analyses the effect of exercise programmes on cardiac power output in both health and disease. Finally the chapter provides recommendations for future investigations in cardiac power output.

4.1 Introduction – The Concept of Cardiac Power Output and Its Definition

The heart is a muscular mechanical pump with an ability to generate both flow and pressure (Cotter et al., 2003). The main function of the heart is to provide hydraulic energy to maintain the circulation through which the body supplies nutrients (oxygen) and removes waste products to and from metabolising tissues (Tan, 1987; Tan 1991). Bergel et al. (1969) were the first to consider the heart as a power generator and measured cardiac power output. It is only since the 1980s that the measurement has received more attention (Firth et al. 1981) and has gained wider acceptance in clinical practice. In the middle 1980s, Lip-Bun Tan described the mechanical pumping capability of the heart and its practical implications in acute and chronic heart failure (Tan, 1986). Of all haemodynamic variables in use, Tan (1986) advocated that hydraulic power output best represents the performance of the cardiac pump. Furthermore hydraulic power output is a measure of the heart's capability to act as a pump and maintain circulation (Cotter et al. 2003). The corollary statement of this concept is that the function of the heart is to provide hydraulic energy to maintain the circulation (Tan, 1991).

Cardiac performance consists of two important terms (Tan, 1987): 1) *cardiac pumping capability* which presents the maximum performance that can be achieved by the heart during stimulation, and 2) *cardiac pumping reserve* which is the difference in performance between the basal resting state and the maximally stimulated state (Figure 4.1). Cardiac reserve has been found to be a major determinant of exercise capacity in heart failure, and pumping capability a major determinant of prognosis in patients with severe heart failure (Tan, 1991). The concept of cardiac reserve provides further insight into pathological and clinical mechanisms that contribute to heart failure (Wright and Tan, 1999). Nevertheless each heart has its own ceiling peak pumping performance that is physically impossible to exceed (Cotter et al., 2003). This peak value would alter only if the intrinsic condition of the heart is altered, e.g. after an acute myocardial infarction or after successful relevant cardiac surgery (Williams et al., 2005a). Cardiac pumping capability is a direct and objective indicator of how relatively good or impaired the heart is as a fluid pump (Williams et al., 2005a).

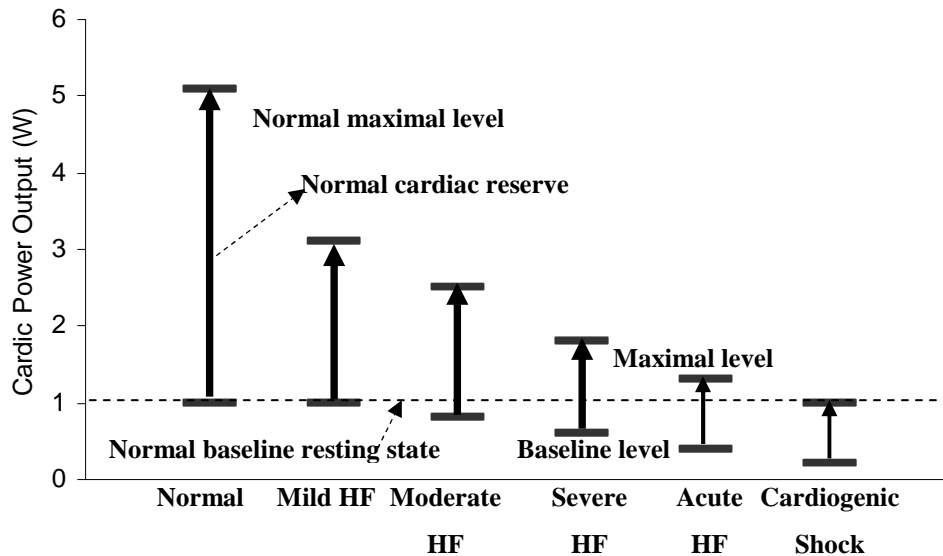


Figure 4-1 Schematic diagram demonstrating cardiac functional reserve of individual hearts on a normal functional state, in various degrees of heart failure (HF) and cardiogenic shock. Adapted from Williams et al. (2005a).

The delivery of oxygen to metabolising tissues depends on the rate of blood flow – cardiac output. An increase in blood flow can be achieved by vasodilatation or by increasing the arterial perfusion pressure (Tan, 1987). Since all vessels have an upper limit of vasodilatation, and since the vasculature of other organs cannot vasoconstrict to an infinite extent, the only way to increase blood flow is by increasing the arterial perfusion pressure through greater pressure generation by the heart (Tan, 1991). This increase in pressure assumes an even greater importance in the perfusion of exercising skeletal muscle because of the higher tissue pressure developed during muscle contraction, in particular during isometric exercise (Williams et al., 2005a). The product of cardiac output and aortic (arterial) pressure gives the term cardiac hydraulic power output or *cardiac power output* (Tan, 1986).

A continuous supply of hydraulic energy from the pumping action of the heart is required to maintain the circulation. Thus, the heart is a generator of hydraulic energy (Tan, 1987). Without this energy, circulation would come to a standstill due to the opposing frictional and separational forces (Tan, 1991; Cotter et al., 2003). The rate at which the heart imparts energy into the circulation is cardiac power output, which presents an ideal measure of heart’s pumping performance. Therefore Tan (1987) suggested that cardiac pumping capability may be redefined as the maximum power

output achieved by the heart during maximal stimulation. Cardiac pumping reserve is defined as the increase in power output as its performance is increased from the basal resting state to the maximally stimulated state. It has been suggested that cardiac power output is the most logical variable to represent cardiac performance (Tan et al. 1989). Also Bain et al. (1990) reported that cardiac power output is an expression of the hydraulic power output of the heart and as such derived from both central and peripheral haemodynamic measurements, cardiac output and mean arterial pressure. From the aspect of physics, ‘power’ is ‘energy per unit of time’.

The following equation is used to calculate cardiac power output:

$$\text{CPO} = \dot{Q}_T \times \text{MAP} \times K \dots\dots\dots(1)$$

Where CPO is cardiac power output in watts (W), \dot{Q}_T is cardiac output in $\text{l}\cdot\text{min}^{-1}$, MAP is the estimated mean arterial pressure in mmHg, and K the conversion factor ($=2.22 \times 10^{-3}$). The formula for calculation of the mean arterial pressure (below) has been suggested by Meaney et al. (2000):

$$\text{MAP} = \text{DBP} + 0.412 (\text{SBP} - \text{DBP}) \dots\dots\dots(2)$$

Where DBP is diastolic blood pressure in mmHg, SBP systolic blood pressure in mmHg. Hodges (2004) reported that from a regression analysis, cardiac output has the greater influence ($r = 0.89$, $\text{SEE} = 0.53 \text{ l}\cdot\text{min}^{-1}$) on cardiac power output than mean arterial pressure ($r = 0.48$, $\text{SEE} = 1.02 \text{ mmHg}$).

The normal resting value of cardiac power output for an average sized man with a cardiac output of $5 \text{ l}\cdot\text{min}^{-1}$ and blood pressure of 120/80 mmHg is about 1 watt, but at peak exercise it may rise to 4-8 watts (Tan, 1991).

While cardiac output is commonly used to assess cardiac function, it clearly overestimates the changes in the overall function of the normal heart (Goldspink, 2005). This is because pressure generation increases with healthy ageing and is not allowed for when measuring only flow-generating capacity of the heart. In contrast, in patients with heart failure measurements of cardiac output alone underestimate overall

cardiac function (Chantler et al., 2006). This is because both the flow and pressure generating capacities of the heart decline in these patients. Taken together, these examples clearly illustrate the need to measure both the flow and pressure generating capacities of the heart to determine overall cardiac function meaningfully (Goldspink, 2005).

Cooke et al. (1998) were the first who assessed physiological cardiac reserve using a non-invasive CO₂ rebreathing method. They tested 70 subjects with a wide range of cardiac function, from heart failure patients to athletes. In previous studies involving evaluation of cardiac power output and cardiac reserve (Tan, 1986; Tan, 1987; Tan et al., 1991; Timmins et al., 1992), the haemodynamic variables were measured invasively using Swan-Ganz catheters. In these studies cardiac stimulation was also achieved pharmacologically, using incremental dobutamine infusion. However, it is not necessarily indicative or representative of physiological cardiac reserve which is obtained during exercise (Cooke et al., 1998). Wright and Tan (1999) concluded that exercise testing plays an essential and integral role in the evaluation and treatment of chronic heart failure. In addition, Cooke et al. (1998) pointed out two important clinical implications. Firstly, it is no longer reasonable to assume that haemodynamic measurement of cardiac function is unimportant in the management of patients with heart failure, and secondly that cardiac reserve is probably the best available objective indicator of overall cardiac function.

Cardiac power output has been studied in both healthy and diseased populations. This chapter concentrates on review of the existing literature on cardiac power output. It is divided in the following sections: 1) cardiac power output in healthy adults; 2) cardiac power output and its role in heart failure patients; 3) cardiac power output in patients with peripheral vascular disease; 4) cardiac power output and its relationship to other cardiorespiratory variables in health and disease; and 5) exercise and cardiac power output in health and disease.

4.2 Cardiac Power Output in Healthy Adults

Many studies over the last two decades have evaluated cardiac power output in a clinical population, while only a few recent studies have analysed cardiac power output in healthy adults. This may be explained by the fact that cardiac power output appears to be of great value in evaluation and prognosis in clinical, especially heart failure, populations. Cardiac power output is a measure which clearly not only differentiates the function of healthy from impaired hearts, but also contributes to the further management of those with variable impaired heart function (Cooke et al., 1998). It seems logical that more data should be available about cardiac power output in healthy populations. Data obtained from healthy people may be used as a 'standard' against which cardiac capacity can be evaluated for the purposes of research and for clinical studies in a population with cardiac disease (Bromley et al., 2006).

It has been suggested that heart rate may respond to strenuous exercise by increasing from about 70 beats per minute to about 180 beats per minute and stroke volume from about 70 ml to 110 ml or more (Tan, 1991). In these circumstances cardiac output increases from 5 l min^{-1} to 20 l min^{-1} or even more. As stated above, the normal resting cardiac power output for an average sized man is about 1 W, but at peak exercise it may rise to 4-8 W (Tan, 1991). Nicholls and Riley (2001) reported that the normal range for cardiac power output has not yet been established. Thus Bromley et al. (2006) were the first to define the normal physiological range for peak cardiac power output in healthy adults. In addition they evaluated age and sex related variations of cardiac output.

In Bromley et al.'s study, 102 healthy adults (50 males and 52 females, age range from 19 to 64 years) performed an incremental exercise test protocol described by Bruce et al. (1973). Oxygen consumption, carbon dioxide production, minute ventilation, tidal volume and respiratory exchange ratio were obtained using an online breath-by-breath metabolic gas analysis system. Also, at peak exercise blood pressure was recorded manually by auscultation over the right brachial artery. Following the peak exercise test and a rest period of 40 minutes, subjects performed the second bout of exercise which was a constant load test with a workload set to achieve $\dot{V}O_2$ levels

within 5% of the $\dot{V}O_2$ peak obtained during the incremental test. Cardiac output was measured using the CO_2 rebreathing method described by Defares (1958). Once near peak values had been reached, the metabolic system was switched to the cardiac output measurement screen and the cardiac output value was obtained within 15 seconds. Bromley et al. (2006) used one-way analysis of variance and t-tests to establish difference in peak cardiac power output between the subgroups. Results of this study showed that peak cardiac power output ranged from 3.11 to 7.94 W (mean 5.26 ± 1.03 W) in men and from 2.53 to 5.57 W (mean 3.69 ± 0.64 W) in women. The difference in peak cardiac power output between men and women and between younger (<45 years) and older (45-65 years) subjects was significant. When men <45 years were compared with men 45-65 years the difference in peak cardiac power output was also significant. However, there was a non-significant difference between women <45 years and women 45-65 years. Additionally the findings of this study suggest that sex accounts for a greater proportion of the variance in peak cardiac power output than age. Bromley et al. (2006) concluded that age-related loss of functional myocardial mass in the male heart (see below) is accompanied by a significant reduction in peak cardiac power output. Although Bromley et al. (2006) did not measure resting cardiac power output, they reported that cardiac pumping reserve was 3.36 ± 1.16 W in their study. This conclusion was drawn from previous suggestions that resting cardiac power output in healthy adults to be between 1 and 1.2 W (Tan, 1986, 1991; Cooke et al., 1998). However, Bromley et al. (2006) were not able to assess any possible differences in resting cardiac power output between men and women, and possible effect of aging on resting cardiac power output. If resting cardiac power output is affected by gender and ageing then people with the same peak cardiac power output will have different peak cardiac reserves due to different starting points (resting cardiac power output). Additionally, Chantler et al. (2005) illustrated the impact and importance of normalizing data for differences in body size before interpreting measurements of overall cardiac function between different populations of subjects. This study yielded novel findings that highlight the fact that cardiac power output is significantly affected by body size and composition. Thus valuable results reported by Bromley et al. (2006) on 'normal' physiological range of cardiac power output, should be considered with caution because differences in body size were not taken into account.

Olivetti et al. (1995) reported that ageing was associated with ventricular myocardial mass, aggregate number of mononucleated and binucleated myocytes, and average cell diameter and volume in the female heart. Further, it has been observed that the male heart loses nearly 1 g per year of myocardium, affecting both the left and right sides of the heart and accounting for the loss of approximately 64 million cells. Olivetti et al. (1991) showed that about one third of the cardiomyocytes are lost from the human male heart between the ages of 17-90 years. Although some of the remaining viable cardiomyocytes undergo adaptive hypertrophy, this does not compensate for the progressive decline in myocyte numbers. Interestingly, the rate of cardiomyocyte attrition in the female heart is considerably less (Olivetti et al., 1995). There is no doubt that the loss of these contractile cells compromises the pumping capability of the heart (Goldspink, 2005). It is, however, important to emphasize that these age-related effects based on measuring cardiac power output are not pronounced as when cardiac output alone is used as the index of cardiac function (Goldspink, 2005).

Chantler et al. (2004) tested the hypothesis that healthy ageing is associated with a decrease in peak cardiac power output and cardiac reserve and also that endurance training improves cardiac power output. Results revealed that in sedentary men peak cardiac power output and cardiac reserve declined significantly by 16 and 18% between the ages 20 and 60 years. In contrast with these effects of ageing, the veteran athletes demonstrated significantly higher peak cardiac power output and cardiac reserve values than their age-matched sedentary counterparts at both 50 and 60 years. Moreover, these trained individuals demonstrated similar or better cardiac function than the sedentary 20 year-old subjects (Chantler et al., 2004). In subsequent study Chantler et al. (2006) determined whether the functional impacts of cardiac impairment through ageing and heart failure are similar or different. Study population consisted of three groups of subjects: 1) twelve sedentary untrained healthy men aged 21 years, 2) fourteen sedentary untrained men aged 60 years, 3) eleven patients with heart failure (NYHA III) aged 58 years. In consistency with previous, this study revealed that ageing from early (20 years) to later (60 years) resulted in a reduction of peak aerobic capacity by about 30%. Additionally, heart failure produced a further reduction of about 30% in aerobic exercise capacity in the same 60 year old age

group. The most prominent difference between the impact of ageing and of heart failure on cardiac function was their opposite effects on cardiac pressure generating capacity of the aging hearts was preserved and even slightly enhanced, whereas heart failure significantly compromised cardiac pressure generating capacity. When compared with the same age group of healthy controls, heart failure diminished the pressure generating capacity of patients by 23%. Further, the flow generating capacity, on the other hand, was reduced 22% secondary to ageing, with further reduction of about 27% due to heart failure. Finally, the power generating capacity of the heart was reduced to a smaller extent of 15% through ageing, but by a much greater further reduction of 57% by heart failure. The reserve capacity of the heart to impart hydraulic energy to maintain the circulation during peak exercise stress test was reduced by 16.5% through ageing and a much greater further reduction of 72% by heart failure.

From a practical and clinical perspective it has been suggested that it would be useful to estimate peak cardiac power output from measurements taken at lower exercise intensities (Hodges, 2004). Thus Hodges (2004) examined whether peak cardiac power output could be predicted accurately from submaximal values. A study evaluated the relationship between oxygen consumption, blood lactate concentration, carbon dioxide production and cardiac power output at submaximal levels of exercise. Also, the study by Hodges (2004) determined the effect that the accumulation of lactic acid has during progressive exercise on the measurement of cardiac power output. In Hodges' study, 19 healthy adults completed three five minutes stages of exercise on a treadmill at 25%, 50% and 75% of each subject's predetermined maximal oxygen consumption. Cardiac output was measured every four minutes into each exercise stage using the exponential rebreathing technique. Capillary blood sampling was accomplished three minutes into each stage and lactate analysed immediately. Metabolic data were obtained online using the breath-by-breath CardioO₂ system, while blood pressure was measured manually every two minutes. Results of this study demonstrated that a high correlation exists between blood lactate and cardiac output ($r = 0.8, p < 0.05$) and cardiac power output, ($r = 0.9, p < 0.05$). Prediction of peak cardiac power output from submaximal values was calculated following regression analysis and the use of multiple regression. The backward regression indicated that the

variables included in the equation were blood lactate at 25% and 75% of peak oxygen consumption and cardiac power output measure at 25% and 75% of peak oxygen consumption. This model represented 82% of the variance and a standard error of estimate of 0.38 W. It has been argued that this model combines practicality and economy, as it would involve only two stages of submaximal exercise (Hodges, 2004). Furthermore results illustrated that it was not possible to exclude the highest measurement, cardiac power output at 75% of peak oxygen uptake from the regression equation, as this was the most important variable used in the equation and accounted for approximately 50% of the variance alone. If this regression equation were to be used in the future investigations, the patient would have adequate time to recover between predictor measures and would not need to exercise to volitional fatigue (Hodges, 2004). However, in order to calculate someone's submaximal functional capacity (e.g. 75% of $\dot{V}O_2$), the investigator must know what is the maximal functional capacity (e.g. 100% of $\dot{V}O_2$). Hodges (2004) did not clearly suggest which method should be used to predict peak $\dot{V}O_2$ in the case when no maximal exercise test is performed. There is evidence which shows that $\dot{V}O_2$ peak may be predicted based on age, gender, height and weight in both healthy and diseased populations (Wasserman et al., 1999). However, the formulae for calculating predicted $\dot{V}O_2$ peak should be treated with caution, especially when working in a clinical environment and with seriously ill patients. Furthermore, the practical implication of assessing peak cardiac power output from submaximal values comes into a question when there is a need for measuring peak cardiac power output, but the patient is not able to achieve 75% of predicted $\dot{V}O_2$ peak (e.g. severe heart failure). Also, taking blood samples twice to measure blood lactate combined with metabolic measurements at a high breathing frequency, places this model on the periphery of clinical use. Nonetheless, Hodges' study produces better understanding of the concept of cardiac power output and expands its theoretical framework.

There are limited number of studies which evaluated cardiac power output in healthy subjects (Bain et al., 1990; Bromley et al., 2006; Cooke et al., 1998; Hodges, 2004; Marshall et al., 2001). Some of these studies examined the relationship between peak cardiac power output and other cardio-respiratory variables, while others evaluated

the effect of exercise programme in cardiac power output in healthy adults. These aspects of cardiac power output in healthy and also diseased populations will be discussed in some of the following subheadings of this chapter.

4.3 Cardiac Power Output and Its Role in Heart Failure Patients

Tan (1991) reported that one major shortcoming in the management of cardiac dysfunction is the lack of a satisfactory definition of heart failure. It has been suggested that without a clear definition, there is no common ground for research and treatment (Tan, 1991). Before defining heart failure, Tan (1991) turned firstly on the heart function, which is *de facto* to provide hydraulic energy in order to maintain circulation. Following this idea, Tan (1991) pointed out that the definition of heart failure can then be simply stated as ‘the failure of the heart to function as it should’. Also, Williams et al. (2005) pointed out that heart failure is impairment of function, instead of structure which may or may not have contributed to the dysfunction. Thus morbidity experienced by patients with chronic heart failure is due to a reduction in functional capacity (Wright and Tan, 1999). Alteration in central haemodynamic, ventilation, peripheral circulation, neurohormonal activity and skeletal muscle all contribute to impaired clinical status (Wright and Tan, 1999). According to Tan (1991) two essential questions are whether the patient’s heart is in terminal failure, and what is the most suitable treatment.

In 1986 Tan pointed out that in the management of severe heart failure, clinicians would value an objective means of determining the point at which a patient’s heart has failed critically (Tan, 1986). Tan (1986) further suggested that the three major determinants of prognosis in heart failure are (1) mechanical pumping capability of the heart, (2) its electrical state, and (3) the rate of progression of the underlying disease. It has been clearly stated that cardiac power output has a more than theoretical value in defining maximum cardiovascular capacity, particularly in patients who are limited in their exercise capacity by both cardiac and other physical conditions (Bain et al., 1990).

In heart failure, when the pumping mechanism deteriorates, the earliest result is a

reduction in the maximum performance of the pump (Tan, 1986). With a major impairment, the heart occasionally cannot maintain its normal resting pumping level (the proposed level of 1 W). When the mechanical function of a cardiac pump has deteriorated to the extent that, however hard to may be stimulated, its maximum performance no longer exceeds its 'normal' resting level, then the condition of the failing heart is incompatible with sustained survival (Tan, 1986). In other words, if the maximum cardiac power output of the failing heart is below 1 W, then the likelihood of long-term survival of the patient is very small. Conversely, if the maximum performance greatly exceeds the normal resting level, then factors other than the mechanical state of the heart become more dominant in determining the prognosis (Tan, 1986) e.g. malignant arrhythmia, further myocardial infarction (Tan, 1987). It has also been suggested that haemodynamic measurements during stress (e.g. exercise or pharmacological intervention) gives a clearer indication of failing cardiac function than haemodynamic evaluation at rest (Tan et al., 1989).

Tan (1986) studied 63 patients of which 26 had acute chronic heart failure due to myocardial infarction, and remainder were in chronic or acute heart failure, symptom class III-IV according to New York Heart Association (NYHA) classification. Cardiac output and arterial pressure were measured invasively using thermodilution catheters and cannula. Baseline control data were recorded at least 10 min after insertion of the catheter and cannula. Maximum stimulation was achieved by using the incremental infusion of dobutamine. Maximum stimulation was determined by the absence of a further rise in cardiac power output, the onset of angina, or serious arrhythmia. Each patient was followed up for one year. Student's t test and Wilcoxon rank sum were used to determine significant differences. The results of this study showed that of the 23 patients with a peak cardiac power output of less than 1 W, all but three died of progressive heart failure within one year of the study; 1 of the 3 survivors had cardiac transplantation; 36 of the 40 patients with a peak cardiac power output of more than 1 W survived more than one year. Based on these results it seems possible to identify patients whose hearts are in terminal mechanical failure. These results are consistent with the findings of Tan and Littler (1990), who evaluated the prognostic value of cardiac power output and cardiac pumping reserve in cardiogenic shock patients. This study showed that in patient with a basal resting cardiac power output of ≤ 0.35 W the

outcome was uniformly death. Above this level, some patients had sufficient cardiac reserve to be able to respond to the dobutamine stimulation to produce peak cardiac power output of >1 W. These patients survived more than a year.

Tan (1986) suggested that cardiac response on dobutamine infusion gives valuable information on prognosis in heart failure. Also it has been suggested that maximal exercise testing provides the best form of classification for cardiac failure patients (Wright and Tan, 1999). Tan (1986) further reported that the use of a pharmacological agent was based on expediency, since clearly physiological stimulation (e.g. an exercise stress test) was neither feasible nor desirable in many of the patients (Tan, 1986). However, it was logical to assess the possible relationship between the pharmacological and the physiological stimulation of peak cardiac power output. Thus in the following investigation, Tan et al. (1989) compared cardiac pumping capability measured during an incremental dobutamine infusion with that measured during symptom limited exercise. They studied 31 patients with moderate to severe heart failure. Baseline and peak haemodynamic data were measured invasively using thermodilution and arterial cannulas. Patients firstly performed maximal cycle ergometry in a semierect position starting at 10 to 25 W and increasing in steps of 10-25 W every three minutes. The workloads were selected so that the patients reached peak exercise in less than 10 minutes. After patients had rested for four hours, they were given increasing doses of dobutamine starting at $2.5 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ and increasing by 2.5 to $5.0 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ every 5-10 minutes to a maximum of $15\text{-}30 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. The maximum dose was reached when there was no further increase in cardiac output and cardiac power output, or when a symptom became intolerable or important arrhythmia developed (Tan et al., 1989). This study showed that both dobutamine and exercise increased heart rate, cardiac index, cardiac power output and left ventricular stroke work index. Results demonstrated that peak cardiac pumping capability measured during dobutamine stimulation correlates well with that measured during symptom limited exercise testing. However, the correlation coefficient was not reported. The peak values of all variables (except cardiac index) produced by both forms of stimulation were not statistically different. However it was noticed that maximal cardiac output values were higher in the dobutamine group. This may be associated with the fact that dobutamine caused more vasodilatation than exercise and

the heart converted more of its pressure generating capacity into a flow generating capacity (Williams et al., 2005a). Bland-Altman analysis showed good agreement between the cardiac pumping capability as evaluated by measuring peak cardiac power output during maximal dobutamine challenge and maximal exercise. Also, it was pointed out that dobutamine challenge may be the best method of assessing cardiac pumping capability particularly when the patient is unable or unwilling to undergo maximal exercise testing (Tan et al., 1989). This study concluded that pharmacological stress using dobutamine is as good as physiological stress for cardiac stimulation. There is no doubt, however, that cardiopulmonary exercise testing provides more data than the pharmacological stimulation (e.g. oxygen uptake, anaerobic threshold etc). Taken together with cardiac power output and cardiac reserve these data are likely to provide deeper insight into the clinical status of a patient. Therefore it is reasonable to suggest that physiological rather than pharmacological stimulation of the heart should be used wherever possible.

At present no single exercise test is able to provide complete evaluation of a patient with cardiac dysfunction (Wright and Tan, 1999). However, the main objectives of exercise testing in patients with chronic heart failure are to improve understanding of pathophysiological mechanisms, to confirm the quantity of symptoms and their severity, to predict prognosis and to assess treatment (Wright and Tan, 1999). In addition to exercise testing, it is important to notice that the type of exercise chosen to stress the heart is also important in determining the extent of impairment of cardiac reserve (Tan, 1987). Tan (1987) using the data from Saltin et al. (1973) pointed out that in young healthy subjects there is a pronounced difference between the cardiac power output obtained at maximal workload tolerated for just 3-4 minutes (mean cardiac power output 7.7 W) and obtained during a maximal effort sustained for 6-9 minutes (6.6 W). Similarly, in heart failure patients, a faster rise in exercise workload appears to stress the heart more than a slower protocol by virtue of the greater maximal cardiac power output attained with the faster protocol (Lipkin et al., 1986).

The information based on peak cardiac performance is most helpful in determining the prognosis and in formulating management plans (Tan, 1991). There is a view that patients with poor prognosis should be resuscitated only if definitive treatment is to be offered (e.g. with cardiac assist devices if necessary or cardiac transplantation) (Tan,

1991). Further it has been suggested that similar principles can be applied to patients with less severe heart failure with the only difference being that the mechanical dysfunction of the heart is not as immediately responsible for the prognosis as in cardiogenic shock (Tan, 1991). Other factors may also be influential in determining the prognosis of heart failure such as arrhythmia. This is more likely to occur in those with heart failure than without, and may effect progression of the underlying disease (e.g. further myocardial infarction) (Tan, 1991). The survival rate becomes less dependant on pure mechanical factors and more dependant on these other factors when the pump failure is less severe (Tan, 1991).

An earlier suggestion was that the only way to improve cardiac pumping capability is by altering the design of the pump by surgery or with compensatory hypertrophy and dilatation (Tan, 1991). Therefore, the principal consideration in treating any heart failure patient should be identification and correction of structural defects (e.g. pericardial aspiration in tamponade or valvular replacement in valve lesion) (Tan, 1991). However, more recently it has been shown that cardiac pumping reserve and consequently peak cardiac power output may be improved with exercise training in both healthy and heart failure populations (Marshall et al., 2001; Patwale et al., 2006; Wright et al., 2002). The effect of exercise on cardiac power output will be discussed later in this chapter.

Accurate classification of heart failure patients according to severity of illness is essential in order to formulate a management strategy (Wright and Tan, 1999). This study pointed out that no system presently exists which adequately classifies patients. The New York Heart Association provided a valuable classification system which has been used almost universally for about half of century (Wasserman et al., 1999). It has four functional classifications based on the perceived activity level (peak $\dot{V}O_2$) of the patient. Specifically, it has been suggested that a peak $\dot{V}O_2$ level of $\leq 14 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ be used as a 'cut off' point and as a key criterion for the acceptance of ambulatory patients for transplantation (Chomsky et al., 1996). Furthermore, patients with a peak $\dot{V}O_2 > 20 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ have a good prognosis and those with peak $\dot{V}O_2 < 10 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ have a limited prognosis (Roul et al., 1995). Conversely, it has been well reported that peak exercise $\dot{V}O_2$ may be influenced by non cardiac factors such as

muscle deconditioning, obesity, motivation, gender, and age (Chomsky et al., 1996; Fleg and Lakata, 1988; Wilson et al., 1995). However, the NYHA system continues to be widely used despite its poor sensitivity in determination of functional capacity (Cohen-Solal and Gourgon, 1991; Franciosa, 1984) and prediction of prognosis (Van Den Broek et al., 1992; Wright and Tan, 1999). It has been further suggested, because of good correlation with peak $\dot{V}O_2$, that maximal cardiac output and the derived peak cardiac power output and cardiac reserve are used as alternative measures (Tan, 1991). On the other hand Wilson et al. (1995) reported dissociation between peak $\dot{V}O_2$ and haemodynamic dysfunction in transplant candidates. They concluded that more than 50% of the potential heart transplant candidates with a reduced peak $\dot{V}O_2$ level exhibit only mild or moderate haemodynamic dysfunction during exercise. Wilson et al. (1995) recommended that haemodynamic responses to exercise should be directly measured in the potential transplant candidates to confirm severity of circulatory dysfunction. It has been therefore suggested that the role of peak $\dot{V}O_2$ in risk stratification of heart failure should be reconsidered. Thus Wright and Tan (1999) reported that a more integrated approach incorporating measurement of exercise haemodynamic should be in use, focusing on cardiac power output. It has also been reported that some other variables such as anaerobic threshold (Gitt et al., 2002) and ventilatory efficiency (Kleber et al., 2000) have higher prognostic importance than $\dot{V}O_2$.

Roul et al. (1995) were the first group to evaluate the prognostic value of peak cardiac power output during maximal exercise testing. They examined 50 patients with chronic heart failure in functional class II and III of the NYHA, with an average age and ejection fraction of 54 years and 20%, respectively. The haemodynamic data were obtained by thermodilution at rest and during exercise which was performed on a recumbent cycle ergometer (25 W every three minutes). $\dot{V}O_2$ of all patients was determined during a new exercise test on a cycle ergometer. Patients were followed up for an average of 21.2 months. Cox analysis showed that exercise cardiac power output, exercise left ventricular work indices and exercise peak $\dot{V}O_2$ were the most useful factors for assessing the prognosis of patients with NYHA II and III chronic heart failure. An exercise cardiac power output <2 W accurately identified those

patients with a short-term poor prognosis, and peak $\dot{V}O_2$ was also accurate to predict prognosis. Roul et al. (1995) concluded that invasive haemodynamic parameters are best for determining the prognosis of patients with chronic heart failure, while peak $\dot{V}O_2$ can, however, be as useful. It may be noted that cardiac power output and cardiac reserve play an important role in prognosis of heart failure not only in severe heart failure, but also in earlier stages of heart failure (e.g. NYHA II and III).

Furthermore, a study by Williams et al. (2001) assessed the prognostic value of peak cardiac power output, measured non-invasively using CO₂ rebreathing method at rest and during maximal cardiopulmonary exercise testing. The study group included 219 unselected consecutive patients, mean age 56 years, with stable congestive heart failure. They were followed up for a mean period of 4.64 years. Peak cardiac power output (< and >1.96 W) and peak $\dot{V}O_2$ (< and >14 ml·kg⁻¹·min⁻¹) were entered as categorical variables. Results demonstrated that of the patients with a peak cardiac power output of <1.96 W, the mortality rate (32%) was considerably higher than those with a peak cardiac power output >1.96 W (8%). Univariate analysis revealed that rest and peak cardiac power output (either continuous or dichotomized at 1.96 W), resting and peak cardiac output and peak $\dot{V}O_2$ predicted survival. However, when peak $\dot{V}O_2$ was dichotomized at 14 ml·kg⁻¹·min⁻¹, this did not predict survival using a univariate model. Multivariate analysis identified peak cardiac power output as the only independent predictor of mortality. In conclusion, this study reported that peak cardiac power output at a level of 1.96 W is the best predictor of outcome in this group of patients with congestive heart failure. According to Williams et al. (2001) the non predictive value of peak $\dot{V}O_2$ may be linked to the fact that it is only an indirect indicator of peak cardiac performance. This study clearly described a critical cut-off value of peak cardiac power output which differentiates heart failure patients with a good and bad prognosis. It is remarkable that despite marked differences in methods and patient population, the results of studies by Roul et al. (1995) and Williams et al. (2001) are highly consistent.

Further, Marmor and Schneeweiss (1997) estimated peak cardiac power output and cardiac reserve in 42 patients with chronic heart failure in NYHA classes II-IV and in

10 healthy volunteers. They were followed up for three years after haemodynamic assessment at rest and after incremental dobutamine stimulation. Cardiac power output was estimated non-invasively using Doppler ultrasonography. They found that patients with good cardiac reserve (>1.5 W) survived well. However, eight of the nine patients with a cardiac reserve of less than 1.5 W died. In this study, using multiple logistic regression analysis, cardiac reserve was found to be the only significant predictor of survival. Moreover Fincke et al. (2004) evaluated clinical, angiographic, and significance in prognosis of haemodynamic variables of 541 patients with suspected cardiogenic shock secondary to left ventricular dysfunction after acute myocardial infarction. Haemodynamic variables were obtained by right heart catheterization. Fincke et al. (2004) attempted to determine a cut-off value for cardiac power output that is most accurately related to outcome of cardiogenic shock. A resting cardiac power output of 0.53 W was found to be most accurate predictor of in hospital mortality. The probability of in hospital mortality with cardiac power output ≤ 0.53 W was 58%, whereas the probability of survival given a >0.53 W was 71%. Fincke et al. (2004) concluded that in acute heart failure the patient becomes haemodynamically unstable, and most of the cardiac pumping potential is recruited in order to sustain life. Hence, cardiac power output measurements in patients with acute heart failure at rest represent most of recruitable reserve available during the acute event, and their measurement reflects the severity of the patient's condition (Fincke et al., 2004). Recently, Mendoza et al. (2007) also evaluated the prognostic value of cardiac power output in a broad spectrum of patients with acute cardiac disease undergoing pulmonary artery catheterization. Results indicated that the inhospital mortality rate was significantly higher among patients with cardiac power output ≤ 0.53 W compared with those with cardiac power output >0.53 W. Mendoza et al. (2007) concluded that cardiac power output is a strong, independent predictor of inhospital mortality in a broad spectrum of patients with primary cardiac disease undergoing pulmonary artery catheterization.

Most recently, Lim et al. (2008) using non-invasive inert gas rebreathing methodology compared the prognostic value of peak cardiac output, left ventricular stroke work index and cardiac power output to peak oxygen consumption in heart failure patients referred for heart failure and transplant evaluation. Bicycle exercise test was

performed in 171 heart failure patients with mean ejection fraction of 24%. Follow-up period averaged 337 days. Endpoints consisted of death, urgent transplant or left ventricular assist device implantation. Peak oxygen consumption was $12.9 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ and peak cardiac power output 1.7 W. The variables analysed included peak oxygen consumption, peak cardiac output, left ventricular stroke work index, ventilatory response to exercise, anaerobic threshold and peak cardiac power output. On multivariable Cox regression analysis, only ventilatory response to exercise, peak cardiac output and peak cardiac power output were predictive, with cardiac power output being the most powerful predictor. Lim et al. concluded that peak cardiac power output, measured non-invasively, is an independent predictor of outcome that can enhance the prognostic power of peak oxygen consumption in the evaluation of heart failure patients.

In summary, this section described the role of cardiac power output and cardiac reserve in patients with heart failure. As earlier suggested, the pumping capability (peak cardiac power output) is the most powerful predictor of prognosis in heart failure, while cardiac pumping reserve is a major determinant of exercise capacity in heart failure (Cotter et al., 2003; Tan, 1991).

4.4 Cardiac Power Output in Patients with Peripheral Vascular Disease

As pointed out above, the aim of this chapter was to review all existing literature on cardiac power output, including healthy and diseased populations. Only one study has been published which evaluated cardiac power output in patients with peripheral vascular disease (Hodges et al., 2006). Surprisingly, this study reported similar peak cardiac power output values as those reported in severe heart failure.

‘Peripheral vascular disease is a condition characterized by atherosclerotic occlusive disease of the lower extremities’ (Association, 2003; page 3334). Commonly measured clinical parameters (e.g. $\dot{V}O_2$, \dot{Q}_T and other metabolic data) are not routinely measured in patients with peripheral disease. Claudication free walking time or distance and maximal claudication-limited walking time or distance are the most common used measures to assess functional capacity in this group of patients (Hodges

et al., 2006). This study uniquely examined cardiovascular variables in patients with peripheral vascular disease.

Fifty consecutive patients completed an incremental treadmill exercise test with two minutes stages. Speed and inclination were increased every two minutes by $3.2 \text{ km}\cdot\text{h}^{-1}$ and 2%. Results showed that mean peak cardiac power output was 2.86 watts. Nineteen percent of patients had a peak cardiac power output of <1.96 watts. Further, results demonstrated that mean cardiac output was $9.8 \text{ l}\cdot\text{min}^{-1}$, mean arterial pressure 126.8 mmHg and $\dot{V}\text{O}_2$ $13.85 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. Hodges et al. (2006) indicated that surprisingly there is a relative lack of research concerning systematic measurements with this group of patients. Based on previous research, the authors reported that patients with peripheral vascular disease have the same relative risk of mortality and morbidity from cardiovascular events as patients with a history of established coronary disease.

Based on this study it is suggested that assessment of cardiac power output is not only a useful measure in heart failure patients, but also in those with peripheral vascular disease. This consideration should have more implication in clinical practice helping doctors and consultants to make the right decisions for their patients.

4.5 Cardiac Power Output and Its Relationship to Other Cardiorespiratory Variables in Health and Disease

In normal subjects the maximum oxygen uptake is limited by the ability of the cardiovascular system to deliver oxygen to the muscle rather than by the tissue's ability to utilise oxygen (Clausen, 1977). This limitation is, according to Tan (1987), more acute in heart failure. In heart failure the reduction in maximal oxygen transport to the muscle results from three major factors: 1) reduced cardiac pumping reserve, 2) reduced constrictor reserve of vessels supplying the non exercising tissues, and 3) reduced vasodilatory capacity of the vessels perfusing the exercise muscles (Tan, 1987).

Only a few studies exist which analysed the relationship between cardiac power output and other cardio-respiratory variables in healthy adults. On the other hand

several studies exist which assessed this relationship in diseased populations.

Hodges (2004) examined the relationship between peak cardiac power output and peak oxygen uptake in 102 healthy adults (50 males and 52 females). This relationship was assessed by the Pearson product moment correlation coefficient. Analysis revealed that a high ($r=0.8$, $p<0.05$) correlation between the two variables. Subgroup analysis by gender showed a moderate correlation between cardiac power output and peak oxygen uptake (males, $r=0.58$, females, $r=0.61$, $p<0.05$). This difference was explained by the difference in heart size and fat free mass between males and females. Furthermore Hodges (2004) reported the correlation between peak cardiac power output and circulatory power was high ($r=0.86$). Circulatory power has been used as 'surrogate' marker of cardiac power output (Cohen-Solal et al., 2002). Also, Hodges (2004) reported that the correlation between peak cardiac power output and peak cardiac index was high ($r=0.81$). In addition, Hodges (2004) also found that there was a non-linear relationship between cardiac power output and blood lactate concentration. There was an exponential relationship between the two variables, but it could be explained as two distinct linear relationships with a break point at 3.2 W. However, Hodges (2004) suggested that there were insufficient data points to make a judgment about whether the break point indicates the lactate threshold. Overall the relationship between blood lactate and cardiac power output was high ($r=0.95$).

Cooke et al. (1998) tested the hypothesis that cardiac power output and cardiac reserve correlated with peak oxygen consumption. In this study 70 subjects with a wide range of cardiac function, from trained athletes to transplant candidates, performed treadmill cardiopulmonary exercise tests with non-invasive estimation of haemodynamic parameters (CO_2 rebreathing method). Bruce or modified Bruce protocols were used. It was found that at peak exercise, cardiac power output was significantly related to maximal aerobic capacity ($r=0.87$, $p<0.001$). The relationship between cardiac output and maximal oxygen consumption was also high ($r=0.92$, $p<0.001$). Furthermore, peak cardiac power output correlated well with exercise duration ($r=0.62$, $p<0.001$), suggesting that cardiac reserve is a major determinant of exercise capacity. In this study cardiac reserve ranged from 0.27 to 5.65 W, indicating a 20-fold difference between the most impaired cardiac function and that of the fittest subject.

Bain et al. (1990) investigated whether resting cardiac power output can be used to predict maximum cardiovascular function and reserve as determined by exercise. They also investigated whether the relationship between exercise time and cardiac power output is stronger than the relationship between the more traditional haemodynamic variables and exercise time. Forty-one patients with moderately severe to severe chronic heart failure were exercised on a cycle ergometer. The mean ejection fraction was 25.9%. Haemodynamic data at rest and during exercise were obtained by the thermodilution method using a Swan-Ganz catheter. Patients exercised commencing at 25 W and increasing by 15 W increments every three minutes until stopped by dyspnoea or exhaustion. Results of this study revealed that resting cardiac power output moderately correlated with exercise duration ($r=0.53$), while peak cardiac power output had a high correlation with exercise duration ($r=0.79$). Cardiac reserve was also highly correlated with exercise duration ($r=0.8$). Furthermore, resting cardiac index was moderately correlated ($r=0.51$) with exercise duration, while maximum cardiac index correlated well with exercise duration ($r=0.73$). This study pointed out that diuretic therapy increased activation of various neuroendocrine mechanisms and may have caused increased catecholamine levels, increased plasma rennin activity (which may subsequently fall as diuresis progresses) and increased arginine-vasopressin levels causing an increased heart rate and systematic vascular resistance. This leads to a rise in mean arterial blood pressure, whilst stroke volume decreases. Bain et al. (1990) concluded that resting cardiac power output is a poor predictor of cardiovascular functional potential. On the other hand, the authors indicated that maximum cardiac power output and the ability to increase cardiac power output through exercise are closely correlated with exercise time and are therefore good descriptors of functional cardiac reserve. Further it has been suggested that cardiac power output has a more than theoretical value in defining maximum cardiovascular capacity, particularly in patients who are limited in their exercise capacity by both cardiac and other physical conditions (Bain et al., 1990).

Roul et al. (1995) reported that none of the exercise variables obtained during catheterization were strongly correlated to data at rest. As previous studies have shown, peak cardiac power output in this study was well correlated to peak cardiac index ($r=0.94$) and peak oxygen consumption ($r=0.84$).

Finally, Williams et al. (2005b) using non-invasive methods, evaluated the relationship between direct and indirect indices of cardiac pumping capacity in 219 patients with chronic heart failure. Results demonstrated that circulatory power correlated well with cardiac power output ($r=0.84$) at peak exercise. However, there was a weak but statistically significant relationship between circulatory power at rest and cardiac power output at rest ($r=0.48$). In addition this study revealed a simple linear regression equation to allow the calculation of cardiac power output from circulatory power: $CPO=0.905 \times CP - 0.409$, with a good fit (adjusted $R^2=70.5\%$). Circulatory power as an index of cardiac function is the product of systolic blood pressure and oxygen uptake. Therefore it should be considered with caution although oxygen uptake may be influenced by non-cardiac factors.

Many studies have shown that resting haemodynamic parameters poorly correlated with exercise capacity. On the other hand it has been frequently shown that peak cardiac power output has a high correlation with peak oxygen uptake, cardiac index, circulatory power and exercise time.

4.6 Exercise Training and Cardiac Power Output in Health and Disease

Controlled clinical studies have recently demonstrated that both in-hospital and home-based exercise training programmes of various intensities induce favourable clinical effects by significantly increasing aerobic capacity, delaying the onset of anaerobic metabolism, reducing the sympathetic drive, and increasing the vagal tone (Belardinelli et al., 1999). According to Tan (1991), whether a therapeutic intervention can increase the exercise capacity of a heart failure patient depends on its ability to: 1) augment the effective cardiac pumping reserve; 2) improve the way the vasculature distributes the pump output; and 3) improve the way the active skeletal muscles utilise the substrates delivered to them (e.g. oxygen extraction). It has been suggested that in normal healthy subjects exercise training improves cardiac reserve and also exercise capacity (Saltin et al., 1968). Apart from exercise training it has also been suggested that pharmacological conditioning using vasodilators (e.g. dobutamine) has a positive effect on exercise capacity (Tan, 1987). However further description of the pharmacological influence on exercise capacity is out of scope of

this review.

A few studies have investigated the effect of exercise training on cardiac power output in healthy and diseased populations.

Marshall et al. (2001) examined the effect of an unsupervised low-budget home based exercise training programme of moderate intensity on peak cardiac power output, cardiac reserve and aerobic capacity. Nine healthy middle-aged subjects participated in a randomized cross-over study. Each subject was tested following eight weeks of training (training phase) and eight weeks of 'non-exercising' using a 1-min incremental treadmill test. During the exercise training protocol, participants trained for eight weeks at home using a static upright cycle. They were instructed to exercise at 50 rev·min⁻¹ for a 20 min period on five days per week. The resistance on the flywheel was set to produce a heart rate that was consistent with a $\dot{V}O_2$ of 75-80% of the $\dot{V}O_2$ max achieved during the control incremental test. Participants also completed a daily exercise diary. During the non-exercise control phase, all participants were instructed to carry out their pre-baseline activities and to avoid any additional exercise. Also, during each visit a self-assessment questionnaire, based on a Likert scale was completed. An ANOVA and Student's t test were used to analyse data between each period of the study. Results of this study revealed that peak cardiac power output increased significantly by 16% and cardiac reserve by 21%. A major contribution to these improvements was observed in the significant 11.2% rise in peak stroke volume and peak cardiac output which increased by 12%. There were non-significant changes in resting cardiac power output as well as in mean arterial pressure between both experimental conditions. Following the training period, when compared with the non-exercise control period, all subjects had a significantly lower heart rate at rest. Also at submaximal exercise the mean heart rate was lower after training than after the non-exercise control phase. $\dot{V}O_2$ max increased significantly by 9% as well as exercise time after the training phase. Mean body weight did not alter significantly following exercise phase. Peak heart rate and anaerobic threshold did not alter from exercise training. Although the intensity of the exercise programme was the same for all participants (75-80% of peak $\dot{V}O_2$) and individual differences in anaerobic threshold were not considered, it is not surprising that anaerobic threshold did not

change following exercise. The improvement in aerobic capacity and cardiac power output do not result in an increase in anaerobic threshold. However the relationship between these variables, particularly cardiac power output and anaerobic threshold, has not yet been established. It has been also shown that in regard to the responses to the self-assessment questionnaire, subjects were significantly more positive in their perception of their health, fitness and levels of activity. Marshall et al. (2001) concluded that home-based, unsupervised exercise training on a cycle ergometer can improve cardiac function, aerobic capacity, exercise duration and quality of life. However, it was noted that the exercise programme was the same throughout the eight weeks. Based on evidence that changes in intensity and volume of exercise training can lead to further improvement of functional abilities (Bompa, 1994), it is prudent to suggest that the reported results could have been even better.

A study by Wright et al. (2002) investigated whether exercise rehabilitation improves cardiac performance as well as functional capacity following coronary artery bypass grafting. Six weeks postoperatively, 22 patients were randomised either to attend the hospital based exercise rehabilitation programme or supervise their own recovery. The patients performed a maximal cardiopulmonary exercise test one week before and one week after rehabilitation. Those in the rehabilitation group attended once a week for six weeks. On each occasion they completed 12 aerobic exercise stations specifically designed to incorporate the use of different skeletal muscle groups. Each week the level of exercise was increased to incorporate more repetitions or a greater workload. The two study groups were similar in size and demographic characteristics. At baseline, both groups demonstrated similar resting and exercise cardiopulmonary responses. Following the six week study period, neither group showed any significant changes in resting parameters. However, there was significant increase in peak cardiac output (11.3 ± 2.2 to 12.2 ± 1.7 $\text{l} \cdot \text{min}^{-1}$), peak cardiac power output (2.97 ± 0.84 to 3.31 ± 0.7 W) and overall cardiac reserve (1.92 ± 0.72 to 2.19 ± 0.53 W) in those who underwent formal rehabilitation, while no significant changes were shown in control group. Furthermore exercise time and peak $\dot{V}O_2$ increased significantly in the rehabilitation group (11.2 ± 3.6 to 13.2 ± 3.1 min, and 20.5 ± 4.6 to 22.3 ± 3.4 $\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) and also in the control group (10.8 ± 4.9 to 12.3 ± 4.7 min, and 20.4 ± 6.4 to 22.7 ± 6.9 $\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$), respectively. It has been also shown that during exercise, the rate of

ventilation/rate of oxygen uptake ($\dot{V}_E/\dot{V}O_2$) at 1 l·min⁻¹ of $\dot{V}O_2$, and the rate of ventilation/rate of carbon dioxide ($\dot{V}_E/\dot{V}C_2$) at 1 l·min⁻¹ of $\dot{V}C_2$, decreased significantly in the rehabilitation group (28 ± 5 to 26 ± 4 l·min⁻¹ and 33 ± 5 to 31 ± 4 l·min⁻¹) respectively. In conclusion Wright et al. (2002) suggested that the provision of cardiac rehabilitation post coronary artery bypass graft in many UK centres may be insufficient and needs to include more frequent exercise training sessions over a sustained period. The study pointed out that the benefits of exercise training on functional capacity and cardiopulmonary function in patients with ischemic heart disease are absolutely clear. In contrast with Marshall et al.'s (2001) study, Wright et al. (2002) increased the level of exercise each week. Further comparison of these two studies show that benefits gained by an exercise programme were very similar. However patients performed exercise less frequently and the exercise training was two weeks shorter compared with the healthy population. This suggests that, due to exercise training, patients with ischemic heart disease tend to increase cardiac power output and aerobic capacity the same as healthy adults.

Patwala et al. (2006) performed a randomised controlled trial to assess whether exercise rehabilitation increases the benefits of cardiac resynchronisation therapy (CRT). Twenty-eight patients were recruited and tested pre, three months post and six months post CRT. At each visit triplicate resting cardiac output measurements were made using the equilibrium method. A modified Bruce protocol was performed to assess peak $\dot{V}O_2$ and peak cardiac output was measured after 30 min rest using the exponential method. After the three months test the patients were randomised into either on exercise group or a control group. The exercise group underwent a programme consisting of three visits per week. Each visit was made up of 20 min of treadmill walking and 10 min cycling. After three months of the exercise programme, the patients were tested at the six months stage along with the control group. Results demonstrated that there were no significant differences between the groups at baseline. By three months there was a significant improvement in NYHA class, exercise duration, peak $\dot{V}O_2$, peak cardiac power output and cardiac reserve in both the control and the exercise group ($p < 0.05$). After a period of randomization to exercise rehabilitation, the exercise group showed further significant improvement in

the exercise haemodynamic measures ($p < 0.05$), while the control group showed no significant changes over this period in any of measured variables. Patawala et al. (2006) concluded that exercise rehabilitation leads to an improvement in exercise haemodynamic measures. It has been suggested that exercise rehabilitation should be considered for all patients following CRT.

Hodges (2004) evaluated the influence of a 12-week exercise therapy programme on cardiovascular and respiratory dynamics in patients with peripheral vascular disease. Forty-one patients with mean age of 63 years completed an initial graded exercise test to maximum claudication. Then patients were randomly assigned to one of three groups: 1) home-based exercise, 2) supervised exercise, and 3) and control group for 12 weeks. Patients were retested at six weeks, 12 weeks and 12 weeks post intervention. Patients in the home-based intervention were asked to go walking three times per week for a period of 30 min. In the supervised group, patients visited the hospital twice weekly. Each supervised exercise session lasted for approximately 45 minutes. During this session patients were encouraged to walk on a treadmill (2 mph and 75% of initial grade achieved during the exercise test) until they reached stage three or four on the peripheral vascular pain scale and had accrued up to thirty minutes of exercise. Repeated measures ANOVA was used to identify any differences between the groups. In contrast with previously cited studies, the results demonstrated that there were no significant changes in oxygen consumption and peak cardiac power output between or within groups. However, significant change was reported in maximum walking distance in the supervised group. Hodges (2004) suggested that a greater intensity, duration and frequency of exercise sessions appear to be required before improvements in oxygen consumption and peak cardiac power output are demonstrated. A more intense intervention may result in the patients being able to sustain longer periods of exercise training, which could result in cardiovascular adaptations (Hodges, 2004).

4.7 Recommendation for Future Research

1. The anaerobic threshold has been proposed as a submaximal index of exercise capacity, independent of the subject's motivation, and has been classically defined as the point where lactate increases in plasma during exercise, as a consequence of the transition from total aerobic to aerobic plus anaerobic metabolism (Corra et al., 2004). Also it has been shown that anaerobic threshold identified patients at high risk of early death from chronic heart failure better than peak $\dot{V}O_2$ (Gitt et al., 2002). Surprisingly there is no study which has examined the relationship between anaerobic threshold and peak cardiac power output in either healthy or heart failure population. Hence more investigation is required to evaluate possible relationship between the two variables.

2. In patients with severe (advanced) heart failure, prolonged unloading of the myocardium with the use of a left ventricular assist device (LVAD) has been reported to lead to myocardial recovery in small numbers of patients for varying periods of time (Birks et al., 2006). LVADs are increasingly used as a bridge to cardiac transplantation and may represent a permanent alternative therapy for the management of end stage heart failure (Mancini et al., 1998). Only a few studies have evaluated exercise performance, while no study has reported cardiac power output and cardiac reserve in this group of patients. Therefore it will be useful to evaluate cardiac power output and cardiac reserve and their relationship to other commonly measured variables in those with LVADs.

3. Research over the past 15 years expanded the understanding and knowledge about the role of exercise training in patients with chronic heart failure (Gianuzzi et al., 2001). A commonly used type of exercise training in patients with chronic heart failure is aerobic training. However, a study by Maiorana et al. (2000) demonstrated that use of combined aerobic and resistance training improves functional capacity as well as strength in chronic heart failure. Further research is needed to determine the effect of different types of exercise on cardiac power output and cardiac reserve in chronic heart failure.

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CHAPTER 5: RELATIONSHIP BETWEEN PEAK CARDIAC POWER OUTPUT AND SELECTED CARDIO-RESPIRATORY VARIABLES IN HEALTHY ADULTS

Abstract

Introduction: Several studies have demonstrated relationships between overall cardiac function represented by cardiac power output and other most commonly reported cardio-respiratory variables in both healthy and diseased populations. There is, however no evidence to show how peak cardiac power output (CPO) correlates with anaerobic threshold (AT), carbon dioxide production ($\dot{V}C_2$), minute ventilation (\dot{V}_E) and oxygen pulse (OP). The purpose of this study was to assess the relationship between peak CPO and AT, $\dot{V}C_2$, \dot{V}_E and OP. This study additionally, evaluated the relationship between CPO and the following variables at peak exercise: oxygen consumption ($\dot{V}O_2$), circulatory power (CP), cardiac index (CI), cardiac output (\dot{Q}_T), stroke volume (SV), heart rate (HR) and mean arterial pressure (MAP).

Methods: Following local ethics committee approval and informed consent, 37 healthy adults (23 males and 14 females, means and SD, age 38 ± 12 years, weight 74 ± 15 kg, height 173 ± 10 cm) performed an incremental exercise test to volitional fatigue on a motorised treadmill using the Bruce protocol. Cardio-respiratory measurements were recorded on a breath-by-breath basis constantly throughout the test using an on-line metabolic analyzer (CardioO₂, Medical Graphics, St Paul, Minnesota, USA). Blood pressure was measured at the end of each stage as well as at peak exercise. Anaerobic threshold was calculated after the exercise test using the V slope method. Followed a 40 min recovery, the subjects performed a constant maximum workload exercise test for at least 4 min to a $\dot{V}O_2$ of at least 95% of the maximum level obtained during the incremental test. Cardiac output was measured using the exponential CO₂ rebreathing method. **Results:** Mean and SD values for the variables investigated were: CPO= 4.72 ± 1.13 W; $\dot{Q}_T = 19.7 \pm 4.6$ l·min⁻¹; MAP= 108 ± 7.8 mmHg; HR= 179.5 ± 14.4 beats·min⁻¹; SV= 109.4 ± 22.7 ml·beat⁻¹; CI= 10.4 ± 2.1 l·min⁻¹·m²; CP= 500 ± 169 mmHg·l·min⁻¹; $\dot{V}O_2 = 2.78 \pm 0.84$ l·min⁻¹; AT= 1.60 ± 0.45 l·min⁻¹; OP= 15.5 ± 4.1 ml·beat⁻¹; $\dot{V}C_2 = 3.46 \pm 1.13$ l·min⁻¹ and $\dot{V}_E = 97.9 \pm 32.4$ l·min⁻¹. In a

linear regression model, the following variables were independent predictors of peak CPO: AT ($r^2=0.22$, $p<0.01$); \dot{V}_E ($r^2=0.28$, $p<0.01$); OP ($r^2=0.32$, $p<0.01$); $\dot{V}C_2$ ($r^2=0.41$, $p<0.01$); $\dot{V}O_2$ ($r^2=0.59$, $p<0.01$); CP ($r^2=0.45$, $p<0.01$); CI ($r^2=0.58$, $p<0.01$); \dot{Q}_T ($r^2=0.90$, $p<0.01$); SV ($r^2=0.88$, $p<0.01$); HR ($r^2=0.12$, $p<0.05$). Non significant association between CPO and MAP at peak exercise was found ($r^2=0.05$, $p=0.16$). **Conclusion:** In healthy adults AT, $\dot{V}C_2$, \dot{V}_E and OP explain 22% to 41% of the variance, while $\dot{V}O_2$ and CI explain 59% and 58% of the variance in peak CPO. \dot{Q}_T and SV explain 90% and 88% of the variance respectively. Only central haemodynamic measures such as peak cardiac output and stroke volume are good predictors of maximal cardiac pumping capability, while those others routinely measured cardio-respiratory variables, including oxygen consumption, should be considered with caution in interpretation of overall cardiac function.

5.1 Introduction

The measurement of hydraulic power (cardiac power output) generated by the heart provides a supreme opportunity for quantifying cardiac pumping capability (Tan, 1987). Cardiac power output offers a major advantage over simply measuring cardiac output or blood pressure within individual compartments of the cardiovascular system (Bain et al., 1990). Cardiac power output is a unique measure which takes into account both blood pressure and flow. It represents the heart's ability to act as a mechanical pump and produce hydraulic energy which is used to maintain circulation (Tan, 1991). It is therefore not surprising that cardiac power output has been proposed to be a direct and probably the best indicator of overall cardiac function (Tan, 1986). Peak cardiac power output is a major determinant of exercise capacity (Tan, 1986; Cooke et al., 1998) and a powerful predictor of prognosis in heart failure (Tan, 1986; Roul et al., 1995; Williams et al., 2001).

Until now, the majority of the studies that have investigated measurement of cardiac power output have been conducted in clinical populations, particularly in heart failure (Tan, 1986; Tan et al., 1989, Bain et al., 1990; Cooke et al., 1998; Roul et al., 1995; Williams et al., 2001; Williams et al., 2005). There are only few studies that have

included measurements from a healthy population. Cooke et al. (1998) measured gas-exchange and haemodynamic responses in 70 subjects with widely ranging cardiac function but only eight of the subjects were healthy normal volunteers with no known cardiac or pulmonary disease. Marshall et al. (2001) measured resting and peak cardiac power output together with other cardio-respiratory variables in nine healthy subjects before and after an eight-week exercise training programme. More recently, Bromley et al. (2006) determined physiological range of peak cardiac power output in healthy adults (n=102). Only Hodges (2004) investigated the relationship between cardiac power output and other exercise variables in large cohort of healthy adults, but this study did not include measures of anaerobic threshold.

Anaerobic threshold is a good predictor of performance in a variety of endurance activities (e.g. running, cycling, race walking) in both trained and untrained populations (Weltman, 1995). Anaerobic threshold is also an effective index of cardiopulmonary exercise capacity in patients with different cardiopulmonary disorders (Wasserman, 1999) and an excellent predictor of prognosis in heart failure (Gitt et al., 2002).

At present there are no data which assess the possible relationship between cardiac power output and anaerobic threshold in either healthy or diseased subjects. Peak cardiac power output has not been previously correlated with measure of: carbon dioxide production, minute ventilation and oxygen pulse taken at peak exercise.

5.1.1 Definitions and Physiological Bases of Measured Variables

5.1.1.1 Cardiac power output (CPO)

Cardiac power output has been defined as a direct indicator of overall cardiac function which is calculated from the product of cardiac output and mean arterial pressure expressed in Watts (Tan, 1986). The concept of cardiac power output has been described in more details in the Chapter 4 of this thesis.

5.1.1.2 Anaerobic (ventilatory) threshold (AT)

Anaerobic threshold is the point at which the metabolic demands of exercise can no longer be met by available aerobic sources and at which an increase in anaerobic metabolism occurs, reflected by an increase in blood lactate concentration (Wilmore and Costill, 2004). It is the point at which lactate begins to accumulate in the blood, when the rate of lactate appearance in the blood exceeds the rate of its removal, causing an increase in ventilation (Myers and Ashley, 1997). Anaerobic threshold is also known as the lactate threshold, lactic acid threshold, gas exchange threshold or ventilatory threshold, regardless of which methodology is used in determination. Non significant difference and high relationship was reported between lactate and ventilatory thresholds (Beaver et al., 1986; Wyatt, 1999; and Gaskill et al., 2001).

The basis behind the link between the lactate and ventilatory threshold is an increased chemoreceptor drive (Swanson, 1979; and Whipp, 1994). As lactate accumulates, there is a reduction in pH. This increases chemoreceptor drive to the respiratory centres (Astrand and Rodahl, 1986). Because of buffering of lactic acid, there is an increase in C_2 and H^+ (Ganong, 1983). When there is a rise in arterial P_2 due to increased tissue metabolism and insufficient alveolar ventilation, ventilatory stimulation takes place (Wasserman et al., 1999). Also Wasserman (1976) found that the delivery of C_2 to the lungs drives ventilation.

5.1.1.3 Peak (maximal) oxygen consumption ($\dot{V}O_2$)

Maximum oxygen consumption ($\dot{V}O_{2\max}$) is defined as the highest rate of oxygen that can be taken up and utilized by the body during severe exercise (Bassett and Howley, 2000). It is one of the main variables in the field of exercise physiology, and is frequently used to indicate the cardio-respiratory fitness of an individual. $\dot{V}O_2$ can be computed from blood flow and O_2 extraction by the tissues, as expressed in the Fick equation. Factors that can influence O_2 availability are: oxygen carrying capacity of the blood (available hemoglobin, arterial O_2 saturation, and dissociation curve shifts with temperature, C_2 and pH), cardiac function (heart rate, stroke

volume), redistribution of peripheral blood flow, and extraction by the tissues (capillary density, mitochondrial density and function, adequacy of perfusion, and tissue diffusion).

As $\dot{V}O_2$ increases with increasing external work, one or more determinants of $\dot{V}O_2$ approach limitations (e.g. stroke volume, heart rate, or tissue extraction) and $\dot{V}O_2$ versus work rate may begin to plateau. Achieving a clear plateau in $\dot{V}O_2$ has traditionally been used as the best evidence of $\dot{V}O_{2\max}$ which is the best index of aerobic capacity and the gold standard for cardio-respiratory fitness (Johnson et al., 2003). However, in clinical testing situations, a clear plateau may not be achieved before symptom limitation of exercise (Myers et al., 1989). Consequently, $\dot{V}O_{2\text{peak}}$ is often used as an estimate for $\dot{V}O_{2\max}$ indicating that for practical purposes $\dot{V}O_{2\max}$ and $\dot{V}O_{2\text{peak}}$ may be used interchangeably (Johnson et al., 2003).

5.1.1.4 Carbon dioxide production ($\dot{V}C_{O_2}$)

Carbon dioxide production has been defined as the amount of C_{O_2} produced by the body's metabolic processes and in some circumstances released by buffering reactions within the body (Wasserman et al., 1999). During exercise $\dot{V}C_{O_2}$ is determined by factors similar to those that govern O_2 uptake such as cardiac output, C_{O_2} carrying capacity of the blood and tissue exchange (Johnson et al., 2003). During short-duration exercise, glycogen is used primarily by the muscles for energy, and the relationship between O_2 consumption and C_{O_2} production is almost equimolar. As such, during progressive exercise $\dot{V}C_{O_2}$ increases nearly as much as does $\dot{V}O_2$ over the lower work rate range, with an average $\dot{V}C_{O_2} - \dot{V}O_2$ relationship slightly less than 1.0 (Wasserman, 1999). There is typically a relatively sharp change in $\dot{V}C_{O_2} - \dot{V}O_2$ slope toward the midrange of the $\dot{V}O_2$ response. This results in a steeper, but typically quite linear, profile over the upper work rate range (Wasserman et al., 1999). The steeper slope reflects the C_{O_2} generated in excess of that produced by aerobic metabolism. This is due to bicarbonate buffering of increased lactic acid production at

these high work rates. With anaerobic metabolism, $\dot{V}C_2$ increases as results of a chemical reaction between hydrogen ions from lactate and dissolved C_2 .

5.1.1.5 Minute ventilation (\dot{V}_E)

Minute ventilation is defined as the volume of air taken into or exhaled from the body in one minute and is the product of tidal volume and breathing frequency (Wasserman et al., 1999). Increased ventilation during exercise is one of the primary means by which arterial blood regulates gases and acid-base status under of the augmented metabolic demands of exercising muscles (Johnson et al., 2003). The rise in \dot{V}_E with exercise is associated with an increase in both tidal volume and frequency of breathing. In health, increases in tidal volume are primarily responsible for increases in ventilation during low levels of exercise (Gallagher et al., 1987). As exercise progresses, both tidal volume and breathing frequency increase until 70-80% of peak exercise and thereafter an increase in breathing frequency predominates (Gallagher et al., 1987). In both the steady-state and during exercise transients, \dot{V}_E responds in close proportion to C_2 (Wasserman et al., 1999).

5.1.1.6 Oxygen pulse (OP)

The ratio of $\dot{V}O_2$ to heart rate is conventionally termed as the “oxygen pulse” (OP) and reflects the amount of O_2 extracted by the tissues of the body per heart beat (Wasserman et al., 1999). According to the modified Fick equation, OP is numerically equal to the product of stroke volume and arterial-venous O_2 difference. It is not, therefore, surprising that OP has been used by some authors as an estimator of stroke volume during exercise (Wasserman et al., 1999). At any given work rate, the subject with the greatest maximal working capacity normally has the highest OP, and the subject with the lowest maximal working capacity normally has the lowest OP (Wasserman et al., 1967).

5.1.1.7 Circulatory power (CP)

Circulatory power represents the volume of O_2 added to the mixed venous blood by the lungs and transferred to the systematic arterial circulation, against a pressure gradient, by the heart (Nicholls et al., 2002). It is calculated as the product of oxygen uptake and systolic blood pressure (Cohen-Solal et al., 2002). Cohen-Solal et al. suggested that circulatory power may be assumed to mirror the cardiac power output at peak exercise. This is only true if arterial-venous O_2 difference does not differ much at peak exercise among subjects, and systolic and mean arterial pressure increase in parallel during exercise. These assumptions may be acceptable in a healthy population, whereas in those with cardiovascular disorders they must be considered with caution. Cohen-Solal et al. (2002) therefore recommended that the circulatory power should not be viewed as a perfect surrogate of cardiac power output, but as a new global 'easy to measure' index that incorporates, besides arterial-venous O_2 difference, heart rate, stroke rate, and blood pressure responses.

5.1.1.8 Cardiac index (CI)

Cardiac index is defined as cardiac output to body surface area ratio. The original reason for using the cardiac index as a means for expressing cardiac output for individuals of different sizes was that the basal metabolic rate in human beings is generally expressed in terms of surface area (Guyton, 1996). One would expect the cardiac output to be greater in a large person compared with a small person (Guyton, 1996). In the clinical environment cardiac index is widely used as an indicator of cardiac function and blood flow. However this may not be the best method of normalizing cardiac output for body size (Hodges, 2004). Cardiac output may be better related to body volume, as this takes into account how far the blood has to travel in order to meet the demands during exercise (Hodges, 2004).

5.1.1.9 Cardiac output (\dot{Q}_T)

Cardiac output is the flow of blood from the heart in a particular period of time. It is the product of the average stroke volume per beat and the heart rate (Wasserman et al.,

1999). Cardiac output increases with exercise to support the increasing metabolic demands of the tissues. In healthy subjects, \dot{Q}_T is a linear function of $\dot{V}O_2$ and does not vary as a function of either sex or state of training (Johnson et al., 2003). Also Proctor et al. (1998) demonstrated that neither age nor gender has significant impact on the \dot{Q}_T - $\dot{V}O_2$ relationship during submaximal cycle ergometry among chronically endurance-trained individuals. Increases in \dot{Q}_T are initially accomplished by increases in stroke volume and heart rate, and then at moderate to high intensity exercise almost exclusively by increases in heart rate. The increase in \dot{Q}_T is largely driven by vagal withdrawal and by increases in either circulating or neurally produced catecholamines.

5.1.1.10 Stroke volume (SV)

Stroke volume is the amount of blood ejected from left ventricle during contraction. Stroke volume also changes during exercise to allow the heart to work more efficiently. However there are conflicting data about stroke volume changes as a person goes from very low rates of work to maximal work or exhaustion. Most researchers agree that stroke volume increase with increasing rates of work but only up to 40-60% of maximal capacity (Wilmore and Costill, 2004). At that point, stroke volume is thought to plateau, remaining essentially unchanged up to and including the point of exhaustion. Others have reported that SV continues to increase up through maximal exercise intensities (Zhou et al., 2001). The mechanism of SV increase during exercise has commonly been explained by the Frank-Starling law, which states that the primary factor in controlling stroke volume is the extent to which the ventricle stretches and consequently contract.

5.1.1.11 Heart rate (HR)

Heart rate reflects the amount of work the heart must do to meet the increased demands of the body when engaged in activity (Wilmore and Costill, 2004). In healthy subjects, HR increases linearly with increasing $\dot{V}O_2$. Increases in HR are initially mediated by a decrease in parasympathetic activity (vagal withdrawal) and, subsequently, almost exclusively by increased sympathetic activity.

5.1.1.12 Mean arterial pressure (MAP)

As exercise intensity increases, reflex control of the distribution of cardiac output causes some characteristic changes in blood pressure and vascular resistance (Perloff et al., 1993). In working muscles, there are local mediators that cause intense vasodilatation that increases blood flow to support metabolic demands. In addition, non-working muscles are vasoconstricted from reflex increases in sympathetic nerve activity. The net result is a fall in systematic vascular resistance, but systolic blood pressure typically rises progressively with an increase in $\dot{V}O_2$. Diastolic blood pressure typically remains constant or may decline slightly (Johnson et al., 2003). Mean arterial pressure is calculated from the following equation: $DBP + 0.412 \times (SBP - DBP)$, where SBP is systolic blood pressure and DBP is diastolic blood pressure (Meaney et al., 2000).

5.1.2 *Non-invasive Methods for Determination of Anaerobic Threshold*

Increases in lactic acidosis can be determined non-invasively by observing the patterns of change in $\dot{V}C_2$ and \dot{V}_E relatively to $\dot{V}O_2$ as exercise intensity increases. The following are the two most commonly used methods.

5.1.2.1 Ventilatory equivalent method

The ventilatory equivalent method involves the simultaneous analysis of the ventilatory equivalent of oxygen ($\dot{V}_E/\dot{V}O_2$), the ventilatory equivalent for carbon dioxide $\dot{V}_E/\dot{V}C_2$, end-tidal P_{O_2} (P_{ETO_2}) and end-tidal P_{CO_2} (P_{ETCO_2}). According to this method anaerobic threshold is defined as the intensity of activity (e.g. $\dot{V}O_2$) which causes the first rise in $\dot{V}_E/\dot{V}O_2$ without a simultaneous rise in $\dot{V}_E/\dot{V}C_2$ (Reinhard et al., 1979).

In response to a progressive exercise test, the linear pattern of increase in $\dot{V}C_2$ and \dot{V}_E seen at low work rates changes to a curvilinear pattern at high work rates (Wasserman et al., 1999). On the other hand $\dot{V}O_2$ continues to increase relatively

linearly. \dot{V}_E and $\dot{V}C_2$ initially accelerate in a proportional manner above the AT. Therefore, $\dot{V}_E/\dot{V}O_2$ and P_{ETO_2} increase, whereas $\dot{V}_E/\dot{V}C_2$ and P_{ETO_2} remain constant for a brief period of time (isocapnic buffering) due to the lack of hyperventilation with respect to C_2 , despite the development of metabolic acidosis (Wasserman et al., 1999).

5.1.2.2 V-Slope method

Beaver et al. (1986) aimed to derive an objective mathematical method, based on buffering of lactic acid, which could reliably locate anaerobic threshold. Importantly it should be independent of the sensitivity of ventilatory control mechanisms. The method involves the analysis of the behaviour of $\dot{V}C_2$ as a function of $\dot{V}O_2$ during progressive exercise tests. The point of exceeding the lactate threshold is accompanied by the buffering of lactic acid by $[HCO_3^-]$ with a consequent increase in $\dot{V}C_2$ (Beaver et al., 1986). This results in a transition in the relationship between the $\dot{V}C_2$ and $\dot{V}O_2$ which is the underlying element on all methods of anaerobic threshold detection by gas exchange (Wasserman et al., 1999). Since the method to detect AT is based on analyzing the slopes of O_2 and C_2 volume curves, Beaver et al. (1986) termed this procedure V-slope method. As this method uses simultaneous measurements of $\dot{V}C_2$ and $\dot{V}O_2$, it is independent of the subject's ventilatory response and insensitive to irregularities of breathing. It is therefore inappropriate to use the term ventilatory but rather anaerobic, lactate or lactate acidosis threshold (Wasserman et al., 1999).

Wasserman et al. (1999, p. 74) explained V-slope method as following: "When the net increase in lactate accumulation produces an acidosis, $\dot{V}C_2$ accelerates relative to $\dot{V}O_2$. When these variables are plotted against each other, the relationship is composed of two apparently linear components, the lower of which (S1) has a slope of slightly less than 1.0, whereas the upper component (S2) has a slope steeper than 1.0. The intercept of these two slopes is the AT as measured by gas exchange".

Computerized detection of AT using the V-slope method today is available in many of

automated metabolic gas analyzers. For the purpose of the present study the V-slope method will be used to identify the point of AT.

5.1.3 Rationale and Purposes of the Study

There are few studies which have evaluated the relationship between overall cardiac function (represented by cardiac power output) and other commonly reported cardio-respiratory variables in healthy adults. Anaerobic threshold has been used as a criterion of the ability of the circulatory system to deliver and utilize oxygen during exercise (Cohen-Solal et al., 1994) and an objective parameter of cardiopulmonary exercise capacity (Gitt et al., 2002). At present there is no study which has examined the relationship between peak cardiac power and a submaximal index of cardiopulmonary exercise capacity such as anaerobic threshold (AT) in healthy adults. Also peak cardiac power output has not previously been correlated with: carbon dioxide production ($\dot{V}C_{O_2}$), minute ventilation (\dot{V}_E) and oxygen pulse (OP), as measured at peak exercise. The first purpose of the present study was, therefore, to assess the relationship between peak CPO and AT, $\dot{V}C_{O_2}$, \dot{V}_E and OP in healthy adults. Furthermore the study evaluated the relationship between cardiac power output (CPO) and the following cardio-respiratory variables measured at peak exercise: oxygen consumption ($\dot{V}O_2$), circulatory power (CP), cardiac index (CI), cardiac output (\dot{Q}_T), stroke volume (SV), heart rate (HR) and mean arterial pressure (MAP).

5.1.4 Research Hypotheses

H_1 – There will be a significant positive relationship between peak CPO and AT, $\dot{V}C_{O_2}$, \dot{V}_E and OP.

H_2 – There will be a significant positive relationship between peak CPO and $\dot{V}O_2$, CP, CI, \dot{Q}_T , SV, HR and MAP, as measured at peak exercise.

5.2 Methods

5.2.1 Subjects

Healthy subjects were recruited from a South-East UK University. The advertisement of the study used the university website, e-mail addresses and posters. Contact details of the research team were clearly displayed. All subjects who volunteered to participate in the study received an information sheet, medical history/lifestyle and physical activity readiness questionnaire (PARQ).

Twenty-three healthy men and 14 women ranging from 20 – 63 years of age were enrolled. Subjects with any history of cardiovascular, pulmonary, metabolic and neuromuscular problems or taking prescribed medications known to affect cardiovascular or respiratory function were excluded. All subjects were asked to refrain from eating two-hours prior to testing. Subjects were instructed to abstain from caffeine and alcohol 12 hours prior to exercise testing, to abstain from cigarette smoking three hours prior testing, and to avoid heavy physical exertion during the 48 hours preceding the test. This study was approved by the appropriate Faculty Ethics Committee. All subjects gave their written informed consent.

5.2.2 Experimental Design

This study took the form of a correlation study with various cardiovascular (OP, CP, CI, \dot{Q}_T , SV, HR, MAP) and respiratory ($\dot{V}O_2$, $\dot{V}C_{2}$, \dot{V}_E) measures being designated as the independent variables and CPO being designated as the dependent variable.

5.2.3 Equipment

Exercise tests were performed using a treadmill adjustable for gradient and speed (Cardio Control, Delft, The Netherlands). Breath-by-breath $\dot{V}O_2$, $\dot{V}C_{2}$, end-tidal partial pressure of C_{2} , tidal ventilation, and respiratory rate were all measured using an online metabolic gas analyser (CardiO₂, Medical Graphics Corporation, St Paul, Minnesota, USA). The CardiO₂ system has an integrated 12-lead ECG system

(Cardio Perfect ST 2001) which was used to monitor heart rate and rhythm prior and during the exercise test. Blood pressure was measured manually by auscultation using a sphygmomanometer (ERKA, Kallmeyer Medizintechnik, Germany) and Littman stethoscope (3M Health care, St Paul, MN, USA).

5.2.4 Procedure

5.2.4.1 Pre-test procedure

On arrival at the laboratory, subjects were asked for their completed PARQ forms and questioned about their medical health. Subjects were then required to complete the informed consent form in front of the researcher who countersigned it as a witness. Subjects had their mass measured using a floor scale (Seca mode 761, Vogel and Halke, Germany) and height recorded using a freestanding stadiometer (Leicester Height Measure, Invicta Plastics, Oadby, Leicester, UK) prior to exercise testing.

Three out of 37 subjects were unfamiliar with using a treadmill and they were asked to complete a familiarisation procedure. During this process subjects were instructed on treadmill walking, balance and posture. All other subjects were familiar with whole testing procedure, including the fitting face mask, as they had participated in a previous exercise testing study with similar characteristics. Subject were asked not to talk during the test and instead, they were instructed to use hand signals to express their feelings: 1) “thumbs up” – meant that the subject was feeling good and able to carry on, 2) “thumbs to the side” – meant that the subject was starting to get tired, 3) “thumbs down” – meant that the subject wanted to stop the exercise test. In addition subjects were familiarised with the use of the Borg Scale (Borg, 1970) and also instructed how to use to an emergency stop button which was located at the front of the treadmill.

ECG electrodes (Blue Sensor, Medicotest, Olstykke, Denmark) were attached according to the standard lead configuration for exercise testing and the ECG cables were connected. In order to minimise both interference with the exercise limbs and the signal to noise ration, the cables were secured around the subject’s waist be means of a neoprene belt. The blood pressure cuff was placed around the upper arm. Resting

blood pressure was measured and a resting ECG was also monitored prior to the of exercise test.

5.2.4.2 Testing procedure

Exercise testing included two stages separated by a 40 min recovery period, as described below.

Stage 1 – Determination of maximal aerobic capacity. In this stage all subjects performed an incremental exercise test (Bruce et al., 1973) to determine peak oxygen consumption. The Bruce protocol begins with 3 min stages of walking at 1.7 mph and 10% gradient. Thereafter, the grade is incremented 2% every 3 minutes, and the speed is incremented 0.8 mph every 3 minutes until the treadmill reaches 18% grade and 5 mph. After this, the speed is increased by 0.5 mph every 3 min. The Bruce protocol has been widely used for exercise stress testing (ACSM, 2000). Blood pressure was measured every two minutes into each stage and during peak exercise. Following blood pressure measurements, the subject pointed on the Borg scale which was located a front of him to indicate the subjective feeling of exercise. On approximately every minute of the test, subjects were also asked “Are you feeling ok?” They replied with thumb signals as described above. The test was terminated when the subject desired to stop or when the researcher considered the subject was unable to continue exercising. For an early test termination, the researcher used the criteria recommended by the ACSM (2000): 1) onset of angina or angina like symptoms, 2) significant drop (20 mmHg) in systolic blood pressure or a failure of the systolic blood pressure to rise with an increase in exercise intensity, 3) excessive rise in blood pressure: systolic > 260 mmHg or diastolic pressure >115 mmHg, 4) signs of poor perfusion: light headiness, confusion, ataxia, pallor, cyanosis, nausea or cold and clammy skin, 5) failure of heart rate to increase with increased exercise intensity, 6) noticeable change in heart rhythm, 7) subjects requests to stop, 8) physical and verbal manifestation of severe fatigue, and 9) failure of the testing equipment. The criteria adopted by the researcher for the achievement of peak $\dot{V}O_2$ were the absence of a rise in $\dot{V}O_2$ with an increase in exercise intensity and a respiratory exchange ratio >1.15.

At termination of the exercise test, subjects undertook an active recovery. The ECG

and heart rate were continuously monitored and the treadmill was stopped when the subject's heart rate returned within 5% of the initial resting values.

Stage 2 – Cardiac output measurement. Stage 2 was performed following a 40-minute rest period. During the rest period the equipment was reconfigured and also recalibrated. Recalibration was necessary because there was a change in the dead space of equipment. The configuration used for monitoring cardiac output has a dead space of 80 ml and the normal mouthpiece and pneumotach configuration used during the first test has a dead space of 50 ml. The anaesthetic bag was filled with 4% carbon dioxide, 35% oxygen and the balance nitrogen. A 6 l anaesthetic rubber bag was filled with approximately 1.5 to 2 times the subject's tidal volume. Peak cardiac output was measured at maximal exercise by the exponential C_{O_2} rebreathing method described by Defares (1958). The exponential C_{O_2} rebreathing method was described in more details in Chapter 3.

The second stage of the testing procedures was a constant maximal workload exercise tests of approximately five minutes in duration. The treadmill speed and incline were initially set to the highest completed or nearly completed stage of the incremental protocol. The gradient and the speed were then adjusted on an individual basis to enable the subject to sustain the exercise for at least five minutes and a $\dot{V}\text{O}_2$ of at least 90% of the maximum attained during incremental test. Once the subject had reached 95% of peak $\dot{V}\text{O}_2$, the researcher pushed the plunger to switch the subject to rebreathing the gas mixture from the bag for 15 seconds after which the plunger was pulled out and the subject breathed room air. An exponential capnograph tracing was produced whilst the subject rebreathed the gas mixture. The line of best fit was plotted through the end-tidal C_{O_2} pressure points using the technique described by DaSilva et al. (1985). The first point in the graph was rejected. Once the line of best fit had been completed the computer systems generated the cardiac output estimate by means of the indirect Fick method as described in Chapter 3. Peak blood pressure was measured by the other researcher during rebreathing procedure.

5.2.5 Calculations and Statistical Analysis

The cardiac power output was calculated from the product of cardiac output and mean arterial pressure using the following equation (Cooke et al., 1998): $CPO = (\dot{Q}_T \times MAP) \times K$, where CPO is cardiac power output in Watts (W), \dot{Q}_T is cardiac output in $l \cdot min^{-1}$, MAP is mean arterial pressure in mm Hg and K is the conversion factor (2.22×10^{-3}). The mean arterial pressure was calculated as $DBP + 0.412 \times (SBP - DBP)$, where SBP is systolic blood pressure and DBP is diastolic blood pressure (Meaney et al., 2000).

All statistical analysis was carried out using SPSS version 13.0 (SPSS inc. Chicago, Illinois, USA). Prior to statistical analysis, data were checked for univariate and multivariate outliers using standard Z-distribution cut-offs and Mahalanobis distance tests respectively. Normality of distribution was assessed using a Kolmogorov-Smirnov test. Correlation between peak cardiac power output and selected cardio-respiratory variables were assessed by univariate linear regression analysis. When data met parametric assumptions the relationship between cardiac power output and other cardio-respiratory variables was assessed using Pearson's product moment coefficient of correlation. The Spearman rank-difference correlation was used when data did not meet parametric assumption. The meaningfulness of coefficient of correlation was evaluated by calculating the coefficient of determination (r^2). Differences in measured variables between men and women were determined using independent samples t-tests and percentage differences were calculated. Statistical significance was indicated if $p < 0.05$. Values are expressed as means \pm SD unless otherwise indicated.

5.3 Results

Demographic details and physical characteristics of the studied population are presented in Table 5.1.

Table 5.2 shows the peak values of cardiac power output and other measured cardio-respiratory variables at peak exercise. The range of peak $\dot{V}O_2$ indicates clearly that subjects come from a wide variety of aerobic capacities. The range of peak cardiac power output illustrates the wide variety of power output generated by the heart in healthy adults. The subjects achieved the following results during the incremental exercise test: exercise duration 11.9 ± 2.6 minutes, relative peak oxygen consumption $37.7 \pm 9.9 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, anaerobic threshold $21.8 \pm 5.7 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and respiratory exchange ratio 1.23 ± 0.10 . During the second test when \dot{Q}_T was measured, subjects achieved a mean peak $\dot{V}O_2$ of $102 \pm 11\%$ of that attained in the first test.

Table 5.1 Descriptive Statistics of Subjects' Demographic and Physical Characteristics Details

Parameter	Men, N=23		Women, N=14		All subjects, N=37	
	Mean \pm SD	Range	Mean \pm SD	Range	Mean \pm SD	Range
Age (years)	34 \pm 9.7	20-59	44.5 \pm 12.3*	24-63	38.2 \pm 11.8	20-63
Weight (kg)	80.2 \pm 14.3	55.5-116	64.1 \pm 8.9*	52.5-80	74.5 \pm 14.6	52.5-116
Height (cm)	178.9 \pm 7.2	165-194.3	163.3 \pm 5.6*	153.2-172.5	173.3 \pm 10.0	153.2-194.3
BMI (kgm ²)	24.9 \pm 3.6	20.1-29.2	24.2 \pm 3.6	19.1-31.3	24.7 \pm 3.5	19.2-29.3
BSA (m ²)	2.0 \pm 0.2	1.6-2.4	1.7 \pm 0.1*	1.5-1.9	1.9 \pm 0.2	1.5-2.4

BMI-body mass index, BSA-body surface area;

*significantly different from men ($p < 0.01$)

From all cardio-respiratory variables measured at peak exercise only mean arterial pressure was not significantly different between men and women ($p=0.38$) (Table 5.2). The percentage difference between men and women for CPO and \dot{Q}_T were 33 and 32%, respectively.

In order to decrease the effect of body size on peak CPO, allometric scaling model was used as suggested by Chantler et al. (2005). The positive relationship between peak CPO and body surface area was found ($r=0.64$, $p<0.01$). Therefore peak CPO was allometrically scaled to body surface area using the exponent for body surface area of 0.81 as suggested (Chantler et al., 2005). Peak CPO was then not significantly different between men and women (3.02 ± 0.44 vs. 2.35 ± 0.35 W/m², $p=0.23$) with mean percentage difference between men and women of 22%.

Table 5.2 Gender Differences in Measured Cardio-respiratory Variables

Cardio-respiratory Variables	Men, N=23		Women, N=14		All Subjects, N=37	
	Mean±SD	Range	Mean±SD	Range	Mean±SD	Range
CPO (W)	5.40±0.78	4.06-7.18	3.60±0.55*	2.72-4.41	4.72±1.13	2.72-7.18
\dot{Q}_T (l·min ⁻¹)	22.4±3.5	16.5-28.7	15.2±2.0*	10.7-17.8	19.7±4.6	10.7-28.7
CI (l·min ⁻¹ ·m ²)	11.4±2.0	8.6-15.6	9.0±1.3*	5.8-11.4	10.5±2.1	5.8-15.6
HR (beats·min ⁻¹)	185±12	156-205	171±14*	154-192	180±14	154-205
SV (ml·beat ⁻¹)	121.5±18.2	80.5-151.9	89.5±13.5*	68.2-115.6	109.4±22.7	68.2-151.9
MAP (mmHg)	109±7.1	96.3-121.6	106.6±8.9	89.8-123.0	108.1±7.8	89.8-123
CP (mmHg·l·min ⁻¹)	610±110	377-791	320±45*	247-408	500±109	247-791
OP (ml·beat ⁻¹)	18.0±2.9	12.5-24.0	11.3±1.7*	9.0-15.0	15.5±4.1	9.0-24.0
AT (l·min ⁻¹)	1.84±0.37	1.33-2.69	1.20±0.23*	0.89-1.61	1.60±0.45	0.89-2.69
$\dot{V}O_2$ (l·min ⁻¹)	3.30±0.58	2.12-4.40	1.92±0.32*	1.49-2.43	2.78±0.84	1.49-4.40
$\dot{V}C_2$ (l·min ⁻¹)	4.18±0.76	2.59-5.69	2.28±0.38*	1.61-2.82	3.46±1.13	1.61-5.69
\dot{V}_E (l·min ⁻¹)	117.6±22.6	62.3-166.4	65.5±14.8*	46.6-89.4	97.9±32.4	46.6-166.4

CPO-cardiac power output, \dot{Q}_T -cardiac output, CI-cardiac index, HR-heart rate, SV-stroke volume, MAP-mean arterial pressure, CP-circulatory power, OP-oxygen pulse, AT-anaerobic threshold, $\dot{V}O_2$ -O₂ uptake, $\dot{V}C_2$ -C₂ production, \dot{V}_E -minute ventilation, * $p<0.01$.

When men and women data were pooled, coefficients of correlation were significant between peak absolute values of CPO and other cardio-respiratory variables as shown in Figures 5.1 – 5.10. Only peak mean arterial pressure was not significantly correlated with peak CPO ($r=0.23$, $p=0.16$).

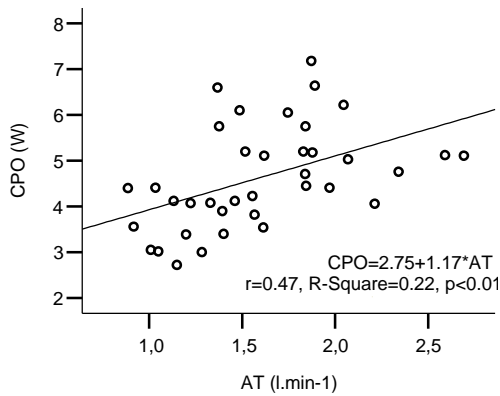


Figure 5-1

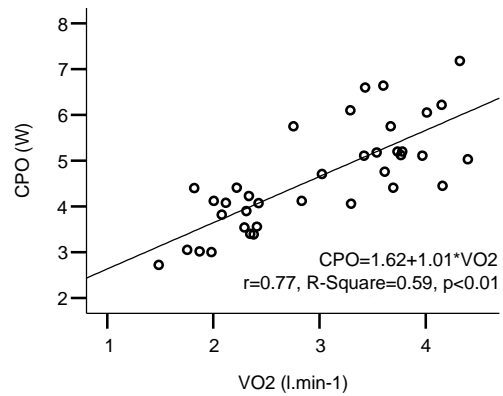


Figure 5-2

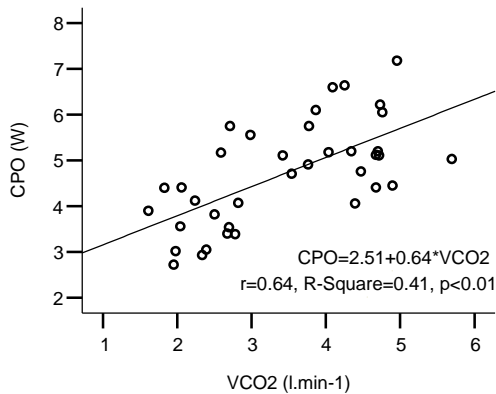


Figure 5-3

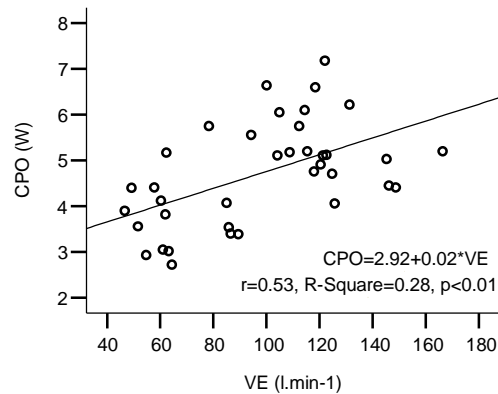


Figure 5-4

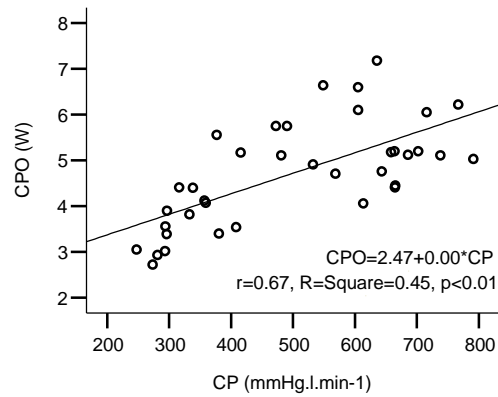
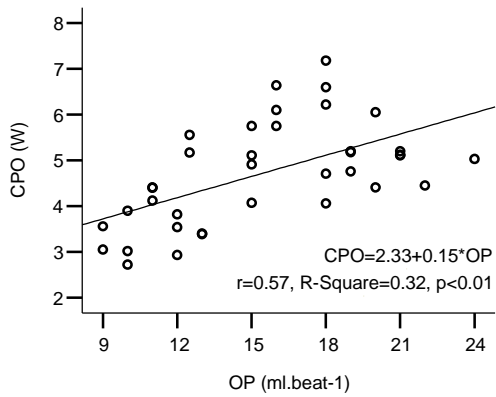


Figure 5-5

Figure 5-6

Figures 5-1 – 5-6 Relationship between peak cardiac power output (CPO) and anaerobic threshold (AT), peak oxygen consumption ($\dot{V}O_2$), peak carbon dioxide production ($\dot{V}C_2$), peak minute ventilation (\dot{V}_E), peak oxygen pulse (OP) and peak circulatory power (CP).

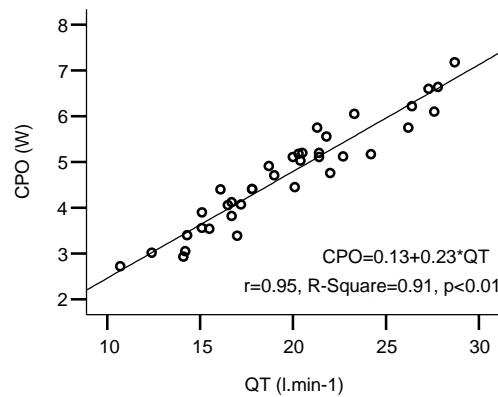
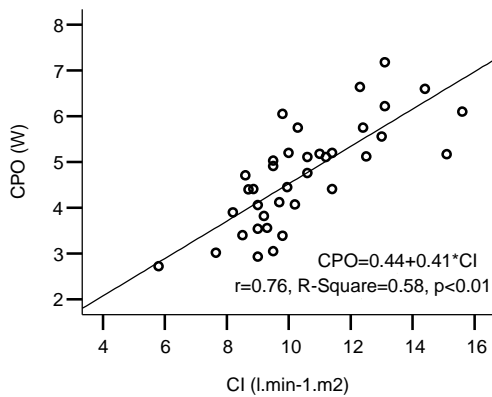


Figure 5-7

Figure 5-8

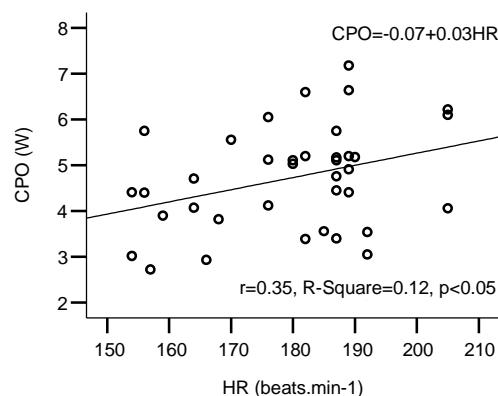
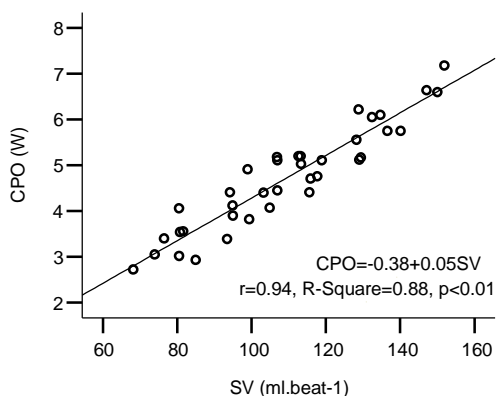


Figure 5-9

Figure 5-10

Figures 5-7 – 5-10 Relationship between peak cardiac power output (CPO) and peak cardiac index (CI), peak cardiac output (\dot{Q}_T), peak stroke volume (SV), peak heart rate (HR).

Peak cardiac power output correlated well with exercise duration ($r=0.66$, $p<0.01$).

Subjects achieved 96 and 92% of maximal predicted heart rate during incremental and single stage exercise test. When these values were correlated with peak CPO there was none significant relationship between peak CPO and peak heart rate ($r=0.10$ and 0.14 , $p>0.05$).

Subgroup analysis by gender demonstrated that peak CPO correlated to \dot{Q}_T , SV, CI and $\dot{V}O_2$ in the similar way in men and women as shown in Table 5.3.

Table 5.3 Relationship between Peak CPO and Selected Variables in Men and Women

	Men, N=23			Women, N=14		
	Mean \pm SD	Correlation with peak CPO		Mean \pm SD	Correlation with peak CPO	
		r	p		r	p
\dot{Q}_T (l \cdot min $^{-1}$)	22.4 \pm 3.5	0.90	<0.01	15.2 \pm 2.0	0.82	<0.01
SV (ml \cdot beat $^{-1}$)	121.5 \pm 18.2	0.89	<0.01	89.5 \pm 13.5	0.88	<0.01
CI (l \cdot min $^{-1}$ \cdot m $^{-2}$)	11.4 \pm 2.0	0.64	<0.01	9.0 \pm 1.3	0.62	<0.05
$\dot{V}O_2$ (l \cdot min $^{-1}$)	3.30 \pm 0.58	0.74	<0.01	1.92 \pm 0.32	0.68	<0.01

CPO-cardiac power output, \dot{Q}_T -cardiac output, SV-stroke volume, CI-cardiac index, $\dot{V}O_2$ - O_2 uptake.

5.4 Discussion

Numerous cardio-respiratory indices of exercise tolerance are routinely measured during exercise test. Many of these are used either to grade severity or provide prognosis in many cardiovascular diseases. The present study aimed to assess the relationship between peak cardiac power output and a number of cardio-respiratory variables which are commonly measured during cardio-pulmonary exercise testing. This is the first study to analyse the relationship between peak cardiac power output and anaerobic threshold, carbon dioxide production, minute ventilation and oxygen pulse. Also for the first time the relationship between peak cardiac power output and peak stroke volume as a component of cardiac output has been analysed.

One novel finding from this study is that AT, $\dot{V}C_{O_2}$, \dot{V}_E and OP explain only 22% to 41% of the variance in peak CPO in healthy adults, whereas $\dot{V}O_2$ and CI explain 59% and 58% of the variance. Cardiac output and stroke volume, however explain 90% and 88% of the variance in peak cardiac power output. This suggests that most of the cardio-respiratory variables routinely measured during cardiopulmonary exercise testing are only weakly related to overall cardiac function. Overall cardiac function is much more strongly associated with central haemodynamic variables such as cardiac output and stroke volume.

5.4.1 Relationship between Peak Cardiac Power Output and Anaerobic Threshold

The anaerobic threshold is an objective parameter of cardiopulmonary exercise capacity (Wasserman et al., 1999) which has been considered to be a good predictor of performance in a variety of endurance activities (e.g. running, cycling, race walking) and for both trained and untrained populations (Weltman, 1995). Myers and Ashley (1997) also suggested that the level of work that can be sustained prior to lactate accumulation is an accurate predictor of endurance performance. In a clinical population (e.g. heart failure), whose cardiac function response to incremental exercise is impaired in proportion to the severity of pump dysfunction, determination of the anaerobic threshold is a useful clinical tool to grade severity of heart failure

(Matsumura et al., 1983) and to predict outcome (Gitt et al., 2002). Finally, the anaerobic threshold has been used as a criterion of the ability of the circulatory system to deliver and utilize O_2 during exercise (Cohen-Solal et al., 1994).

Taking into account the above facts and considering cardiac power output as direct indicator of overall cardiac function, one would expect a strong positive relationship between the CPO and AT. The present results from healthy adults demonstrate only a moderate relationship between these variables suggesting that a higher anaerobic threshold does not necessarily indicate better cardiac performance as represented by peak cardiac power output. More precisely, calculated coefficient of determination indicates that differences in peak cardiac power output may explain only 22% of the variance observed in anaerobic threshold. This may in part be attributable to the contribution of the peripheral muscles characteristics (e.g. mitochondrial content, capillary density) to the anaerobic threshold (Basset and Howley, 2000), whereas cardiac power output is reflection of central haemodynamics.

5.4.2 Relationship between Peak Cardiac Power Output and Peak Carbon Dioxide Production and Minute Ventilation

Carbon dioxide production is linked to both circulation through the Fick equation and respiration through the level of ventilation (Hachamowitch et al., 1991). During exercise $\dot{V}C_{O_2}$ is determined by factors similar to those that govern O_2 uptake such as cardiac \dot{Q} output, C_{O_2} carrying capacity of the blood and tissue exchange (Johnson et al., 2003). On the other hand \dot{V}_E is closely linked to $\dot{V}C_{O_2}$ at all times. During rest or very mild exercise, the relationship between \dot{V}_E and $\dot{V}C_{O_2}$ can vary widely, predominantly because of psychogenic factors and difference in partial arterial CO_2 pressure (P_{aCO_2}) and dead space-tidal volume ratio (Sun et al., 2002). During heavy exercise above anaerobic threshold, however, the increases in \dot{V}_E relative to $\dot{V}C_{O_2}$ is variable and depended on the decrease in pH and P_{aCO_2} induced by the lactic acidosis (Wasserman et al., 1999). An increase in \dot{V}_E out of proportion to the increase in $\dot{V}C_{O_2}$ is correlated with the onset of metabolic acidosis (Wasserman et al., 1967).

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For respiratory compensation of metabolic acidosis, alveolar ventilation must increase and remain increased to eliminate CO₂ produced at a reduced mean alveolar CO₂ tension (Wasserman et al., 1967).

An increase in \dot{V}_E is partially affected by an increase in $\dot{V}C_{O_2}$ during exercise in healthy subjects, while the transport of $\dot{V}C_{O_2}$ is depended on blood flow (Wasserman et al., 1999). Results from the present study support the interaction of different physiological mechanisms (e.g. metabolic, circulatory and ventilatory) during progressive exercise (Wasserman et al., 1967). This is reflected by positive moderate correlation between peak cardiac power output on one side and peak $\dot{V}C_{O_2}$ and \dot{V}_E on the other.

5.4.3 Relationship between Peak Cardiac Power Output and Peak Oxygen Pulse

As previously stated oxygen pulse is the ratio of $\dot{V}O_2$ and HR and reflects the amount of oxygen extracted from the blood per heart beat. From the modified Fick equation, the O₂ pulse is numerically equal to the product of stroke volume and arterial-mixed venous O₂ content difference. Therefore the O₂ pulse has also been used as an estimator of stroke volume during exercise (Wasserman et al., 1999). The O₂ pulse normally increases with incremental exercise test because of increases in both SV and O₂ extraction. However, a low, unchanging, flat O₂ pulse reflects deconditioning, cardiovascular disease (e.g. heart failure, coronary artery disease), and early exercise limitation due to ventilatory constraints or symptoms (Johnson et al., 2003). Therefore O₂ pulse may be used as an index of cardiovascular function or dysfunction (Johnson et al., 2003).

The present study is the first to assess the relationship between peak cardiac power output and peak O₂ pulse. Results clearly demonstrate moderate positive relationship between the two variables as measured at peak exercise. Based in this finding it appears that O₂ pulse has the capacity to represent cardiac response to exercise

partially but clearly can not be considered as an index of cardiac function only.

5.4.4 Relationship between Peak Cardiac Power Output and Peak Cardiac Output, Stroke Volume, Heart Rate and Mean Arterial Pressure

During progressive exercise test there is a linear relationship between cardiac output and work rate (Wilmore and Costill, 2004). This is not surprising as the major purpose of the increase in \dot{Q}_T is to meet the muscles' increased demand for O_2 . During an incremental exercise test both components of cardiac output (stroke volume and heart rate) increase linearly up to 40 – 60% of maximal $\dot{V}O_2$, and thereafter an increase in \dot{Q}_T is mainly due to an increase in HR (Wilmore and Costill, 2004). It has been shown that SV increases up to exercise intensities of 40 – 60% of maximal $\dot{V}O_2$ in sedentary normal young subjects and normal men (Astrand et al., 1964; Higginbotham et al., 1986). In contrast, a plateau in SV does not occur at specific exercise intensity, but rather continues to increase with further increase in work rate. This has mostly been reported in highly trained endurance athletes (Zhou et al., 2001). Proctor et al. (1998) found that SV continued to increase between 40 – 70% of maximal $\dot{V}O_2$ in endurance trained men but not in woman. As exercise intensity increases to near maximal level (90% of maximal $\dot{V}O_2$) there is a significant age-related difference in the maintenance of SV (Proctor et a., 1998). In younger men SV continued to increase slightly but in older men was maintained. At higher work intensities there is also trend for a decline in SV within the older groups (men and women combined) (Proctor et al., 1998).

Cardiac power output takes into account both blood flow, represented by cardiac output, and pressure represented by mean arterial pressure. Results from the present study clearly demonstrate that peak cardiac power output is highly correlated with peak cardiac output but not significantly with its other component, mean arterial pressure. This is in agreement with finding reported by Hodges (2004) who also found that cardiac output has a greater influence than mean arterial pressure on total cardiac power output. Based on these findings one may speculate that, in order to assess cardiac function, measurement of cardiac output only will be sufficient. However,

measurement of cardiac output only may overestimate overall cardiac function of the normal heart (Goldspink, 2005). This is because pressure generation increases with healthy ageing and is not allowed for when measuring only flow-generating capacity of the heart. In contrast, in patients with heart failure, measurements of cardiac output alone underestimate overall cardiac function (Chantler et al., 2006). This is because both the flow and pressure generating capacities of the heart decline in these patients. Taken together, these examples clearly illustrate the need to measure both the flow and pressure generating capacities of the heart to determine overall cardiac function meaningfully (Goldspink, 2005). Also considering the heart as a hydraulic pump which produces hydraulic energy used to maintain circulation (Tan, 1986), it is necessary to evaluate not only the aspect of flow but also the pressure generating capacity of the heart. This is one of the main reasons why cardiac power output has been proposed to be the best indicator of overall cardiac function (Tan, 1986).

Furthermore none of the previous studies have evaluated the relationship between peak cardiac power output and the components of cardiac output such as stroke volume and heart rate. The results of the present study clearly demonstrated that in healthy adults, peak cardiac power output was strongly correlated with peak stroke volume but weakly correlated with peak heart rate. Moreover stroke volume explains 88% while heart rate only 12% of the variance in cardiac power output.

5.4.5 Relationship between Peak Cardiac Power Output and Peak Circulatory Power

Cohen-Solal et al. in 2002 established a new measure termed 'circulatory power' which they believe may be used as a surrogate of cardiac power output in heart failure population. Circulatory power (CP) is the product of peak $\dot{V}O_2$ and systolic blood pressure and as such has a high prognostic value in heart failure (Cohen-Solal, 2002). Circulatory power used $\dot{V}O_2$ as a surrogate for \dot{Q}_T , and systolic blood pressure for mean arterial pressure. According to Nicholls et al. (2002) CP is therefore not as appropriate as cardiac power output, but the information for its calculation is available from any cardiopulmonary exercise test without the need for special equipment. It has been also shown that CP have greater prognostic power than peak $\dot{V}O_2$ (Cohen-Solal

et al., 2002).

Hodges (2004) was the first to analyse the relationship between peak cardiac power output and peak circulatory power. The study indicated positive high correlation between the two variables in 102 healthy adults ($r=0.86$). Williams et al. (2005) also reported high correlation between peak CPO and peak CP ($r=0.84$), although in 219 chronic heart failure patients. In the present study, this relationship between the two variables was lower ($r=0.67$). Although Hodges (2004) and Williams et al. (2005) also used C_2 rebreathing methodology to determine \dot{Q}_T , one may expect stronger relationship between peak CPO and peak CP in the present study. Presumably the number of subjects, which in Hodges' study was almost tripled and in Williams et al. even more, may contribute to the stronger relationship between peak CPO and peak CP previously reported.

5.4.6 Relationship between Peak Cardiac Power Output and Peak Oxygen Consumption

It is well known that maximal oxygen consumption has been highly dependent on cardiac output. It is not surprising as direct Fick equation clearly shows that $\dot{V}O_2$ is the product of cardiac output and arterial-venous O_2 content difference. In the exercising human, maximal $\dot{V}O_2$ is limited by the ability of the cardio-respiratory system to deliver O_2 to the exercising muscles, not by the ability of skeletal muscles to extract O_2 (Basset and Howley, 2000). This statement has been supported by the following three points: 1) when O_2 delivery is altered (by e.g. blood doping, hypoxia, or beta-blockade), maximal $\dot{V}O_2$ changes accordingly, 2) the increase in maximal $\dot{V}O_2$ with training results primarily from an increase in cardiac output (not an increase in arterial-venous O_2 difference), and 3) when a small muscle mass is overperfused during exercise, it has an extremely high capacity for consuming oxygen (Basset and Howley, 2000).

When peak cardiac power output has been correlated with peak $\dot{V}O_2$ in either healthy

or heart failure populations, almost all studies have reported high coefficients of correlation between peak CPO and peak $\dot{V}O_2$. Hodges (2004) reported coefficient of correlation of 0.80 between peak CPO and $\dot{V}O_2$. Cooke et al. (1998) reported $r=0.92$ between the two variables in 70 subjects with a wide range of cardiac function, from trained athletes to transplant candidates, and finally Roul et al. (1995) found an r of 0.84 between peak CPO and peak $\dot{V}O_2$ in 50 chronic heart failure.

In the present study the finding regarding the relationship between peak cardiac power output and peak oxygen consumption agrees well with those mentioned above, clearly indicating that 59% of peak CPO may be predicted by peak $\dot{V}O_2$. It is well known that $\dot{V}O_2$ may be influenced also by non-cardiac factors (e.g. muscle conditioning, motivation, obesity). Therefore evaluation of cardiac function by measurement $\dot{V}O_2$ only may lead to wrong conclusions.

5.4.7 Relationship between Peak Cardiac Power Output and Peak Cardiac Index

In a clinical environment, cardiac index is widely used as an indicator of cardiac function and blood flow (Guyton and Hall, 1996). The original reason for using the cardiac index as a means for expressing cardiac output for individuals of different body sizes was that the basal metabolic rate in human beings is generally expressed in terms of body surface area (Guyton and Hall, 1996). Berkson and Boothby (1936) found a higher correlation between basal metabolic rate and body surface area than basal metabolic rate and mass.

In the present study coefficient of correlation between peak cardiac power output and peak cardiac index was high. High coefficient of correlation between the two variables has also been previously reported in healthy adults ($r=0.81$), and in heart failure ($r=0.94$) (Hodges, 2004; Roul et al., 1995). From these and previous results it is not difficult to conclude that body dimensions influence cardiac power output as shown by Chantler et al. (2005).

5.4.8 Gender and Body Size Related Differences in Measured Variables and Reported Relationships

Hutchinson et al. (1991) examined the relationship between cardiac size to maximal oxygen consumption in males and females. They found that left ventricular mass accounted for 63.8% of the gender for maximal $\dot{V}O_2$ and the combination of left ventricular mass and fat free mass accounted for 98.7% of the gender related difference. Hutchinson and colleagues provided an explanation that differences in body size dimensions contributed to difference in cardio-respiratory variables between men and women. From the present study it was also possible to illustrate a significant difference in gender in most of the measured cardio-respiratory variables except peak mean arterial pressure (Table 5.2).

It seems that the mean arterial pressure is independent of body size (Dobein, 1956). In contrast, cardiac output is known to be influenced by body size with a larger body mass creating a greater O_2 demand (Collis et al., 2001).

In the present study the absolute values of peak cardiac power output in men were 33% higher than those in women. Chantler et al. (2005) found that CPO is significantly affected by body size and composition, and strongly suggested that whenever possible CPO should be allometrically scaled for lean body mass. Chantler and colleagues also suggested that in the absence of research tools such as dual-energy X-ray absorption (DEXA), body surface area or even body mass should be used in a clinical or field setting to generate body size independent CPO data. When peak CPO data were allometrically scaled to body surface area in the present study, the difference between men and women was 11% less when compared with the absolute peak CPO values. In agreement with Chantler et al. (2005) this result indicates the importance of normalizing CPO data for differences in body size when comparing different groups of subjects. This will avoid wrong interpretations and conclusions which may have practical implications and consequences.

Furthermore in the present study subgroup analysis revealed that strength of the relationships between peak CPO and peak \dot{Q}_T , SV, CI and $\dot{V}O_2$ were similar

between men and women (Table 5.3). It also appears that in the present study the difference in age between men and women of ~10 years does not affect these relationships. This finding is in agreement with one reported by Proctor et al. (1998) who found that neither gender nor age has a significant impact on \dot{Q}_T - $\dot{V}O_2$ relationship.

5.4.9 Study Limitations

Total number of subject participated in the present study was 37 (23 men and 14 female). In those previously cited studies which also evaluated the relationship between cardiac power output and other cardio-respiratory variables the number of participant was higher than in the present study. This possibly may explain some lower coefficient of correlation obtained in the present study compared with previous similar studies. Nevertheless it appears that even the lower number of participants recruited in the present study was enough to identify relationships which have not been previously reported between CPO and e.g. AT, $\dot{V}C_{O_2}$, \dot{V}_E , OP and SV.

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The C_{O_2} rebreathing method used in the present study does not allow continuous measurement of \dot{Q}_T , and it has been recognised as major limitations of this technique in the present but also in the previous studies which used the same methodology. However continuous monitoring would reveal if cardiac power output reaches a similar plateau during exercise to that of oxygen consumption.

In the present study no resting measurement of \dot{Q}_T , and consequently CPO were taken. This was due to the issues surrounding the technicality of the two very different measurements. In the Chapter 3 it was clearly indicated that resting \dot{Q}_T is measured more accurately and precisely using the equilibrium C_{O_2} method. To use both, the exponential method for \dot{Q}_T measurement at peak exercise and the equilibrium method for resting \dot{Q}_T , would mean that two gas mixtures would be required. Also a different configuration of the equipment would be necessary. It was therefore decided that due to this technical reasons and also due to time constraints, resting measurement would not be taken. Thus, possible relationships between cardiac

pumping reserve and other variables in a cohort of healthy adults were not examined.

5.5 Conclusion

The present study is the first to analyse the relationship between overall cardiac function represented by cardiac power output and a variety of routinely measured physiological variables. Novel findings of the present study clearly indicate that peak cardiac power output moderately correlated not only with a submaximal index of cardiopulmonary exercise capacity such as anaerobic threshold, but also with carbon dioxide production, minute ventilation and oxygen pulse, all measured at peak exercise.

In healthy adults, anaerobic threshold, peak carbon dioxide production, minute ventilation and oxygen pulse explain 23% to 41% of the variance, while peak oxygen consumption and cardiac index explain 59% and 58% of the variance in peak cardiac power output. Cardiac output and stroke volume explain 90% and 88% of the variance. This clearly suggests that only central haemodynamic measures such as peak cardiac output and stroke volume are good predictors of maximal cardiac pumping capability, while those other routinely measured cardio-respiratory variables, including oxygen consumption, should be considered with caution in interpretation of cardiac function.

The results from the present study demonstrate that gender does not affect the strength of the relationship between peak cardiac power output and cardiac output, stroke volume, cardiac index and peak oxygen consumption.

Finally the present findings support existing evidence that special attention is needed when comparing cardiac power output data between different groups of subjects when differences in body size are emphasized (e.g. men and women). When data were allometrically scaled to body surface area, the difference in cardiac power output between men and women was reduced by 11%.

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CHAPTER 6: COMPARISON OF CARDIAC POWER OUTPUT AND EXERCISE PERFORMANCE IN PATIENTS WITH LEFT VENTRICULAR ASSIST DEVICES, EXPLANTED (RECOVERED) PATIENTS AND THOSE WITH MODERATE TO SEVERE HEART FAILURE

Abstract

Introduction: Originally a left ventricular assist device (LVAD) was considered as a bridge to transplantation. However recent reports demonstrated that the use of an LVAD can in many patients prevent the need for subsequent transplantation, being considered as a bridge to recovery. A limited number of studies have evaluated exercise performance in patients implanted with LVADs and those explanted due to recovery, but none of these investigations evaluated cardiac power output (CPO). Therefore the aim of the present study was to assess CPO and exercise performance in patients implanted with LVADs, those explanted due to myocardial recovery and in those with moderate to severe heart failure. **Methods:** In this cross-sectional study design, measurements at rest and at peak exercise of the Bruce or modified Bruce protocol (two preliminary stages with inclination of 0% and 5%) were undertaken using non-invasive, inert gas, rebreathing haemodynamic and respiratory gas procedures. They were performed on 54 male patients – 20 moderate to severe heart failure (HF) patients (age 45 ± 10 yrs), 18 implanted LVAD (IMP) patients (age 39 ± 14 yrs) and 16 explanted LVAD (EXP) patients (age 41 ± 14 yrs). **Results:** At rest there was a non significant difference in cardiac power output between the HF, IMP and EXP patients ($p > 0.05$), whereas cardiac output in the IMP group was higher compared with the HF group (5.5 ± 2.1 vs. 4.1 ± 1.3 $\text{l} \cdot \text{min}^{-1}$, $p < 0.05$). Peak CPO was significantly higher in the EXP than the HF and the IMP patients (HF, 1.90 ± 0.45 ; IMP 2.37 ± 0.55 ; EXP 3.39 ± 0.61 W; $p < 0.01$) as was peak cardiac output (HF, 9.1 ± 2.1 ; IMP, 12.4 ± 2.2 ; EXP, 14.6 ± 2.9 $\text{l} \cdot \text{min}^{-1}$; $p < 0.01$). Peak CPO was higher in IMP than in HF patients ($p < 0.05$). Mean arterial pressure at rest was not significantly different between the HF, IMP and EXP patients ($p > 0.05$), whereas at peak exercise mean arterial pressure in IMP patients was significantly lower than in EXP patients ($p < 0.01$). Peak oxygen consumption was higher in the EXP than the HF and the IMP patients (HF, 15.8 ± 4.1 ; IMP, 19.8 ± 5.8 ; EXP, 28.2 ± 5.0 $\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$; $p < 0.05$) as was anaerobic threshold (HF, 11.2 ± 1.9 ; IMP, 14.7 ± 4.9 ; EXP, 21.4 ± 5.0 $\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$; $p < 0.05$). **Conclusion:** The

results from the present study suggest that peak cardiac power output differentiates well during cardiac restoration using LVADs and emphasizes the benefits of this therapy. The use of LVAD improves overall cardiac function and also exercise performance. A peak CPO of 1.96 W is considered to be a “cut-off” value for good and poor prognosis in heart failure, therefore studied IMP and particularly EXP patients appear to have better prognosis than HF patients. Cardiac power output has the potential to be a key physiological marker of heart failure severity and can guide management of LVAD patients.

6.1 Introduction

According to the ACC/AHA Guideline (2005), heart failure (HF) is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood (inability of the heart to function as a pump to support physiological circulation). Typical symptoms and signs of heart failure are fatigue and dyspnoea, either at rest or during exercise, and fluid retention, which may lead to pulmonary congestion and peripheral oedema (ESC Task Force, 2005). Coronary artery disease, hypertension, valvular heart disease, and dilated cardiomyopathy are some of the causes of heart failure in the Western world (ACC/AHA Guideline, 2005).

The definition of advanced heart failure, (also called severe, end-stage, refractory heart failure) includes symptoms which limit daily activities (NYHA III and IV) despite the inclusion of strong pharmacological therapy with angiotensin-converting enzyme inhibitors, β -blockers, digoxin and diuretics (Adams and Zannad, 1998). Despite advances in the medical management of heart failure the only really effective form of therapy for patients with advanced heart failure is cardiac transplantation (Yacoub, 2001). Transplantation offers an effective alternative for many patients with advanced heart failure, yet the lack of donors still currently limits the number of transplantations performed annually nationwide. The success and limitations of transplantation have stimulated alternative therapies for patients with advanced heart failure.

6.1.1 Left Ventricular Assist Devices – from Idea to the REMATCH

Mechanical circulatory support (MCS) is a viable therapy for severe end-stage heart failure (Frazier, 2002). To date a number of clinical trials have shown clear benefits of MCS in terms of survival and improved quality of life. The MCS is not therefore considered as bridge to cardiac transplantation only, but also as destination therapy (Lietz et al., 2007; Rose et al., 2001) and bridge to recovery (Birks et al., 2006).

The first application of a ventricular assist system was in 1963 by DeBakey for support of postoperative cardiogenic shock, with successful device removal after one week of support with improvement of cardiac function (DeBakey, 1971). In 1968 Cooley and colleagues first used a circulatory assist device as temporary support until cardiac transplantation (Cooley et al., 1969). Since that time, ventricular assist devices have been applied as an assist to recovery for postcardiotomy support, the experience of which has been documented in multiple studies (Pae et al., 1992; Pennington et al., 1985). In these experiments, approximately 45% of supported patients were weaned from device support, with approximately half of that group surviving to hospital discharge, subsequently achieving long-term survival (Pae et al., 1992; Pennington et al., 1985).

With the advances in cardiac transplantation during 1980s, ventricular assist systems were used as left ventricular devices (LVADs) or as biventricular assist devices for support of patients with severe heart failure accompanied by shock and multiple organ dysfunction (Kumpati et al., 2001).

Various circulatory-support devices have been developed for short-term use in patients with end-stage heart failure since the beginning of the artificial heart programme at the American National Institute of Health in 1964 (Hogness and VanAntwerp, 1991). In 1994 the US Food and Drug Administration approved pneumatically driven LVADs to be used as a bridge to transplantation, and self-contained, vented electrical devices were approved for this purpose in 1998 (Goldstein et al., 1998).

The successful use of LVADs as a bridge to transplantation for extended periods of time led to their consideration for destination therapy, as originally proposed for the artificial heart development programme (Frazier et al., 1992; Oz et al., 1997). The use of LVADs as destination therapy was proposed in a prospective study called Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) (Rose et al., 1999).

The REMATCH trial was the first scientific approach validating the original goal of destination (permanent) therapy for patients with end-stage heart failure for whom donor hearts were not available. This trial had a long period of development from proposal in 1993 to initial enrolment of patients in 1998. This prospective randomized trial was performed by Rose and colleagues (2001). Inclusion criteria included left ventricular ejection fraction $\leq 25\%$ with severe heart failure symptoms (NYHA class IV) for >90 days despite attempted therapy with ACE inhibitors, diuretics, and digoxin. Severe limitation had to be documented by peak oxygen consumption of ≤ 12 $\text{ml kg}^{-1} \cdot \text{min}^{-1}$ with evidence of anaerobic metabolism. Rose and colleagues randomized 129 patients who were ineligible for cardiac transplantation to LVAD group (N = 68) or “optimal medical therapy” group (N = 61). Kaplan-Meier survival analysis showed a 48% reduction in risk of death in LVAD-supported patients. Survival in LVAD-supported patients was twice that in medically treated controls after 1 year (52% vs. 25%) and triple after 2 years (23% vs. 8%). Quality of life was also significantly improved in those supported with the LVAD. Rose and colleagues (2001) concluded that the use of LVADs in patients with advanced heart failure resulted in an improvement in survival and quality of life.

6.1.2 Different Models of Mechanical Circulatory Support

Mechanical circulatory support can be used as short- or long-term support. The incidence of mechanical circulatory support after open-heart surgery is reported to be between 0.5% and 3% (Smedira and Blackstone, 2001). The overall survival rate of patients treated with mechanical circulatory support for long-term use as a bridge to heart transplantation was reported to be between 70% and 80% (McCarthy et al., 1998; Sun et al., 1999).

Pump systems can be divided into five groups, depends on the operating principles: 1) intra-aortic balloon pump, 2) centrifugal pumps, 3) displacement pumps, 4) axial blood flow pumps, and 5) total artificial hearts.

6.1.2.1 Intra-aortic balloon pump (IABP) as circulatory support for postcardiotomy heart failure

The IABP was first introduced in clinical practice in 1967 (Kantrowitz et al., 1968). The IABP affects cardiac function positively in several ways. It decreases myocardial oxygen demand (systolic unloading) and increases the supply of oxygen to the myocardium (diastolic augmentation) (Frazier, 1995). This should favourably influence the myocardial oxygen supply demand relationship which can improve the myocardial performance.

6.1.2.2 Centrifugal pumps

In the Bio-pumpTM the blood is accelerated in a pump house by centrifugal force and a nonpulsatile flow is generated. There is need for venous and arterial cannulae and an extracorporeal circuit. The tubings may be heparin coated and thereby systemic anticoagulation can be reduced. It can include an oxygenator and give full cardiopulmonary support. The system is flexible and can be used as an left ventricular assist device (LVAD), right ventricular assist device (RVAD), or biventricular assist device (BVAD) (Hosenpud and Greenberg, 2006).

6.1.2.3 Displacement pumps

The principle is that blood enters the artificial pump from the heart and is ejected into the aorta by the movement of a diaphragm creating pressure variations in the pump. Pulsatile flow is created. These pumps can be extracorporeal as the ThoratecTM and the AbioMedTM, or as implantable as the NovacorTM and HeartMateTM.

6.1.2.4 Axial blood flow pumps

The principles of the axial flow pumps are based on the Hemopump™ (Wampler et al., 1988) which is described in more detail below. A rotating impeller ejects blood from the left ventricular to the systemic circulation with continuous flow. An electromagnetic motor runs the impeller. The pumps are small, valveless, and without a compliance chamber. Compared with other pumps, they require less surgery for implantation. A variety of pumps for long-term use have been developed, like the MicroMed DeBakey™, the HeartMate II™, and the Jarvik 2000 Heart™.

6.1.2.5 Artificial hearts

The CardioWest™ is a pulsatile biventricular cardiac replacement system. It is a displacement rigid polyurethane pump and contains a smooth, flexible polyurethane diaphragm that separates the blood and two air chambers. Mechanical valves provide unidirectional flow. Compressed air from an external drive console moves the diaphragm causing ejection of the blood (Copeland et al., 1996).

6.1.3 Continuous versus Pulsatile Left Ventricular Assist Devices

In the United States, according to Miller et al. (2007), most of the patients undergoing implantation of LVAD as a bridge to heart transplantation have received support from pulsatile, volume-displacement devices such as the HeartMate XVE (Thoratec Inc, Pleasanton, Calif) or Novacor (WorldHeart, Oakland, Calif) (Figures 6.1 and 6.2). These devices fill with and eject blood in a cyclic fashion that is equivalent to the systole and diastole of the native heart.

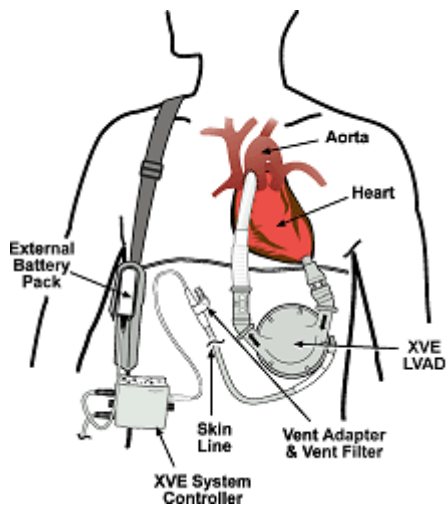


Figure 6-1 HeartMate XVE LVAD

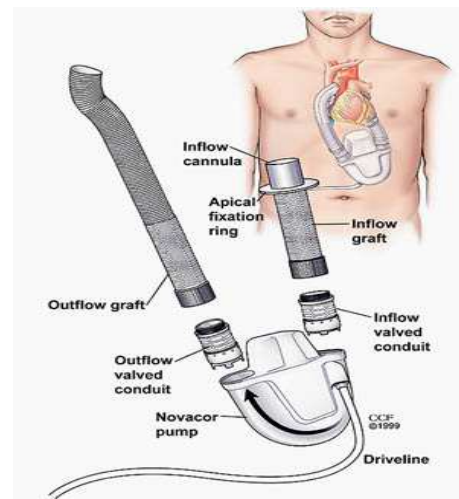


Figure 6-2 Novacor LVAD

Most of the LVAD explanted patients in the present study have been previously implanted with the HeartMate XVE LVAD. Therefore basic technical characteristics of the HeartMate XVE LVAD are described below.

The HeartMate XVE (extended lead vented electric) LVAD consists of an implanted blood pump, external XVE system controller, and external power supply components. The blood pump is a pusher-plate type device that is capable of producing a stroke volume of 83 ml, generating approximately 10 litres of blood per minute, and a beat rate of up to 120 beats per minute (Thoratec Corporation, 2004). The pump consists of a rigid titanium housing divided in half by a flexible diaphragm. One half functions as the blood chamber, while the opposite half serves as a chamber for the electric motor. This motor chamber is connected to the external control and power components via a percutaneous tube. Displacement of the diaphragm by rotation of the electric motor results in pumping of the blood. The inflow and outflow conduits of the device each contain a 25-mm porcine valve within a titanium cage to ensure unidirectional blood flow. The HeartMate XVE is typically operated in a full-to-empty cycle. Beat rate is regulated by an external computer controller from information provided by sensors on filling volume within the pump. Beat rate automatically increases or decreases to changes in left ventricular preload and filling rate of the pump chamber.

The HeartMate XVE LVAD is intended for use as bridge to transplantation in cardiac transplant candidates at risk of imminent death from non-reversible left ventricular failure. The HeartMate XVE is also indicated for use in patients with NYHA class IV end-stage left ventricular failure who have received optimal medical therapy for at least 60 of the last 90 days, who have life expectancy of less than two years, and who are not candidates for cardiac transplantation. The device is intended for use both inside and outside hospital. The HeartMate XVE is contraindicated for patients whose body surface area is less than 1.5 m² (Thoratec Corporation, 2004).

Pulsatile left ventricular assist devices provide excellent haemodynamic support and improve survival to transplantation but have substantial constraints, including the need for extensive surgical dissection, the requirement that the patient has a large body size, the presence of a large-diameter percutaneous lead, audible pump operation, and limitation in long-term mechanical durability that frequently require subsequent operations for device exchange (Frazier and Kirklin, 2006).

More recently, several left ventricular assist devices have been designed incorporating continuous-flow rotary pump technology with axial configuration. One advantage of these newer pumps is a smaller device size, with the potential for extending therapy to other populations, including some women and adolescents (Griffith et al., 2001). Another advantage is the potential for greater long-term mechanical reliability owing to a simplified design that requires only a single moving part, an internal rotor (Miller et al., 2007). Other benefits include less noise from the device and greater comfort for patients than with a typical pulsatile pump. Continuous-flow pumps are the HeartMate II left ventricular assist system (Thoratec), the MicroMed DeBakey ventricular assist device (MicroMed), the Jarvik 2000 Heart (Jarvik Heart), and the VentrAssist left ventricular assist system (Ventracor).

Most of the LVAD implanted patients in the present study have been implanted with the HeartMate II LVAD, and therefore technical characteristics of this device will be described.

The HeartMate II LVAD has been successfully tested in more than 40 calves since 1997 and the first human implant occurred in July 2000 (Griffith et al., 2001). The

HeartMate II LVAD (Figure 6.2) is a continuous-flow device consisting of an internal axial-flow blood pump with a percutaneous lead that connects the pump to an external system driver and power source. The pump contains an internal rotor with helical blades that curve around a central shaft. When the rotor spins on its axis, kinetic energy is imparted to the blood, which is drawn continuously from the left ventricular apex through the pump and into the ascending aorta. The pump has an implant volume of 63 ml and operating revolutions per minute range of 6000 to 15000, and can generate up to 10 litres per minute of flow at a mean pressure of 100 mm Hg (Thoratec Corporation, 2006). The hydrodynamic performance of continuous flow pumps is determined primarily by speed of the rotor and by the pressure difference that exists across the pump (Griffith et al., 2001).

The HeartMate II has a manual speed control that can be accessed only by a technical operator and that is for use intraoperatively and perioperatively. During this period of fluid shift and physiologic adjustment, Griffith et al. (2001) suggested that slow rates corresponding to lower flow more reliably maintain left heart preload and prevent sudden and dramatic negative left atrial and ventricular pressures. Griffith et al. (2001) recommended operating in the safe margins of the pressure-flow relationship and have been most successful at rates of 8000 to 9000 revolutions per minute with pressure differentials of 80 to 100 mm Hg and flows of 3 to 4 litres per minute.

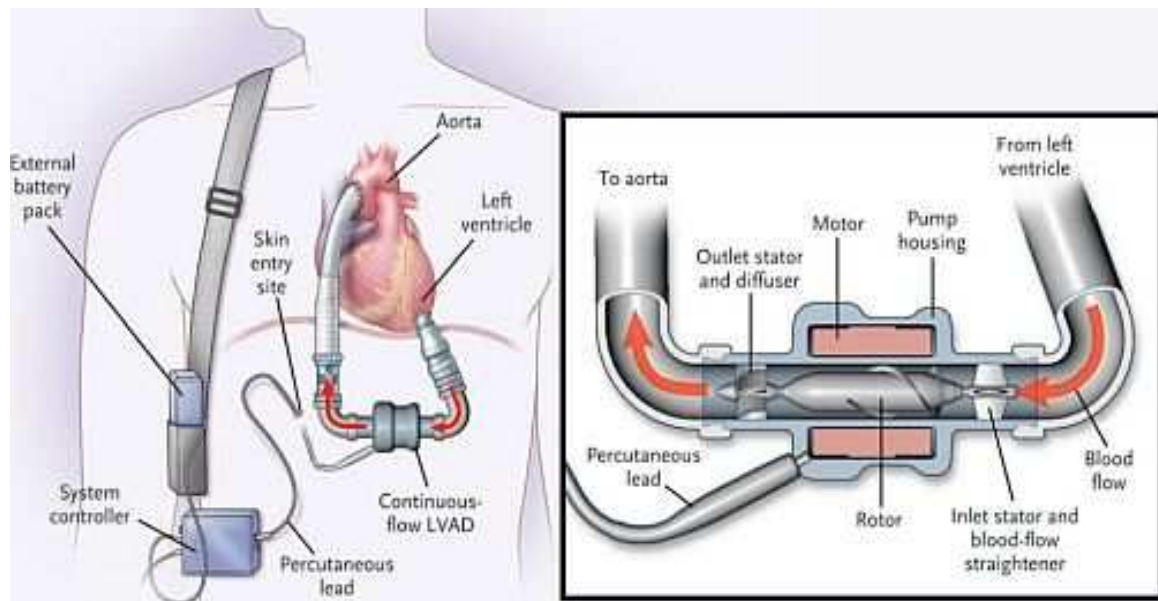


Figure 6-3 Components of the continuous-flow left ventricular assist device-HeartMate II. The inflow cannula is inserted into the apex of the left ventricular assist device, which pumps throughout cardiac diastole and systole into the ascending aorta, with the rotor being the only moving part. The LVAD is placed within the abdominal wall or peritoneal cavity. A percutaneous lead carries the electrical cable to an electronic controller and battery packs, which are worn on a belt and shoulder holster.

It has been suggested that as the speed of pump goes up, the flow and blood pressure follow the same trend. At a certain point, with further increase in pump speed, there is no increase in blood pressure, and if the speed is further increased the blood pressure goes down (in Kormos, 2001). Dr Magovern (Pittsburgh, PA) argued that pump flows around 3.5 to 4 litres in most of the patients, and they are “hoping to get another litre or two out from the patients native heart” (in Kromos, 2001). This discussion indicates that it is not clear how much of the total cardiac output is delivered by the pump and how much from the native heart. Westaby et al. (2006), who used the Jarvik 2000 LVAD, suggested that at a pump-rotor speed of 10000 revolutions per minute produced the resting cardiac output of 5.5 litres per minute with a mean blood pressure of 70 to 80 mm Hg.

According to Myers et al. (2006) blood flow through continuous-flow LVADs depends primarily on the differential pressure across the pump when the impeller speed is constant. This differential pressure is the difference between left ventricular pressure and aortic pressure, which is always changing throughout the cardiac cycle. At the start of diastole, left ventricular pressure is at its lowest; this is also when the differential pressure is the greatest (Myers et al., 2006). At the end of systole, left ventricular pressure and aortic pressure are nearly equal; this is when the differential pressure is lowest. As the left ventricular pressure rises during systole, pump flow increases because the differential pressure decreases Myers et al. (2006). During diastole when the left ventricular pressure decreases (thus increasing the differential pressure), the blood flow through the pump also decreases. However, when the pump is turned off, blood flow may flow through the pump in both directions.

In a prospective, multicenter study Miller and associates (2007) recruited 133 patients with end-stage heart failure who were on a waiting list for heart transplantation to assess the efficacy of HeartMate II LVAD in providing mechanical circulatory support as a bridge to heart transplantation. The survival rate and quality of life were also evaluated. Results of this study demonstrated that survival rate was 75% at 6 months and 68% at 12 months. Furthermore, at 3 months there was significant improvement in functional status (according to NYHA class and results of a 6-minute walk test). At 24 hours after implantation of the device, the cardiac index increased from a mean of 2.0 l/m^2 preoperatively to 2.8 l/m^2 . The average pump flow index was 2.6 l/m^2 on the first day at a mean pump speed of 9236 revolutions per minute, and increased to 2.8 l/m^2 at one month at a mean pump speed of 9502 revolutions per minute, with systolic and diastolic arterial blood pressure averaging 96 and 73 mm Hg. There was also significant improvement in quality of life. Significant adverse events included postoperative bleeding, stroke, right heart failure, and percutaneous-lead infection. Miller and colleagues concluded that effective haemodynamic support for periods of at least 6 months can be achieved with continuous-flow LVAD, with improved functional status and quality of life. Miller et al (2007) outlined some of possible issues in a use of continuous flow devices. These include the risk of pump thrombosis and thromboembolism, with requirement for higher levels of antithrombotic therapy than required for some pulsatile devices and a consequent risk of bleeding.

Infection remains a potential concern, as with all circulatory devices that have a percutaneous component. Also mechanical failure may not be totally avoided by continuous flow pump technology, although it appears to be less frequent than with some pulsatile pumps. Other issues include the need to determine the optimal pump-speed settings to provide sufficient blood flow without ventricular arrhythmias and difficulty in detecting vital signs in a systemic circulation with reduced pulsatility (Miller et al., 2007). In clinical findings some pulsatility is present even in very weak hearts during the early post-operative phase, but this pulsatility increases in most patients during myocardial recovery (Thalmann et al., 2005).

Haft et al. (2007) investigated the effects of LVAD support with either a pulsatile, volume displacement pump (HeartMate XVE) or continuous-flow rotary pump with axial design (HeartMate II) on haemodynamic and exercise performance in 34 patients, 16 implanted with HeartMate XVE and 18 implanted with HeartMate II. Patients were evaluated with right heart catheterization and echocardiography preoperatively and at three months postoperatively and cardiopulmonary exercise testing three months postoperatively. Support with either the XVE or II resulted in significant increases in cardiac output and reduction in mean pulmonary artery and pulmonary wedge pressures. Exercise capacity at three months was similar between groups (% predicted peak $\dot{V}O_2$ - XVE: ~47% versus II: ~49%). Echocardiography at three months demonstrated a significantly greater reduction in left ventricular end-diastolic volume, left ventricular end-systolic volume, and percent mitral valve regurgitant volume for the XVE compared with II. Haft et al. (2007) concluded that the HeartMate XVE and II provided equivalent degrees of haemodynamic support and exercise capacity. The XVE was associated with greater left ventricular volume unloading. Similarly Garcia et al. (2008) found that continuous flow LVADs (HeartMate II) are as effective as pulsatile flow LVADs (HeartMate XVE) with regard to degree of left ventricular unloading and cardiac haemodynamic.

Finally, according to manufacturer (Thoratec Corporation, 2006) some of the complications associated with the HeartMate LVADs that may occur in greater than 1% of patients include hepatic dysfunction, renal dysfunction, need for reoperation, infection, bleeding, death, neurological dysfunction, right heart failure, haemolysis,

thrombo-embolism, pulmonary dysfunction, cardiac arrhythmia and myocardial infarction.

6.1.4 Left Ventricular Assist Device as Bridge to Recovery in Clinical Trials – Aspects of Cardiac Recovery during Support with LVAD

Different aspects of cardiac recovery have been reported following LVAD insertion. This section describes some mechanisms of cardiac remodelling as suggested by Bristow (1998), Francis (1998), Goldstein et al. (1998) and Mann (1999).

Heart failure is a wide spectrum of anatomic, physiologic and clinical abnormalities in the heart. Heart failure is a syndrome whereby some injurious event causes myocardial injury which results in abnormal mechanical properties that, in conjunction with the injurious process, produces cardiac remodelling. These processes can be sudden or insidious in their development. Injurious events can include a chronic myocardial ischemia, exposure to toxins, infectious agents, inflammatory responses to systematic illnesses, cardiac volume and pressure overload, genetic abnormalities, or unknown (idiopathic) causes. Alterations in myocyte biology associated with heart failure include attenuation of normal excitation contraction coupling mechanisms with a reversion to myosin heavy chain foetal gene expression and beta-adrenergic receptor desensitization. These and additional changes in cytoskeletal protein production lead to myocyte hypertrophy, myocytolysis, and interstitial fibrosis, setting the stage for cardiac chamber enlargement and myocardial hypertrophy. Systolic dysfunction ensues with interstitial fibrosis, causing a stiffening of the heart and diastolic dysfunction. Programmed cell death, or premature apoptosis, leads to an accelerated loss of functional myocytes. Altered contractility of the heart with chamber geometry remodelling toward more spherical state causes mitral regurgitation and diminished stroke volume, which leads to perfusion abnormalities in systemic organs. This then causes perpetuation of the heart failure milieu by eliciting expression in a variety of neurohumors and mediators of inflammation. Indeed, the growth of myocytes seems primarily related to many growth factors subsequently liberated, including catecholamines, endothelin, growth hormone, tumor necrosis factor, angiotensin-II, and insulin-dependent growth factor. Mechanical stretch is also important and is likely to stimulate cell growth directly. Myocyte stretch also induces

release of intracellular angiotensin-II. This is a very important observation because ventricular assist device insertion might effect cardiac recovery primarily by attenuating these stretch-induced responses with ventricular unloading.

As previously mentioned, mechanical circulatory support holds promise not only as a bridge to transplantation and as destination therapy, but also as bridge to recovery. Today there is evidence that prolonged, near complete unloading of the ventricle with the use of an LVAD is associated with structural reverse remodelling (Zafeiridis et al., 1998) that can be accompanied by functional improvement (Terracciano et al., 2003). However, recovery that is sufficient to permit explantation of the device has been observed in only 5 to 24% of patients in various series (Dandel et al., 2005; Farrar et al., 2002; Frazier and Myers, 1999; Frazier et al., 2004; Liden et al., 2007; Mancini et al., 1998a; Maybaum et al., 2007; Miller et al., 2007; Simon et al., 2005) with a relatively high incidence of early recurrence (Simon et al., 2005).

According to Frazier (2002) as early as 1992, mechanical, histological, and metabolic improvements in LVAD supported patients were being reported including histological improvements characterized by normalization of myocyte diameter, decreased fibrosis, and decreased myocytolysis. Also normalisation in calcium transport mechanisms with sarcoplasmic reticulum, enhanced myocyte contraction, improved glucose use, decreased tissue necrosis factor levels, decreased apoptosis of the native heart, and improved beta-receptor density were observed (Frazier, 2002).

Frazier et al. (1996) studied 31 patients after 30 days of implantation. Results of echocardiography indicated significant decrease in left-ventricular end-diastolic dimension (6.81 to 5.35 cm) and significant improvement in ejection fraction (11% to 22%) when the device was switched off. In eight patients with advanced idiopathic dilated cardiomyopathy Altemose and colleagues (1997) found a decrease in left ventricular mass from 505 to 297 g, whereas myocyte diameter also decreased significantly after 42 days of support with an LVAD. Also Nakatani and colleagues (1996) reported a decrease in left atrial and left ventricular diastolic and systolic diameters after an LVAD insertion from 4.6 to 3.5, 6.3 to 4.1, and 5.9 to 3.6 cm, respectively. Left ventricular wall thickness increased from 1.0 to 1.4 cm for the interventricular septum. Myocardial histological findings demonstrated a reduction in

myocyte damage as estimated by the decreased appearance of wavy band fibres and contraction band necrosis. There was, however, a slight increase in fibrosis but no significant change in myocyte diameter (Nakatani et al., 1996). Furthermore Levin and associates (1995) demonstrated that chronic unloading of the failing ventricle with the use of an LVAD resulted in deremodeling, or reversal of the chamber enlargement associated with heart failure. Scheinin and associates (1992) found that following an LVAD insertion myocardial tissue demonstrated significant decrease or disappearance of stretched fibres with a slight increase in interstitial replacement fibrosis, as well as an increase in the diameter of the myocardial fibres. This finding was supported also by McCarthy and colleagues (1995). These observations support the concept the morphologic parameters are normalized with mechanical circulatory support. Dipla et al. (1998) reported that the magnitude of myocyte contraction was greater, the time to peak contraction was significantly abbreviated, and the time to 50% relaxation reduced in patients supported by the ventricular assist device. Myocytes removed from the ventricular assist device patients had greater contraction than control myocytes at all frequencies of stimulation (Dipla et al., 1998). Findings by Zafeiridis and colleagues (1998) also indicated that long-term ventricular assist device support was associated with significant reduction in myocyte volume, cell length, cell width, and length-to-thickness ratio. These changes were associated with reductions in left ventricular dilation and left ventricular mass measured by echocardiography and further support the concept of that reverse remodelling occurs in response to chronic ventricular assist device sustenance. These findings were stressed by Soloff (1998) who argued that morphologic changes were more consistent with atrophy of the myocardium than normalization of a severely remodelled heart.

From the view of molecular remodelling, it was found that patients with advanced heart failure undergoing ventricular assist device insertion have extensive cardiac myocyte apoptosis, and that prolonged mechanical unloading with an LVAD affect apoptosis-inhibiting genes and cardiac myocyte apoptosis by decreasing the extent of myocyte apoptosis overall in the ventricle (Belland et al., 1999). Changes in neurohormones were also noted in patients with LVADs as follows: plasma renin activity decreased from 57 to 3 nm, angiotensin-II decreased from 237 to 14 U/L, plasma epinephrine fell from 6,800 to 46 pg/mL, as was norepinephrine from 2,953 to

518 pg/mL, and arginine vasopressin decreased from 6 to 0.8 pg/mL (James et al., 1995). Accompanying these changes were dramatic improvements in cardiac index and central haemodynamics. These observations indicate that circulatory support normalizes the peripheral milieu of the heart failure to such an extent that the sympathetic and parasympathetic nervous system and neurohumoral expression markers characteristic of heart failure are attenuated.

Takeishi et al. (2000) explored the relationship of mechanical assist device support to improved calcium (Ca) cycling. The investigators specifically examined whether protein kinase-C activation and decreased Ca-cycling protein levels could be reversed by support with a LVAD. Changes were found in protein levels of g-alpha-q, phospholipase-C-beta-1, regulators of g-protein signalling, sarcoplasmic reticulum calcium ATPase, phospholamban, and translocation of protein kinase-C isoforms. The paired pre- and post-LVAD samples revealed that a selective inhibitor of g-alpha-q was significantly decreased, while the status of g-alpha-q phospholipase-C-beta-1 and regulators of g-protein signalling were unchanged after LVAD implantation. Translocation of protein kinase-C isoforms also remained unchanged. The LVAD support increased sarcoplasmic reticulum Ca ATPase protein level with phospholamban concentration unaffected. Takeishi and colleagues (2000) concluded that altered protein expression and stoichiometry of the major cardiomyocyte Ca cycling proteins, rather than reduced phospholipase-C-beta-1 activation occurred during support with a LVAD, improving mechanical function. Furthermore Terracciano et al. (2003) examined changes in Ca handling at the cellular level in failing left ventricular tissue taken at LVAD implantation and LVAD removal. The results showed that in myocytes from patients after LVAD support there is more Ca entry to trigger Ca release and more sarcoplasmic reticulum Ca content, leading to improved contractile function. Also improvement in myocardial mitochondrial function after LVAD support was found (Lee et al., 1998). The respiratory control index was higher in LVAD patients than in the heart failure patients. Lee et al. concluded that cardiomyocyte dysfunction in heart failure may actually be reversed with LVAD support.

Holman et al. (1991) were the first to report a patient receiving an LVAD as bridge to transplantation with the device being removed because of satisfactory native heart function after longer term support. Cardiac function improvement was noted in a 19-year-old man after four weeks of circulatory assistance and at the 70-day mark the device was removed with a patient developing normal rest and exercise cardiac systolic function. The patients did not have coronary artery disease (Holman et al., 1991). Furthermore, Nakatani and associates (1995) reported that out of 31 LVAD supported patients, six patients supported more than three weeks were able to be weaned from the ventricular assist device, with four patients doing well, but four deteriorating to the point where cardiac transplantation was necessary. Of these six patients weaned from the device, two have ischemic heart disease, one valvular heart disease, and three idiopathic cardiomyopathy. Loebe and colleagues (1997) reported a case of a 36-year-old man with dilated cardiomyopathy who was supported with LVAD for more than two years. During the support interval, gradual functional recovery occurred, but a suitable donor organ finally came available. In the preparation for the transplant operation, the LVAD was switched off and native ventricular function assumed the total cardiac load. Because cardiac performance was judged acceptable, the LVAD was explanted and transplantation not performed with the patient continuing to improve. Long-term effects of ventricular unloading on cardiac function, humoral anti-beta-1 adrenoreceptor autoantibodies, and myocardial fibrosis were studied by Muller et al. (1997). Seventeen patients with nonischemic dilated cardiomyopathy were implanted with LVADs for a mean duration of 230 days. Results indicated that six patients died, four transplanted, and two supported at the time of publication. Five patients (29%) were noted to have significant recovery and were weaned after 160 to 794 days of support with follow-up post-device removal of 51 to 592 days. Antiadrenoreceptor antibodies disappeared during mechanical circulatory support and did not increase during after weaning. Cardiac function (represented by left ventricular ejection fraction only) and volume density of fibrosis remained normal in the successfully weaned patients. It should be noted, however, that nine patients did not have any improvement in ventricular function. Frazier and Myers (1999) demonstrated data on five patients having devices removed after 46 to 447 days. In three patients, the system was removed electively after patients showed signs of myocardial recovery, and in two patients, the device was removed because of

pump malfunction. One patient died of cardiac-related causes 10 days after ventricular assist system removal, with the remaining patients noted to be alive and well at 35, 33, 14, and three months after system removal. None of the patients had ischemic heart disease as the underlying pathologic difficulty. Hetzer and Muller (1999) provided evidence that out of 19 LVAD patients supported for up to 26 months, seven patients had persistently restored cardiac function for more than eight months and five patients for less than five months. Hetzer and Muller suggested that markers of successful device removal included decreased ventricular volumes and improved ejection fraction as the pump contribution to circulation was decreased. In 2005 Dandel et al. reported successful weaning in 32 (24%) out of 131 patients, with a 5-year survival rate of 78% after explantation.

In contrast with previous suggestions, recent reports by Liden et al. (2007) and Maybaum et al. (2007) reported that a degree of cardiac recovery was insufficient for the device to be explanted in most of the patients with chronic heart failure. Liden et al. (2007) studied 18 LVAD patients. Cardiac recovery was defined as off-pump left ventricular ejection fraction (LVEF) $\geq 40\%$ together with significant improvement in invasive haemodynamic measurements (cardiac index ≥ 2.5 and pulmonary capillary wedge pressure ≤ 20 -23 mm Hg). Patients who met this criterion were considered for weaning. Results demonstrated that only three out of 18 patients fulfilled the predefined criteria for cardiac recovery and were subjected to device explantation. In one patient, a young female with acute myocarditis, the following course was uneventful. In the second patient, a male with dilated cardiomyopathy, heart failure reoccurred only a few days later. The third patient had a relapse of giant cell myocarditis and was transplanted. In conclusion, Liden et al. (2007) argued that patients with severe advanced heart failure are unlikely to show significant cardiac recovery following treatment with LVAD. Furthermore Maybaum et al. (2007) in the LVAD Working Group Recovery Study enrolled 67 patients on LVADs and found that after 30 days of device implantation there was significant improvement in LVEF (17% vs 34%) and a reduction in left ventricular end-diastolic diameter (7.1 vs 5.1 cm) and left ventricular mass (320 vs 194 g). Furthermore 34% of patients had LVEF $>40\%$ with partial device support. The LVEF decreased over the time to pre-LVAD measurement by 120 days. Tissue analysis revealed significant reduction in myocyte

size, collagen content, and cardiac tumor necrosis factor- α . Only six subjects (9%) underwent LVAD explantation for recovery. Maybaum et al. (2007) concluded that cardiac function improves significantly after device implantation, but the degree of clinical recovery is insufficient for device explantation in most of the patients with chronic heart failure.

At present there is only one study, Birks and associates (2006) from Harefield Hospital, UK, to demonstrate cardiac recovery with the use of LVADs at significantly higher rate than any other in the literature. Data presented in this and the following chapter were also collected in Harefield Hospital in collaboration with Dr Birks and associates, and therefore description and review of the paper by Birks et al. (2006) is emphasized below.

6.1.5 Harefield Heart Science Centre Study from 2006

Birks and colleagues (2006) recruited 15 patients with severe heart failure due to nonischaemic cardiomyopathy and with no histologic evidence of active myocarditis. All patients had markedly reduced cardiac output and were receiving inotropes before implantation with LVAD. Compared with all previous reports, Birks et al. (2006) clearly emphasized so called “combination therapy” which does not only includes left ventricular unloading with the use of LVAD but also “specific pharmacological therapy” which together result in cardiac “reverse remodelling”. The preliminary overview of combination therapy used in Harefield has been described by Prof Yacoub in 2001 (Yacoub, 2001).

In the study by Birks et al. (2006) pharmacologic regimen consisted of two stages. In the first stage, intended to enhance reverse remodelling, treatment with four drugs commenced immediately after the patient had been weaned from inotropic therapy with adequate end-organ recovery. The four drugs and the maximum titrated doses were as follows: lisinopril, 40 mg daily; carvedilol, 50 mg twice daily; spironolactone, 25 mg daily; and losartan, 100 mg daily. The second stage of pharmacologic therapy was induced after maximal regression in the left ventricular end-diastolic diameter had been achieved while the left ventricular assist device was in place. When a constant size of left ventricular had been maintained for at least 2

weeks according to echocardiography assessment, clenbuterol was administered at an initial dose of 40 µg twice daily, when at a dose of 40 µg three times daily, and finally at a dose of 700 µg three times daily. The dose was adjusted to maintain the resting heart rate at a level below 100 beats per minute. Before clenbuterol was started, carvedilol was replaced by the selective β_1 -blocker bisoprolol.

Results of the study (Birks et al., 2006) demonstrated that 11(73%) out of 15 patients had sufficient recovery to meet the explantation criteria. The mean duration of support with a left ventricular assist device was 320 days (range, 63 to 603). In one patient, explantation was required because of device failure. In three patients, severe infection was present at the time of explantation. The mean LVEF with the pump off for 15 minutes was 64% before explantation as compared with 12% before implantation; the mean left ventricular end-diastolic diameter was ~56 mm as compared with ~75 mm, and the mean end-systolic diameter was ~40 mm as compared with 67 mm. Before explantation, the mean walking distance in 6 minutes (with the pump off) was 632 m, and the mean $\dot{V}O_2$ max (with the pump off) was 20.7 ml·kg⁻¹·min⁻¹, with a mean $\dot{V}_E/\dot{V}C_2$ slope of 32.5. Cardiac catheterization before explantation (with pump off) showed a mean right atrial pressure of 5.6 mm Hg, a pulmonary-capillary wedge pressure of 9.0 mm Hg (as compared with 23.8 mm Hg during inotropic therapy before implantation), a cardiac output of 5.4 litres per minute, a cardiac index of 2.8, and a pulmonary artery oxygen saturation of 66.9%.

Four patients underwent heart transplantation after completing the full course of combination therapy. Transplantation was performed because of lack of myocardial recovery in three patients and the development of appreciable mitral, tricuspid, and aortic regurgitation in one. No patient died during the combination therapy. The survival rate one and four years after explantation was 90.8% and 81.8%. The minimum period of follow-up after explantation was approximately 4 years (range, 1519 to 2058 days, mean, 1799 days). All surviving patients continued to be in NYHA class I except one, in whom severe heart failure recurred. Finally quality of life also improved in those patients, and this was also reported in separate study by George et al. (2008). Birks et al. (2006) concluded that sustained reversal of severe heart failure secondary to nonischaemic cardiomyopathy could be achieved in

selected patients with the use of an LVAD and specific pharmacologic regimen.

According to Birks et al. (2006) the objective of the initial phase of mechanical and pharmacological therapy is to reverse ventricular remodelling. Mechanical support with an LVAD has been shown to lead to a reduction in neuroendocrine activation (James et al., 1995) and myocyte hypertrophy (Zafeiridis et al., 1998). Also there is evidence to demonstrate that beta-blockers, angiotensin converting-enzyme inhibitors, angiotensin II-receptor blockers, and aldosterone antagonists can all reduce left ventricular remodelling (Greenberg et al., 1995; Groenning et al., 2000; Tsutamoto et al., 2001; Wong et al., 2002). Beta-blockers have multiple beneficial effects: slowing heart rate, lowering blood pressure, as well as a direct effect on the myocardium by reversing remodelling and upregulating β -receptors (Yacoub, 2001). The combination of ACE inhibitor and angiotensin 1 receptor antagonists has the advantage of full blockade of the receptors, together with enhanced endothelial function due to increased concentration of bradykinin produced by ACE inhibition (Pitt, 1998). Apart the effect on reverse remodelling, these drugs have a direct effect on the sarcoplasmic reticulum which improves calcium handling and diastolic function (Boateng et al., 1998). The addition of spironolactone has been shown to enhance survival in heart failure (Pitt et al., 1999) and reduce myocardial fibrosis (Zannad et al., 2000).

Once maximal reverse remodelling has been achieved, a programme of inducing physiological hypertrophy is instituted (second stage of pharmacologic therapy) (Birks et al., 2006; Yacoub, 2001). This consists of administering the β_2 agonist clenbuterol which has been shown to have beneficial effects on excitation-contraction coupling and myocardial metabolism in experimental models (Soppa et al., 2005; Wong et al., 1997). In addition, clenbuterol has been found to induce physiological hypertrophy in the myocardium (Wong et al., 1998). Such hypertrophy may actually confer a physiological benefit, because studies of myocardial tissue during long-term use of LVADs suggest that myocyte atrophy may occur in response to long-term mechanical unloading (Soloff, 1998; Zafeiridis et al., 1998). This may be prevented or reversed by clenbuterol (Birks et al., 2006). However, Birks and colleagues also stressed that some adverse effects of clenbuterol use may be present including apoptosis and necrosis of myocytes, particularly when the drug is given without β_1 -

blockade (Burniston et al., 2002). In their study Birks et al. (2006) reported that the only adverse effects were mild tremor and muscles cramp, but no serious side effects were observed.

According to Maybaum et al. (2007) the Harefield strategy will be tested in a US multicentre study that is due to commence recruitment in the near future.

6.1.6 Exercise Capacity in Patients on Left Ventricular Assist Devices

It has been suggested that supine cycle and upright treadmill exercise are safe during chronic support with LVAD (Jaski et. 1997). Cardio-pulmonary exercise testing and evaluation of exercise capacity is standardized procedure of heart failure evaluation in the most world heart transplantation centres. However, up to date there are only several studies which investigated functional capacity using cardiopulmonary exercise test in patients implanted with an LVAD.

Murali et al. (1991) compared metabolic stress test performance in 7 LVAD patients (class IV) with those patients with NYHA class III. The mean peak oxygen consumption for the LVAD patients slightly exceeded that of the class III patients: 16.2 vs. 14.8 ml·kg⁻¹·min⁻¹, indicating improvement in exercise tolerance in the LVAD patients. Furthermore Jaski et al. (1993) assessed haemodynamics and exercise performance in three patients one month following LVAD implantation. All three patients underwent graded supine bicycle exercise (maximal work load 100 to 150 W) with measurements of central haemodynamics, including continuous pulmonary artery oxygen saturation and oxygen consumption. Two of the patients also underwent upright treadmill exercise with oxygen consumption measurement only. During supine cycle exercise, the heart rate increased from 93 to 119 beats per minute. Oxygen consumption increased from 3.0 to 8.7 ml·kg⁻¹·min⁻¹. Cardiac output increased from 6.0 to 9.6 l·min⁻¹. The patients assessed during treadmill exercise achieved a maximal oxygen consumption of 14.3 and 16.7 ml·kg⁻¹·min⁻¹. Jaski et al. (1993) concluded that significant work loads compatible with activities of daily life and adequate exercise haemodynamics were demonstrated in LVAD patients.

Levin and colleagues (1994) assessed changes in NYHA class, mean arterial pressure, resting cardiac output, exercise oxygen consumption and exercise cardiac output in 12 LVAD patients. Nine patients improved to NYHA class I. Resting cardiac output increased from $3.1 \text{ l}\cdot\text{min}^{-1}$ preoperatively to $5.7 \text{ l}\cdot\text{min}^{-1}$ at two months, and mean arterial pressure from 60 to 91 mm Hg at two months. Four patients underwent maximal treadmill exercise testing (modified Naughton protocol) average 10 weeks after LVAD implantation. Patients achieved a peak exercise oxygen consumption of $15 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ and cardiac output of $\sim 9 \text{ l}\cdot\text{min}^{-1}$. These data indicated that functional recovery occurs during LVAD support.

Foray and associates (1996) performed a serial assessment of submaximal exercise capacity in patients with LVADs early (<3 months), mid (3 to 6 months), and late (>6 months) after device implantation to determine whether submaximal exercise capacity increased over the time and whether this was related to improvements in the cardiac output response. Additionally Foray et al. compared submaximal exercise capacity of LVAD patients with those of normal subjects and patients with mild to severe heart failure dependent on dobutamine. A six minute test with metabolic measurements was performed in 14 LVAD patients, 20 patients with mild to moderate congestive heart failure, 14 patients dependent on dobutamine and six normal subjects. The LVAD patients demonstrated significantly greater walked distance than dobutamine dependent patients and similar to that for patients with mild heart failure. Oxygen consumption was also greater in the LVAD than in dobutamine dependent or mild heart failure patients (16.3 vs. 9.8 vs. $11.2 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$). Serial assessment of submaximal exercise capacity in LVAD patients demonstrated continued sustained improvement over the time. However, cardiac output response was not significantly changed over the time (early 8 , mid 8.6 , and late $8.6 \text{ l}\cdot\text{min}^{-1}$). Foray et al. concluded that a significant sustained improvement in submaximal exercise capacity occurs with chronic LVAD therapy. Lack of the alteration of cardiac output response to exercise suggests that functional improvement results from peripheral mechanisms.

Mancini and colleagues (1998b) compared the exercise performance of 20 LVAD patients with that of 65 ambulatory heart failure patients who were transplant candidates. Time since device implantation averaged 2.6 months, with a range of 1 to 5 months. Patients performed in incremental cycle test. Peak oxygen consumption was

significantly higher in the LVAD patients (15.9 vs. 12.0 ml·kg⁻¹·min⁻¹) as was anaerobic threshold (12.2 vs. 8.1 ml·kg⁻¹·min⁻¹). At rest, mean arterial blood pressure was higher in LVAD patients (94 vs. 87 mmHg) as was cardiac output (4.9 vs. 4.1 l·min⁻¹). At peak exercise, heart rate was also higher in LVAD patients (148 vs. 125 beats per minute) as were blood pressure (96 vs. 87 mm Hg) and cardiac output (11.2 vs. 7.6 l·min⁻¹). Mancini et al. concluded that haemodynamic measurements at rest and during exercise are significantly improved in patients with LVADs compared with those awaiting cardiac transplantation. Similarly, the exercise capacity of the device patients is better than that of transplant candidates.

Jaski and associates (1999) compared the functional capacity of LVAD patients vs. heart transplant. Eighteen patients who received LVAD as a bridge to heart transplantation underwent treadmill testing one to three months post-LVAD and again post-heart transplantation. Most of the patients performed a modified Naughton protocol with 2-minute stages, and one patient underwent a modified Bruce protocol as the investigator felt this would lead to a better assessment of the patient's maximum exercise capacity. Patients exercise a mean of 52 days post-LVAD, and 59 days post-heart transplantation. Results demonstrated that peak oxygen consumption was 14.5 ml·kg⁻¹·min⁻¹ post-LVAD and 17.5 ml·kg⁻¹·min⁻¹ post-heart transplantation. Exercise duration was significantly lower in post-LVAD than post-heart transplantation, while the mean peak exercise systolic blood pressure and heart rate were not significantly different between post-LVAD and post-heart transplantation.

De Jonge and colleagues (2001) assessed exercise capacity at different point of LVAD implantation and compared the results with those obtained at different points after heart transplantation. Fifteen patients underwent treadmill exercise testing using a 2-min staged Naughton protocol or modified Bruce protocol. In 10 patients exercise capacity was assessed at 8 and 12 weeks after LVAD implantation. Results indicated that peak oxygen consumption increased from 21.3 to 24.2 ml·kg⁻¹·min⁻¹, while peak minute ventilation and carbon dioxide production ratio decreased from 39.4 to 36.3. Anaerobic threshold was not significantly changed (14.8 vs. 15.8 ml·kg⁻¹·min⁻¹). Furthermore in nine patients peak oxygen consumption 12 weeks after LVAD implantation was comparable to that of 12 weeks and one year after heart transplantation: 22.8 vs. 24.6 and 26.2 ml·kg⁻¹·min⁻¹. The patients' anaerobic threshold

increased from $14.4 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ with a LVAD to 15.9 and $18.7 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ 12 weeks and one year after heart transplantation. The ventilatory responses 12 weeks after LVAD implantation and 12 weeks and one year after transplantation were not significantly different. De Jonge et al. (2001) concluded that exercise capacity in patients with LVADs increases over the time. Similarly, Maybaum et al. (2007) found that peak oxygen consumption and exercise duration increase over the time with LVAD support. Patients performed cardiopulmonary exercise test at 30, 60, 90 and 120 days following LVAD insertion and peak oxygen consumption results were as follows: 13.7 vs. 16.1 vs. 17.4 vs. $18.9 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, respectively. A similar trend was demonstrated in time of exercise duration. Recent study by Pruijsten et al. (2008) compared functional and haemodynamic capacity after LVAD implantation and after heart transplantation. Forty-four patients who underwent LVAD implantation performed an exercise test (modified Naughton or modified Bruce protocol) three months after implantation of the device. Of the 44 patients, 29 performed a second exercise test three months after heart transplantation. Peak oxygen consumption was $20.0 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ following LVAD implantation and $24.0 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ following heart transplantation. Anaerobic threshold and ventilatory response were $13.8 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ and 35.6 after LVAD implantation and $15.7 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ and 34.7 after heart transplantation. The authors concluded that exercise performance in patients with severe end-stage heart failure, treated with a LVAD, is compatible with activities of normal daily life.

Functional capacity is an important aspect of quality of life in patients with cardiovascular disease (Jaski et al., 1999). From the above cited investigations there is no doubt that most of the patients implanted with left ventricular assist devices demonstrate improvement in exercise performance.

6.1.7 Rationale and Purposes of the Study

A number of cited studies have demonstrated that the use of LVAD in severe end-stage heart failure lead to positive molecular, cellular, biochemical, and structural changes in the myocardium, often referred as reverse remodelling that is also accompanied with functional improvement. Also several studies assessed exercise performance in patients with LVADs usually expressed as peak oxygen consumption, anaerobic threshold, ventilatory response, exercise duration, and walked distance. Non-invasive, central haemodynamic measures have been less frequently reported compared with other markers of exercise capacity.

Cardiac power output (CPO) is a novel haemodynamic measure that is the product of simultaneously measured cardiac output and mean arterial pressure (Cotter et al., 2003). By incorporating both pressure and flow domains of the cardiovascular system, CPO is an integrative measure of cardiac hydraulic pumping ability. Cardiac power output has been shown to be a powerful predictor of prognosis and mortality in patients with chronic heart failure and those with cardiogenic shock (Fincke et al., 2004; Mendoza et al., 2007; Roul et al., 1995; Tan, 1986; Tan and Littler, 1990; Williams et al., 2001) while cardiac reserve has been shown to be a major determinant of exercise capacity in heart failure (Tan, 1991). Surprisingly, cardiac power output has not been evaluated yet in patients supported with LVADs, and those explanted due to myocardial recovery.

Therefore the first purpose of the present study was to assess and compare peak cardiac power output and cardiac reserve between patients implanted with LVADs, those explanted due to recovery and patients with moderate to severe heart failure. Additionally, the study evaluated and compared different aspects of exercise performance in these three groups of patients.

6.1.8 Research Hypotheses

H_1 – There will be a significant difference in peak cardiac power output between patients implanted with LVADs, those explanted due to recovery and patients with moderate to severe HF.

H_2 – There will be a significant difference in cardiac reserve between patients implanted with LVADs, those explanted due to recovery and patients with moderate to severe HF.

H_3 – There will be a significant difference in peak oxygen consumption, anaerobic threshold and ventilatory response to exercise between patients implanted with LVADs, those explanted due to recovery and patients with moderate to severe HF.

6.2 Methods

6.2.1 Patients

The study population consisted of 54 male patients who attended cardiopulmonary exercise testing at Harefield Hospital, Harefield, United Kingdom. Data were collected in period from August 2006 to May 2008. Exclusion criteria included inability to perform treadmill exercise tests, inability to exercise beyond anaerobic threshold, symptomatic angina limiting exercise, unwillingness to provide consent form. Out of 54 patients, 20 were patients with moderate to severe heart failure (HF), 18 patients were implanted with LVAD (IMP) and 16 patients were explanted with LVAD due to myocardial recovery (EXP). Only male patients were studied as there were no available female patients with an LVAD *in situ*. Only two LVAD explanted female patients and only five female heart failure patients were available for exercise testing. These female patients were excluded from analysis in order to avoid gender differences in measured physical and physiological variables. Patients' clinical characteristics are presented in table 6.1.

Patients with moderate to severe heart failure consisted of available patients who were referred from other local and national hospitals to Harefield Hospital for further heart

failure evaluation and, where appropriate, heart transplantation. Forty-five percent of patients with moderate severe heart failure had NYHA class IV and 55% had class III heart failure symptomatology. The pathogenesis of heart failure was ischaemic heart disease in 15%, and dilated cardiomyopathy in 85% of patients. Left ventricular ejection fraction (LVEF) averaged $32\pm 14\%$, with a range of 15 to 55% (reported by Dr RG). All patients were receiving treatment with medication as described in Table 6.1. Eighteen patients had a prior exercise test as part of their heart failure evaluation, while two patients were performing exercise test for the first time. Patients were diagnosed with heart failure for a mean period of 29 ± 7.1 months.

Eighteen patients implanted with LVAD were studied (Table 6.1). All patients were implanted with a continuous blood flow left ventricular assist device. Fifteen patients had HeartMate II (Thoratec Corporation, CA, USA) LVAD and three patients had HeartWare (HeartWare Limited, Sydney, AU) LVAD. At the time of the test, 44% of LVAD patients were in NYHA class I, 22% in class II, 11% in class III and 22% in class IV. All LVAD patients had dilated cardiomyopathy. LVEF averaged $50\pm 8\%$, with a range of 45 to 68% (reported by Dr RG). All LVAD patients had a prior exercise test as evaluation for cardiac transplantation. Time since device implantation averaged 219 ± 87 days, with a range of 62 to 388 days. According to Dr Birks, the indication for insertion of the LVAD was the development of severe heart failure that was not responsive to intensive medical treatment, including inotropic support, with evidence of impeding or actually multiorgan failure due to low cardiac output. At the time of data collection in all LVAD patients the device was set up at fixed speed rate 9000 to 9600 revolutions per minute for HeartMate II LVAD and between 2600 and 3500 revolutions per minute for HeartWare LVAD. Patients with LVADs were diagnosed with heart failure for a mean period of 46 ± 24 month.

Sixteen patients explanted with LVAD due to myocardial recovery were studied (Table 6.1). At the time when LVAD was *in situ* 12 patients were implanted with pulsatile LVAD (HeartMate XVE, Thoratec Corporation, CA, USA) and three patients had continuous LVAD (Jarvik 2000, Jarvik Heart, Inc., MA, USA). At the time of the exercise test, 87% of LVAD explanted patients were in NYHA class I, and 13% patients were in class II, respectively. All LVAD explanted patients had dilated cardiomyopathy. LVEF averaged $58\pm 14\%$, with range of 50 to 72% (reported by Dr

RG). All LVAD explanted patients had a prior exercise test as evaluation for cardiac transplantation (LVAD implantation) as well as during follow up period when LVAD was *in situ*. The mean period of LVAD support was 396 days, with a range of 22 to 638 days. According to Dr Birks, explantation was considered if the following criteria were met while the LVAD was off for 15 minutes: a left ventricular end-diastolic diameter of less than 60 mm, a left ventricular end-systolic diameter of less than 50 mm, and a LVEF of more than 45%; a left ventricular end-diastolic pressure (or pulmonary-capillary wedge pressure) of less than 12 mm Hg; a resting cardiac index of more than 2.8 litres per minute per square meter of body surface area; and maximal oxygen consumption with exercise of more than $16 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ and an increase in minute ventilation relative to the carbon dioxide production ($\dot{V}_E / \dot{V}C_{O_2}$, ventilatory response) of less than 34. Patients in the present study were tested average 3.3 ± 1.1 years (range from 0.3 to 5.8 years) following device explantation. All LVAD explanted patients completed two stages of pharmacologic regimen suggested by Birks and associates (2006). Patients explanted with LVAD were diagnosed with heart failure for a mean period of 54 ± 19 months.

The study was approved by the ethics committee of the Royal Brompton and Harefield National Health Service. All patients who participated in the study provided written informed consent.

Table 6.1 Clinical Characteristics of Studied Population

	HF	IMP*	EXP
No.	20	18	16
Age, yrs	45±10	39±14	41±14
Range, yrs	22-64	19-58	18-63
LVEF, %	32±14	50±08	58±14
Aetiology of HF			
DCM	17	18	16
IHD	3	-	-
NYHA class, n			
I	-	8	14
II	-	4	2
III	11	2	-
IV	9	4	-
Medical Therapy			
ACE inhibitors	15 (75%)	13 (72%)	12 (75%)
β-blockers	17 (85%)	15 (83%)	13 (81%)
Diuretics	18 (90%)	16 (89%)	12 (75%)
Angiotensin II antagonists	7 (35%)	3 (17%)	6 (38%)
Aldosterone antagonists	17 (85%)	15 (83%)	9 (56%)
Digoxin	15 (75%)	11 (61%)	13 (81%)
Antiarrhythmics	5 (25%)	4 (22%)	6 (38%)
Clenbuterol	-	4 (22%)	-

HF, moderate to severe heart failure patients; IMP, LVAD implanted patients; EXP, LVAD explanted patients; DCM, dilated cardiomyopathy; ICM, ischaemic heart disease; LVEF, left ventricular ejection fraction; ACE inhibitors, angiotensin converting enzyme inhibitor

*LVAD turned on with optimal operation speed: 9,000 – 9,600 rpm for HeartMate II; 2,600 – 3,500 rpm for HeartWare. Time since LVAD was implanted averaged 219±87 days, range 62 – 388 days.

ACE inhibitors: Lisinopril; Ramipril; Perindopril

β-blockers: Carvedilol; Bisoprolol

Diuretics: Frusemide; Bendrofluazide; Bumetanide

Angiotensin II antagonists: Losartan; Candesartan; Valsartan

Aldosterone antagonists: Spironolactone; Eplerenone

Antiarrhythmics: Amiodarone

6.2.2 Study Design

This study took the form of a cross sectional study in which cardiac and respiratory measures were compared between the three groups of patients: 1) patients with moderate to severe heart failure, 2) patients implanted with an LVAD, and 3) patients explanted with LVAD due to myocardial recovery.

6.2.3 Testing Procedure

Upon the arrival in the transplant exercise laboratory, the patients' weight and height were measured. ECG electrodes were attached according to the standard lead configuration for exercise testing and the ECG cables were connected. The patient then sat on a chair and following a five minutes resting period, arterial blood pressure was assessed from the brachial artery by cuff sphygmomanometry. This was followed by measurement of cardiac output in a seated position using the inert gas rebreathing methodology (Innocor, Innovision, Denmark) as described in details in the Chapter 3. Following explanation, the subject performed rebreathing technique in the demonstration mode of the Innocor first to ensure patient's familiarisation with rebreathing manoeuvre. After a three minute wash out period, while the patient remained in a seated position, the rebreathing test was performed and cardiac output estimated by the Innocor.

Following cardiac output measurement the patient was connected to the Oxycon Pro (Jaeger, the Netherlands) Metabolic Cart via a disposable pneumotach attached to the face mask. Oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}C_{O_2}$) and minute ventilation (\dot{V}_E) were measured. After three minutes of resting metabolic measurements patient with severe heart failure and those implanted with LVAD performed a modified Bruce protocol while those patients explanted with LVAD performed Bruce protocol. Continuous breath-by-breath sampling of respiratory gases and heart rate measurements were made, while the last 30 seconds of each exercise stage arterial blood pressure was measured and Borg scale recordings for dyspnea and fatigue were performed (Borg, 1982). At peak exercise, cardiac output was measured using the inert gas rebreathing methodology. The Innocor respiratory valve unit with

bacterial filter was inserted into the pneumotach of the Oxycon Pro and patient was asked to breathe with required breathing frequency and to empty the rebreathing bag with each inspiration. At the same time during rebreathing manoeuvre, peak arterial blood pressure was measured.

The moment of cardiac output measurement at peak exercise was determined by the following criteria: respiratory exchange ratio of 1.05 and higher, achievement of maximal oxygen consumption (the absence of a rise in $\dot{V}O_2$ with further increase in exercise intensity) and patient's subjective feeling of high intensity work as indicated on the Borg scale (>17).

Peak $\dot{V}O_2$ was defined as the average $\dot{V}O_2$ during the last minute of exercise, expressed as ml per kg of body weight per min, as well as ml per kg. Oxygen consumption at the ventilatory (anaerobic) threshold (AT) was identified as the oxygen uptake before the systematic increase in the ventilatory equivalent for oxygen ($\dot{V}_E/\dot{V}O_2$), without a concomitant increase in the ventilatory equivalent for carbon dioxide ($\dot{V}_E/\dot{V}C_2$), together with the V-slope method (Beaver, 1986; Wasserman, 1999). ○

Echocardiography at rest was performed in all studied patients on the same day when cardiopulmonary exercise test was conducted. Most of the echocardiographic results (e.g. left ventricular systolic and diastolic diameters, left ventricular mass, etc.) were utilised for the other clinical research project. In the present study patients' left ventricular ejections fractions were reported.

6.2.4 Calculations and Statistical Analysis

The cardiac power output was calculated from the product of cardiac output and mean arterial pressure using the following equation (Cooke et al., 1998): $CPO = (\dot{Q}_T \times MAP) \times K$, where CPO is cardiac power output in Watts (W), \dot{Q}_T is cardiac output in $l \cdot min^{-1}$, MAP is mean arterial pressure in mm Hg and K is the conversion factor (2.22×10^{-3}). The physiological cardiac reserve is equal to the difference in between peak CPO and baseline resting CPO (Cooke et al., 1998). The mean arterial pressure was calculated as $DBP + 0.412 \times (SBP - DBP)$, where SBP is systolic blood pressure and DBP is diastolic blood pressure (Meaney et al., 2000). The ventilatory response to exercise ($\dot{V}_E / \dot{V}C_{O_2}$ slope) was calculated by linear regression analysis using the values of minute ventilation and carbon dioxide output as previously described (Chua et al., 1997). Age- and gender-adjusted maximal predicted oxygen consumption was determined by using the treadmill equation of Wasserman et al. (1999) as following: $W \times (56.36 - 0.413 \times Age)$, where W is normal weight (in kg) to height (H, in cm); $W = 0.79H \times 60.7$ for men. In addition, systematic vascular resistance to blood flow (SVR) at peak exercise was estimated as MAP / \dot{Q}_T and as per convention multiplied by a factor of 80 to convert units to $dyn \cdot s^{-1} \cdot cm^{-5}$.

All statistical analysis was carried out using SPSS version 13.0 (SPSS inc. Chicago, Illinois, USA). Prior to statistical analysis, data were checked for univariate and multivariate outliers using standard Z-distribution cut-offs and Mahalanobis distance tests respectively. Normality of distribution was assessed using a Kolmogorov-Smirnov test. To test difference in measured variables between patients with severe heart failure, those implanted and explanted with LVAD one-way analysis of variance (ANOVA) was used. To identify the groups that differed significantly from one another, a post hoc Tukey's test was performed. Statistical significance was indicated if $p < 0.05$. All data are presented as means \pm SD unless otherwise indicated.

6.3 Results

Physical characteristics of the studied patients are presented in Table 6.2. There were non significant differences in age and body dimensions between patients with moderate to severe heart failure (HF), LVAD implanted (IMP) and LVAD explanted (EXP) patients ($p>0.05$).

Table 6.2 Physical Characteristics of the Patients

	HF, N=20		LVAD IMP, N=18		LVAD EXP, N=16	
	Mean±SD	Range	Mean±SD	Range	Mean±SD	Range
Age (yrs)	45±10	22-64	39±14	19-58	41±14	18-63
Weight (kg)	84.6±14.1	55-108	79.3±15.3	57-88	85.4±14.2	53-116
Height (cm)	177.7±5.5	165-194.3	177.2±6.1	153.2-172.5	178.8±7.8	153.2-194.3
BMI (kg/m ²)	26.8±4.7	20.1-29.2	25.5±4.1	19.1-31.3	26.7±4.0	19.2-29.3
BSA (m ²)	2.1±0.2	1.9-2.4	2.0±0.2	1.6-1.9	2.1±0.2	1.5-2.4

BMI-body mass index, BSA-body surface area

6.3.1 Central Haemodynamic Measurements

The ANOVA revealed that cardiac power output at rest was not significantly different between the HF, LVAD IMP and LVAD EXP patients ($p>0.05$). In the HF patients resting cardiac power output ranged from 0.38 to 1.10 W, while in the LVAD IMP and LVAD EXP patients ranged from 0.43 to 1.26 W and from 0.73 to 1.42 W, respectively. At peak exercise, cardiac power output in LVAD IMP and LVAD EXP patients was significantly higher compared with HF patients ($p<0.01$). Also peak cardiac power output in LVAD EXP patients was significantly higher compared with LVAD IMP ($p<0.01$) (Figure 6.3). Peak cardiac power output ranged in 1) HF patients from 1.15 to 2.64 W, 2) LVAD IMP patients from 1.33 to 3.71 W, and 3) LVAD EXP patients from 2.20 to 4.50 W.

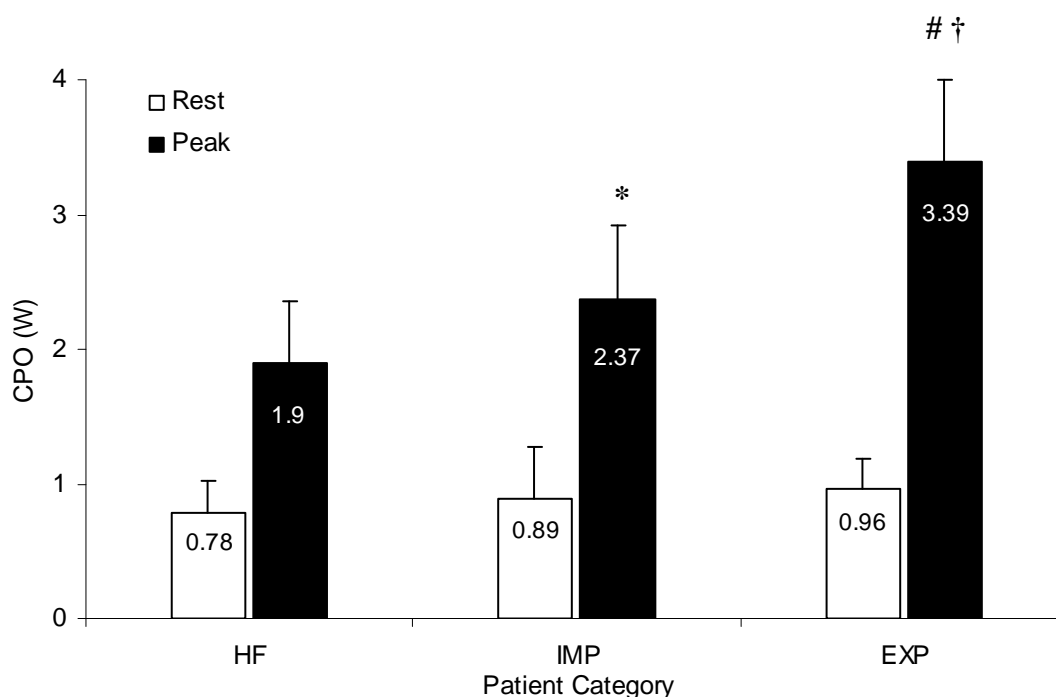


Figure 6-4 Cardiac power output (CPO) at rest and at peak exercise in heart failure (HF) patients, LVAD implanted (IMP) and LVAD explanted (EXP) patients.

* $p < 0.05$ IMP vs. HF, [#] $p < 0.01$ EXP vs. HF, [†] $p < 0.01$ EXP vs. IMP.

The mean physiological cardiac reserve of 2.43 ± 0.54 W in LVAD EXP patients was significantly higher than in LVAD IMP (1.48 ± 0.55 W) and HF patients (1.12 ± 0.40 W) ($p < 0.01$). The mean difference in cardiac reserve of 0.36 W between LVAD IMP and HF was not significantly different ($p > 0.05$).

Cardiac output at rest was significantly greater (by $1.4 \text{ l} \cdot \text{min}^{-1}$ or 25%) in the LVAD IMP than in the HF patients ($p < 0.05$), as were stroke volume and cardiac index by 25 and 30% respectively (Table 6.3). In the LVAD IMP and EXP patients, resting cardiac index was greater than in the HF patients ($p < 0.05$). Resting heart rate values and systolic, diastolic and mean arterial blood pressures were all comparable between the groups and were not significantly different (Table 6.3).

Table 6.3 Baseline and Peak Exercise Haemodynamic Measurements in the HF, IMP and EXP patients

	<i>Haemodynamic Variables</i>						
	\dot{Q}_T (l·min ⁻¹)	HR (beats·min ⁻¹)	SV (ml·beat ⁻¹)	CPO (W)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)
<i>Sitting Rest</i>							
HF	4.1±1.3	74.6±18.3	56.8±20.8	0.78±0.24	103.4±13.8	68.9±9.7	84.2±10.8
IMP	5.5±2.1*	72.6±14.5	76.0±21.2*	0.89±0.39	94.2±20.1	59.9±16.2	75.2±16.6
EXP	5.2±0.8	73.2±6.6	70.8±11.9	0.96±0.22	104.6±16.8	70.9±13.6	86.2±14.1
<i>Peak Exercise</i>							
HF	9.1±2.1	126.3±27.3	71.1±14.1	1.90±0.45	123.2±22.1	75.0±12.6	95.9±16.2
IMP	12.4±2.2*	142.2±27*	87.2±16.4**	2.37±0.55*	110.7±24.1	67.7±11.5	87.4±14.5
EXP	14.6±2.9 ^{##}	163±18.1 ^{##}	89.4±15.1 ^{##}	3.39±0.61 ^{##††}	137.8±22.4 ^{††}	76.6±12.7	102.8±15.0 [†]

\dot{Q}_T -cardiac output, HR-heart rate, SV-stroke volume, CPO-cardiac power output, SBP-systolic blood pressure, DBP-diastolic blood pressure, MAP-mean arterial pressure

*p<0.05, **p<0.01 IMP vs. HF

[#]p<0.05, ^{##}p<0.01 EXP vs. HF

[†]p<0.05, ^{††}p<0.01 EXP vs. IMP

At peak exercise, cardiac output was significantly higher in the IMP and EXP patients compared with the HF patients, as were heart rate, stroke volume and cardiac index (Table 6.3). At peak exercise, pressure generating capacity of the heart tended to be lower in LVAD IMP patients compared with the LVAD EXP and HF patients (Table 6.3). Systematic vascular resistance at peak exercise was significantly higher (p<0.05) in the HF patients (845±281 dyn·s·cm⁻⁵) than in the LVAD IMP (572±155 dyn·s⁻¹·cm⁻⁵) and LVAD EXP patients (556±192 dyn·s⁻¹·cm⁻⁵).

6.3.2 Oxygen Consumption Measurements and Exercise Duration

Oxygen consumption measured at rest was not significantly different between the HF, LVAD IMP and LVAD EXP patients. Oxygen consumption at anaerobic threshold in LVAD EXP patients ($21.4 \pm 5.0 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) was significantly greater than that in LVAD IMP ($14.7 \pm 4.9 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) and HF patients (11.2 ± 1.9) ($p < 0.01$). The anaerobic threshold occurred at 71% of peak oxygen consumption in the HF patients. In the LVAD IMP and LVAD EXP patients anaerobic threshold occurred at 74 and 76% of peak oxygen consumption. Peak oxygen consumption averaged $15.8 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (range 10.4 - $19.8 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) in HF patients, $19.8 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (range 12.4 - 25.1) in LVAD IMP patients, and 28.2 (range 20.5 - $34.8 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) (Figure 6.4).

Using the modified Bruce protocol, the exercise duration was higher in the LVAD IMP than in the HF patients (633 ± 207 vs. 563 ± 172 seconds, $p < 0.05$). The LVAD EXP patients scored 645 ± 190 seconds at Bruce protocol. The Borg scale results for ratings of perceived exertion were not significantly different between the patients (HF, 18.6 ± 1.1 ; IMP, 18.2 ± 1.3 ; EXP, 19.2 ± 1.2).

The HF patients achieved $46 \pm 13\%$ (range, 34% to 69%), whereas LVAD IMP and LVAD EXP patients achieved $57 \pm 16\%$ (range, 41% to 77%) and $83 \pm 17\%$ (range, 52% to 93%) of maximal predicted oxygen consumption calculated as suggested by Wasserman et al. (1999).

Patients reported that they terminated cardiopulmonary exercise test due to fatigue, dyspnoea, both or other factors. Sixty-eight percent of the HF patients, and 59 and 74% of LVAD IMP and LVAD EXP patients were limited by fatigue. Twenty-seven percent of the HF patients, and 32 and 19% of LVAD IMP and LVAD EXP were limited by dyspnoea. Between 3 and 6% of all patients reported that they had to stop the exercise test due to both fatigue and dyspnoea, and between 2 and 3% of patients terminated the test due to some other factors.

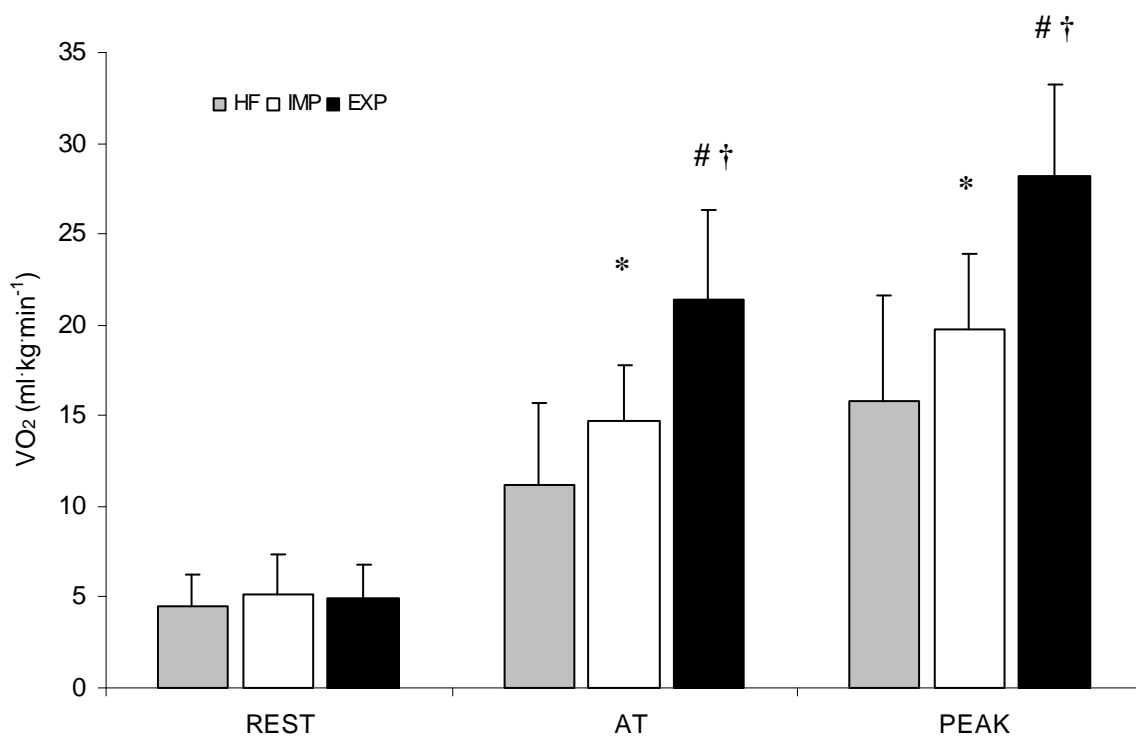


Figure 6-5 Oxygen consumption (VO₂) at rest, anaerobic threshold (AT), and peak exercise (peak), measured by Oxycon Pro - Jaeger, in heart failure (HF) patients, LVAD implanted (IMP) and LVAD explanted (EXP) patients

*p<0.05 IMP vs. HF, #p<0.01 EXP vs. HF, †p<0.01 EXP vs. IMP

6.3.3 Ventilatory and Metabolic Measurements

At rest, there was non significant difference in respiratory exchange ratio between the patients (HF, 0.86; LVAD IMP 0.83; and LVAD EXP 0.78). The mean absolute values for carbon dioxide output and oxygen consumption at rest were in HF patients 338.4±62.6 and 394.5±84.6 ml·min⁻¹, in LVAD IMP patients 337.5±53.9 and 406.6±92.3 ml·min⁻¹, and in LVAD EXP patients 324.5±64.1 and 415.5±87.1 ml·min⁻¹.

Metabolic and respiratory measures obtained at peak exercise are summarized in Table 6.4. Absolute values of peak oxygen consumption, carbon dioxide output and minute ventilation were higher in the LVAD EXP patients than in the HF and LVAD IMP patients (p<0.01). Respiratory exchange ratio was similar between the patients. The HF patients had an increased ventilatory response to exercise compared with

LVAD IMP and LVAD EXP patients.

Table 6.4 Metabolic and Respiratory Measurements at Peak Exercise

	$\dot{V}O_2$ (ml·min ⁻¹)	$\dot{V}C_2$ (ml·min ⁻¹)	RER	\dot{V}_E (l·min ⁻¹)	$\dot{V}_E / \dot{V}C_2$ slope
HF	1384±375	1591±378	1.14±0.12	53.7±10.8	35.8±7.8
IMP	1592±554	1846±401	1.15±0.14	62.2±17.7*	30.9±9.1*
EXP	2511±468 ^{#†}	2837±550 ^{#†}	1.12±0.11	88.6±28.0 ^{#†}	29.3±5.2 ^{##}

$\dot{V}O_2$ -oxygen consumption, $\dot{V}C_2$ -carbon dioxide output, RER-respiratory exchange ratio, \dot{V}_E -minute ventilation, $\dot{V}_E / \dot{V}C_2$ slope-ventilatory efficiency, all measured by Oxycon Pro, Jaeger.

*p<0.05 IMP vs. HF, [#]p<0.01 EXP vs. HF, ^{##}p<0.05 EXP vs. HF, [†]p<0.01 EXP vs. IMP.

6.3.4 Longitudinal Data – A Case Report

A twenty-year-old male patient (height 188 cm, weight 80 kg) was supported with the HeartMate II LVAD. After 211 days of LVAD support he was explanted due to sufficient cardiac recovery. Cardiopulmonary exercise tests with non-invasive cardiac power output measurements were performed at different time points: 90 days since implantation (Test I) and 47, 76 and 148 days since the device was explanted (Tests II, III, IV).

Resting cardiac power output values at Tests I, II, III and IV were 0.99, 1.24, 1.23, 1.13 W, respectively. Peak cardiac power output increased over the time (from 2.10 W at Test I to 3.11 W at Test IV) as was peak oxygen consumption (from 17.5 ml·kg⁻¹·min⁻¹ at Test I to 26.8 at Test IV) (Figure 6.5). Peak oxygen consumption at 47 days explanted was similar to that at 76 days explanted (24.7 and 24.4 ml·kg⁻¹·min⁻¹).

Resting cardiac output and cardiac index ranged from 5.9 to 6.8 l·min⁻¹ and from 2.7 to 3.1 l·min⁻¹·m². Maximal cardiac output and mean arterial pressure also increased

over the time. Cardiac output increased from 11 l·min⁻¹ at Test I to 14.4 l·min⁻¹ at test IV, whereas mean peak arterial pressure increased from 86 to 100 mm Hg.

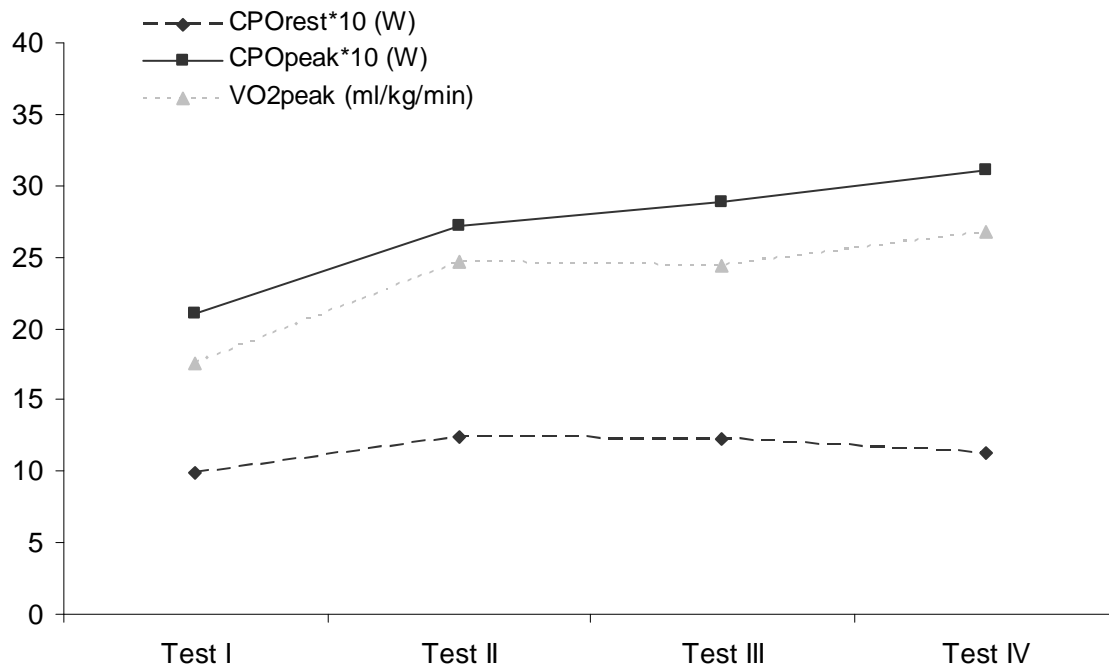


Figure 6-6 Cardiac power output (CPO) and oxygen consumption (VO₂) measured at 90 days since device implantation (Test I), and 47, 76 and 148 days since device was explanted (Tests II, III, IV).

6.4 Discussion

Cardiac power output determined non-invasively at rest and at peak exercise has not been previously described in patients implanted with LVADs and those to whom LVAD was explanted do to sufficient myocardial recovery. Together with central haemodynamic measurements, the present study evaluated exercise performance represented by peak oxygen consumption and anaerobic threshold and ventilatory response to exercise in patients with moderate to severe heart failure, those implanted and explanted with an LVAD.

In this cross sectional study design, different physiological variables were compared between the three different categories of heart failure patients (moderate to severe heart failure, LVAD implanted and LVAD explanted patients). When comparing cardiac power output between different subgroups of subjects it is very important to minimize the effect of body dimension using appropriate scaling model (Chantler et al., 2005). The reported population in the present study consisted of male patients only. Analysis of variance revealed that there were non significant differences in measured body dimension variables and age between the three groups of patients. This important finding allowed direct comparison of cardiac power output to be made between the groups of patients.

The important findings of this study are as follows: (1) Cardiac power output was not significantly different between the patients at rest as was the pressure generating capacity of the cardiac pump. However, blood flow generating capacity at rest was significantly higher in LVAD IMP than in HF patients. (2) Overall cardiac function represented by peak cardiac power output was significantly higher in LVAD EXP than in LVAD IMP and HF patients. Similar trend of higher peak cardiac power output was demonstrated in LVAD IMP versus HF patients. (3) Physiological cardiac reserve was significantly higher in LVAD EXP than in LVAD IMP and HF patients. (4) Exercise capacity represented by peak oxygen consumption and anaerobic threshold was also higher in LVAD EXP than in LVAD IMP and HF patients, and finally ventilatory response to exercise was increased in HF compared with LVAD IMP and EXP patients.

6.4.1 Patients Clinical Characteristics

Analysis of the aetiology of heart failure revealed that all LVAD implanted and LVAD explanted patients had nonischaemic dilated cardiomyopathy as were 85% of heart failure patients. This is consistent with previous studies which indicate that the majority of patients needed mechanical circulatory support had dilated cardiomyopathy. Furthermore, medication (e.g. β -blockers, ACE inhibitors, diuretics) were comparable between the groups. Level of the usage of angiotensin II antagonists were lower in LVAD implanted compared with LVAD explanted and heart failure patients as was digoxin. The use of aldosterone antagonists (spironolactone or eplerenone), however, was lower in LVAD explanted than in LVAD implanted and heart failure patients. The effect of medication on heart failure and exercise performance is described in more details in Appendix IV.

Twenty-two percent of LVAD implanted patients used a selective β_2 -adrenergic agonist (clenbuterol). It has been shown that clenbuterol induced significant myocyte necrosis in the heart and soleus muscle of the rat at doses previously used to demonstrate its anabolic properties (Burniston et al., 2002). However, Birks et al. (2006) suggested that clenbuterol prevents myocardial atrophy which may be caused during long-term mechanical unloading of the heart with LVAD. Moreover, Wong et al. (1998) found that clenbuterol causes mild myocardial hypertrophy. George et al. (2006) evaluated the effect of high-dose clenbuterol on cardiac and skeletal muscle in heart failure patients during LVAD support. Results revealed that cardiac function (represented by left ventricular ejection fraction) and exercise capacity did not change, but there was improvement in skeletal muscle mass and strength. It was also noted that clenbuterol prevented the expected decrease in myocyte size during LVAD support. Similarly, one recent study by Kamalakkannan and colleagues (2008) determined the effect of clenbuterol on skeletal muscle function, cardiac function, and exercise capacity in patients with heart failure. Results showed that maximal strength increased by 27% in clenbuterol group, but patients' endurance and exercise duration decreased after clenbuterol.

6.4.2 Cardiac Performance

The results from the present study suggest that LVAD implanted patients, and particularly those who have been explanted due to sufficient myocardial recovery, had better overall cardiac function than those patients with moderate to severe heart failure as represented by higher peak cardiac power output and physiological cardiac reserve. The results show that in LVAD explanted patients, both the flow- and pressure-generating capacity of the heart were higher than those patients with moderate to severe heart failure and LVAD IMP patients. This confirms previous finding by Birks et al. (2006) that the use of LVAD and specific pharmacologic therapy (so called “combination therapy”) improves cardiac function which in the present study has been assessed primarily by cardiac power output and physiological cardiac reserve.

Peak cardiac pumping capability and physiological cardiac reserve measured in LVAD explanted patients were similar to that in patients with mild heart failure (~3 and 2 W) as suggested by Williams et al. (2005). This finding is supported by the fact that the most of the LVAD explanted patients (77%) were in NYHA functional class I and 13% of the patients were in NYHA class II. Maximal cardiac pumping capability was higher in LVAD explanted patients by 30 and 44% compared with LVAD implanted and those patients with moderate to severe heart failure, respectively. Similarly, physiological cardiac pumping reserve was higher in LVAD explanted patients by 39 and 53% than in LVAD implanted and those patients with moderate to severe heart failure. At peak exercise, cardiac output, heart rate and stroke volume were higher in LVAD explanted than in moderate to severe heart patients by 38, 23 and 20%, respectively.

A number of previously mentioned studies suggested that ventricular pressure and volume unloading provided by LVAD support led to reverse remodelling on genetic, biochemical, histological and functional levels. To date, however, limited numbers of heart transplantations centres were able to demonstrate cardiac recovery that is sufficient to permit explantation of the LVAD. Only few studies presented data obtained from cardiopulmonary exercise testing in LVAD explanted patients, while none study has shown central haemodynamics measured either invasively or non-

invasive during exercise. A report from Germany by Muller et al. (1997) identified five (29%) of 17 patients with dilated cardiomyopathy supported by LVAD for >160 days in whom the device was successfully explanted and who maintain stable cardiac function (represented by resting LVEF only) between 52 and 594 days after explantation. Further Dandel et al. (2005) reported successful weaning in 32 (24%) out of 131 patients with dilated cardiomyopathy with a 5-year survival rate of 78%, respectively. Compared with the previous study from Germany (Muller et al., 1997), Dandel et al. (2005) reported that patients performed incremental treadmill exercise test (Naughton's protocol) between the third and fourth year after weaning. However, only predicted metabolic and ventilatory, but not any of central haemodynamic variables were presented, as discussed below. Significantly lower incidence of myocardial recovery has been reported by Mancini (1998a) and Maybaum et al. (2007). In study by Mancini et al. only 5% of patients met explantation criteria which was defined as peak oxygen consumption $>20 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ and cardiac output $>10 \text{ l}\cdot\text{min}^{-1}$ when LVAD contribution to circulation was decreased. However, Mancini et al. (1998a) did not report any cardiopulmonary exercise test data in patients following weaning of the device. Similarly, Maybaum et al. (2007) successfully explanted 9% of their patients but they also did not report central haemodynamic data following certain time since device explantation. Only Birks and associates (2006) reported cardiac output and cardiac index but only at rest in LVAD explanted patients. One year after explantation cardiac output and cardiac index averaged $4.9 \text{ l}\cdot\text{min}^{-1}$ and $2.4 \text{ l}\cdot\text{min}^{-1}\cdot\text{m}^2$, while in the present study the mean cardiac output and cardiac index averaged $5.2 \text{ l}\cdot\text{min}^{-1}$ and $2.5 \text{ l}\cdot\text{min}^{-1}\cdot\text{m}^2$. It should be noted that the average time since the device explantation in the present study was 3.3 years. Data from the present case report suggest that cardiac function at rest is stable during the first five months since the device was explanted (resting cardiac power output ranged between 1.13 and 1.24). Resting cardiac output and cardiac index ranged from 5.9 to $6.8 \text{ l}\cdot\text{min}^{-1}$ and from 2.7 to $3.1 \text{ l}\cdot\text{min}^{-1}\cdot\text{m}^2$ between 1.5 and 5 months since explantation. Higher resting cardiac output values may be explained by body dimensions of the studied patient (height, 188 cm; weight, 80 kg), with the bigger body demanding higher metabolic rate. Importantly, data from this case report demonstrate that maximal cardiac pumping capability of the heart and peak oxygen consumption increased by 12% (from 2.72 W) and 8% (from $24.7 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) between 1.5 and 5 months since the device was

explanted (Figure 6.5). This indicates that overall cardiac function and exercise performance improve during first months of LVAD explantation.

Compared with limited number of studies which evaluated cardiac performance during exercise in LVAD explanted patients, a few studies reported central haemodynamics in patients supported with an LVAD. Mancini and colleagues (1998a) reported that Fick cardiac output measured in 15 LVAD patients increased in response to exercise from resting value of $5.4 \text{ l}\cdot\text{min}^{-1}$ to peak exercise value of $11.4 \text{ l}\cdot\text{min}^{-1}$ and mean arterial pressure changed from 90 to 98 mm Hg. These results were obtained approximately three months after device implantation. Calculated peak cardiac power output based on data from Mancini's study ($\sim 2.5 \text{ W}$) is similar to that found in the present study in LVAD IMP patients. Peak cardiac output was lower by $0.9 \text{ l}\cdot\text{min}^{-1}$ than that found in the present study whereas peak mean arterial pressure was higher by 11 mmHg (98 vs. 87 mm Hg). Furthermore in a separate study, Mancini et al. (1998b) compared cardiac and exercise performance between patients with congestive heart failure ($N = 65$) and LVAD patients ($N = 20$). Cardiac output was higher in LVAD than patients with congestive heart failure (rest, 4.9 vs. $4.1 \text{ l}\cdot\text{min}^{-1}$, peak exercise 11.2 vs. $7.6 \text{ l}\cdot\text{min}^{-1}$). Pressure generating capacity, however, was higher in LVAD than in heart failure patients, which is in contrast with findings of the present study. The difference shown in mean arterial pressure between the studies by Mancini et al. (1998a; 1998b) and present study may possibly be explained by different model of the pump which was implanted. Patients in studies by Mancini and associates were implanted with pulsatile devices, while in the present study continuous-flow left ventricular assist devices were used. Pulsatile devices fill with and eject blood in a cyclic fashion that is equivalent to the systole and diastole of the native heart. On the other hand continuous-flow devices produce kinetic energy imparted to the blood which is drawn continuously from the left ventricular apex to the pump and into the ascending aorta. Continuous blood flow devices demonstrate difficulty in detecting vital signs in a systematic circulation with reduced pulsatility (Miller et al., 2007) which may possibly lead to lower blood pressure detected in the present study. Systolic blood pressure measured at rest was similar to that reported by Miller et al. (2007) who also evaluated patients implanted with continuous LVAD. At one month after device implantation resting systolic blood pressure averaged 96 mm

Hg in a study by Miller et al., while in the present study (~7 months after device implantation) systolic blood pressure averaged 94 mm Hg. However, Miller et al. did not report results from an exercise test.

The present study differed from Mancini et al. (1998a and 1998b) in that the exercise test was performed at different time points since LVAD was implanted. Time since device implantation averaged 3 months, with a range of 1 to 5 months in Mancini et al. (1998a and 1998b) while in the present study time averaged ~7 months, with a range of ~2 to 13 months. However, cardiac output data obtained three months after device implantation in the present study (case report) are similar to that found by Mancini et al. (1998a and 1998b). There is evidence to show that the improvement in central haemodynamics gained within the first few months after device implantation is maintained in the following months. Levin and associates (1994) demonstrated that resting cardiac (device) output and mean arterial pressure are stable from two to 10 months since device implantation. Foray and associates (1996) revealed that cardiac output was not significantly different between different time points after device implantation. In study by Foray et al., LVAD patients performed 6-minute walk test with metabolic and cardiovascular measurements at early (<3 months), mid (3 to 6 months) and late stage (>6 months) after device implantation. Peak cardiac output, estimated by the device sensor, was unchanged over the time (early, 8 l·min⁻¹; mid, 8.6 l·min⁻¹; and late, 8.6 l·min⁻¹). Similar observation was also reported by Maybaum et al. (2007) at 30, 60, 90, and 120 days after device implantation.

Similar average values of peak cardiac (device) output were reported elsewhere with a range of 7.5 and 9 l·min⁻¹ (de Jonge et al., 2001; James et al., 1998; Jaski et al. 1999; Levin et al., 1994; Maybaum et al., 2007). While only a few studies (Jaski et al., 1997; Mancini et al., 1998a and 1998b; the present study) have reported total cardiac output (as measured by invasive or non-invasive methods) in LVAD patients, others (de Jonge et al., 2001; James et al., 1998; Jaski et al. 1999; Levin et al., 1994; Maybaum et al., 2007) have used the device sensor to illustrate resting but also peak exercise cardiac output. This sensor takes into account only the volume of blood which flows through the pump, but not the output which is ejected directly from left ventricular into the aorta. The sum of the two should present total cardiac output. It is likely, therefore, that device (cardiac) output obtained by the device sensor underestimates

total cardiac output at rest and during exercise. This assumption is supported by Mancini et al. (1998a) who found that LVAD output was lower than cardiac output measured by the direct Fick method (rest 5.1 vs. 5.4 l·min⁻¹; peak exercise, 8.1 vs. 11.6 l·min⁻¹). Interpretation of device output leads to an underestimation of cardiac performance. Therefore, in order to obtain an objective image of the heart function and performance, cardiac output, and particularly cardiac power output should be measured at rest but also during exercise by the use of either invasive or non-invasive methods rather than reporting the device output only. In the present study patients were not connected to external device control unit which displays the device output results and, therefore, data regarding estimated LVAD output were not available for analysis.

The present study demonstrates that cardiac performance, represented by cardiac power output and physiological cardiac reserve differentiates well during cardiac restoration using LVADs, and emphasizes the benefits of this therapy. The results confirm previous evidence that the use of LVAD in combination with specific pharmacologic regimen, as suggested by Birks et al. (2006) improves overall cardiac function and performance. A peak CPO of ~ 2 W is considered to be a “cut-off” value for good and poor prognosis in heart failure (Roul et al., 1995; Williams et al., 2001). Therefore LVAD implanted, and particularly LVAD explanted patients, appear to have better prognosis than heart failure patients evaluated in the present study.

6.4.3 Peak Exercise Performance and Ventilatory Measurements

Few studies compared exercise performance of LVAD implanted with severe heart failure patients (Mancini et al., 1998b) and patients after heart transplantation (de Jonge et al., 2001; Jaski et al., 1999; Pruijsten et al., 2008). However, this is the first comparison of maximal upright exercise in LVAD explanted patients with LVAD implanted and severe heart failure patients. The peak oxygen consumption was higher in LVAD explanted patients compared with LVAD implanted and heart failure patients. LVAD explanted patients achieved 83% of the maximal predicted oxygen consumption. These patients were explanted at an average of 3.3 years (range of 0.3 to 5.8). To date, only one study is available to demonstrate exercise performance in LVAD explanted patients (Dandel et al., 2005). In that study data on exercise

performance were obtained between three and four years after device explantation. Seventeen patients in Dandel et al. study reached 78% of maximal predicted oxygen consumption what is only 5% lower than that found in the present study. The improvement in exercise performance of these LVAD explanted patients is extremely dramatic and is similar to that observed in sedentary healthy adults. Moreover, data from case report from this chapter indicates that peak oxygen consumption increased from 24.7 to 26.8 ml·kg⁻¹·min⁻¹ between 1.5 and 5 months after device explantation.

Peak oxygen consumption has been reported in the most studies which evaluated exercise performance in patients implanted with LVADs. Three months following device implantation peak oxygen consumption ranged from 14.3 to 17.4 ml·kg⁻¹·min⁻¹ (Foray et al., 1996; Haft et al., 2007; Jaski et al., 1993; Jaski et al., 1997; Levin et al., 1994; Mancini et al., 1998a; Mancini et al., 1998b; Maybaum et al., 2007; Murali et al., 1991). In the present study peak oxygen consumption in LVAD patients averaged 19.8 ml·kg⁻¹·min⁻¹. Several factors may account for this difference. Firstly in some of the cited studies (Jaski et al., 1997; Mancini et al., 1998a and 1998b) exercise testing was performed on a cycle ergometer compared with treadmill exercise used in the present study. This may render 10 to 25% lower values of peak oxygen consumption (Richard et al., 1999). In the rest of the cited studies, exercise performance in LVAD patients was measured using a treadmill protocol (e.g. Naughton or modified Bruce protocol) or 6-minute walk test. The difference in peak oxygen consumption between these and the present study is likely to be explained by different time points of exercise test after device implantation (~3 vs. ~7 months). This supposition that peak oxygen consumption improves over the time while the patient is on mechanical circulatory support, is supported by Maybaum and colleagues (2007). They measured peak oxygen consumption at 30, 60, 90 and 120 days following LVAD implantation and reported values of 13.7, 16.1, 17.4 and 18.9 ml·kg⁻¹·min⁻¹. De Jonge and associates (2001) reported that peak oxygen consumption at 8 and 12 weeks after LVAD implantation was 21.3 and 24.2 ml·kg⁻¹·min⁻¹ (de Jonge et al., 2001). However it should be emphasized that LVAD patients performed an intensive post-implantation exercise training program which clearly resulted in an excellent exercise performance.

The oxygen consumption at the anaerobic threshold was significantly higher in LVAD explanted than in LVAD implanted and heart failure patients. Moreover, anaerobic

threshold was significantly higher in LVAD than in heart failure patients. The oxygen consumption at anaerobic threshold in LVAD patients is similar to that reported by de Jonge and colleagues three months after device implantation (15.2 vs. 14.7 ml·kg⁻¹·min⁻¹). The data from the present study suggest that endurance capacity is improved in LVAD implanted and particularly LVAD explanted patients compared with severe heart failure patients. The delay in onset of anaerobic metabolism would help to explain the observed improved exercise performance of the LVAD explanted and implanted patients. The mechanisms responsible for the delayed onset of the anaerobic threshold may be improved skeletal muscle perfusion. With the improved cardiac output at rest and throughout exercise, it is likely that skeletal muscle perfusion was enhanced. This assumption may be explained by findings in the present study that systematic vascular resistance at peak exercise was lower in LVAD implanted and explanted patients compared with heart failure patients. Impaired exercise performance in heart failure patients may be inferred not only from impaired haemodynamic condition, but also skeletal muscle abnormalities (Gibbs et al., 1990; Maskin et al., 1983; Wilson et al., 1995) like atrophy (Mancini et al., 1992), as well as alterations in muscle histology and biochemistry (Massie et al., 1996).

Finally, better exercise performance found in LVAD implanted and explanted compared with heart failure patients was accompanied by a significant decrease in ventilatory response to exercise. This variable is often increased in patients with severe heart failure and is considered an independent and even better prognostic marker than reduced peak oxygen consumption (Chua et al., 1997; Robbins et al., 1999). During exercise, patients with heart failure have an excessive ventilatory response, possibly due to early onset of lactic acidosis, ventilation-perfusion mismatching from hypoperfusion leading to an increase in dead space ventilation (Wasserman et al., 1999). A cut off value of 34 has been proposed to differentiate severe heart failure patients with good and poor prognosis (Chua et al., 1997).

6.4.4 Study Limitations

The present study has a number of limitations. Firstly, this study had cross-sectional design as only limited data obtained at different time points (e.g. baseline data prior LVAD implantation with that after short and medium term following implantation

and/or explantation) were available. Data from one patient only, who was implanted and, after sufficient recovery, explanted are presented. Secondly, this study is limited in that it is observational. The mechanisms which resulted in improved cardiac function and performance were not investigated in either LVAD implanted and/or explanted patients. Thirdly, the exercise test was not performed at precise time points (with a wide range) after LVAD implantation and explantation. This may have skewed results and limited generalisation of the whole population of patients. Finally, the Innocor system was not used for metabolic but only for cardiac output measurements as it was not standard equipment in the Harefield Transplant Exercise laboratory. Therefore in order to estimate peak cardiac power output the Innocor respiratory valve unit with a bacterial filter was inserted into the pneumotach of the Jaeger system at peak exercise. Eight patients (5 EXP, 1 IMP, 2 HF) continued rebreathing manoeuvre within the first few seconds following test termination. This may underestimate cardiac power output results obtained at peak exercise in these patients.

6.5 Clinical Implications and Conclusions

The present study demonstrated that the use of LVAD with specific pharmacologic regimen (so called “combination therapy” proposed by Birks and associates in 2006) provides patients with greater functional capacity than that observed in patients with moderate to severe heart failure. Moreover, those patients who successfully completed combination therapy (LVAD explanted patients) demonstrated level of central haemodynamics and exercise performance similar to that in patients with mild heart failure and sedentary healthy adults.

The results from this study have shown that overall cardiac function represented by peak cardiac power output and physiological cardiac reserve is better in LVAD implanted and particularly LVAD explanted patients than those with heart failure. Not only peak cardiac power output, but also the other powerful surrogate indicators of prognosis such as anaerobic threshold, ventilatory response and peak oxygen consumption were all shown to be significantly different in LVAD implanted and LVAD explanted patients compared with heart failure patients. It is, therefore, fair to say that LVAD implanted and particularly LVAD explanted patients have better long-

term prognosis than HF patients.

Furthermore, this study has shown that the absence of significant differences in cardiac function at rest does not necessarily mean that there is not going to be significant difference during exercise between LVAD implanted, explanted and heart failure patients. It is important to assess variables which reflect both the flow- and pressure-generating capacity of the heart. Cardiopulmonary exercise testing with non-invasive measurement of central haemodynamics including cardiac power output has been reported for the first time in LVAD implanted and explanted patients. Results confirm feasibility and importance of cardiac power output measurement in these patients. Therefore, future LVAD investigations should evaluate central haemodynamics during exercise, particularly cardiac power output, which has the potential to be a key physiological marker of heart failure severity and can possibly guide management of LVAD patients.

Future studies should evaluate overall cardiac function and exercise performance in LVAD patients with limited device support, assessing the response of the native heart to exercise. Also the association between cardiac power output and other powerful prognostic surrogates obtained from cardiopulmonary exercise testing in LVAD implanted and explanted patients should be assessed.

6.6 References

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CHAPTER 7: RESTING AND EXERCISE HAEMODYNAMIC AND METABOLIC RESPONSES TO ACUTE REDUCTION OF LVAD SUPPORT: ASSESSMENT OF MYOCARDIAL RECOVERY

Abstract

Introduction: Patients with left ventricular assist device (LVAD) become stable after a few weeks following device implantation. The LVAD explantation criteria is based on data obtained when the LVAD is either switched off (pulsatile LVADs) or operates at reduced, very low speed (continuous LVADs). It has been suggested that assessment of myocardial recovery during reduced LVAD support is safe and well tolerated. Only a few studies have reported haemodynamic and metabolic measurements at rest and at peak exercise in patients with reduced LVAD support, but none have evaluated its effect on the power generating capacity of the heart. The purpose of the present study was to assess the effect of acute reduction of continuous-flow LVAD support on resting and peak exercise cardiac power output and other haemodynamic and metabolic measurements **Methods:** Twelve male patients (age 37 ± 10 yrs, weight 77 ± 9 kg, height 178 ± 7 cm) implanted with continuous-flow LVADs (Heart Mate II), visited the exercise laboratory twice during the same day with at least four hours rest between the two visits. During the first visit LVAD support was optimal with speeds ranging from 9,000 to 9,600 revolutions per minute. During the second visit the LVAD support was reduced and ranged from 5,800 to 6,000 revolutions per minute. Measurements at rest and at the peak exercise of the modified Bruce protocol were undertaken using non-invasive, inert gas, rebreathing haemodynamic and respiratory gas procedures. **Results:** In response to reduced LVAD support, resting cardiac power output decreased by 21% (from 0.87 to 0.69 W, $p=0.068$) as was cardiac output by 13% (from 5.3 to 4.6 $\text{l}\cdot\text{min}^{-1}$, $p=0.141$) and mean arterial pressure by 9% (from 74.1 to 67.3 mm Hg, $p=0.123$). Resting stroke volume decreased by 18% (from 71.4 to 58.2 $\text{ml}\cdot\text{beat}^{-1}$, $p=0.072$) while resting heart rate increased by 5% (from 74 to 79 $\text{beats}\cdot\text{min}^{-1}$, $p=0.126$). At peak exercise most of the measured haemodynamic and metabolic variables decreased significantly in response to reduced device support. Cardiac power output decreased by 39% (from 2.31 to 1.40 W, $p<0.001$), cardiac output by 30% (from 12.2 to 8.6 $\text{l}\cdot\text{min}^{-1}$, $p<0.001$), mean arterial

pressure by 13% (from 85.4 to 74.3 mm Hg, $p=0.006$), stroke volume by 24% (from 88.4 to 67.5 ml·beats⁻¹, $p=0.039$) and heart rate by 9% (from 138 to 126 beats·min⁻¹, $p=0.046$). Peak oxygen consumption reduced by 23% (from 18.2 to 14.1 ml·kg⁻¹·min⁻¹, $p=0.004$) whereas exercise time decreased by 18% (from 628 to 516 seconds, $p=0.032$). None of the patients demonstrated any short- or long-term adverse effects after the tests. **Conclusion:** The present study shows that acute reduction of LVAD support is safe and well tolerated by the patients both at rest and during exercise. There is a decrease in cardiac pumping capability and exercise performance as a consequence of acute reduction of LVAD support. A decrease at rest and at peak exercise, expressed in percentages, was higher in central haemodynamics, particularly in cardiac power output, than in the conventionally measured oxygen consumption. This may suggest that cardiac power output is more sensitive to acute reduction of LVAD support than oxygen consumption. Further ‘reduced LVAD support’ studies in larger cohorts of patients are required to find out the “cut-off” value of peak cardiac power output which may indicate sufficient myocardial recovery for the LVAD to be explanted.

7.1 Introduction

Left ventricular assist devices (LVADs) have been used as an effective therapeutic option in patients with advanced heart failure either as a bridge to transplantation, as destination therapy or as a bridge to recovery (Birks et al., 2004; Birks et al., 2006; Frazier et al., 2001; Long et al., 2005; Stevenson et al., 2004). Improvement in myocyte histology and biochemistry, as well as in left ventricular anatomy, physiology and haemodynamics have been observed in patients with advanced heart failure receiving prolonged mechanical circulatory support (Frazier et al., 1996). The improvement in cardiac function may be such that the pump could be removed and transplantation avoided (Muller et al., 1997).

Sufficient recovery to allow device explantation has been observed in only 5% to 24% of patients (Frazier et al., 1999; Dandel et al., 2005; Manicini et al., 1998). A strategy of combined mechanical and pharmacological therapy has been proposed with the β_2 -adrenoreceptor agonist clenbuterol used to stimulate physiologic hypertrophy during LVAD support (Yacoub, 2001). This strategy (so called ‘Harefield Recovery

Protocol') resulted in sufficient myocardial recovery that allowed LVAD to be explanted in >70% of non-ischaemic cardiomyopathy patients.

The utility of the LVAD may depend on aetiology of advanced heart failure (e.g. myocarditis vs. dilated cardiomyopathy). In the case of myocarditis, the LVAD may simply provide the circulatory needs of the body, including improved coronary flow, for the time necessary to resolve the disease process naturally, or burnout the inflammatory process (Rose and Frazier, 1997). However, in the case of dilated cardiomyopathy, reverse remodelling during chronic left ventricular unloading with an LVAD is clearly taking place with normalization of cardiac structure (reversal of chamber enlargement) and function (Levin et al., 1995; Madigan et al., 2001).

When patients with advanced heart failure implanted with an LVAD demonstrate restoration of heart function, according to Hetzer et al. (2001), two questions continue to await definitive answers. Firstly, which criteria indicate complete and long-term cardiac recovery while the patient is on an LVAD, and secondly what is the ideal time to remove the device once recovery appears to have occurred? Similarly, Farrar et al. (2002) argued that after the device is implanted it is not known what methods of patient and device management should be undertaken to optimize the chances for recovery.

7.1.1 LVAD Explantation Criteria

The LVAD explantation criteria is usually based on results obtained by echocardiography, cardio-pulmonary exercise testing, catheterization and myocardial tissue analysis. Echocardiography and cardio-pulmonary exercise testing may be performed when the device operates in full (optimal mode) but also when the device is either switched off (pulsatile device), or operates at very low speed (continues axial flow device) at rest and/or during exercise. This procedure allows evaluation and monitoring of myocardial recovery.

To date, only a few studies have clearly defined the LVAD explantation criteria. It is surprising that in a prospective big multicenter study of the LVAD working group performed by Maybaum and colleagues (2007) there were no protocol-specified

criteria for device explantation. However, Liden et al. (2007) defined cardiac recovery as off-pump left ventricular ejection fraction (LVEF) $\geq 40\%$ together with significant improvement in invasive haemodynamic measurements (cardiac index ≥ 2.5 and pulmonary capillary wedge pressure ≤ 20 - 23 mm Hg). Further Dandel et al. (2005) considered LVAD removal to be safe if, during repeated off-pump trials performed over several days, the maximum left ventricular end-diastolic diameter (LVEDd) was 55 mm and the minimum LVEF 45%, while the right ventricular diameters and function remained stable.

In contrast with Dandel et al. (2005) and Liden et al. (2007), the following two studies included data obtained from cardiopulmonary exercise test as important information in making the final decision for an LVAD to be explanted. Yacoub (2001) reported that explantation of the device was considered, if the device was 'switched off' and ventricular dimensions were normalized, LVEF $\geq 45\%$, LV end-diastolic pressure ≤ 8 mmHg, cardiac index more than $2.8 \text{ l}\cdot\text{min}^{-1}\cdot\text{m}^2$, and most importantly maximal oxygen consumption $\geq 20 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ and ventilatory response to exercise < 34 . According to Birks et al. (2006) explantation was considered if the following criteria were met while the LVAD was off for 15 minutes: a left ventricular end-diastolic diameter of less than 60 mm, a left ventricular end-systolic diameter of less than 50 mm, and a LVEF of more than 45%; a left ventricular end-diastolic pressure (or pulmonary-capillary wedge pressure) of less than 12 mm Hg; a resting cardiac index of more than $2.8 \text{ l}\cdot\text{min}^{-1}\cdot\text{m}^2$; and maximal oxygen consumption with exercise of more than $16 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ and ventilatory response < 34 . Finally, Mancini and associates (1998) suggested that the ability to exercise at reduced LVAD support to an oxygen consumption of more than $20 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ and/or a peak cardiac output higher than $10 \text{ l}\cdot\text{min}^{-1}$ provides sufficient cardiovascular reserve for the patient to tolerate device explantation. Echocardiographic parameters such as consistent aortic valve opening, normal shortening fraction, and absence of marked ventricular dilation are clinical variables that may also be used to identify explant candidates.

7.1.2 Monitoring of Myocardial Recovery – ‘On Pump vs. Off Pump’ Studies

Today, it is well known that myocardial recovery occurs after LVAD implantation. However, evaluation and monitoring of myocardial recovery of an LVAD patient still remains an issue (George et al., 2007). Some investigators have relied on examination of the patients while the device is on, after reducing the speed of the device and hence reducing its power, or after momentary discontinuation of the device (Hetzer et al., 2001; Maybaum et al., 2003; Slaughter et al., 2001). However, it remains difficult to determine whether the heart has had significant recovery that can be sustained once the device has been removed.

Hetzer and associates (2001) reported that the LVEDd and LVEF served as the main parameters to assess changes in cardiac performance. Under the conditions of a running device, an LVEDd below 60 mm and an LVEF above 40% were the criteria to do further echocardiographic studies. Firstly, the pump was set at the lowest possible pumping frequency, and eventually, the pump was stopped to evaluate the heart without mechanical support. To avoid thrombus formation inside the pump, 10,000 international units of heparin were administered before stopping the pump. These off-pump studies were conducted once a week after device placement. Hetzer et al. (2001), however, did not present any data to demonstrate response of the native heart to an acute interruption of LVAD support. They concluded that no reliable parameters predicts outcome after weaning and none determines the possibility of the device removal before implantation in advance.

Slaughter and colleagues (2001) suggested a new method for monitoring myocardial recovery and weaning a pulsatile LVAD. They differentiated two phases, recovery and weaning phase. During recovery phase, neurohormonal markers (to include plasma norepinephrine and tumor necrosis factor- α) are monitored and echocardiography is performed. Weekly bioimpedance is performed which allows an accurate non-invasive assessment of the patient's cardiac output. After the second postoperative week, the patients undergo cardiopulmonary exercise testing using the modified Naughton protocol which they performed preoperatively. This is repeated every week until the patient has a 10% increase in their peak oxygen consumption.

The weaning phase begins once an improvement in echocardiography, neurohormonal markers and cardiopulmonary exercise test results have been observed. During this phase, LVAD support gradually decreases in four steps over several days with daily echocardiography and bioimpedance monitoring. Once the device has reached a final setting for two days, the native left ventricle will have been providing a significant portion of total cardiac output. The patient then undergoes repeat cardiopulmonary exercise test, and if peak oxygen consumption remains unchanged or improved, the patient is scheduled for operation the following day. If the peak oxygen consumption decreases or the total cardiac output decreases during the weaning process, the device mode is changed back to full support and the recovery phase continued. Slaughter et al. (2001) concluded that gradual reloading of the ventricle would be ideal. This would avoid a sudden increase in wall stress and stretching of the myocyte. Also it would allow a longer period to observe the ventricle to see how it handles the new workload and its ability to sustain that work.

Maybaum et al. (2003) described the assessment of myocardial recovery in a 35-year-old male patient with acute myocarditis who required LVAD support as a bridge to recovery. A combination of echocardiography, right heart catheterization, exercise testing and serial endomyocardial biopsies was used to determine the resolution of myocarditis, recovery of cardiac function and timing for device explantation. Successful device explantation was performed after 37 days of device support. After two weeks postoperatively, LVAD rate was progressively decreased from full device support in auto mode (LVAD output of $6.5 \text{ l}\cdot\text{min}^{-1}$) to reduced LVAD support with flow of $2.5 \text{ l}\cdot\text{min}^{-1}$. Results revealed that there were no significant changes in LVEF, LVEDd, blood pressure, pulmonary capillary wedge pressure, right atrial and pulmonary artery pressures, and resting cardiac output. On the 36th post-operative day, cardiopulmonary exercise testing was performed, with simultaneous haemodynamic and echocardiographic measurements. The patient initially performed symptom-limited cycle exercise testing with full device support in the auto mode. Then LVAD flow was reduced over the period of 40 minutes to 2 litres per minute, and the patient repeated the exercise test with reduced LVAD flow. In response to reduced LVAD support, peak oxygen consumption and thermodilution cardiac output slightly decreased from 14.7 to $14.5 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ and from 14.3 to $12.6 \text{ l}\cdot\text{min}^{-1}$. Due to good

haemodynamic response to exercise with reduced LVAD flow, device explanation was planned for the following day. This study demonstrates that central haemodynamic measures (e.g. cardiac output) rather than peak oxygen consumption should be used in LVAD explantation decision making process.

George and associates (2007) from Harefield Heart Science Centre developed a test involving short-term interruption of LVAD support with measurements of several haemodynamic (heart rate and blood pressure) and echocardiographic parameters such as left ventricular end-systolic diameter (LVESd) and LVEDd, and LVEF at rest and, whenever possible, after exercise. After full heparization, the HeartMate I XVE device was switched off and echocardiographic measurements were obtained at 5, 10 and 15 minutes following device cessation. If device cessation was tolerated for 15 minutes, a 6-minute walk test was performed with repeat measurements thereafter to determine inotropic reserve. Results revealed that short-term discontinuation of the LVAD is safe and well tolerated by the patients. Cessation of the device was associated with an immediate drop in resting mean arterial blood pressure, a rise in resting heart rate, a reduction in LVEF, and increases in ventricular dimensions. After an exercise test, the recovered group had a significant rise in heart rate and LVEF and non-significant increase in mean arterial pressure, whereas, the non-recovered group had a significant drop in mean arterial pressure compensated by a rise in heart rate. George et al. (2007) concluded that acute discontinuation of the device to assess recovery is safe and well tolerated and is followed by specific changes in haemodynamic and echocardiographic parameters.

Mancini and colleagues (1998) performed echocardiographic and haemodynamic measurements in patients implanted with pulsatile LVAD. Tests were performed when the device was operating in the auto mode (full device support) and then with the device at the lowest fixed rate (50 cycles per minute) with full heparization of the patients. The electrical device was interfaced with a pneumatic stroke volume limiter so that the device rate could be reduced to 20 cycles per minute. Downtitration of the LVAD rate by 10 cycles per minute was performed with haemodynamic and echocardiographic measurements every 10 minutes until the patients developed symptoms or a device rate of 20 cycles per minute was achieved. Because the stroke volume of the device is 80 ml, a fixed rate of 20 cycles per minute generates ~1.6

$l\text{min}^{-1}$. Patients then performed cycling exercise test with metabolic and invasive central haemodynamic measurements. During downtitration of the device, resting heart rate increased significantly from 99 to 106 beats per minute, whereas blood pressure and cardiac output decreased significantly, from 91 to 71 mmHg and from 5.3 to 4.2 $l\text{min}^{-1}$. Only 7 out of 18 patients were able to exercise at a fixed device rate of 20 cycles per minute. At peak exercise heart rate, mean arterial blood pressure, cardiac output and oxygen consumption were significantly lower when the LVAD rate was reduced to 20 cycles per minute compared with auto mode. Additionally, reduction in LVAD support resulted in significant increase in LVEDd and LVESd both at rest and at peak exercise. Mancini et al. (1998) concluded that exercise testing may be a useful modality to identify those patients with sufficient myocardial recovery for the device to be explanted.

In continuous-flow LVADs the blood flow through the pump is dependant on the rotation of its impeller and the differential pressure across the pump. When the impeller is not rotating, as when pump is off, blood may flow from the aorta to the left ventricle, causing shunting and ineffectual blood flow.

Myers and colleagues (2006) were the first to evaluate haemodynamic and patient safety during pump-off studies of an axial-flow LVAD. Thirty patients were supported with the Jarvik-2000 LVAD for the mean duration of 170 days (range from 13 to 763 days). Patients were monitored by echocardiography during brief periods of no more than 5 minutes with the pump off. All patients received anti-coagulation therapy to achieve an international normalized ratio (INR) of 1.5 to 2.0, and the mean INR value for the group was 1.5. In each case, 5,000 U of heparin was administrated just before the pump was turned off. When the LVAD was switched off, there was an regurgitant flow of 0.42 $l\text{min}^{-1}$. The systolic blood pressure was not significantly different with the pump on or off, whereas the diastolic and mean arterial blood pressures significantly decreased when the device was off. With the pump off, the mean values for LVEDd and LVESd were 74 and 65 mm. With the pump-on, LVEDd and LVESd progressively decreased as pump speed increased. When compared with the pump-off, these changes became significant when the pump was operating at speed of $\geq 10,000$ rpm. The LVEDd decreased to 67 mm at 10,000 rpm, and further to 62 mm at 12,000 rpm. Likewise, the LVESd was 59 mm at 10,000 rpm, and 56 mm at

12,000 rpm. The mean heart rate and respiratory rate did not change significantly at any of the experimental settings. In the most of the patients, when the pump speed reached 12,000 rpm, the cardiac output was largely represented by the pump flow. Myers et al. (2006) concluded that regurgitant flow through axial-flow LVAD is minimal and does not have immediate clinical consequences. Whether this holds true when the pump is turned off for longer periods will depend on the degree to which the patient's native heart function recovers (Myers et al., 2006).

7.1.3 Rationale and Purposes of the Study

Monitoring of myocardial recovery after LVAD implantation remains an issue. It is, however, essential to know whether there is sustained recovery of the native heart in the LVAD patient. A number of procedures have been proposed, as described above. It seems that the best way to evaluate the degree of myocardial recovery in LVAD patients is to reduce LVAD support by switching the device off or reducing its speed.

Although a number of studies evaluated the effect of reduced LVAD support on heart function and structure at rest, only a few have assessed cardiovascular and metabolic response to maximal exercise. No study, however, examined the effect of reduced LVAD support on power generating capacity of the heart (cardiac power output) either at rest or at peak exercise.

Moreover, over the last few years continuous-flow rather than pulsatile LVADs have been mostly implanted in the clinics worldwide. Only Myers et al. (2006) reported their experience with switching off continuous-flow LVAD for a period of five minutes. At present, the effect of reduced speed of a continuous-flow LVAD on haemodynamic and metabolic measurements either at rest or at peak exercise has not been assessed.

Therefore, the purpose of the present study was to assess the effect of acute reduction of continuous-flow LVAD support on resting and peak exercise haemodynamic and metabolic measurements.

7.1.4 Research Hypotheses

H_1 – Acute reduction of continuous-flow LVAD support will not significantly reduce cardiac power output, and other haemodynamic and metabolic measurements at rest.

H_2 – Acute reduction of continuous-flow LVAD support will significantly reduce cardiac power output, and other haemodynamic and metabolic measurements at peak exercise.

7.2 Methods

7.2.1 Patients

In this study 12 male patients were recruited who were prospectively enrolled in the Harefield Bridge-to-Recovery Programme. Patients were implanted with a HeartMate II LVAD between August 2006 and January 2008. The cause of chronic heart failure was dilated cardiomyopathy. The average age of these patients was 37 ± 10 years. Average weight and height were 77.3 ± 8.7 kg and 178.1 ± 6.7 cm, and LVEF of 44 ± 12 %. Duration of implant averaged 186 ± 72 days. Eight patients were in the first phase of specific Harefield pharmacological regimen and they were treated with ACE inhibitors, β -blockers, aldosterone antagonists, angiotensin II antagonists and diuretics. Four patients were in the second stage of pharmacologic therapy in which additionally the β_2 -adrenergic-receptor agonist clenbuterol was administered. Patients who were unable to exercise above anaerobic threshold were excluded from analysis. The study was approved by the ethics committee of the Royal Brompton and Harefield National Health Service. Participants provided written informed consent.

7.2.2 Testing Procedure

Patients visited the transplant exercise laboratory twice during the same day with at least four hours rest between the two visits. During the first, morning visit (Test I), the LVAD support was optimal with speed ranging from 9,000 to 9,600 rpm. During the second, afternoon visit (Test II), the LVAD support was reduced and ranged from 5,800 to 6,000 rpm. The pump speed was adjusted manually in increments of 1,000

rpm. During the pump speed reduction and during the cardiopulmonary exercise test with reduced device support, the patients were closely observed clinically for any untoward symptoms such as dizziness, sweating and palpitations. During both visits, measurements at rest and at peak exercise of the modified Bruce protocol were undertaken using non-invasive, inert gas, rebreathing haemodynamic and respiratory gas procedures, as described in details in the Chapter 6 of this thesis. During the reduced LVAD support session, measurements were undertaken following pump speed reduction.

7.2.3 Calculations and Statistical Analysis

Cardiac power output (CPO), mean arterial pressure (MAP), ventilatory response to exercise ($\dot{V}_E/\dot{V}C_{2}$) and systematic vascular resistance (SVR) were calculated as described earlier ^Q in the Chapter 6.

All statistical analysis was carried out using SPSS version 13.0 (SPSS inc. Chicago, Illinois, USA). Prior to statistical analysis, data were checked for univariate and multivariate outliers using standard Z-distribution cut-offs and Mahalanobis distance tests respectively. Normality of distribution was assessed using a Kolmogorov-Smirnov test. To test difference in measured variables between Test I (optimal LVAD support) and Test II (reduced LVAD support), a t-test for paired samples or Wilcoxon signed rank test were used. Statistical significance was indicated if $p < 0.05$. All data are presented as mean \pm SD unless otherwise indicated.

7.3 Results

7.3.1 Resting Measurements

Table 7.1 shows haemodynamic and metabolic variables measured at rest during Test I (morning session with optimal LVAD support) and Test II (afternoon session with reduced LVAD support). Although changes varied between one and 21%, none of these changes were significantly different between the two tests. As soon as the LVAD speed was reduced the power generating capacity of the heart decreased by 0.19 W. Similarly pressure and flow generating capacities of the heart decreased by ~7 mm Hg and 0.7 l·min⁻¹. There was slight rise in heart rate by 5 beats⁻¹ and reduction in stroke volume by ~13 ml·beats⁻¹ following a decrease of LVAD speed.

Table 7.1 Resting Haemodynamic and Metabolic Variables Measured during Test I and Test II (N=12)

	Test I*	Test II**	% diff.	p-value
CPO, watts	0.87±0.36	0.69±0.26	21	0.068
SV, ml·beat ⁻¹	71.4±16.1	58.2±12.2	18	0.072
Innocor \dot{Q}_T , l·min ⁻¹	5.3±1.7	4.6±1.4	13	0.141
SBP, mm Hg	95.6±20.1	85.7±20.0	10	0.154
DBP, mm Hg	60.8±16.2	54.5±10.9	10	0.179
MAP, mm Hg	74.1±16.8	67.3±13.6	9	0.123
$\dot{V}O_2$, ml·kg ⁻¹ ·min ⁻¹	4.3±0.4	4.6±0.3	6	0.323
HR, beats·min ⁻¹	74±16	79±13	5	0.126
RER	0.83±0.03	0.84±0.05	1	0.791

$\dot{V}O_2$ -oxygen consumption, RER-respiratory exchange ratio, CPO-cardiac power output, HR-heart rate, SV-stroke volume, \dot{Q}_T -cardiac output, SBP-systolic blood pressure, DBP-diastolic blood pressure, MAP-mean arterial blood pressure. *optimal LVAD support-operation speed 9,000-9,600 rpm, **reduced LVAD support-operation speed 5,800-6,000 rpm.

7.3.2 Exercise Measurements

At peak exercise most of the measured haemodynamic and metabolic variables were significantly lower when LVAD support was reduced (Table 7.2). Peak power generating capacity of the heart was lower by ~0.90 W following Test II, as were flow- and pressure generating capacities by ~4 l·min⁻¹ and ~11 mm Hg. Peak cardiac power output ranged from 1.36 to 3.51 W (Test I) and from 0.85 to 2.51 W (Test II). Maximal exercise time and peak oxygen consumption were lower by 112 seconds and ~4 ml·kg⁻¹·min⁻¹. As a consequence of reduced LVAD support there was a significant increase in systematic vascular resistance and ventilatory response to exercise.

Table 7.2 Exercise Haemodynamic and Metabolic Variables Measured during Test I and Test II (N=12)

	Test I	Test II	% diff.	p-value
Peak CPO, watts	2.31±0.58	1.40±0.50	39	<0.001
Innocor Peak \dot{Q}_T , l·min ⁻¹	12.2±2.1	8.6±2.5	30	<0.001
Peak SVR, dyn·s·cm ⁻⁵	612±162	823±226	26	0.008
Peak SV, ml·beat ⁻¹	88.4±16.4	67.5±14.7	24	0.039
Peak $\dot{V}O_2$, ml·kg ⁻¹ ·min ⁻¹	18.2±4.5	14.1±5.3	23	0.004
Exercise time, seconds	628±192	516±119	18	0.032
$\dot{V}_E/\dot{V}C_2$ slope	35.5±4.6	41.3±7.1	16	0.038
Peak SBP, mm Hg	110.7±24.1	96.5±23.5	13	0.016
Peak MAP, mm Hg	85.4±15.4	74.3±14.9	13	0.006
Peak \dot{V}_E , l·min ⁻¹	58.4±6.2	52.8±9.5	10	0.046
Peak HR, beats·min ⁻¹	138±27	126±26	9	0.046
Peak DBP, mm Hg	59.9±16.2	54.9±10.9	9	0.015
Peak RER	1.12±0.10	1.09±0.06	3	0.083

$\dot{V}O_2$ -oxygen consumption, RER-respiratory exchange ratio, \dot{V}_E -minute ventilation, $\dot{V}_E/\dot{V}C_2$ -ventilatory response to exercise, CPO-cardiac power output, HR-heart rate, \dot{Q}_T -cardiac output, SV-stroke volume, SBP-systolic blood pressure, DBP-diastolic blood pressure, MAP-mean arterial blood pressure, SVR-systematic vascular resistance.

The ability of the patients to increase haemodynamic and metabolic responses to exercise from resting level was higher when LVAD support was optimal (Test I) compared to that when LVAD support was reduced (Test II) (Table 7.3).

Table 7.3 Changes from Resting to Peak Exercise Values in Selected Haemodynamic and Metabolic Variables

	Δ absolute		Δ %	<i>p</i> -value
	Test I	Test II		
CPO*, W	1.44±0.58	0.71±0.38	51	<0.001
\dot{Q}_T , l·min ⁻¹	6.9±2.8	4.0±2.1	42	0.001
MAP, mm Hg	11.3±3.2	7±2.4	38	0.222
SV, ml·beats ⁻¹	17.0±4.6	9.3±3.8	45	0.014
$\dot{V}O_2$, ml·kg ⁻¹ ·min ⁻¹	13.9±2.1	9.5±2.4	32	0.082
HR, beats·min ⁻¹	64±9	47±8	27	0.021

Δ absolute – difference between peak and resting value, Δ % – percentage difference in Δ absolute between Test I and Test II. * – the difference between peak and resting cardiac power output is physiological cardiac reserve.

All patients tolerated well acute reduction in the pump speed and were able to perform a cardiopulmonary exercise test. There were no short- or long-term adverse effects in any of the patients as a consequence of reduced LVAD support either at rest, during or after high intensity exercise.

7.4 Discussion

This is the first study to address the effect of acute reduction of continuous-flow LVAD support on cardiac pumping capability and other haemodynamic and metabolic measurements at rest but also at peak exercise. Others have evaluated myocardial recovery in 'off-pump' studies when patients were implanted with a pulsatile LVADs (George et al., 2007; Hetzer et al., 2001; Mancini et al., 1998; Maybaum et al., 2003; Slaughter et al., 2001), while only Myers et al. (2006) reported their experience with a continuous-flow LVAD. Myers et al. (2006), however, did not perform a 'stress' test.

The major finding of the present study is that reduced continuous-flow LVAD support decreases cardiac pumping capability (cardiac power output) by 21% at rest and by 39% at peak exercise. Reduced LVAD support also decreases the patients' ability to increase cardiac power output from resting to peak exercise value (physiological cardiac reserve) by half. In non-pulsatile LVADs (as used in this study), where the flow is continuous, reducing the pump speed to a rate at which there is no forward or back flow (an 'off-pump' equivalent study) is an alternative for assessing recovery (George et al., 2006). It has been shown that the device output is $<2 \text{ l min}^{-1}$ when the HeartMate II LVAD operates at very low speed (e.g. 6,000 rpm) (Myers et al., 2006) as used in the present study. Therefore cardiac output obtained with reduced LVAD support (speed of 6,000 rpm) is mostly produced by the native heart rather than by the device.

Different approaches have been proposed in the assessment of myocardial recovery while a patient is implanted with an LVAD (George et al., 2007; Hetzer et al., 2001; Mancini et al., 1998; Maybaum et al., 2003; Myers et al., 2006; Slaughter et al., 2001). Performing a number of echocardiographic and exercise tests measurements when the device is switched off or operates at low speed has commonly been used to evaluate a degree of myocardial recovery in LVAD patients. Some authors evaluated cardiac structure and function at rest only (Hetzer et al., 2001), whereas others have performed exercise test with measurement of central haemodynamics and oxygen consumption (Mancini et al., 1998; Maybaum et al., 2003; Slaughter et al., 2001).

Although there is an agreement that myocardial recovery should be evaluated with reduced LVAD support, it seems that there is no consensus yet regarding the best measure to evaluate myocardial recovery in LVAD patients. In an attempt to address this issue, Dr Tan's concept of cardiac power presented in Copenhagen (2007) will be described. Firstly, it should be stressed that cardiac function, rather than structure, should be prioritised in evaluation of myocardial recovery. Secondly, the degree to which the myocardium has recovered may only be objectively evaluated not with measurements at rest, but at peak exercise. The key role of the cardiac pump is to produce hydraulic energy to maintain physiological circulation (Tan, 1991). From evidence available so far only one parameter has the capacity to express hydraulic energy produced by the heart. That measure is cardiac power output which accounts not only for flow-, but also pressure-generating capacity of the heart. It is, therefore, not surprising that cardiac power output has been proposed to be the best, direct indicator of overall cardiac function (Tan, 1986). It may, therefore be suggested that probably the best method and measure to assess the degree of myocardial recovery in LVAD patients is the measurement of cardiac power output at rest and peak exercise with reduced LVAD support.

7.4.1 Optimal vs. Reduced LVAD Support at Rest

Results from the present study show that the acute reduction of continuous-flow LVAD support decreases cardiac pumping capability, cardiac output, stroke volume and mean arterial pressure. It causes slight increase in heart rate, oxygen consumption and respiratory exchange ratio at rest. None of these changes were significantly different between optimal and reduced LVAD support. It should be noted, however, that some of these changes require attention as the magnitude expressed in percentages may have some practical implications.

Firstly, and most importantly, as soon as LVAD support was reduced, cardiac pumping capability (CPO) decreased by 21% as a consequence of reduced flow (\dot{Q}_T)- and pressure (MAP)-generating capacity of the heart by 13 and 9%. While heart rate increased by 5%, stroke volume decreased by 18%. Therefore reduced cardiac pumping capability is mostly due to reduced stroke volume.

Reduced rate of pulsatile LVAD at rest is associated with a rise in the heart rate by ~9% (George et al., 2007) or by 11% (Mancini et al., 1998). In contrast, when the continuous LVAD was turned off from the speed of 9,000 rpm, there was an increase of 3% in the heart rate (Myers et al., 2006). These findings are in agreement with those from the present study. Reduced LVAD support causing a decreased mean arterial blood pressure has also been previously shown (George et al., 2007; Mancini et al., 1998; Myers et al., 2006). Only Mancini et al. (1998) demonstrated that reduced LVAD support was associated with a reduction in direct Fick cardiac output by 1.1 $\text{l}\cdot\text{min}^{-1}$, whereas in the present study cardiac output reduced by 0.7 $\text{l}\cdot\text{min}^{-1}$. Slight increase in resting oxygen consumption by 6% found in the present study is consistent with finding by Mancini et al. (1998).

These resting data suggest that minimal changes associated with reduced LVAD support in routinely measured haemodynamics (e.g. heart rate, arterial pressure) do not mirror changes in overall cardiac function. Moreover, presenting only changes in either flow- or pressure-generating capacity of the heart may overestimate overall cardiac function. It remains an issue as to what minimal level of decrease in cardiac pumping capability at rest (e.g. <5%) may represent sufficient myocardial recovery. However, it seems reasonable to suggest that the smaller the decrease in cardiac power output with reduced LVAD support, the better will be the overall cardiac function. Stressing the heart with a cardiopulmonary exercise test with central haemodynamic measurements at peak exercise is probably the best method to determine a degree of myocardial recovery in LVAD patients.

7.4.2 Optimal vs. Reduced LVAD Support at Peak Exercise

The present results obtained at peak exercise demonstrate the following important findings. Firstly, the ability of the heart to generate hydraulic power was reduced by 39% when LVAD support was reduced. Probably as a direct consequence of reduced cardiac pumping capability there was a significant reduction in exercise capacity (exercise time, peak oxygen consumption) and an increase in ventilatory response to exercise. Secondly, the results show that the ability of the patients to increase haemodynamic and metabolic response from rest to peak exercise was significantly lower when the LVAD support was reduced. Moreover, physiological cardiac reserve,

which represents the difference between rest and peak exercise cardiac power output, was halved as a consequence of reduced LVAD support. Similarly, the patients' ability to increase flow- and pressure-generating capacity was lower by 42 and 38% with reduced LVAD support. Finally, performing a treadmill exercise test is safe and well tolerated in LVAD patients when the device operates at low speed (reduced LVAD support).

Only few studies have shown exercise results in response to reduced LVAD support. George et al. (2007) used a 6-minute-walk test and performed a series of measurements not during and/or peak exercise, but following cessation of exercise. Apart from echocardiography, from central haemodynamic measurements, George et al. (2007) only evaluated blood pressure and heart rate. They showed an increase in mean arterial blood pressure due to an increase in systolic, but not diastolic blood pressure. Also a significant increase in heart rate following 6-minute-walk test was reported. Furthermore, Mancini and associates (1998) performed haemodynamic and metabolic measurements at rest but also at peak exercise (cycling) with optimal and reduced LVAD support. Results showed that cardiac output and peak oxygen consumption were lower by 25%, whereas mean arterial pressure was lower by 13% when LVAD support was reduced. These findings are similar to those found in the present study where cardiac output, peak oxygen consumption and mean arterial pressure were lower by 30, 23, and 13% respectively when LVAD support was reduced.

Great difference in physiological cardiac reserve between optimal and reduced LVAD support found in the present study may indicate that insufficient reverse remodelling and myocardial recovery have occurred in this cohort of patients following LVAD implantation. This supposition may be supported by the fact that only four of 12 patients were in the final, second phase of 'Harefield Recovery Protocol' which includes the β_2 -adrenoreceptor agonist clenbuterol (Birks et al., 2006). The present study demonstrates that cardiac pumping reserve was 0.71 W when LVAD support was reduced. Whether this result may indicate any myocardial recovery in this group of LVAD patients remains an issue as no such pre-implantation data are available.

The results from the present study show that peak cardiac power output and

physiological cardiac reserve were dramatically decreased when support from a continuous-flow LVAD was reduced. On the other hand, the study demonstrates great haemodynamic and metabolic benefits when LVAD operates with optimal speed. More importantly, the study demonstrates feasibility of cardiac pumping capability measurements in LVAD patients with optimal and reduced device support. Due to the capacity to represent overall cardiac function directly, cardiac power output should become a standard measure of myocardial recovery evaluation in LVAD patients. This will assist in making important decisions such as LVAD explantation.

Finally, a decrease at rest and at peak exercise, expressed in percentages, was higher in central haemodynamics, particularly in cardiac power output, than in conventionally measured oxygen consumption. This may suggest that cardiac power output is more sensitive to acute reduction of LVAD support than the oxygen consumption. This fact additionally supports the view that cardiac power output should be prioritized among other more conventionally measured cardio-respiratory variables such as oxygen consumption.

7.4.3 Study Limitations

The major limitation of this study is that no baseline (pre-implantation) data are available. Thus, it is difficult to suggest whether measured cardiac power output and physiological cardiac reserve demonstrate an improvement in myocardial function, particularly in situation with reduced LVAD support. This study is also limited by the small sample size. Although a greater number of LVAD patients was available for cardiopulmonary exercise testing as shown in Chapter 6, not all of them attended afternoon session with reduced LVAD support. Additionally, the present study is descriptive. No attempt was made to identify the mechanism of improved (non-improved) myocardial function.

7.5 Clinical Implications and Conclusions

The present study shows that performing a cardiopulmonary exercise test with non-invasive haemodynamic and metabolic measurements in patients implanted with continuous-flow LVAD is safe and well tolerated when the device operates at low speed. The results demonstrate that cardiac pumping capability at rest and peak exercise is dramatically impaired when continuous-flow LVAD support is reduced. Physiological cardiac reserve was halved in response to reduced LVAD support. This may indicate that insufficient myocardial recovery occurred in this cohort of patients.

Stressing the heart with a cardiopulmonary exercise test with central haemodynamic measurements at rest and peak exercise is probably the best method to determine a degree of myocardial recovery in LVAD patients, particularly when the device support is reduced. Measurement of cardiac pumping capability in LVAD patients with reduced LVAD support is feasible. Cardiac power output estimated at rest and peak exercise should become a standard measure in evaluation of myocardial recovery in LVAD patients based on which important decisions can be made (e.g. LVAD explantation). There is no reason why cardiac power output, as a direct measure of overall cardiac function, should not be prioritized among other cardio-respiratory variables (e.g. oxygen consumption, ventilatory response) as the latter may be influenced not only by cardiac but also by non-cardiac factors (e.g. muscle conditioning). Results from the present study show that cardiac power output is more sensitive to acute reduction of LVAD support than the oxygen consumption. A decrease at rest and at peak exercise, expressed in percentages, was higher in cardiac power output, than in conventionally measured oxygen consumption.

Further ‘reduced LVAD support’ studies in larger cohorts of patients are required to find out the “cut-off” value of peak cardiac power output which may indicate sufficient myocardial recovery for the device to be explanted.

7.6 References

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CHAPTER 8: RELATIONSHIP BETWEEN PEAK CARDIAC PUMPING CAPACITY AND EXERCISE-DERIVED PROGNOSTIC INDICATORS IN PATIENTS WITH MODERATE TO SEVERE HEART FAILURE AND THOSE IMPLANTED AND EXPLANTED WITH A LEFT VENTRICULAR ASSIST DEVICE

Abstract

Introduction: The cardiopulmonary response to exercise in patients with chronic heart failure has been established as an important prognostic indicator. Several exercise-derived variables have been shown to be strong predictors of prognosis in chronic heart failure (peak oxygen consumption, anaerobic threshold, peak circulatory power, ventilatory efficiency- $\dot{V}_E/\dot{V}C_{O_2}$ slope and peak oxygen pulse). The purpose of the present study was to assess the relationship between peak cardiac pumping capacity represented by peak cardiac power output (CPO) and peak oxygen consumption ($\dot{V}O_2$), anaerobic threshold (AT), ventilatory efficiency slope ($\dot{V}_E/\dot{V}C_{O_2}$), circulatory power (CP) and peak oxygen pulse (OP) in moderate to severe chronic heart failure patients (HF), and those implanted (IMP) and explanted (EXP) with a left ventricular assist device (LVAD). **Methods:** Fifty-four patients (20 HF, 18 IMP, 16 EXP) performed a cardiopulmonary exercise test (the Bruce or modified Bruce protocol) with respiratory gas and non-invasive haemodynamic measurements. **Results:** When all data were combined (n=54), peak CPO was strongly correlated with peak $\dot{V}O_2$ (r=0.87, p<0.01), AT (r=0.79, p<0.01) and circulatory power (r=0.82, p<0.01). Peak CPO was well correlated with peak oxygen pulse (r=0.69, p<0.01) and moderately with $\dot{V}_E/\dot{V}C_{O_2}$ slope (r=-0.51, p<0.01). Subgroup analysis revealed that the strength of relationship between peak CPO and other prognostic indicators was generally lower in HF patients and IMP than in EXP patients. Peak $\dot{V}O_2$ was highly correlated with peak CPO in EXP (0.85, p<0.01), whereas in HF and IMP this relationship was moderate (r=0.55 and r=0.53, p<0.05). The AT was only modestly correlated with peak CPO in HF and EXP patients (r=0.46 and r=0.54, p<0.05) and weakly in IMP patients (r=0.37, p<0.05). Peak CPO was highly correlated with peak CP in EXP patients (r=0.82, p<0.01), whereas in IMP and HF patients the r values were 0.63 (p<0.01) and 0.31 (p>0.05). $\dot{V}_E/\dot{V}C_{O_2}$ slope

was only moderately correlated with peak CPO in EXP patients ($r=-0.52$, $p<0.05$) but a non significant relationship was found in HF and IMP patients. Similarly the relationship between peak CPO and peak OP was good in EXP patients ($r=0.63$, $p<0.02$), but not in severe HF ($r=0.45$, $p<0.05$) and IMP patients ($r=0.32$, $p>0.05$).

Conclusion: The present study demonstrates that the strength of the relationship between direct and indirect indicators of cardiac pumping capacity is weaker in patients with moderate to severe heart failure and those implanted with a LVAD, compared with LVAD explanted patients. It is important to assess maximal cardiac pumping capability directly by measuring peak cardiac power output rather than using the other surrogates of cardiac pumping function, particularly in moderate to severe heart failure patients and those implanted with a LVAD.

8.1 Introduction

Cardiopulmonary exercise testing has been widely used in chronic heart failure patients to assess functional capacity, to evaluate responses to medical treatment and exercise therapy, to assess progression of disease process, and to determine prognosis (Ingle, 2008). According to Wright and Tan (1999) the objectives of cardiopulmonary exercise testing in patients with chronic heart failure are: 1) to improve understanding of pathophysiological mechanisms, 2) to confirm the quantity of symptoms and their severity, 3) to predict prognosis, and 4) to assess therapeutic success.

Despite surgical, technological and pharmacological advances used in management of heart failure patients, the prognosis remains generally poor (Nieminen et al., 2005). In order to identify patients who are at the highest risk of cardiac event, researchers reported a number of exercise-derived parameters which have been shown to be powerful prognostic indicators. Peak oxygen consumption, anaerobic threshold, ventilatory response to exercise (ventilatory efficiency) and circulatory power have been used in the prognosis of heart failure, in addition to functional and treatment assessment. It should, however, be emphasized, that these variables are indirectly related to cardiac function, and therefore can only be considered as markers of severity of organ failure. The practical implication is that an improvement in these values does not necessarily indicate an improvement in cardiac function (Williams et al., 2005a). More direct measurements of cardiac function represented by peak stroke

work index (Griffin et al., 1991; Metra et al., 1999), cardiac output response to exercise (Chomsky et al., 1996) and cardiac power output (Roul et al., 1995; Williams et al., 2001) have emerged as powerful independent predictors of prognosis over the more commonly reported peak oxygen consumption.

8.1.1 Exercise-Derived Prognostic Indicators in Heart Failure

8.1.1.1 Peak oxygen consumption in heart failure

The prognostic value of exercise testing in the heart failure population is well established. Peak oxygen consumption ($\dot{V}O_2$) has consistently demonstrated prognostic significance (Francis et al., 2000; Mancini et al., 1991; Myers et al., 2000) and is the most frequently analyzed cardiopulmonary exercise test parameter (Gibbons et al., 1997). In conjunction with other typically more invasive evaluation techniques, peak $\dot{V}O_2$ is used to assess survival and the need for heart transplantation (Gibbons et al., 1997). American Heart Association consensus reports have recommended that peak $\dot{V}O_2$ be used to help determine the timing of heart transplantation in ambulatory patients with chronic heart failure (Costanzo et al., 1995). Specifically, it has been suggested that a peak $\dot{V}O_2$ level of less than or equal to $14 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ be used as a key criterion for the acceptance of ambulatory patients for transplantation. This recommendation is based on several studies demonstrating that peak $\dot{V}O_2$ is a valuable prognostic marker in patients with chronic heart failure and that transplantation can be safely deferred in patients with peak $\dot{V}O_2$ levels of more than $14 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ (Mancini et al., 1991; Szlachcic et al., 1985). The 24th Bethesda Conference for Cardiac Transplantation listed peak $\dot{V}O_2$ less than $10 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ with achievement of anaerobic metabolism as an accepted indication for heart transplantation (Mudge et al., 1993).

Patients with chronic heart failure have a reduced physical (exercise) capacity, which can be characterized by a reduction in oxygen consumption at peak exercise (Weber et al., 1982). Weber et al. (1982) proposed a functional classification of heart failure in four stages (A to D) according to the peak $\dot{V}O_2$ and oxygen consumption at

anaerobic threshold (Table 8.1). The latter will be discussed in the section 8.1.1.2 of this chapter.

Table 8.1 Weber Functional Classification for Heart failure

Weber Class	Peak $\dot{V}O_2$ ml·kg ⁻¹ ·min ⁻¹	Anaerobic threshold ml O ₂ ·kg ⁻¹ ·min ⁻¹	Deterioration of functional capacity
A	>20	>14	Mild or absent
B	16-20	11-14	Mild-Moderate
C	10-15	8-11	Moderate-Severe
D	<10	<8	Severe

Oxygen uptake is determined by cellular oxygen demand and can be calculated from blood flow and oxygen extraction by the tissue. According to the Fick equation, oxygen uptake is equal to the product of cardiac output and the difference between arterial and venous oxygen ($a-\bar{v} O_2$). Figures 8.1 and 8.2 show central and peripheral determinants of maximal oxygen uptake.

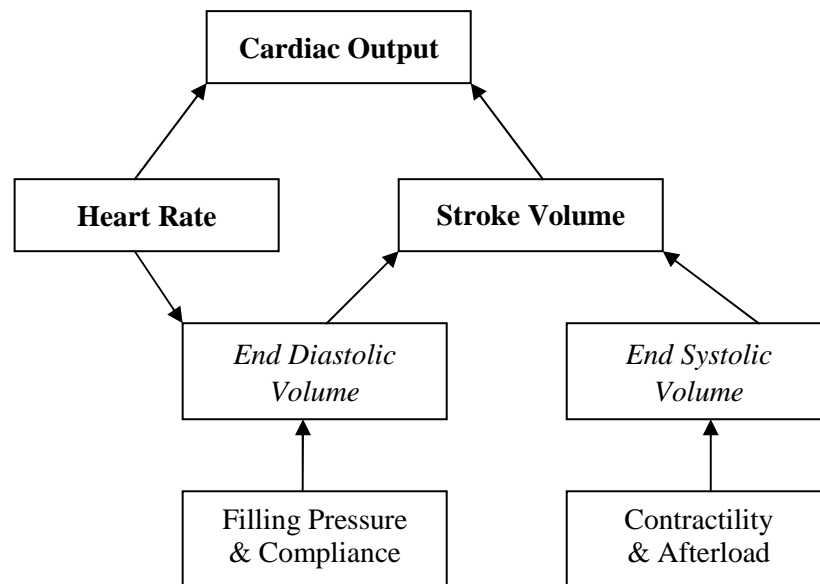


Figure 8-1 Central determinants of maximal oxygen uptake (modified from Myers and Froelicher, 1991).

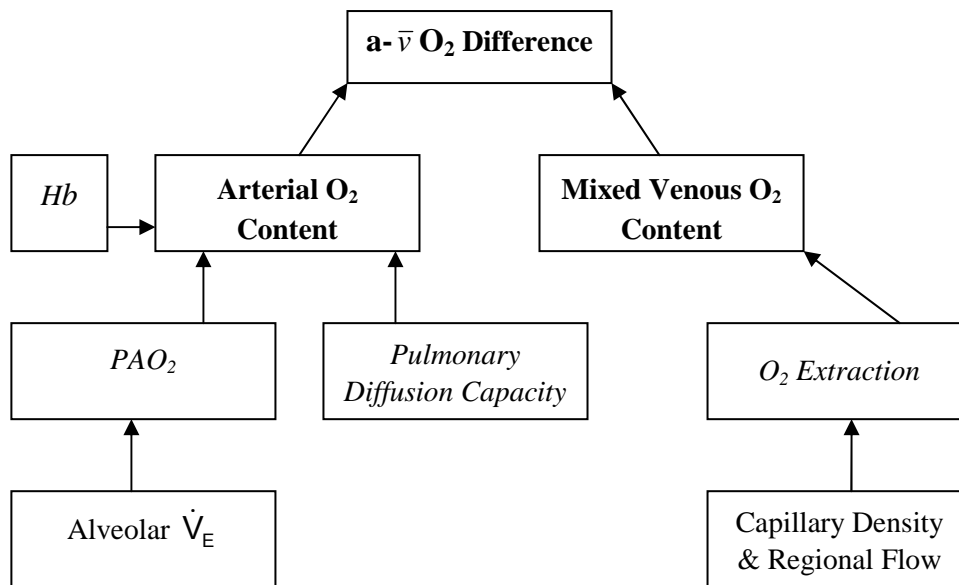


Figure 8-2 Peripheral determinants of maximal oxygen uptake. $a-\bar{v}$ O₂ difference = the difference between arterial and venous oxygen; Hb = haemoglobin; \dot{V}_E = minute ventilation; PA O₂ = partial pressure of alveolar oxygen (modified from Myers and Froelicher, 1991).

The upper limit of oxygen uptake could be determined by limitations in maximal cardiac output, pulmonary gas exchange, or the ability of the working muscles to extract and use supplied oxygen. It has been traditionally believed that in the absence of pulmonary disease, peak $\dot{V}O_2$ is not limited by pulmonary gas exchange (Rowel, 1986). In healthy individuals the most important factor limiting maximal oxygen uptake is the heart's ability to deliver oxygen (Basset and Howley, 2000). In contrast to healthy individuals, patients with heart failure demonstrate many central, peripheral, and ventilatory abnormalities during exercise (Myers and Froelicher, 1991). Therefore, peak $\dot{V}O_2$ in heart failure patients may be limited by central (systolic function, pulmonary haemodynamics, diastolic function, neurohumoral mechanisms), peripheral (blood flow abnormalities, vasodilatory capacity, skeletal muscle biochemistry) and ventilatory factors (pulmonary pressure, physiological dead space, ventilation-perfusion mismatch, respiratory control, breathing pattern (Clark et al., 1996; Myers and Froelicher, 1991). A detailed literature review about exercise limitation in chronic heart failure is provided in chapter 10.

Central haemodynamic parameters measured at rest do not correlate with maximal exercise capacity represented by peak $\dot{V}O_2$ (Cohen-Solal et al., 1999). Earlier studies have shown that resting haemodynamic measurements fail to predict subsequent exercise performance (Bain et al., 1990; Cooke et al., 1998; Engler et al., 1982; Gelberg et al., 1979; Higginbotham et al., 1983; Roul et al., 1995). Left ventricular ejection fraction and cardiac output have not been shown to be good predictors of exercise capacity (Benge et al., 1980; Higginbotham et al., 1983; Franciosa et al., 1984; Lipkin and Wilson, 1986; Weber et al., 1984), with one study showing that 50% of the patients with ejection fraction of less than 30% had normal exercise capacity (Benge et al., 1980). Calculated indices of resting left ventricular function such as pre-ejection time, velocity of circumferential shortening, stroke volume index and stroke work index all fail to predict exercise capacity. Bain et al. (1990) were the first to correlate cardiac power output measured at rest with exercise capacity represented by exercise time. As with other resting haemodynamic measurements, cardiac power output was also a poor predictor of exercise capacity (Bain et al., 1990; Cooke et al., 1998).

Cohen-Solal et al. (1999) reported two main reasons to explain the poor relationship between peak $\dot{V}O_2$ and haemodynamic parameters measured at rest: 1) none of the resting measurements is able to demonstrate the reserve of cardiac pump function, which can only be evaluated during either physiological (exercise test) or pharmacological (inotropic) stimulation; 2) resting haemodynamic measurements do not account for peripheral factors (circulatory and muscular) that appear to play an important role in the limitation of exercise capacity of patients with heart failure (Cohen-Solal et al., 1999).

Peak $\dot{V}O_2$ has emerged as a powerful predictor of prognosis in patients with heart failure as it provides an indirect assessment of the cardiac functional reserve. Therefore it is not surprising that a significant positive correlation between peak $\dot{V}O_2$ and maximal exercise cardiac output has been reported by several investigators (Franciosa et al., 1984; Higginbotham et al., 1983; Metra et al., 1990; Weber et al., 1982). Similarly several studies have shown that peak $\dot{V}O_2$ and/or exercise duration

was well correlated with peak cardiac power output and functional cardiac reserve in heart failure patients (Bain et al., 1990; Cooke et al., 1998; Roul et al., 1995).

Over the years, peak $\dot{V}O_2$ has been used as a “gold” standard among other cardiopulmonary exercise measures in heart failure evaluation and prognosis. It has several key limitations in the assessment of cardiac function. In chronic heart failure, peak $\dot{V}O_2$ can be influenced by comorbidities and non-cardiac factors such as muscle conditioning, motivation for performing exercise, anaemia, abnormal reflex response, and obesity (Fleg and Lakata, 1988; Wilson et al., 1995). Additionally many years ago it was noted that the expected peak $\dot{V}O_2$ varies according to the age and sex of the individual (Becklake et al., 1965). Further, no statistical difference in survival between patients with peak $\dot{V}O_2$ levels of 10-14 ml·kg⁻¹·min⁻¹ and those with levels of 14-18 ml·kg⁻¹·min⁻¹ has been shown (Stevenson et al., 1995). Myers and colleagues (2000) carried out a large study consisting of 664 patients during a 10 year period follow-up. A multivariate analysis revealed peak $\dot{V}O_2$ to be an independent predictor of mortality above and below a range of 10-17 ml·kg⁻¹·min⁻¹, rather than at a cut-off point of 14 ml·kg⁻¹·min⁻¹. It seems that a cut-off of 14 ml·kg⁻¹·min⁻¹ is no longer viewed as appropriate for cardiac transplantation because of improved survival in patients treated with beta-blockers. It has been shown that patients on beta-blockers with a peak $\dot{V}O_2$ <14 ml·kg⁻¹·min⁻¹ have a better outcome than non-beta-blocked patients with a peak $\dot{V}O_2$ >14 ml·kg⁻¹·min⁻¹ (Zugck et al., 2002). O’Neill et al. (2005) reported that peak $\dot{V}O_2$ is a determinant of survival in patients in heart failure even in those with beta-blockade. However, because of improved survival in patients treated with beta-blockers, the cut point value of 14 ml·kg⁻¹·min⁻¹ for referral for cardiac transplantation in these patients requires reevaluation, and a lower cut-off point may be more appropriate (O’Neill et al., 2005).

Furthermore, Wilson et al. (1995) investigated the relationship of haemodynamic data (cardiac output and pulmonary wedge pressure) and peak $\dot{V}O_2$ in 64 patients with stable chronic heart failure listed for cardiac transplantation. The data showed no correlation between peak $\dot{V}O_2$ and haemodynamic data recorded at all workloads in a

3-minute Naughton protocol. A significant proportion of the patients (44%) had only mild or moderate haemodynamic dysfunction despite peak $\dot{V}O_2$ values less than the previously recommended limit for transplantation ($<14 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$). Conversely, 33% of patients with a peak $\dot{V}O_2$ greater than $14 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ had severely impaired cardiac output at peak exercise. Finally, Metra et al. (1999) recruited 219 patients with chronic heart failure to test the hypothesis that direct assessment of the haemodynamic response to exercise could improve prognosis. It would also identify those patients in whom the main cause of reduced functional capacity is related to non-cardiac factors. Among the haemodynamic parameters, peak stroke work index was found to be the strongest predictor at both one and two-year follow-ups. Although peak stroke work index was correlated to peak $\dot{V}O_2$, the latter was a weaker predictor. They noted that more than 40% of the patients with normal haemodynamic response had a peak $\dot{V}O_2$ less than $14 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. On this basis, they recommended that haemodynamic measurements during exercise be used in heart failure evaluation to avoid transplantation in patients whose exercise limitation is due more to muscle deconditioning than to pump failure. Cotter et al. (2003) argued that stroke work index demonstrates the heart's ability to produce hydraulic energy, as does cardiac power output, but expressed per heart beat.

The results from above cited studies should not be surprising as peak $\dot{V}O_2$ is only an indirect indicator of peak exercise cardiac output (Szlachic et al., 1985; Meiler et al., 1987; Weber et al., 1982) and cardiac function reserve (Cotter et al., 2003). Therefore peak $\dot{V}O_2$ must be considered with caution in interpretation of cardiac pumping function/dysfunction, particularly in patients with severe heart failure and heart transplant candidates.

8.1.1.2 Anaerobic threshold in heart failure

It is well known that at moderate and severe levels of muscular work, blood lactate concentration is increased particularly in the venous blood draining working muscle (Wasserman et al., 1999). This increase in venous lactate concentration, which indicates the onset of lactate production and a major shift to anaerobic metabolism in

working skeletal muscle was termed the anaerobic threshold (Wasserman et al., 1999). In an early report it has been suggested that anaerobic threshold represents a transition during exercise from a phase of aerobic metabolism to a phase of anaerobic metabolism (Wasserman and McIlroy, 1964). This is the point where oxygen delivery is not sufficient to meet oxygen consumption and anaerobic mechanisms are needed to supplement energy production during exercise (Reybrouck and Ghesquiere 1983; Wasserman et al., 1973).

Reduced cardiac output in heart failure is responsible for decreased perfusion of working skeletal muscle resulting in premature anaerobic metabolism (Wilson et al., 1984; Wiener et al. 1986). As cardiac output response to incremental exercise is impaired in proportion to the severity of pump dysfunction, it has been suggested that determination of the anaerobic threshold may be a useful clinical tool to grade the severity of heart failure (Matsumura et al., 1983; Weber et al., 1982). The anaerobic threshold has been used as a non-invasive index of exercise tolerance, which is independent of patient motivation, and may be more reliable than exercise duration in assessing the effect of drug therapy in chronic heart failure (Matsumura et al., 1983; Weber et al., 1982). Furthermore, peak $\dot{V}O_2$ may be underestimated in clinical practice because of reduced patient motivation as well as premature termination of exercise by the examiner. Thus the anaerobic threshold (oxygen consumption at anaerobic threshold) has been suggested as an objective parameter of cardiopulmonary exercise capacity that can be derived from submaximal exercise testing and is therefore independent of the influences described above (Wasserman et al., 1999). Moreover, Lipkin et al. (1985) showed that oxygen consumption at the anaerobic threshold was able to predict maximal oxygen consumption in chronic heart failure patients ($r=0.93$). Similarly, Myers et al. (2006) and Ingle et al. (2008) reported high relationship between peak oxygen consumption and anaerobic threshold ($r=0.76$ and 0.82).

Only one study investigated the prognostic value of anaerobic threshold in heart failure patients. Gitt et al. (2002) compared anaerobic threshold ($\dot{V}O_2$ at anaerobic threshold) and ventilatory response to exercise with peak $\dot{V}O_2$ to identify chronic heart failure patients at increased risk of death within six months after evaluation.

Cardiopulmonary exercise tests were performed in 223 consecutive patients with chronic heart failure (114 coronary artery disease, 92 dilated cardiomyopathy, 17 others). Peak $\dot{V}O_2 \leq 14 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, $\dot{V}O_2$ at an anaerobic threshold of $<11 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, and $\dot{V}_E/\dot{V}C_{O_2}$ slope of >34 were selected as threshold values for high risk of death. Results revealed that combined, $\dot{V}O_2$ at anaerobic threshold of $<11 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ and $\dot{V}_E/\dot{V}C_{O_2}$ slope >34 better identified patients at high risk for early death from chronic heart failure than did peak $\dot{V}O_2$. Gitt and associates (2002) concluded that $\dot{V}O_2$ at anaerobic threshold and ventilatory response should therefore be considered when prioritizing patients for heart transplantation.

8.1.1.3 Ventilatory efficiency in heart failure

The relationship between minute ventilation and carbon dioxide production, called ventilatory efficiency or ventilatory response to exercise ($\dot{V}_E/\dot{V}C_{O_2}$ slope) is one of the cardiopulmonary exercise test parameters that appears to have important clinical value in heart failure patients. During exercise in normal subjects, there is a linear relation between minute ventilation (\dot{V}_E) and carbon dioxide production ($\dot{V}C_{O_2}$), and the ventilatory response can be characterized by the slope of the relationship between the two (Ingle et al., 2007). In patients with chronic heart failure, the slope of this relation is increased so that for any given level of carbon dioxide production, there is greater ventilation than normal, and the $\dot{V}_E/\dot{V}C_{O_2}$ slope becomes steeper (Banning et al., 1995; Reindl et al., 1998). This steeper slope in chronic heart failure patients is associated with reduced cardiac output during exercise (Metra et al., 1992; Sullivan et al., 1988), increased pulmonary artery and capillary wedge pressures (Metra et al., 1992; Sullivan et al., 1988), increased dead space/tidal volume ratio (Metra et al., 1992; Sovijarvi et al., 1992; Sullivan et al., 1988), and augmented chemoreceptor sensitivity (Chua et al., 1996). Chua et al. (1997) argued that it is not precisely known whether the increased ventilatory response to exercise (ventilatory inefficiency) is predominantly due to reduced pulmonary perfusion and haemodynamic abnormalities causing ventilation-perfusion mismatching or to the altered control of ventilation. Myers (2005) and Arena et al. (2007) suggested that a

primary mechanism for elevated ventilatory efficiency is the impaired cardiac output response to exercise. A decrease in cardiac output affects both left- and right-sided circulation. A decline in pulmonary perfusion and carbon dioxide exchange, in the presence of normal alveolar ventilation, results in an elevated $\dot{V}_E/\dot{V}C_{O_2}$ (Myers, 2005). Furthermore, the theory of peripheral muscle receptors (metabo- or mechanoreceptors) produce an abnormal ergoreflex resulting in an abnormal $\dot{V}_E/\dot{V}C_{O_2}$ slope during exercise has been used to explain breathlessness and fatigue in chronic heart failure (Clark et al., 1996). Witte and Clark (2007) hypothesized that ventilatory inefficiency is caused by weak, structurally abnormal and inefficient skeletal muscle which during incremental exercise produces a greater relative production of metabolic products leading to an increased ergoreflex in chronic heart failure. As a result, there is increased ventilation relative to carbon dioxide production demonstrated by increased $\dot{V}_E/\dot{V}C_{O_2}$ slope and reduced CO_2 partial pressure (Witte and Clark, 2007). In summary, $\dot{V}_E/\dot{V}C_{O_2}$ depends on pulmonary haemodynamics, skeletal muscle ergoreceptor and peripheral chemoreceptor sensitivity, and heightened sympathetic activity.

Elevated $\dot{V}_E/\dot{V}C_{O_2}$ slope is inversely related to cardiac output (Reindl et al., 1998) and cardiac index at peak exercise (Franciosa et al., 1984). Because of its association with cardiac function, the prognostic value of the $\dot{V}_E/\dot{V}C_{O_2}$ slope has been demonstrated in a number of studies (Francis et al., 2000; Ingle et al., 2007; Kleber et al., 2000). Several studies reported that the $\dot{V}_E/\dot{V}C_{O_2}$ slope may also be a better predictor of outcome than peak $\dot{V}O_2$ in a heart failure population (Arena et al., 2002; Corra et al., 2002; Chua et al., 1997; Francis et al., 2000; Kleber et al., 2000). The $\dot{V}_E/\dot{V}C_{O_2}$ has bettered peak $\dot{V}O_2$ in predicting mortality (Corra et al., 2002; Chua et al., 1997; Francis et al., 2000; Kleber et al., 2000) and hospitalization (Arena et al., 2002). O'Neill et al. (2005) prospectively analyzed probably one of the largest datasets of cardiopulmonary exercise testing to date (N=2015 patients). In contrast with others, they found that the $\dot{V}_E/\dot{V}C_{O_2}$ slope did not predict survival in patients with chronic heart failure.

8.1.1.4 Circulatory power in heart failure

Measurement of cardiac output is not as straightforward as that of O_2 consumption, particularly during exercise, and therefore approximations of cardiac power output has been sought (Cotter et al., 2003; Williams et al., 2005a). Cohen-Solal et al. (2002) assessed the prognostic value of a new cardiopulmonary variable derived from an exercise test, which they believed, is a new “surrogate” variable of cardiac power output. The new variable is termed “circulatory power” and is the product of peak $\dot{V}O_2$ and peak systolic blood pressure. Cohen-Solal and associates (2002), using a multivariate analysis, demonstrated that among other cardiopulmonary variables commonly assessed (e.g. ejection fraction, heart rate, systolic arterial pressure, peak $\dot{V}O_2$, $\dot{V}C_{O_2}$, anaerobic threshold, minute ventilation, $\dot{V}_E/\dot{V}C_{O_2}$), the peak circulatory power was the best predictor of outcome in 175 chronic heart failure patients. Williams et al. (2005b) assessed the relationship between circulatory power and cardiac power output in 219 ambulatory patients with chronic heart failure. The results revealed that circulatory power, both overall and at peak exercise, has a direct and consistent relationship with cardiac power output. Williams et al. (2005a) argued circulatory power to be an adequate measure of cardiac pumping capacity when more directly measured cardiac power output is not available.

8.1.1.5 Oxygen pulse in heart failure

Oxygen pulse is the ratio of oxygen consumption to heart rate and reflects the amount of oxygen extracted by the tissue per heart beat. Oxygen pulse has often been used as an estimator for stroke volume as it represents the product of stroke volume and arterio-venous O_2 difference. It seems that peak oxygen pulse is more dependant than peak oxygen consumption on cardiac function reserve (Cohen-Solal et al., 1997). The oxygen pulse increases linearly with incremental exercise in healthy adults (Wasserman et al., 1999). At maximal or near maximal exercise the slope flattens as it is assumed that the arterio-venous mixed oxygen difference is maximal (Wasserman et al., 1999). A low, unchanging or shallow oxygen pulse suggests poor oxygen extraction of the skeletal muscles and is seen in patients who may be deconditioning or suffer from cardiovascular disease (Wasserman et al., 1999). In chronic heart

failure patients, peak oxygen pulse is reduced (Belardinelli et al., 2003). To date, only two studies assessed the prognostic value of peak oxygen pulse in heart failure patients (Cohen-Solal et al., 1997; Lavie et al., 2004). Cohen-Solal et al. (1997) reported that peak oxygen pulse had a lower prognostic value than peak oxygen consumption, whereas Lavie et al. (2004) found that peak oxygen pulse was a stronger predictor for clinical event (e.g. cardiovascular death or transplantation) than any other exercise-derived cardiopulmonary variable, including peak $\dot{V}O_2$.

8.1.2 Rationale and Purposes of the Study

Peak oxygen consumption, anaerobic threshold, ventilatory efficiency, peak circulatory power and peak oxygen pulse are strong predictors of outcome in heart failure patients. These variables have been used to assess functional status of patients, effects of intervention (e.g. surgery, drug, exercise), and risk stratification in heart failure. Very important clinical decisions (e.g. cardiac transplantation) are considered on the basis of such cardiopulmonary exercise test data. This should not be a surprise as these variables are associated with cardiac function. It should, however, be emphasized that these variables may be affected by non-cardiac factors and therefore must be considered as indirect indicators of cardiac function. On the other hand, peak cardiac power output as a direct indicator of overall cardiac function, has been shown to be a superior in prognosis of heart failure (Williams et al., 2001; Roul et al., 1995).

Several studies assessed the association between overall cardiac function, represented by peak cardiac power output, with other exercise derived variables in heart failure patients (Bain et al., 1990; Cooke et al., 1998; Roul et al., 1995; Williams et al., 2005b). No such association was investigated in patients implanted with a left ventricular assist device (LVAD) and those who had an LVAD explanted due to sufficient myocardial recovery. Peak cardiac power output and physiological cardiac reserve have not been correlated yet with anaerobic threshold, ventilatory efficiency and peak oxygen pulse in any category of heart failure patients, including those implanted and explanted with a LVAD. Therefore, the purpose of the present study was to assess the relationship between peak cardiac pumping capability (represented by peak cardiac power output and cardiac pumping reserve) and peak oxygen

consumption, anaerobic threshold, ventilatory efficiency, circulatory power and peak oxygen pulse in severe chronic heart failure patients, and to include those implanted and explanted with a LVAD.

8.1.3 Research Hypotheses

H_1 – There will be a significant positive relationship between peak cardiac power output and peak oxygen consumption, anaerobic threshold, peak circulatory power and peak oxygen pulse in severe chronic heart failure patients, and those implanted and explanted with a LVAD.

H_2 – There will be a significant negative relationship between peak cardiac power output and ventilatory efficiency in severe chronic heart failure patients, and those implanted and explanted with a LVAD.

H_3 – The strength of the relationship between peak cardiac power output and peak oxygen consumption, anaerobic threshold, peak circulatory power, ventilatory efficiency and peak oxygen pulse will be different between severe heart failure, LVAD implanted and explanted patients.

8.2 Methods

8.2.1 Patients

In total 54 male patients were included in the analysis: 20 moderate to severe heart failure (NYHA III and IV), 18 LVAD implanted, and 16 LVAD explanted patients. Patients' clinical and demographics details as well as baseline measurements are detailed in Chapter 6 of this thesis.

8.2.2 Testing Procedure

Testing procedure is detailed in Chapter 6 of this thesis, section 6.2.3.

8.2.3 Calculations and Statistical Analysis

Cardiac power output (CPO), mean arterial pressure (MAP) and ventilatory response to exercise ($\dot{V}_E/\dot{V}C_{O_2}$ slope) were calculated as previously described in this thesis (Chapter 6). Circulatory power was calculated as the product of oxygen consumption and systolic blood pressure, expressed in $\text{mmHg}\cdot\text{l}\cdot\text{min}^{-1}$ (Cohen-Solal et al., 2002). Oxygen pulse was calculated as the ratio between oxygen consumption and heart rate.

Statistical analysis for all variables except circulatory power and oxygen pulse was performed as in Chapter 6. One-way ANOVA with a Tukey's *post hoc* test was used to determine any difference in circulatory power and oxygen pulse between severe heart failure patients, LVAD implanted and explanted patients. The relationship of various parameters was assessed using Pearson's product moment coefficient of correlation. The meaningfulness of coefficient of correlation was evaluated by calculating the coefficient of determination (R^2). A p value of <0.05 was considered statistically significant.

8.3 Results

8.3.1 Resting and Peak Exercise Circulatory Power and Oxygen Pulse Values

Only circulatory power and oxygen pulse values were not determined in Chapter 6. At rest there was non-significant difference among the groups in circulatory power (heart failure patients, 41 ± 14 mmHg \cdot l \cdot min $^{-1}$; LVAD implanted and explanted patients, 36 ± 7 and 42 ± 16 mmHg \cdot l \cdot min $^{-1}$, $p > 0.05$) and oxygen pulse (heart failure patients, 5.3 ± 2.1 ml \cdot beats $^{-1}$; LVAD implanted and explanted patients, 4.7 ± 1.9 and 5.5 ± 2.0 ml \cdot beats $^{-1}$, $p > 0.05$).

Peak circulatory power was significantly lower in patients with moderate to severe heart failure compared with LVAD explanted patients (173 ± 49 vs. 334 ± 56 mmHg \cdot l \cdot min $^{-1}$, $p < 0.01$). This was also the case in LVAD implanted patients compared with LVAD explanted patients (196 ± 56 vs. 334 ± 56 mmHg \cdot l \cdot min $^{-1}$, $p < 0.01$). Peak circulatory power between moderate to severe heart failure patients and LVAD implanted patients was not significantly different ($p > 0.05$).

Peak oxygen pulse was significantly higher in LVAD explanted patients than in heart failure and LVAD implanted patients (LVAD explanted, 16 ± 2 ; LVAD implanted, 12 ± 3 ; severe heart failure, 11 ± 2 ml \cdot beats $^{-1}$, $p < 0.01$). The difference in peak oxygen pulse between moderate to severe heart failure and LVAD implanted patients was not significantly different ($p > 0.05$).

8.3.2 Relationship between Peak Cardiac Power Output and Indirect Indices of Cardiac Work Capacity

When all data were combined (n=54), peak cardiac power output was strongly correlated with peak oxygen consumption ($r=0.87$, $R^2=0.76$, $p<0.01$), anaerobic threshold ($r=0.79$, $R^2=0.62$, $p<0.01$) and circulatory power ($r=0.82$, $R^2=0.67$, $p<0.01$). Peak cardiac power output was well correlated with peak oxygen pulse ($r=0.69$, $R^2=0.48$, $p<0.01$) and exercise duration ($r=0.58$, $R^2=0.34$, $p<0.01$). Modest negative correlation was found between peak cardiac power output and $\dot{V}_E/\dot{V}C_{O_2}$ slope ($r=-0.51$, $R^2=0.26$, $p<0.01$).

Figures 8.3 to 8.8 show subgroup analysis in the relationship between peak cardiac power and peak oxygen consumption, anaerobic threshold, peak circulatory power, ventilatory efficiency, peak oxygen pulse and exercise duration in patients with severe heart failure, those implanted and explanted with a LVAD.

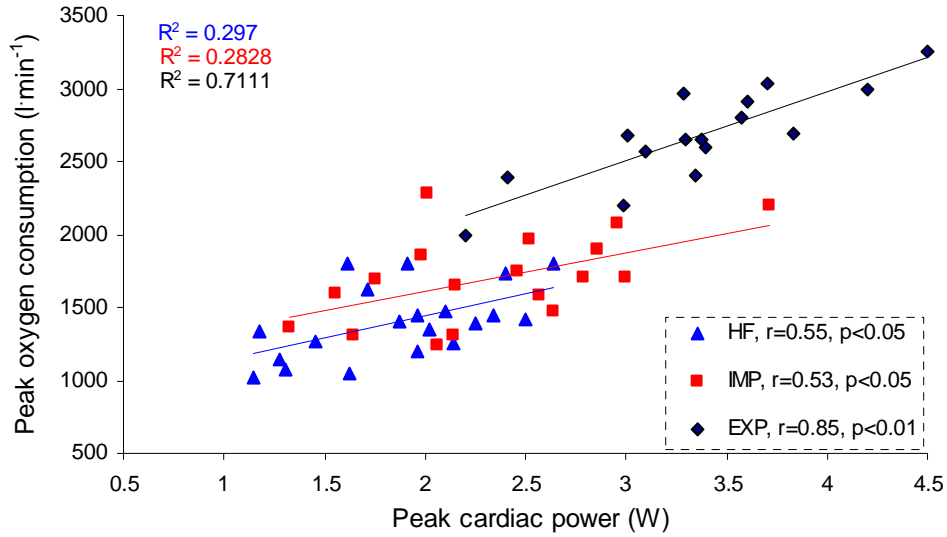


Figure 8-3 Relationship between peak cardiac power output and peak oxygen consumption in patients with moderate to severe heart failure (HF), those implanted (IMP) and explanted (EXP) with a LVAD.

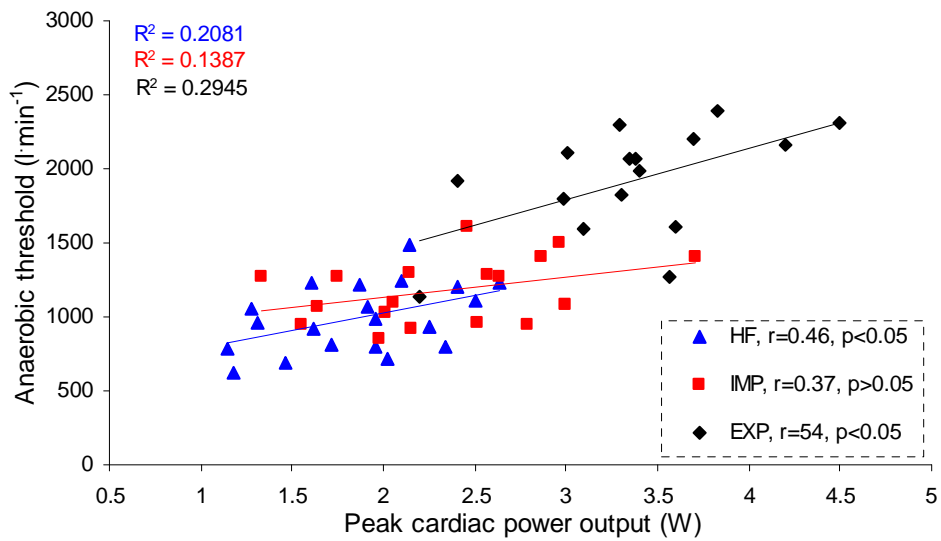


Figure 8-4 Relationship between peak cardiac power output and oxygen consumption at anaerobic threshold in patients with moderate to severe heart failure (HF), those implanted (IMP) and explanted (EXP) with a LVAD.

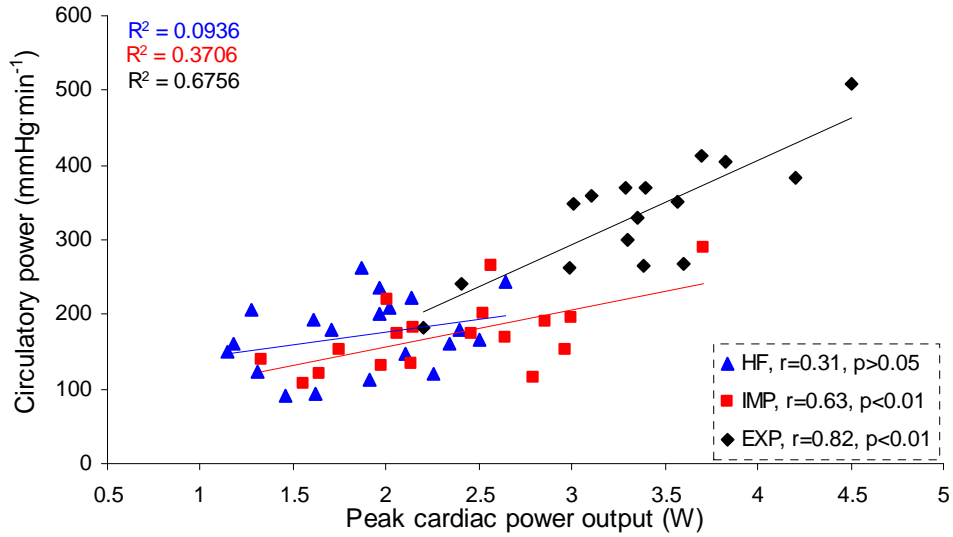


Figure 8-5 Relationship between peak cardiac power output and peak circulatory power in patients with moderate to severe heart failure (HF), those implanted (IMP) and explanted (EXP) with a LVAD.

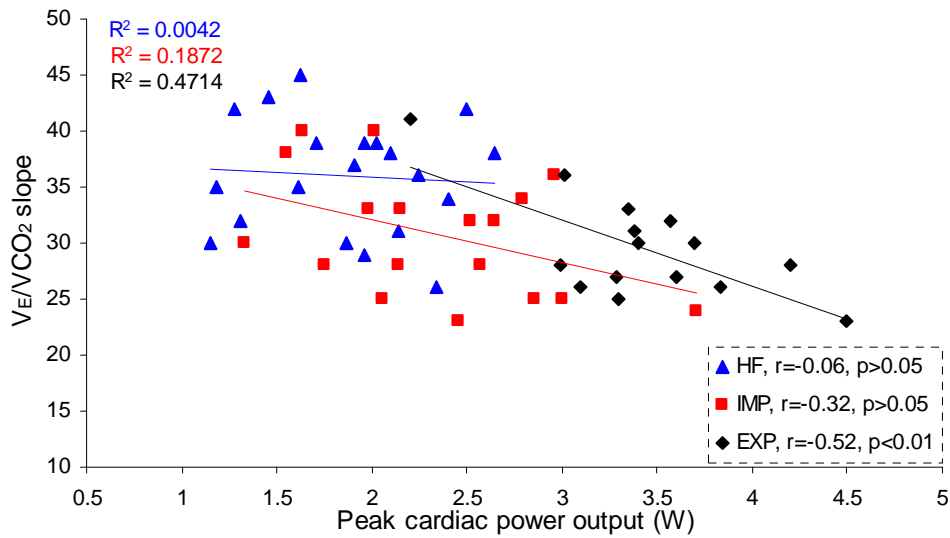


Figure 8-6 Relationship between peak cardiac power output and ventilatory efficiency slope (\dot{V}_E/\dot{V}_{CO_2} slope) in patients with moderate to severe heart failure (HF), those implanted (IMP) and explanted (EXP) with a LVAD.

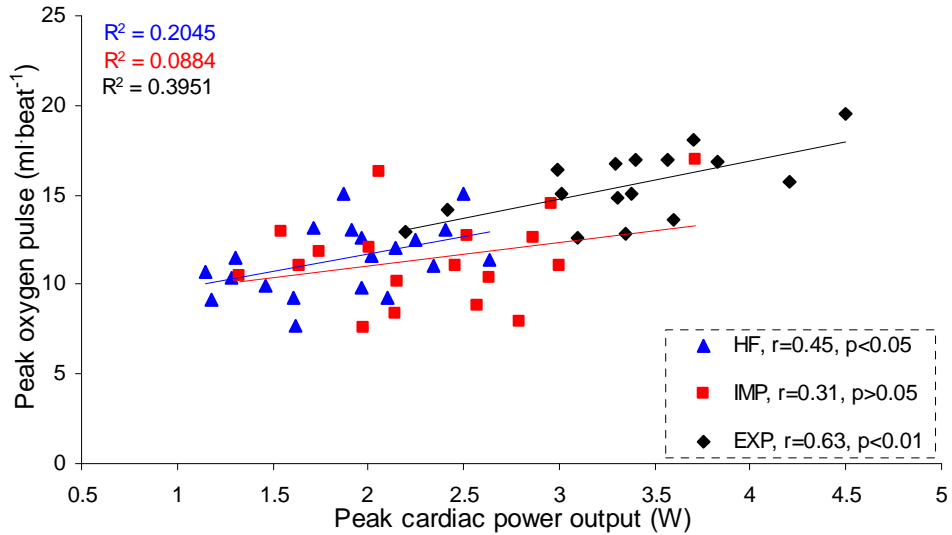


Figure 8-7 Relationship between peak cardiac power output and peak oxygen pulse in patients with moderate to severe heart failure (HF), those implanted (IMP) and explanted (EXP) with an LVAD.

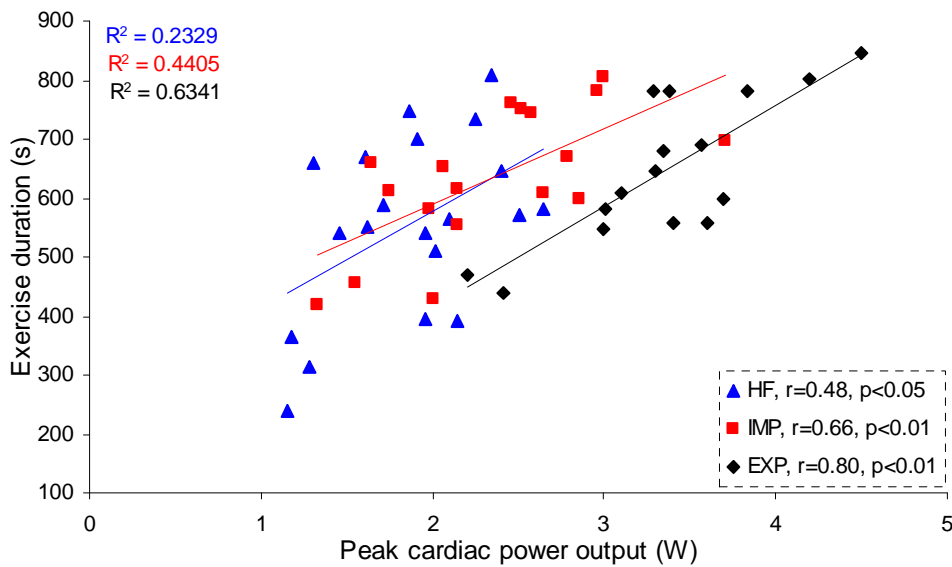


Figure 8-8 Relationship between peak cardiac power output and exercise duration in patients with moderate to severe heart failure (HF), those implanted (IMP) and explanted (EXP) with an LVAD.

8.3.3 Relationship between Peak Cardiac Power Output and Central Haemodynamic Measures

When all data were combined (n=54), peak cardiac power output was strongly correlated with peak cardiac output ($r=0.93$, $R^2=0.86$, $p<0.01$) and peak cardiac index ($r=0.81$, $R^2=0.66$, $p<0.01$). Peak cardiac power output was well correlated with peak heart rate ($r=0.68$, $R^2=0.46$, $p<0.01$) and peak stroke volume ($r=0.69$, $R^2=0.48$, $p<0.01$). There was a weak non-significant relationship between peak cardiac power output and peak mean arterial pressure ($r=0.27$, $R^2=0.07$, $p>0.05$).

Figures 8.9 to 8.13 show subgroup analysis in the relationship between peak cardiac power and peak cardiac output, peak heart rate, peak stroke volume, peak mean arterial pressure and peak cardiac index.

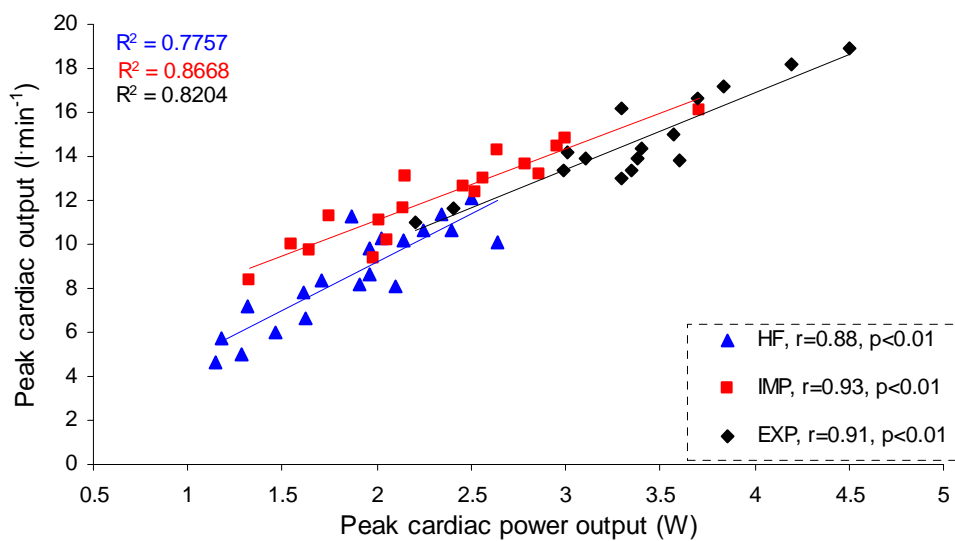


Figure 8-9 Relationship between peak cardiac power output and peak cardiac output in patients with moderate to severe heart failure (HF), those implanted (IMP) and explanted (EXP) with an LVAD.

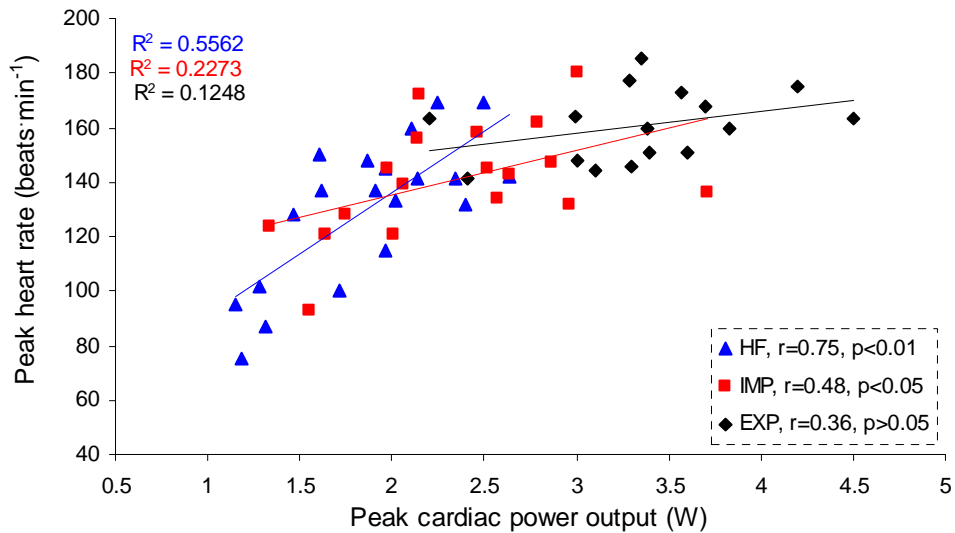


Figure 8-10 Relationship between peak cardiac power output and heart rate in patients with moderate to severe heart failure (HF), those implanted (IMP) and explanted (EXP) with an LVAD.

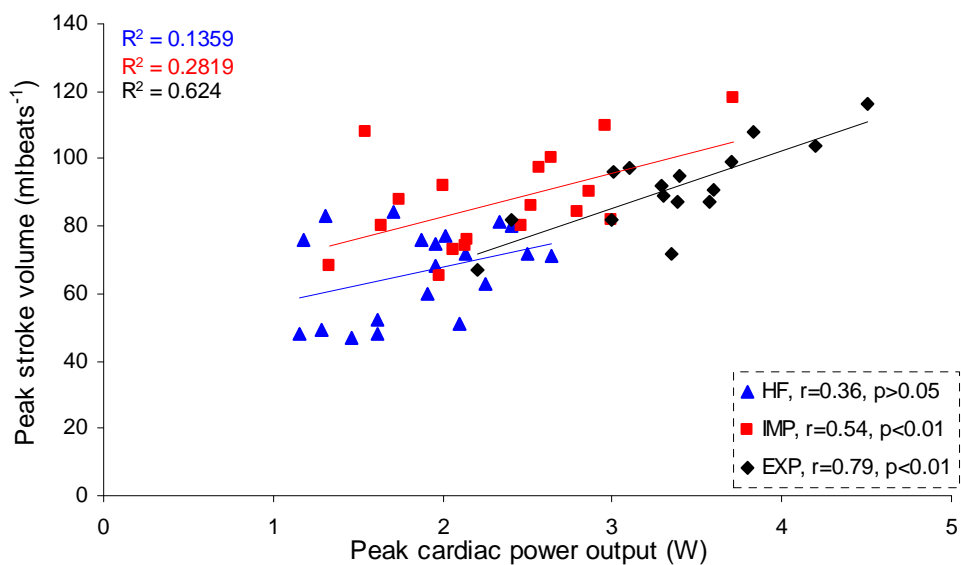


Figure 8-11 Relationship between peak cardiac power output and stroke volume in patients with moderate to severe heart failure (HF), those implanted (IMP) and explanted (EXP) with an LVAD.

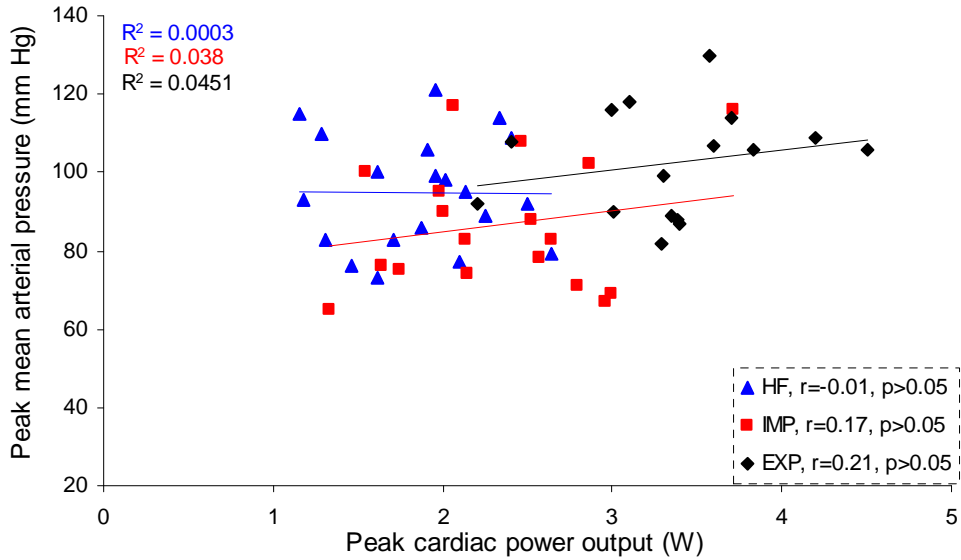


Figure 8-12 Relationship between peak cardiac power output and peak mean arterial pressure in patients with moderate to severe heart failure (HF), those implanted (IMP) and explanted (EXP) with an LVAD.

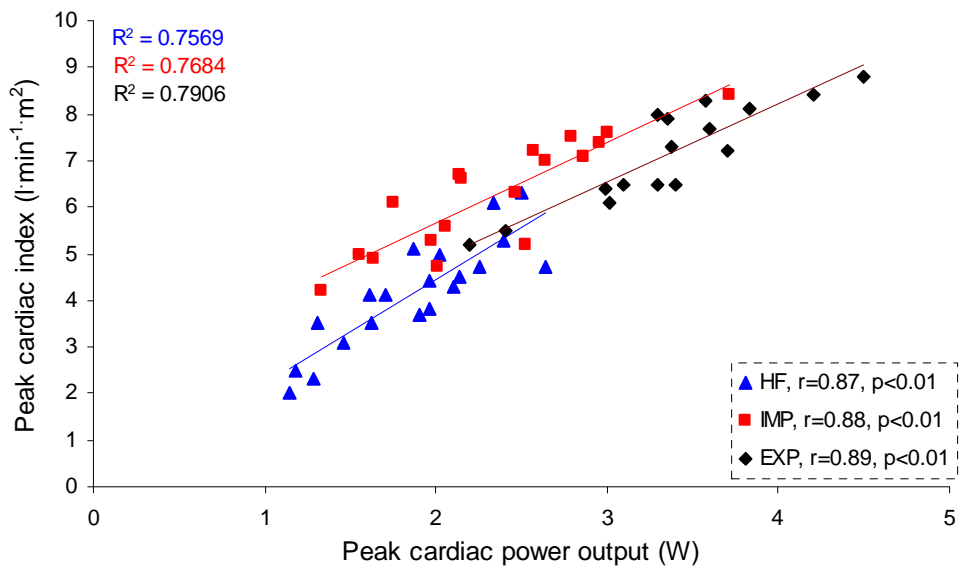


Figure 8-13 Relationship between peak cardiac power output and peak cardiac index in patients with moderate to severe heart failure (HF), those implanted (IMP) and explanted (EXP) with an LVAD.

8.3.4 Relationship between Cardiac Pumping Reserve and Indirect and Direct Indices of Cardiac Work Capacity

Resting and peak exercise values of measured variables are presented in the Results section of Chapter 6 in this thesis. Table 8.2 (below) shows the increase from resting to peak exercise value in the measured variables (physiological reserves).

The relationship between cardiac pumping reserve (the difference between peak and resting cardiac power output) and measured direct and indirect indices of cardiac work capacity are presented in Table 8.3. The strength of the relationship between cardiac pumping reserve and peak exercise values is similar to that between cardiac pumping reserve and physiological reserves (Δ values) of other variables (Table 8.3).

Table 8.2 Absolute Increase in Exercise Variables from Rest to Peak Exercise (Δ values)

	Severe Heart Failure	LVAD Implanted	LVAD Explanted
Δ CPO, W	1.07 \pm 0.40	1.48 \pm 0.55	2.43 \pm 0.54 ^{##,††}
Δ OP, ml·beats ⁻¹	6.2 \pm 2.0	6.8 \pm 2.6	10.1 \pm 2.0 ^{##,††}
Δ CP, mmHg·l·min ⁻¹	131 \pm 50	140 \pm 48	293 \pm 78 ^{##,††}
$\Delta \dot{Q}_T$, l·min ⁻¹	5.0 \pm 2.2	6.9 \pm 2.1*	9.4 \pm 2.2 ^{##,††}
Δ HR, beats·min ⁻¹	51 \pm 27	69 \pm 21	90 \pm 13 ^{##,†}
Δ SV, ml·beats ⁻¹	14.0 \pm 8.2	11.1 \pm 6.7	18.6 \pm 12.4 [#]
Δ MAP, mmHg	12 \pm 10	12 \pm 7	17 \pm 12
Δ CI, l·min·m ²	2.2 \pm 1.1	3.5 \pm 1.2	4.6 \pm 1.1 ^{##,†}
$\Delta \dot{V}O_2$, ml·min ⁻¹	987 \pm 147	1186 \pm 204**	2096 \pm 324 ^{##,††}

CPO-cardiac power output, OP-oxygen pulse, CP-circulatory power, \dot{Q}_T -cardiac output, HR-heart rate, SV-stroke volume, MAP-mean arterial pressure, CI-cardiac index, $\dot{V}O_2$ -oxygen consumption, Δ -the difference between peak and resting value.

*p<0.05, **p<0.01 IMP vs. HF

#p<0.05, ##p<0.01 EXP vs. HF

Table 8.3 Relationship between Cardiac Pumping Reserve and Measured Direct and Indirect Indices of Cardiac Pumping Capacity

	Overall Population		Severe Heart Failure		LVAD Implanted		LVAD Explanted	
	r	R ²	r	R ²	r	R ²	r	R ²
<i>Relation to Peak values</i>								
CR vs CPO	0.94**	0.88	0.85**	0.72	0.92**	0.85	0.96**	0.92
CR vs \dot{Q}_T	0.85**	0.72	0.71**	0.50	0.85**	0.72	0.88**	0.77
CR vs CI	0.80**	0.64	0.72**	0.52	0.77**	0.59	0.75**	0.56
CR vs $\dot{V}O_2$	0.78**	0.61	0.63**	0.40	0.51*	0.26	0.83**	0.69
CR vs CP	0.75**	0.56	0.19	0.04	0.62**	0.38	0.84**	0.71
CR vs AT	0.67**	0.45	0.48*	0.23	0.19	0.04	0.51*	0.26
CR vs SV	0.64**	0.41	0.28	0.08	0.47*	0.22	0.86**	0.74
CR vs HR	0.61**	0.37	0.65**	0.42	0.48*	0.23	0.19	0.04
CR vs OP	0.59**	0.35	0.28	0.08	0.21	0.04	0.65**	0.42
CR vs ET	0.55**	0.30	0.56**	0.31	0.51*	0.26	0.65**	0.42
CR vs $\dot{V}_E/\dot{V}C_{2 \text{ slope}}$	0.40**	0.16	0.01	0.00	-0.09	0.00	-0.53*	0.28
CR vs MAP	0.29**	0.08	-0.04	0.00	0.23	0.05	0.27	0.07
<i>Relation to Δ Values</i>								
CR vs $\Delta\dot{Q}_T$	0.87**	0.76	0.73**	0.53	0.88**	0.77	0.90**	0.81
CR vs Δ CI	0.83**	0.69	0.70**	0.49	0.79**	0.62	0.77**	0.59
CR vs $\Delta\dot{V}O_2$	0.79**	0.62	0.64**	0.41	0.52*	0.27	0.84**	0.71
CR vs Δ CP	0.76**	0.58	0.21	0.04	0.63**	0.40	0.86**	0.74
CR vs Δ HR	0.62**	0.38	0.68**	0.46	0.50*	0.25	0.21	0.04
CR vs Δ OP	0.59**	0.35	0.30	0.16	0.23	0.05	0.67**	0.45
CR vs Δ SV	0.59**	0.35	0.29	0.08	0.49*	0.24	0.87**	0.76
CR vs Δ MAP	0.24	0.06	-0.06	0.00	0.24	0.06	0.28	0.08

CR-cardiac pumping reserve, CPO-cardiac power output, \dot{Q}_T -cardiac output, CI-cardiac index, $\dot{V}O_2$ -oxygen consumption, CP-circulatory power, AT-anaerobic threshold, SV-stroke volume, HR-heart rate, OP-oxygen pulse, ET-exercise time, $\dot{V}_E/\dot{V}C_{2 \text{ slope}}$ -ventilatory efficiency, MAP-mean arterial pressure, Δ -the difference between \dot{O}_{peak} and resting value.

8.3.5 Comparison of the Relationships between Patients and Healthy Adults

Table 8.4 summarizes the relationships between cardiac power output and exercise-derived variables in moderate to severe heart failure patients, LVAD implanted and explanted patients and healthy adults.

Table 8.4 Summary of the Relationships between Peak Cardiac Power Output and Exercise-Derived Variables in Patients (current Chapter) and Healthy Adults (Chapter 5)

	Severe Heart Failure (n=20)		LVAD Implanted (n=18)		LVAD Explanted (n=16)		Healthy Adults (n=37)	
	r	R ²	r	R ²	r	R ²	r	R ²
<i>Indirect Indices</i>								
CPO vs $\dot{V}O_2$	0.55*	0.30	0.53*	0.28	0.85**	0.71	0.77**	0.59
CPO vs AT	0.46*	0.21	0.37	0.14	0.54*	0.29	0.47**	0.23
CPO vs CP	0.31	0.09	0.63**	0.37	0.82**	0.68	0.67**	0.45
CPO vs OP	0.45*	0.20	0.31	0.09	0.63**	0.40	0.57**	0.32
CPO vs $\dot{V}_E/\dot{V}C_{2 \text{ slope}}$	-0.06	0.00	-0.08	0.19	-0.52**	0.47	-	-
CPO vs ET	0.48*	0.23	0.66**	0.44	0.80**	0.63	0.66**	0.44
<i>Central Haemodynamics</i>								
CPO vs \dot{Q}_T	0.88**	0.78	0.93**	0.87	0.91**	0.82	0.95**	0.90
CPO vs CI	0.87**	0.76	0.88**	0.77	0.89**	0.79	0.76**	0.58
CPO vs HR	0.75**	0.55	0.48*	0.23	0.36	0.12	0.35	0.12
CPO vs SV	0.36	0.14	0.54**	0.28	0.79**	0.62	0.94**	0.88
CPO vs MAP	0.01	0.00	0.17	0.04	0.21	0.05	0.23	0.05

CPO-cardiac power output, $\dot{V}O_2$ -oxygen consumption, AT-anaerobic threshold, CP-circulatory power, OP-oxygen pulse, $\dot{V}_E/\dot{V}C_{2 \text{ slope}}$ -ventilatory efficiency, ET-exercise time, \dot{Q}_T -cardiac output, CI-cardiac index, HR-heart rate, SV-stroke volume, MAP-mean arterial pressure.

*p<0.05, **p<0.01

8.4 Discussion

The present study examined the relationship between peak cardiac power output and indirect indexes of cardiac pumping capacity, which have also been shown to be strong predictors of prognosis (e.g. peak oxygen consumption, anaerobic threshold, peak circulatory power, ventilatory efficiency, peak oxygen pulse), in patients with moderate to severe heart failure, and those implanted and explanted with a LVAD. When all data were combined, the results not only showed that peak cardiac power output was strongly correlated to peak oxygen consumption, anaerobic threshold and circulatory power, but also was well correlated with peak oxygen pulse when data from all patients were combined together. Subgroup analysis, however, revealed that the strength of the above relationships is reduced particularly in patients with severe heart failure and those implanted with a LVAD.

8.4.1 Association between Peak Cardiac Power Output and Indirect Indices of Cardiac Pumping Capacity

The finding of the present study that overall peak cardiac power output is strongly correlated to peak oxygen consumption ($r=0.87$) in heart failure patients is in agreement with previous studies (Cooke et al., 1998; Roul et al., 1995). Cooke et al. (1998) showed that in 70 subjects with a wide range of cardiac function, from heart failure patients to athletes, peak cardiac power output was highly related to peak oxygen consumption ($r=0.87$). Cooke and associates also demonstrated good relationship between peak cardiac power output and exercise duration, similar to that found in the present study ($r=0.62$ vs. 0.58). In 52 heart failure patients (NYHA II and III), Roul and colleagues (1995) found the coefficient of correlation of 0.84 between peak cardiac power output and peak oxygen consumption. Bain et al. (1990) determined the relationship between cardiac power output and exercise duration in 41 patients with moderately severe to severe chronic heart failure. Maximum cardiac power output and the ability to increase cardiac power output from resting to peak exercise value (cardiac pumping reserve or physiological cardiac reserve) were highly correlated with exercise duration ($r=0.79$ and 0.80). These three studies (Bain et al., 1990; Cooke et al., 1998; Roul et al., 1995), however, have shown that resting cardiac power output is generally slightly or modestly correlated to maximal aerobic capacity,

suggesting that it is a poor predictor of cardiovascular functional potential together with other resting central hemodynamic measures. Williams et al. (2005b) were the first to evaluate the relationship between cardiac power output and its proposed “surrogate” – circulatory power. In 219 ambulatory patients with chronic heart failure, circulatory power was found to have a strong positive relation with cardiac power output, overall $r=0.93$ and at peak exercise $r=0.84$. This finding at peak exercise is consistent with the present study ($r=0.84$).

Finding of the present study that ventilatory efficiency slope is inversely related ($r=-0.51$) to cardiac function (cardiac power output) is in agreement with Myers et al. (2007) who reported similar relationship between cardiac output and $\dot{V}_E/\dot{V}C_{20}$ slope ($r=-0.47$). Additionally, the present study suggests for the first time that, when data from all patients were combined ($n=54$), peak cardiac power output was well correlated with oxygen consumption at anaerobic threshold and peak oxygen pulse. Moreover, anaerobic threshold and oxygen pulse explain 62% and 48% of the total variance in peak cardiac power output. Previous studies have shown that anaerobic threshold was highly correlated with peak oxygen consumption (Ingle et al., 2008; Lipkin et al., 1985; Myers et al., 2006).

In contrast with relationship results when all data were combined ($n=54$), subgroup analysis of patients (e.g. moderate to severe heart failure, LVAD implanted and explanted patients) revealed dramatically different strength of the relationship among variables, particularly in severe heart failure and LVAD implanted patients. Whereas in LVAD explanted patients, peak oxygen consumption explained 71% of the variance in peak cardiac power output, in moderate to severe heart failure and LVAD implanted patients peak oxygen consumption explained only 30 and 28% of the variance. The finding of the current study that peak cardiac power output was not strongly correlated to other indirect indices of cardiac work capacity (e.g. peak oxygen consumption) in moderate to heart failure and LVAD implanted patients is not surprising as other authors have demonstrated no relationship between peak oxygen consumption and haemodynamic data. That peak oxygen consumption does not reflect the severity of cardiac dysfunction has been reported by Wilson et al. (1995). In 64 potential heart transplant candidates they investigated whether peak oxygen

consumption was primarily determined by the haemodynamic response to exercise. Results revealed that there was no significant correlation between peak oxygen consumption and cardiac index or pulmonary wedge pressure, suggesting that peak oxygen consumption does not reliably reflect the severity of flow impairment. Moreover, Wilson et al. (1995) observed that 18 (28%) patients with peak oxygen consumption less than $14 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ (considered to reflect severe haemodynamic dysfunction) had a normal cardiac response to exercise, whereas seven (11%) patients with severe haemodynamic dysfunction had a peak oxygen consumption level of more than $14 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. Dissociation between peak oxygen consumption and the degree of cardiac dysfunction in patients with chronic heart failure has also been reported by Myers et al. (2006).

None of the prior studies have evaluated the relationship between peak cardiac power output and peak oxygen consumption in patients implanted with a LVAD and those to whom LVAD has been removed due to sufficient myocardial recovery. It seems that peak oxygen consumption and its derived variables (e.g. circulatory power) do not reflect cardiac pumping capability in LVAD implanted and severe heart failure as strong as in LVAD explanted patients. Moreover, in LVAD explanted patients these relationships seem to be similar to that previously observed in larger number of subjects, ranging from healthy adults to patients in NYHA class I-IV (Cooke et al., 1998; Roul et al., 1995; Williams et al., 2005b; Chapter 5 of this thesis). In LVAD implanted patients, the device itself contributes significantly to total cardiac output, particularly at peak exercise. Peak oxygen consumption may be influenced by a number of non-cardiac factors (e.g. muscle conditioning), as previously mentioned. This possibly may indicate the inability of working muscle to extract oxygen, particularly in LVAD implanted patients with optimal device support. Therefore modest relationship between peak cardiac power output and peak oxygen consumption found in LVAD implanted and severe heart failure patients in the present study should not be surprising. Similarly, variables which involve oxygen consumption in the calculation (e.g. circulatory power, oxygen pulse) should be considered with caution in the interpretation of cardiac work capacity. Interestingly, in LVAD implanted patients, peak circulatory power seems to reflect cardiac pumping capacity better than any other assessed variable, including peak oxygen consumption.

Additionally, ventilatory efficiency and anaerobic threshold does not strongly reflect cardiac pumping capability in moderate to severe heart failure and LVAD implanted patients. Finally, exercise duration correlated moderately in severe heart failure patients, whereas in LVAD implanted and explanted patients this correlation was higher ($r=0.66$ and 0.80). When data from all patients were combined ($n=54$) the relationship between exercise duration and peak cardiac power output was only modest ($r=0.58$). The lower overall association between exercise duration and peak cardiac power output may be explained by the fact that LVAD explanted patients performed the Bruce protocol compared with LVAD implanted and those with severe heart failure patients who performed modified Bruce protocol (as described in Chapter 6 of this thesis). Practically, this means that for the same duration of exercise, the intensity of exercise and expected cardiac power output were higher during the Bruce protocol compared with the modified Bruce protocol.

Results from the present study suggest that exercise-derived prognostic indicators in heart failure (e.g. peak oxygen consumption, peak circulatory power, ventilatory efficiency and peak oxygen pulse) present a poor reflection of cardiac power output in patients with moderate to severe heart failure. In contrast with other measured variables, peak circulatory power seems to be a good predictor of cardiac pumping capacity in patients implanted with a LVAD. In LVAD explanted patients, however, the relationship between direct and indirect indices of cardiac work capacity is stronger than that in severe heart failure and LVAD implanted patients. Moreover, in LVAD explanted patients assessed relationships are comparable to those found in healthy subjects (Table 8.4).

8.4.2 Association between Peak Cardiac Power Output and Central Haemodynamic Measures

Findings of the present study suggest that central haemodynamic measures, particularly peak cardiac output and peak cardiac index, do reflect peak cardiac power output better than any of the indirect indexes discussed above in patients with moderate to severe heart failure and those implanted and explanted with a LVAD. This is supported by a strong relationship between the two variables and peak cardiac power output (Table 8.4). Roul et al. (1995) also reported a strong relationship

between peak cardiac power output and peak cardiac index ($r=0.94$).

Although cardiac power output is calculated as the product of cardiac output and mean arterial pressure, not many studies assessed the relationship between peak cardiac power output and other central haemodynamic measures. As previously mentioned, most of the studies on the topic of cardiac power output investigated the relationship between cardiac power output and measures of exercise and functional capacity such as exercise duration and peak oxygen consumption (Bain et al., 1990; Cooke et al., 1998; Roul et al., 1995). It is, however, no less important to investigate which component of cardiac power output (mean arterial pressure or cardiac output) and cardiac output (heart rate or stroke volume) explain most of the variance in cardiac power output. Additionally, the question whether the strength of the relationship between these variables is similar in different categories of subjects (healthy adults, moderate to severe heart failure patients, LVAD implanted and explanted patients) remained unanswered until now.

Results from the current but also from the Chapter 5 clearly suggest that most of the variance in cardiac power output is explained by cardiac output not by mean arterial pressure. In moderate to severe heart failure, LVAD implanted and explanted patients, as well as in healthy adults, cardiac output explains 78%, 87%, 82% and 90% of the variance in peak cardiac power output, respectively (Table 8.4). Further analysis revealed that stroke volume explains most of the variance in peak cardiac power output in healthy subjects (88%) and LVAD explanted patients (62%) whereas in severe heart failure and LVAD implanted patients only 14% and 28% respectively. In contrast, in moderate to severe heart failure and LVAD implanted patients, heart rate explains 55% and 23% of the variance in peak cardiac power output, whereas in LVAD explanted patients and healthy subjects, heart rate explains only 12%.

It has been suggested that oxygen pulse may be used as an estimator of stroke volume (Wasserman et al., 1999). Data from the present study indicate that an estimate of stroke volume by the use of oxygen pulse may not adequately reflect cardiac pumping capacity in severe heart failure and LVAD implanted patients, but may do so in LVAD explanted patients and healthy subjects. This supposition is directly supported by a stronger relationship between peak oxygen pulse and peak cardiac power output

in LVAD explanted patients and healthy subjects than in moderate to severe heart failure and LVAD implanted patients.

The other component of cardiac power output, mean arterial pressure, was not significantly correlated to peak cardiac power output in any of the subgroups (Table 8.4). Although, cardiac output itself is an excellent indicator of cardiac pumping capacity, the measurement of blood pressure should not be ignored from the following reasons: 1) in normal healthy subjects, measurement of cardiac output only may overestimate overall cardiac function. This is because pressure generation increases with ageing in healthy adults and is not allowed for when measuring only flow-generating capacity of the heart (Chantler et al., 2006; Goldspink, 2005); 2) in patients with heart failure, measurement of cardiac output alone underestimates overall cardiac function, because both the flow and pressure generating capacities of the heart decline in this patients. However, from the current results it is reasonable to suggest that whenever difficulties in measuring blood pressure exist (e.g. staff shortage) it is better to measure cardiac output alone than any other indirect or direct index of cardiac pumping capacity. Finally, the present study further provides evidence that measurement of central haemodynamics should be measured prior to all other exercise-derived variables in heart failure (Chomsky et al., 1996; Lang et al., 2007; Metra et al., 1999; Williams et al., 2001; Williams et al., 2005; Wilson et al., 1995). Although, the inclusion of exercise testing is mandatory when designing any study to evaluate treatment of chronic heart failure (Narang et al., 1996), the measurement of exercise haemodynamics is less frequently performed (Wright and Tan, 1999). With non-invasive methods available today (e.g. inert gas rebreathing, C_{2} rebreathing), and more recently bio-reactance method (Myers et al., 2007; Squara et al., 2007), measurement of cardiac output and cardiac power output responses to exercise should become a standard clinical tool for evaluation and management of chronic heart failure, including those implanted with an LVAD.

8.4.3 Relationship between Cardiac Pumping Reserve and Indirect and Direct Indices of Cardiac Work Capacity

Earlier Dr Tan has advocated that peak cardiac power output is a major determine of prognosis in heart failure, whereas cardiac pumping reserve is a major determinant of exercise capacity in heart failure (Tan, 1986; Tan et al., 1991). A number of later studies have also demonstrated that peak cardiac power output is an excellent indicator of prognosis in heart failure (Roul et al., 1995; Williams et al., 2001). Nonetheless, cardiac pumping reserve, which is an increase in cardiac power output from resting to maximum value, has also been shown to be of significant prognostic value during pharmacological stress in ambulatory chronic heart failure patients and patients with cardiogenic shock (Tan, 1986; Tan and Littler, 1990; Marmor et al., 1997), but also during cardiopulmonary treadmill exercise testing in chronic heart failure patients (Williams et al., 2005b).

Findings by Bain et al. (1990) suggest that the magnitude of the augmentation of cardiac power output on exercise (cardiac pumping reserve) shows good correlation with exercise duration ($r=0.80$). Similarly, Cooke et al. (1998) suggested that patients who had higher measured cardiac power output and therefore greater cardiac reserve had greater aerobic exercise capacity. The present study is the first to investigate cardiac pumping reserve and its relationship to a number of direct and indirect indexes of cardiac work capacity. For the first time also the relationship between cardiac pumping reserve and other physiological reserves (increase from resting to peak exercise value) was evaluated.

As expected, cardiac pumping reserve was strongly related to peak cardiac power output, peak cardiac output and peak cardiac index (Table 8.3). Cardiac pumping reserve was also well associated with peak oxygen consumption and peak circulatory power when all data were combined together. However, subgroup analysis revealed that these relationships were only strong in LVAD explanted patients. Similarly, peak stroke volume, peak oxygen pulse and exercise duration were stronger related to cardiac pumping reserve in LVAD explanted than in moderate to severe heart failure or LVAD implanted patients. Therefore, an estimation of the heart's ability to increase cardiac power output on exercise from indirect indexes of cardiac work

capacity may be acceptable in LVAD explanted, but not in severe heart failure and LVAD implanted patients.

Finally, the present study indicates that strength of the relationship between cardiac pumping reserve and other assessed physiological reserves (cardiac output reserve, cardiac index reserve, oxygen consumption reserve, circulatory power reserve, heart rate reserve, oxygen pulse reserve, stroke volume reserve, and mean arterial pressure reserve) is very similar to that between cardiac pumping reserve and peak values of the same variables (Table 8.3). This finding suggests that calculated physiological reserves of exercise-derived indexes of cardiac work capacity do not reflect better cardiac pumping reserve than their peak values.

8.4.4 Study Limitations

The study sample size was relatively small, particularly within each subgroup of patients. However in mitigation, this study requested every available patient who was referred to a major national centre for heart transplantation and/or LVAD utilisation over a period 22 months. The study was limited to men and it remains an issue whether the investigated relationships would be similar in women.

8.5 Clinical Implications and Conclusions

Peak oxygen consumption has been used over the years as an indirect estimate of cardiac pumping capacity and is an important indicator of prognosis in heart failure patients. In addition to peak oxygen consumption, the measured of anaerobic threshold, circulatory power, oxygen pulse, ventilatory efficiency slope, are also consistently reported in heart failure patients as surrogates of cardiac function/dysfunction.

The present study clearly suggests that these indirect markers of cardiac work capacity do not reflect peak cardiac power output in the same way in specific subgroups of heart failure patients. Among other assessed indirect indicators of cardiac work capacity, peak oxygen consumption and peak circulatory power were the only variables which were able explain most of the variance in peak cardiac power

output in LVAD explanted patients but not in moderate to severe heart failure and LVAD implanted patients. In contrast, central haemodynamics measurements such as peak cardiac output and peak cardiac index explained most of the variance in cardiac power output not only in LVAD explanted, but also in moderate to severe heart failure and LVAD implanted patients. Therefore, is it important to assess maximal cardiac pumping capability directly measuring peak cardiac power output (or cardiac output) rather than using other surrogates of cardiac pumping function, particularly in moderate to severe heart failure patients and those implanted with a LVAD.

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CHAPTER 9: REPRODUCIBILITY OF CARDIAC POWER OUTPUT AND SELECTED CARDIO-RESPIRATORY EXERCISE TEST VARIABLES IN PATIENTS WITH STABLE CHRONIC HEART FAILURE

Abstract

Introduction: The reproducibility of cardiac power output has been less frequently reported compared with commonly measured cardiopulmonary exercise test variables. The purpose of the present study was to assess the reproducibility of cardiac power output and other more commonly reported cardiopulmonary exercise test variables in patients with stable chronic heart failure. **Methods:** Metabolic, ventilatory, and non-invasive central haemodynamic measurements at rest and at peak exercise of the modified Bruce protocol have been performed in 14 patients with stable chronic heart failure. The same procedure was repeated seven days later in order to assess reproducibility of cardiac power output (CPO), cardiac output (\dot{Q}_T), heart rate (HR), mean arterial blood pressure (MAP), oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}C_2$), minute ventilation (\dot{V}_E), anaerobic threshold (AT) and respiratory exchange ratio (RER). **Results:** Measured at rest, central haemodynamic variables had a lower coefficient of variation (CV) (ranging from 3.4% for \dot{Q}_T and 5.6% for HR) compared with metabolic and ventilatory measurements (ranging from 8.2% for RER and 14.2 for absolute values of $\dot{V}O_2$). The CV of AT, $\dot{V}O_2$, $\dot{V}C_2$ and RER measured at peak exercise ranged from 3.8% (for AT) to 6.4% (for relative $\dot{V}O_2$), with minute ventilation having CV of 11.1%. Measured at peak exercise CPO, \dot{Q}_T , MAP and HR had CVs of 4.1, 2.2, 6.8 and 4.4%, respectively. **Conclusion:** Cardiac power output measured at rest and at peak exercise has a high degree of reproducibility. Cardiac power output should be assessed as priority compared with other cardiopulmonary exercise test variables in patients with heart failure due to its good reproducibility and the capacity to demonstrate the degree of cardiac dysfunction better than any other currently available measure.

9.1 Introduction

Repeated measurements obtained during cardiopulmonary exercise tests have generally shown good reliability and reproducibility in healthy children (Figuroa-Colon et al., 2000) and adults (Astrand and Rodahl, 1986; Skinner et al., 1999), and in highly trained athletes (Astrand and Rodahl, 1986; Weltman et al., 1990; Weston et al., 2001). A basic requirement for the clinical application of exercise-derived cardiopulmonary variables in follow-up investigations is high reproducibility. Particularly in patients with chronic heart failure, high reproducibility is of great importance because even small changes in cardiopulmonary data due to treatment or disease progression may be detected (Meyer et al., 1997).

Several studies have assessed reproducibility of cardiopulmonary exercise variables in patients with chronic heart failure (Bensihmon et al., 2008; Elborn et al., 1990; Marburger et al., 1998; Meyer et al., 1997; Russell et al., 1998). Those studies have focused on commonly measured cardiopulmonary exercise test variables such as peak oxygen consumption, carbon dioxide production, ventilation, anaerobic threshold, oxygen pulse, heart rate, arterial blood pressure, respiratory exchange ratio and exercise time. Compared with these physiological parameters, reproducibility of cardiac power output and cardiac output, however, has been less frequently reported.

9.1.1 *Rationale and Purposes of the Study*

Evidence available so far suggests that there is only one study which assessed reproducibility of cardiac power output and cardiac output in 12 heart failure patients (NYHA II-III) (Cooke et al., 1998). Cooke et al. (1998) performed an exercise test in two stages with a 40 minutes resting period between the two stages. The first stage was an incremental test to determine the maximum oxygen consumption and the anaerobic threshold, and a second maximum workload stage was used to make cardiac output measurements (the same methodology as used in Chapter 5 of this thesis).

It seems, however, that reproducibility of cardiac output and cardiac power output, measured non-invasively during an incremental exercise test, have not been evaluated yet. Therefore, the purpose of the present study was to examine the reproducibility of

cardiac power output and selected cardiopulmonary variables at rest and at peak exercise in patients with stable chronic heart failure.

9.1.2 Research Hypothesis

H_1 – There will be good reproducibility of cardiac power output and selected cardiopulmonary exercise testing variables in patients with stable chronic heart failure.

9.2 Methods

9.2.1 Patients

The study group consisted of 14 stable chronic heart failure patients with New York Heart Association class I-II. The patients' demographic and clinical characteristics are presented in table 9.1. All patients were symptomatically stable and on the same dose of optimal drug therapy for the preceding two months, including an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker and a β blocker unless a contraindication was present.

The present study was a part of the clinical trial titled “Cardiac power output, heart rate variability and heart rate recovery in response to exercise training in heart failure patients” which was approved by the Hounslow and Hillingdon NHS Research Ethics Committee. An informed written consent form was obtained from each patient prior the investigation.

9.2.2 Study Design

In order to assess reproducibility of cardiac power output and selected cardiopulmonary exercise variables, patients visited the Cardiac Rehabilitation Department of Hillingdon Hospital twice within one week of each other. Measurements were performed at the same time of day under identical conditions and medication. Patients who were not familiar with the use of treadmill were asked to visit laboratory a few days prior the first test to complete a brief familiarisation

protocol.

Table 9.1 Study Patients' Demographic and Clinical Characteristics (N=14)

Age (yrs)	62±11
Men/Women	12/2
Weight (kg)	79.6±17
Height (cm)	172±10
BMI (kg/m ²)	26.6±4.0
BSA (m ²)	1.92±0.25
Cause: ischaemic/nonischaemic	9/5
LVEF (%)	29±12
NYHA I/II	8/6

BMI-body mass index, BSA-body surface area, LVEF-left ventricular ejection fraction, NYHA-New York Heart Association.

9.2.3 Testing Procedure

All patients were exercised at least two hours after any food or drink. They were instructed not to drink alcohol or caffeine containing beverages before the tests. The tests were performed at an ambient room temperature maintained at about 20°C. Upon the arrival in the Cardiac Rehabilitation Department of Hillingdon Hospital, the patients' weight and height were measured. ECG electrodes were attached according to the standard lead configuration for exercise testing and the ECG cables were connected. The patient then sat on a chair and following a five minutes resting period, arterial blood pressure was assessed from the brachial artery by cuff sphygmomanometry (ERKA, Kallmeyer Medizintechnik, Germany). This was followed by measurement of resting gas exchange data over five minutes (Medical Graphics Corporation, St Paul, Minnesota, USA). Following five minutes of metabolic measurements, the face mask was taken off the patient, and cardiac output was measured using the inert gas rebreathing methodology while the patient was still in a seated position (Innocor, Innovision, Denmark). Following explanation, the subject performed a rebreathing technique in the demonstration mode of the Innocor first to ensure the patient's familiarisation with rebreathing manoeuvre. After a three minute wash out period, while the patient remained in a seated position, the rebreathing test was performed and cardiac output estimated by the Innocor.

Following the cardiac output measurement, the patient was again connected to the Medical Graphics metabolic analyser via a disposable pneumotach attached to the face mask. Oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}C_{O_2}$) and minute ventilation (\dot{V}_E) were measured. The patient then performed a modified Bruce protocol. During the test, patients were verbally encouraged to perform as long as possible. Continuous breath-by-breath sampling of respiratory gases and heart rate measurements were made, while during the last 30 seconds of each exercise stage, arterial blood pressure was measured and Borg scale recordings for dyspnea and fatigue were performed (Borg, 1982). At peak exercise, cardiac output was measured using the inert gas rebreathing methodology. The Innocor respiratory valve unit with bacterial filter was inserted into the pneumotach of the Medical Graphics system and the patient was asked to breathe with the required breathing frequency and to empty the rebreathing bag with each inspiration. At the same time during the rebreathing manoeuvre, peak arterial blood pressure was measured. After completion of the rebreathing procedure, the Innocor unit was taken off immediately from the Medical Graphics pneumotach, and patients were encouraged to continue the exercise test if they were able to do so.

The exact moment to determine cardiac output measurement at peak exercise involved the following criteria: respiratory exchange ratio of 1.05 and higher, achievement of maximal oxygen consumption (the absence of a rise in $\dot{V}O_2$ with further increase in exercise intensity) and patient's subjective feeling of high intensity work as indicated on the Borg scale (>17).

Peak $\dot{V}O_2$ was defined as the average $\dot{V}O_2$ during the last minute of exercise, expressed as ml per kg of body weight per min, as well as ml per kg. Oxygen consumption at the ventilatory (anaerobic) threshold (AT) was identified by the V-slope method (Beaver, 1986) by the two researchers.

9.2.4 Statistical Analysis

All statistical analysis was carried out using SPSS version 13.0 (SPSS inc. Chicago, Illinois, USA). Prior to statistical analysis, data were checked for univariate and multivariate outliers using standard Z-distribution cut-offs and Mahalanobis distance tests respectively. Normality of distribution was assessed using a Kolmogorov-Smirnov test. To test difference in measured variables between test I and test II, t-test for paired samples was used. Statistical significance was indicated if $p < 0.05$. To assess the reproducibility of cardiac power output and selected cardiopulmonary variables, the coefficient of variation (CV) and Pearson's correlation coefficient (r) were calculated. For each variable, the coefficient of variation was defined as the (within-person standard deviation/within-person mean) \times 100%. Additionally, Bland-Altman plots were constructed to demonstrate reproducibility of cardiopulmonary exercise test variables measured at peak exercise (Bland and Altman, 1986). All data are presented as means \pm SD unless otherwise indicated.

9.3 Results

All subjects completed each exercise test without any untoward events. All exercise tests were stopped because of dyspnoea or fatigue. Nine patients stopped the first exercise test due to fatigue and five patients stopped due to dyspnoea. Two patients reported a different limiting symptom at the end of the second from the first test. At the end of the second test, seven patients stopped due to dyspnoea.

Six patients were able to continue with the exercise test after the peak cardiac power output measurement during the first test and nine patients during the second test. The time from completion of cardiac power output measurement and termination of the test averaged eight seconds (range from five to 14 seconds).

9.3.1 Reproducibility of Resting Metabolic, Ventilatory and Central Haemodynamic Variables

There were no significant changes in resting metabolic, ventilatory and central haemodynamic variables between the two tests (Tables 9.2 and 9.3). Central haemodynamic variables demonstrated lower coefficient of variation and higher coefficient of correlation compared with metabolic and ventilatory variables between the two tests, suggesting better reproducibility.

Table 9.2 Resting Metabolic and Ventilatory Variables

	Test I	Test II	<i>p</i> -value	<i>r</i>	CV (%)
$\dot{V}O_2$ (ml·min ⁻¹)	304±98	320±100	0.45	0.69	14.2
$\dot{V}O_2$ (ml·kg ⁻¹ ·min ⁻¹)	3.9±0.9	4.0±0.9	0.68	0.43	11.9
$\dot{V}C_2$ (ml·min ⁻¹)	262±87	268±94	0.66	0.83	10.3
$\dot{V}P$ (l·min ⁻¹)	12.4±4.2	12.0±4.7	0.53	0.75	14.4
RER	0.80±0.12	0.80±0.10	0.95	0.44	8.2

$\dot{V}O_2$ -oxygen consumption, $\dot{V}C_2$ -carbon dioxide production, \dot{V}_E -minute ventilation, RER-respiratory exchange ratio.

Table 9.3 Resting Haemodynamic Variables

	Test I	Test II	<i>p</i> -value	<i>r</i>	CV (%)
\dot{Q}_T (l·min ⁻¹)	4.0±1.0	3.9±0.9	0.63	0.99	3.4
HR (beats·min ⁻¹)	62±12	60±9	0.24	0.83	5.6
SBP (mm Hg)	118±11	114±10	0.13	0.55	5.3
DBP (mm Hg)	77±11	75±10	0.31	0.87	4.3
MAP (mm Hg)	94±11	91±9	0.15	0.79	4.5
CPO (W)	0.83±0.24	0.79±0.19	0.15	0.96	5.4

\dot{Q}_T -cardiac output, HR-heart rate, SBP-systolic blood pressure, DBP-diastolic blood pressure, MAP-mean arterial pressure, CPO-cardiac power output.

9.3.2 Reproducibility of Peak Exercise Metabolic and Ventilatory Variables

As listed in Table 9.4, mean exercise time, peak oxygen consumption, anaerobic threshold and minute ventilation increased significantly from test I to test II ($p < 0.05$). The coefficient of correlation was high ($r > 0.90$) and the coefficient of variation was low ($< 10\%$) between the two test for all measured variables except minute ventilation ($CV = 11.1\%$).

Table 9.4 Exercise Metabolic and Ventilatory Variables

	Test I	Test II	p-value	r	CV (%)
Exercise time (s)	684±191	745±190	0.00	0.95	7.1
$\dot{V}O_2$ ($ml \cdot min^{-1}$)	1792±827	1884±767	0.04	0.99	5.7
$\dot{V}O_2$ ($ml \cdot kg^{-1} \cdot min^{-1}$)	21.7±7.0	23.0±5.8	0.03	0.97	6.4
AT ($ml \cdot kg^{-1} \cdot min^{-1}$)	13.7±3.5	14.2±3.4	0.03	0.97	3.8
$\dot{V}C_2$ ($ml \cdot min^{-1}$)	1927±951	2031±1037	0.11	0.98	5.5
\dot{V}_E ($l \cdot min^{-1}$)	53.4±16.9	60.2±21.7	0.02	0.90	11.1
RER	1.06±0.12	1.09±0.15	0.13	0.91	4.2
Borg score	16.8±2.8	17.6±2.1	0.18	0.91	3.2

$\dot{V}O_2$ -oxygen consumption, AT-anaerobic threshold, $\dot{V}C_2$ -carbon dioxide production, \dot{V}_E -minute ventilation, RER-respiratory exchange ratio.

The Bland-Altman analysis revealed that the mean difference between the first and second test for exercise time was -61 seconds (range -196 to 29 seconds) and the limits of agreement were -183 to 61 (Figure 9.1).

The mean difference between the first and the second test for peak oxygen consumption was -92 $ml \cdot min^{-1}$ or -1.3 $ml \cdot kg \cdot min^{-1}$ (range -465 to 195 $ml \cdot min^{-1}$ or -5.4 to 2.2 $ml \cdot kg \cdot min^{-1}$) and the limits of agreement were -394 to 210 $ml \cdot min^{-1}$ or -5.3 to 2.7 $ml \cdot kg \cdot min^{-1}$. Figure 9.2 shows a Bland-Altman plot for absolute values of peak oxygen consumption.

For anaerobic threshold (Figure 9.3), the mean difference between the two tests was -0.6 $ml \cdot kg \cdot min^{-1}$ (range -2.80 to 0.60 $ml \cdot kg \cdot min^{-1}$) and the limits of agreement were -2.4

to $1.2 \text{ ml}\cdot\text{kg}\cdot\text{min}^{-1}$.

For carbon dioxide production at peak exercise (Figure 9.4), the mean difference between the two tests was $-104 \text{ ml}\cdot\text{min}^{-1}$ (range -704 to $243 \text{ ml}\cdot\text{min}^{-1}$) and the limits of agreement were -552 to $344 \text{ ml}\cdot\text{min}^{-1}$.

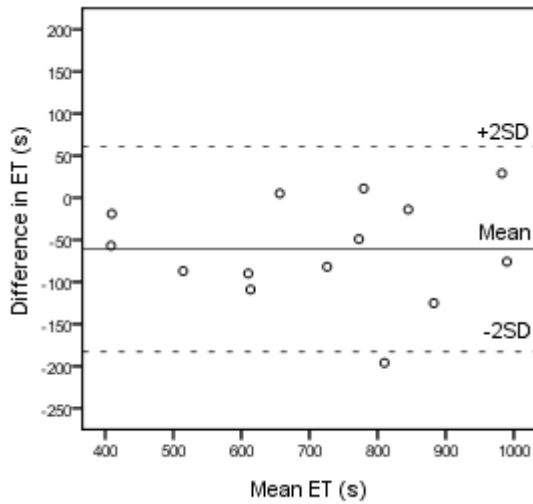


Figure 9-1 Bland-Altman plot of the differences against the means of repeated measurements of maximal exercise time (ET).

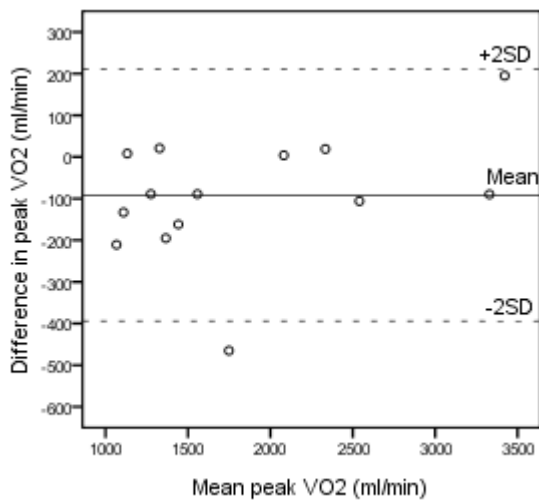


Figure 9-2 Bland-Altman plot of the differences against the means of repeated measurements of peak oxygen consumption (VO₂).

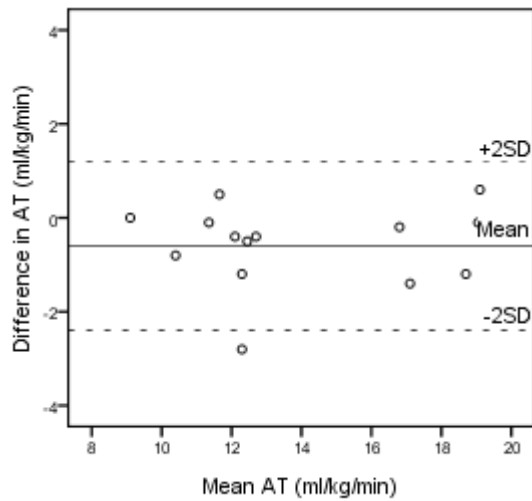


Figure 9-3 Bland-Altman plot of the differences against the means of repeated measurements of anaerobic threshold (AT).

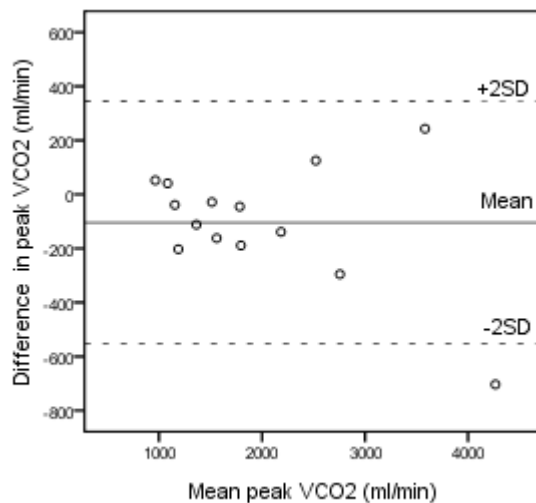


Figure 9-4 Bland-Altman plot of the differences against the means of repeated measurements of peak carbon dioxide production (VCO₂).

For peak minute ventilation and respiratory exchange ratio the mean differences between the two tests were $-6.8 \text{ l} \cdot \text{min}^{-1}$ and -0.03 (range -17.2 to $8.1 \text{ l} \cdot \text{min}^{-1}$ and -0.18 to 0.15). The limits of agreement were -19.8 to $13 \text{ l} \cdot \text{min}^{-1}$ for peak minute ventilation and -0.19 to 0.16 for peak respiratory exchange ratio.

9.3.3 Reproducibility of Peak Central Haemodynamic Variables

There was no significant difference between cardiac output, arterial blood pressures and cardiac power output at peak exercise in the two tests (Table 9.5). For all measured central haemodynamic variables there was a high coefficient of correlation ($r \geq 0.90$) and low coefficient of variation was ($< 10\%$).

Table 9.5 Peak Exercise Haemodynamic Variables

	Test I	Test II	p-value	r	CV (%)
\dot{Q}_T (l·min ⁻¹)	11.2±5.7	11.3±5.6	0.84	0.99	2.2
HR (beats·min ⁻¹)	116±31	118±26	0.42	0.96	4.4
SBP (mm Hg)	148±27	146±25	0.67	0.93	4.5
DBP (mm Hg)	74±13	78±11	0.23	0.90	7.5
MAP (mm Hg)	104±17	106±15	0.51	0.98	6.8
CPO (W)	2.68±1.53	2.69±1.52	0.63	0.96	4.1

\dot{Q}_T -cardiac output, HR-heart rate, SBP-systolic blood pressure, DBP-diastolic blood pressure, MAP-mean arterial pressure, CPO-cardiac power output.

The Bland-Altman analysis revealed that the mean difference between the first and second test for peak cardiac output was -0.02 l·min⁻¹ (range -0.30 to 0.40 l·min⁻¹) and the limits of agreement were -0.40 to 0.36 l·min⁻¹ (Figure 9.5).

The mean difference between the first and the second test for peak heart rate was -2.1 beats·min⁻¹ (range -16 to 17 beats·min⁻¹) and the limits of agreement were -11.4 to 7.2 beats·min⁻¹ (Figure 9.6).

For peak mean arterial pressure, the mean difference between the two tests was -2.3 mm Hg (range -10 to 12 mm Hg) and the limits of agreement were -7.8 to 6.1 mm Hg (Figure 9.7). Additionally, the mean difference for peak systolic and diastolic blood pressures between the two tests was 1.9 mm Hg and -4.2 mm Hg. The difference ranged from -22 to 18 mm Hg for peak systolic blood pressure, and from -10 to 8 mm Hg for diastolic blood pressure. The limits of agreement were -11.2 to 8.8 mm Hg for systolic, and -3.8 to 7.7 mm Hg for diastolic blood pressure.

For peak cardiac power output, the mean difference between the two tests was -0.02 W (range -0.21 to 0.30 W) and the limits of agreement were -0.14 to 0.10 W. (Figure 9.8).

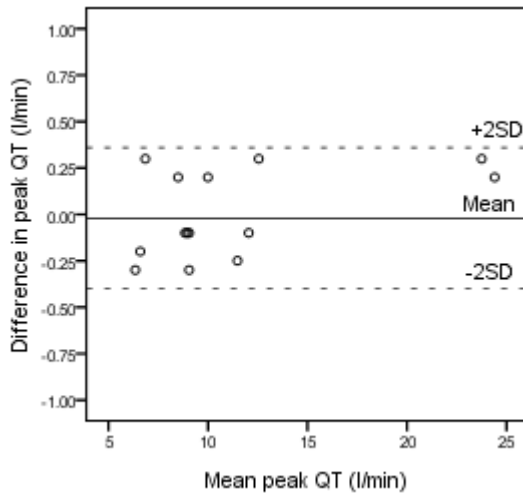


Figure 9-5 Bland-Altman plot of the differences against the means of repeated measurements of peak cardiac output (QT).

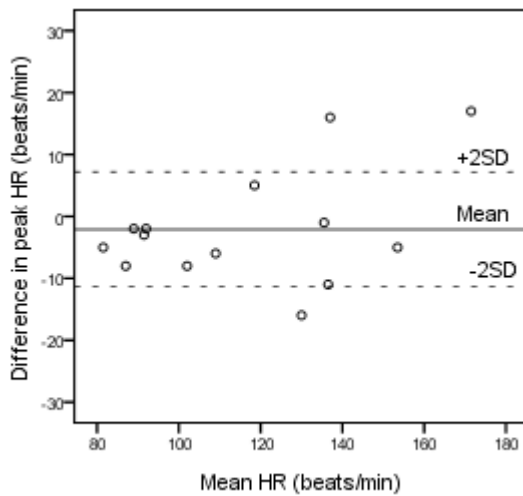


Figure 9-6 Bland-Altman plot of the differences against the means of repeated measurements of peak heart rate (HR).

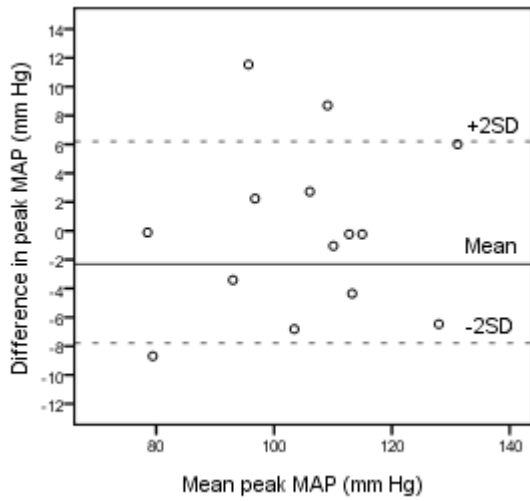


Figure 9-7 Bland-Altman plot of the differences against the means of repeated measurements of peak mean arterial pressure (MAP).

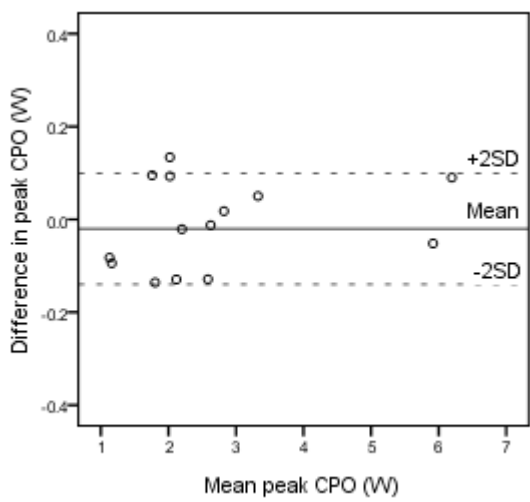


Figure 9-8 Bland-Altman plot of the differences against the means of repeated measurements of peak cardiac power output (CPO).

9.4 Discussion

The present study evaluated the reproducibility of cardiac power output and other important cardiopulmonary exercise parameters in 14 patients with chronic heart failure who underwent two tests within seven days of each other. The major findings were 1) measured at rest, central haemodynamic variables (cardiac power output, cardiac output, heart rate, arterial blood pressure) showed better reproducibility than metabolic and ventilatory variables (oxygen consumption, carbon dioxide production, minute ventilation, respiratory exchange ratio); 2) at peak exercise, central haemodynamic measurements demonstrated a high degree of reproducibility whereas maximal exercise time, peak oxygen consumption, carbon dioxide production and minute ventilation tended to increase on the second of two baseline tests.

Myers and Froelicher (1990) suggested that a common method of assuring a reproducible response to exercise is to have the patient perform two exercise tests on separate days, at the same time of the day. A test is considered “reproducible” if peak oxygen uptake is within $\pm 10\%$ on both days (Myers and Froelicher, 1990).

9.4.1 Reproducibility of Cardiac Power Output and Selected Cardio-respiratory Variables Measured at Rest

Numerous studies have evaluated reproducibility of exercise cardiopulmonary variables in chronic heart failure patients (Bensimhon et al., 2008; Cooke et al., 1998; Elborn et al., 1990; Marburger et al., 1998; Meyer et al., 1997; Russell et al., 1998). Only one study, however, reported repeated measurements of cardiopulmonary variables measured at rest (Elborn et al., 1990). This fact should not be a surprise as of today, resting metabolic and ventilatory measurements (e.g. oxygen consumption, carbon dioxide production, minute ventilation) have not been shown to have significant diagnostic and/or prognostic importance in heart failure patients as those measured during and/or at peak exercise. Elborn et al. (1990) presented the mean and SD values of resting oxygen consumption, carbon dioxide production, minute ventilation and ventilatory rate in addition to heart rate and systolic blood pressure. Similarly, as in the present study, non-significant differences were found between the repeated tests, with coefficient of variation ranging from 8% (for relative oxygen

consumption) to 28% (for carbon dioxide production).

The finding of the present study that cardiac output measured at rest by the inert gas rebreathing methodology is highly reproducible is in agreement with previous studies (Agostoni et al., 2005; Christensen et al., 2000) which also demonstrated the CV below 10% in heart failure patients. Additionally, the present study demonstrates for the first time that resting cardiac power output is highly reproducible in chronic heart failure patients with stable condition using an inert gas rebreathing methodology, having the coefficient of variation of only 5%. Although the reproducibility of blood pressure measurement using cuff manometry has been questioned (Cooke et al., 1998), the present study suggests that measurement of this variable has also a high degree of reproducibility in patients with stable chronic heart failure. This is also consistent with Elborn et al. (1990) who reported a coefficient of variation of 7% for systolic blood pressure measured at rest.

Conversely to resting metabolic and ventilatory variables, resting central haemodynamic measurements demonstrated a higher degree of reproducibility. Moreover, measurement of resting cardiac output and cardiac power output may indicate changes in haemodynamic status caused by e.g. an intervention or progress of the disease, particularly in seriously ill patients.

9.4.2 Reproducibility of Cardiac Power Output and Selected Cardio-respiratory Variables Measured at Peak Exercise

Reproducibility of cardiac power output has been previously assessed by one study only (Cooke et al., 1998). Cooke et al. (1998) repeated the treadmill exercise tests on 12 heart failure patients (NYHA class II-III) under the same conditions at least four weeks apart to investigate the reproducibility of the tests and measurements. In contrast with methodology used in the present study, Cooke et al. (1998) performed exercise test in two stages with a 40 minutes resting period between the two stages. The first stage was an incremental test to determine the maximum oxygen consumption, and a second maximum workload stage was used to make cardiac power output measurements. Similarly as in the present study, cardiac output and cardiac power output measurements were not significantly different between the two

tests. Reported coefficients of variations for cardiac output and cardiac power output were low (below 10%), but compared to the present study coefficients of variations were higher (for cardiac output 7.1% vs. 2.2%, for cardiac power output 9.1% vs. 4.1%). Furthermore, the mean difference and the limits of agreement between the two tests for cardiac output and cardiac power output measurements reported by Cooke et al. (1998) were higher than in the present study (the mean difference for cardiac output and cardiac power output were $-0.15 \text{ l}\cdot\text{min}^{-1}$ vs. $0.02 \text{ l}\cdot\text{min}^{-1}$ and -0.04 W vs. -0.02 W ; the limits of agreement for cardiac output were -2.18 to $0.98 \text{ l}\cdot\text{min}^{-1}$ vs. -0.40 to $0.36 \text{ l}\cdot\text{min}^{-1}$, and for cardiac power output -0.35 to 0.28 W vs. -0.14 to 0.10 W). Similarly to the present study, excellent reproducibility of peak heart rate measurement in heart failure patients has been reported elsewhere (Elborn et al., 1990; Marburger et al., 1998; Meyer et al., 1997). Although Cooke et al. (1998) questioned reproducibility of blood arterial pressure measurement by cuff manometry, they did not report repeated measures of blood pressure measurements, or reproducibility analysis of this variable. Elborn and associates (1990), however, reported the coefficient of variation of 5% for systolic blood pressure measured at peak exercise in chronic heart failure patients. Similarly, Meyer et al. (1997) reported that coefficients of variation for systolic and diastolic blood pressures at peak exercise in patients with severe heart failure were similar as in the present study (2.2% and 6.1%). Results from the present study indicate that coefficient of variation for blood pressure measurement is below 10% in patients with stable chronic heart failure (for mean arterial pressure 6.8%). Also the mean difference between the two tests for mean arterial blood pressure was low (2.3 mm Hg) and the limits of agreement acceptable (-7.8 to 6.1 mm Hg). Therefore, a good reproducibility of cardiac power output measured at peak exercise found in the present study is unsurprising as its both components (cardiac output and mean arterial pressure) appear to have a high degree of reproducibility.

Conversely to cardiac power output, reproducibility of exercise metabolic and ventilatory variables has been investigated by a numerous studies (Bensimhon et al., 2008; Elborn et al., 1990; Marburger et al., 1998; Meyer et al., 1997; Russell et al., 1998). Some investigators have suggested that due to great variability between repeated measurements more than one test should be performed at baseline for clinical

trial purposes. Elborn and associates (1990) performed three consecutive treadmill tests separated by two weeks on 30 patients with heart failure. Mean peak oxygen consumption improved significantly from the first to the second test (14.1 vs. 14.9 ml·kg⁻¹·min⁻¹; p<0.005) with no difference in peak oxygen consumption between the second and the third test (14.9 vs. 14.8 ml·kg⁻¹·min⁻¹, p>0.05). The average within-subject coefficient of variation for the three test was 6%. Additionally Elborn et al. (1990) reported that the first test underestimated exercise time by approximately 20%, and concluded that a single baseline test was not sufficient for measuring cardiopulmonary response to an intervention and suggested the performance of two or more tests for clinical research application.

Conversely, Russell and colleagues performed a series of five baseline maximal treadmill tests (three with gas exchange) in 81 men and women with symptomatic heart failure and found that although there was a significant improvement in exercise time between test 1 and 3 (419 vs. 470 seconds, p<0.05), there was no significant change in peak oxygen consumption (1199 vs. 1105 vs. 1123 ml·min⁻¹, p>0.05). The investigators concluded that a single baseline test was sufficient to measure peak oxygen consumption for the evaluation of therapy or assessment of the prognosis. Similarly, Marburger and associates (1998), in nine elderly patients with heart failure, found a change in peak oxygen consumption and exercise time of 63 ml·min⁻¹ and 32 seconds (the CV of 6.1% and 5.2%) between the two tests with one week apart. Respiratory exchange ratio and anaerobic threshold had coefficient of variation of 5% and 9%. The authors concluded that only one test was necessary to determine physiological responses to exercise in elderly heart failure patients. Furthermore, Meyer et al. (1997) also reported high reproducibility for duplicate measurements during stress exercise test in 11 patients with severe heart failure. The coefficient of variation for peak oxygen consumption, carbon dioxide production, respiratory exchange ratio and minute ventilation ranged from 3 to 6.4% respectively. Most recently, Bensihmnon and colleagues (2008) evaluated inter-subject variability of peak oxygen consumption over two baseline tests in the largest trial including 398 patients with heart failure. More than 90% of patients performed two tests within seven days of each other. Results revealed that peak oxygen consumption was unchanged from test 1 to test 2 (15.2 vs. 15.2 ml·kg⁻¹·min⁻¹, p>0.05). Within subject

absolute change was $1.3 \text{ ml}\cdot\text{kg}\cdot\text{min}^{-1}$ (the CV of 6.6%) with 46% of subjects increasing and 48% decreasing on the second test. The mean exercise time increased significantly from test 1 to test 2 by 4% (in the present study by 8%), whereas the mean values of anaerobic threshold were nearly identical between the two tests (10.5 vs. $10.6 \text{ ml}\cdot\text{kg}\cdot\text{min}^{-1}$, the CV of 7.8%). There was a very small, but statistically significant, difference in peak respiratory exchange ratio between the two tests. Bensihmon and associates (2008) concluded that there is no need to perform more than one baseline cardiopulmonary exercise test in heart failure patients.

It has been suggested that measured oxygen uptake remains relatively stable whereas exercise time continues to increase with serial testing (Tavazzi et al., 2001). In the present study, exercise time, peak oxygen consumption and peak minute ventilation were significantly higher during the second test. Indicating individual differences between test 1 and test 2 for measured variables, the Bland-Altman analysis (1986) shows that the most of the patients tended to score higher values during the second compared with the first cardiopulmonary exercise test. However, despite this statistically significant difference, there was a low coefficient of variation (below 10%) for all variables, except peak minute ventilation (the CV of 11.1%). This finding compares well with those previously mentioned studies which reported coefficient of variation for metabolic and ventilatory variables to be below 10%, indicating good reproducibility of metabolic and ventilatory exercise test variables (Bensihmon et al., 2008; Marburger et al., 1998; Meyer et al., 1997).

9.5 Clinical Implications and Conclusions

Measurement of central haemodynamic variables and particularly cardiac power output is more relevant in the evaluation of the severity of cardiac dysfunction in heart failure patients than any other metabolic or ventilatory variable. Good reproducibility of commonly reported cardiopulmonary exercise tests variables such as peak oxygen consumption, anaerobic threshold, carbon dioxide production, minute ventilation and respiratory exchange ratio has been previously shown. The coefficient of variation for measured peak metabolic and ventilatory variables, except minute ventilation, was low in the present study also, ranging from 4.2% to 7.1%. However, it seems that patients with stable chronic heart failure tend to achieve slightly higher results for

metabolic and ventilatory measurements during second of the two tests.

The present study suggests that cardiac output and cardiac power output, as direct indicators of cardiac function, had lower coefficient of variation than any of the commonly reported gas exchange variables at rest but also at peak exercise, demonstrating a high degree of reproducibility. Therefore, cardiac power output could be assessed together with other cardiopulmonary exercise test variables. Finally, it is reasonable to suggest that cardiac power output should be assessed as priority compared with other cardiopulmonary exercise test variables due to its good reproducibility and the capacity to represent overall cardiac function/dysfunction better than any other currently available measure.

9.6 References

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CHAPTER 10: THE EFFECT OF AEROBIC VERSUS RESISTANCE EXERCISE TRAINING ON CARDIAC POWER OUTPUT AND SELECTED CARDIO-RESPIRATORY VARIABLES IN PATIENTS WITH STABLE CHRONIC HEART FAILURE

Abstract

Introduction: Clinical evidence suggests that both aerobic and resistance exercise training may improve exercise tolerance in patients with chronic heart failure (CHF). Whether the two modalities of exercise training (aerobic and resistance) have similar effect on hemodynamic and metabolic variables remains unclear. The purpose of this study was to assess the effect of aerobic and resistance exercise training on cardiac power output and selected cardio-respiratory variables in CHF patients. **Methods:** Patients were randomized either into aerobic exercise training (AE) group (8 men, 3 women; mean±SD age 65±12 years) or to a resistance exercise training (RE) group (8 men, 2 women; age 63±10 years). At baseline and after 12 weeks of exercise intervention, patients underwent cardiopulmonary exercise testing with metabolic, ventilatory, and non-invasive central haemodynamic measurements at rest and at peak exercise. **Results:** Non-significant differences between the two groups were identified for any variable of interests at baseline level, either at rest or at peak exercise. Resting central haemodynamic or metabolic variables were not significantly changed after AE or RE compared with baseline. Peak cardiac power output increased following AE by 6.2%, although not significantly ($p>0.05$), whereas following RE, it remained almost unchanged. Peak cardiac output significantly increased from baseline by $0.8 \text{ l}\cdot\text{min}^{-1}$ in AE group (from 11.1 to $11.9 \text{ l}\cdot\text{min}^{-1}$, $p<0.05$), whereas no such change was observed in the RE group ($p>0.05$). Systemic vascular resistance was significantly reduced following AE by 8.2% (from 742 to $684 \text{ dyn}\cdot\text{s}^{-1}\cdot\text{cm}^{-5}$, $p<0.05$) and was not significantly changed following RE ($p>0.05$). Peak oxygen consumption significantly increased in AE (from 23.3 to $25.1 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, $p<0.05$) but not in RE (from 22.2 to $23.2 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, $p>0.05$). Changes in cardiac output were significantly correlated to changes in peak oxygen consumption following AE ($r=0.82$, $p<0.01$). Patients in AE group achieved an increase in anaerobic threshold of 7.8% (from 14.2 to $15.5 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, $p<0.05$ vs. RE group). Patients in both groups significantly increased maximal exercise duration, peak minute ventilation and carbon dioxide production compared to

baseline values ($p < 0.05$). **Conclusion:** In contrast with resistance, aerobic exercise training increases maximal flow-generating capacity of the heart and delays anaerobic metabolism during sub maximal exercise in patients with stable chronic heart failure. Improved peak oxygen consumption following aerobic exercise training is closely associated to an exercise-induced increase in cardiac output.

10.1 Introduction

Over the past decades considerable knowledge has accumulated concerning the significance of exercise in the treatment of a number of diseases, including metabolic syndrome-related disorders (insulin resistance, type 2 diabetes, dyslipidemia, hypertension, obesity), heart and pulmonary diseases (chronic obstructive pulmonary disease, coronary heart disease, chronic heart failure, intermittent claudication), muscle, bone and joint diseases (osteoarthritis, rheumatoid arthritis, osteoporosis, fibromyalgia, chronic fatigue syndrome) and other chronic diseases (cancer, depression, asthma, type 1 diabetes) (Oldridge, 2003; Pederson and Saltin, 2006; Roberts and Bernard, 2005). In the medical world, it is traditional to prescribe the evidence-based treatment known to be the most effective and entailing the fewest side effects or risks. The evidence available so far suggests that in selected cases, exercise therapy is just as effective as medical treatment, and in special situations more effective or adds to the effect (Pederson and Saltin, 2006).

Chronic heart failure or cardiac insufficiency is a clinical syndrome defined by the European Society of Cardiology as the presence of the following criteria: symptoms (dyspnoea, fatigue, ankle swelling) and objective evidence of cardiac dysfunction at rest (ESC Task Force, 2005). Heart failure is subdivided into left heart failure (the most frequently studied) and right heart failure, as well as into acute (pulmonary congestion, cardiogenic shock) and chronic heart failure. Heart failure is often caused by ischaemic heart disease, but can also be caused by hypertension, valvular heart disease, and dilated cardiomyopathy.

According to Duscha et al. (2008) pathophysiology of systolic chronic heart failure entails an initial injury to the heart that results in decreased left ventricular function and progressive declines in cardiac output. The pump function of the heart is

inadequate to supply sufficient blood perfusion for systematic metabolic needs. Clinical consequence and the hallmark symptom of chronic heart failure (CHF) is exercise intolerance, often exhibited by early fatigue or shortness of breath with a minimal degree of exertion (Myers, 2008). The pathophysiologic features of CHF that underlie reduced exercise tolerance have been the focus of numerous investigations over the last two decades (Pina et al., 2003).

10.2 Exercise and Chronic Heart Failure

10.2.1 Exercise Limitations in CHF patients

The extent to which exercise capacity is impaired in CHF is typically 30-50% relative to age-matched normal subjects and is 20-30% lower than that among typical patients with coronary artery disease (Myers, 2008). Over two decades of research have demonstrated that exercise intolerance in CHF is very complex and also extends to systems and abnormalities beyond the heart. The multiple mechanisms that are potentially responsible for the impairment of exercise capacity include: 1) cardiac dysfunction, 2) abnormalities in peripheral blood flow, 3) endothelial dysfunction, 4) skeletal muscle abnormalities, 5) ventilatory defects, and 6) abnormalities of autonomic nervous system function (McKelvie, 2008). In other words, factors that contribute to impaired exercise tolerance in CHF patients involve both central (cardiac) and peripheral (skeletal muscle and vascular) abnormalities, including impaired cardiac output response to exercise, abnormal redistribution of blood flow, reduced mitochondrial volume and density, impaired vasodilatory capacity, and heightened systematic vascular resistance (Drexler and Coats, 1996; Kitzman and Groban, 2005; Myers and Froelicher, 1991; Pina et al., 2003).

10.2.1.1 Central (cardiac) factors limiting exercise performance in CHF patients

In normal subjects, maximal exercise capacity seems to be limited by the ability of the cardiovascular system to deliver oxygen to the exercising muscles (Basset and Howley, 2000; Saltin and Rowell, 1980). This is shown by three major lines of evidence: 1) when oxygen delivery is altered (by blood doping, hypoxia, or beta-

blockade), maximal oxygen consumption changes accordingly, 2) the increase in maximal oxygen consumption with exercise training results primarily from an increase in maximal cardiac output, and 3) when a small muscle mass is overperfused during exercise, it has an extremely high capacity for consuming oxygen (Basset and Howley, 2000). Maximal exercise capacity is primarily limited by cardiac output in healthy adults. This is supported by the evidence that increasing the exercising muscle bulk by adding arm to maximal leg exercise does not result in an increase in maximal oxygen consumption (Jondeau et al., 1992). This suggests that cardiac output and oxygen delivery is already maximal (Jondeau et al., 1992). The same study, however, showed that in patients with CHF, the addition of arm to maximal leg exercise does produce a further increase to maximal oxygen consumption (Jondeau et al., 1992). Clark et al. (1996) suggested that the ability of the muscle to extract oxygen, for whatever reason, rather than the heart to deliver oxygen, is the major determinant of exercise capacity in patients with CHF. Clark and colleagues (1996) proposed so called “muscle hypothesis” according to which exercise intolerance and the reduction in peak aerobic power in CHF patients is primarily determined by the peripheral factors such as disease-induced alteration in skeletal muscle. This will be discussed in more details in the following subheading.

The Fick equation makes clear that functional capacity depends both on central cardiac performance as well as on peripherally mediated oxygen utilisation. The potential to increase cardiac output is essentially limited in heart failure patients (Pina et al., 2003) because the hearts of CHF patients tend to be dilated with impaired pumping function even at baseline (Duscha et al., 2008).

The increase in cardiac output during maximal upright exercise is typically four to six fold in healthy adults. This is a consequence of a two- to four-fold increase in heart rate and a 20% to 50% in stroke volume. The stroke volume increase is accomplished both by the use of the Frank-Starling mechanism to maintain left ventricular end-diastolic volume and by more complete left ventricular emptying to reduce end-systolic volume. Both enhanced left ventricular contractility and peripheral vasodilatations contribute to the more complete left ventricular emptying observed during exercise (Pina et al., 2003). A hallmark of heart failure patients, as previously mentioned, is a reduced ability to perform aerobic exercise. This reduction in aerobic

capacity seems to be largely mediated by inadequate blood flow to active skeletal muscle secondary to impaired cardiac output (Sullivan and Cobb, 1992; Wilson et al., 1984). Patients with CHF may achieve <50% of the maximal cardiac output attained by healthy individuals at peak exercise.

In CHF patients, peak exercise heart rate is often decreased (Clark and Coats, 1992). One explanation for such a decrease (apart from heart rate-lowering drugs) is that exercise is submaximal as it is usually stopped due to breathlessness or inadequate motivation. The second explanation is that the chronotropic reserve, as a major determinant of the increase in cardiac output, is significantly reduced (Franciosa et al., 1984; Szlachic et al., 1985). Resting tachycardia is not the only reason for reduced heart rate response to exercise as some CHF patients have a fairly low resting heart rate associated with markedly enlarged heart and preserved stroke volume (Cohen-Solal et al., 1999). In contrast, the kinetics of the heart rate response during exercise is generally abnormal with a rapid increase in more severe heart failure patients (Chidsey et al., 1962). There is an increase in resting sympathetic tone in CHF patients, but it seems to be unknown whether it is smaller or larger during exercise in healthy subjects (Wilson et al., 1989). The plasma noradrenalin level increases less than in healthy subjects (Colucci et al., 1989). The rise in sympathetic myocardial tone is lower than the rise in systemic tone in CHF patients (Rundqvist et al., 1997). Moreover, there is desensitization of β adrenergic receptors, and this is a possibly the main mechanism underlying the limited chronotropic response (Colucci et al., 1989; Bristow et al., 1986).

Furthermore, stroke volume in CHF patients, which is already decreased at rest, rises only modestly up to a peak of 55 to 65 ml (Pina et al., 2003). The inability to increase cardiac output is related primarily to the minimal increase in stroke volume coupled with a lower heart rate (Sullivan and Hobb, 1992). In the dilated left ventricle and with reduced resting left ventricular systolic function, stroke volume typically increases only modestly during exercise because of a reduced ability to increase both left ventricular preload and ejection fraction (Sullivan and Cobb, 1992). The reduced ability to augment left ventricular end-diastolic volume is explained by the fact that the already dilated left ventricle is operating near its maximal volume and has thus exhausted most of its preload reserve (Sullivan and Cobb, 1992). It has further been

suggested that the failure to increase left ventricular systolic emptying and thus augmented ejection fraction is a consequence of a combination of impaired intrinsic contractility, reduced β -adrenergic responsiveness, elevated systemic vascular resistance due to increased activity of the sympathetic and rennin-angiotensin systems, and minimal peripheral arterial vasodilator response to exercise (Pina et al., 2003).

10.2.1.2 Peripheral factors limiting exercise performance in CHF patients

Although the focus is often on abnormalities of the heart, it is well known that peripheral abnormalities, especially involving skeletal muscles, significantly contribute to the functional impairment and reduced exercise tolerance in CHF patients. Nonetheless, due to a compromised cardiac output, characteristics of skeletal muscle become relatively more important in determining maximal oxygen consumption in CHF patients (Duscha et al., 2008). Systematic reviews on peripheral factors limiting exercise performance commonly describe abnormalities of vasodilatory capacity, endothelial function, ergoreflex activation and distribution of cardiac output (Pina et al., 2003).

The failure of muscle blood flow to increase normally during exercise in patients with CHF is due not just to a reduction in cardiac output but also due to an abnormality in peripheral vasodilatation (Pina et al., 2003). In patients with CHF, systematic vascular resistance is higher at rest than in normal subjects. The reduction in resistance during exercise is only slightly less marked than in normal subjects, but nonetheless, systematic vascular resistance always remain higher than in normal subjects at a given workload (Isnard et al., 1996; Roubin et al, 1990; Sullivan and Cobb, 1992). The impairment in vasodilatory capacity has been attributed to excessive sympathetic stimulation causing vasoconstriction, activation of the plasma renin-angiotensin system, and higher than normal levels of endothelin (McMurray et al., 1992; Zelis et al., 1988). An additional mechanism may involve vascular stiffness secondary to increased vascular sodium content (Pina et al., 2003). This is supported by the observations that the capillary basement membranes may be thickened in CHF patients (Longhurst et al., 1975) and that vascular responsiveness is partially improved by diuretic therapy (Sinoway et al., 1987).

It has been suggested that endothelium plays an important role in tissue perfusion in heart failure (Pina et al., 2003). The vascular endothelium releases vasoactive substances that play an important regulatory role in peripheral vasomotor tone (Cohen-Solal et al., 1999). Vasodilating and vasoconstricting factors, including nitric oxide, endothelins, and prostaglandins derived from the endothelium, are released in response to various chemical, pharmacological, mechanical, and exercise stimuli (Pina et al., 2003). Endothelium-dependent dilation of the vasculature is impaired in heart failure. This is supported by the evidence that there is a reduction in release of nitric oxide in response to acetylcholine (Drexler et al., 1992, Kubo et al., 1991). The release of nitric oxide, an important mediator of flow-dependent vasodilation, is stimulated by exercise in healthy individuals but seems to be attenuated in heart failure patients (Drexler et al., 1992). This may contribute to a reduction in peripheral vasodilation and thus tissue perfusion (Pina et al., 2003). It has been shown that the impairment of endothelial-dependent vasodilation is correlated with the degree of exercise intolerance and the severity of New York Heart Association class (Nakamura et al., 1994). Exercise training has been shown to improve endothelial nitric oxide formation and endothelial-dependent vasodilation of skeletal muscle vasculature (Hambrecht et al., 1998).

Patients with CHF compensate for reduced cardiac output with an increased arterio-venous oxygen difference, such that resting and submaximal exercise oxygen consumption are similar to that of normal subjects (Duscha et al., 2008). Despite this increase, CHF patients have increased lactate production, even during submaximal exercise (Weber and Janicki, 1985; Wilson et al., 1984). Early blood lactate production is a function of intramuscular acidosis and not reduced lactate clearance (Wiener et al., 1986). It seems that a prolonged decrease in left ventricular function causes skeletal muscle abnormalities. It is possible, however, that these skeletal muscle changes may be independent of left ventricular function (Duscha et al., 2008). The primary function of the capillary bed in skeletal muscle is to supply oxygen to muscle fibres. It seems, however, that patients with CHF have reduced capillary density in the skeletal muscles between 17% and 32% (Drexler et al., 1992; Duscha et al., 1999; Sullivan et al., 1990; Williams et al., 2004). This finding further supports the argument that peripheral abnormalities play an important role in impaired exercise tolerance in CHF patients.

Further abnormalities in skeletal muscles of CHF patients involve 10-20% decrease in oxidative (red) type I muscle fibre with an increase in glycolytic (white) type IIb muscle fibre compared with normal subjects (Drexler et al., 1992; Lipkin et al., 1988; Sullivan et al., 1990). These shifts have been correlated to peak oxygen consumption and leg fatigue during isokinetic knee extension (Magnusson et al., 1996; Mancini et al., 1989). Furthermore, it has been reported that myosin heavy-chain type I isoforms are decreased in proportion to peak oxygen consumption in CHF patients (Sullivan et al., 1997). Although levels of glycolytic enzymes seem to be unchanged in CHF, levels of oxidative enzymes are decreased (Sullivan et al., 1990). Specifically, mitochondrial enzymes (citrate synthase and succinic dehydrogenase) and enzymes involved in β -oxidation of fatty acids (3-hydroxyl CoA dehydrogenase) have been shown to be decreased (Sullivan et al., 1990). Interestingly, an inverse relationship between oxidative enzyme activity and blood lactate accumulation was found during exercise (Sullivan et al., 1991). In that study CHF patients had less phosphocreatine depletion and lactate accumulation at peak exercise than normal subjects, raising the possibility that intrinsic skeletal muscle abnormalities may be responsible for early anaerobic metabolism (Duscha et al., 2008). Although, the most important determinant in maximal oxygen consumption in healthy subjects is cardiac output (Saltin and Rowell, 1980), it seems that sub-maximal indices rely on skeletal muscle capacity (e.g. mitochondria content) (Holloszy and Coyle, 1984). Mitochondria generate most of a cell's adenosine-three-phosphate and therefore play an intricate role in skeletal muscle energy metabolism. Only Drexler et al. (1992) measured mitochondria in CHF patients compared with healthy subjects. They demonstrated that oxygen consumption correlates with a reduced mitochondrial volume and surface. A decline in mitochondrial number and size indicates a reduced oxidative capacity of the muscle and has been offered as explanation for the rapid fatigue that occurs in CHF patients (Drexler et al., 1992). Taken together, these findings suggest that alterations in skeletal muscle may contribute to abnormal oxygen extraction or substrate delivery/utilization and may further limit exercise tolerance in CHF patients.

In skeletal muscles, there are ergoreceptors, small afferent nerve fibres that are sensitive to changes in metabolism (Piepoli et al., 1996; Ponikowski et al., 2001; Scott et al., 2002). Muscle metabolic abnormalities with overproduction and accumulation of metabolites (a.g. H^+ , C_2 , bradykin) during exercise activate afferents of the

ergoreflex, which leads to an exaggerated increase of ventilatory, haemodynamic, and sympathetic nervous system activity to exertion (Scott et al., 2002). In CHF patients, it has been found that there is an increased activation of the ergoreflex compared with normal subjects, with evidence of more pronounced exercise hyperventilation and more severe symptoms (Piepoli et al., 1996; Ponikowski et al., 2001). These findings suggest that increased activation of the ergoreflex during exercise in CHF is closely related to exercise intolerance (Ponikowski et al., 2001).

The finding of skeletal muscle abnormalities and increased activation of the ergoreflex has provided substantial support for the skeletal muscle hypothesis as an explanation for the exercise intolerance (Piepoli et al., 1996). In this hypothetical model, left ventricular dysfunction reduces blood flow to the periphery and activates a catabolic state causing skeletal muscle myopathy, which contributes to fatigue and dyspnoea. This, in turn, stimulates ergoreceptors in the skeletal muscles leading to increased ventilation and sympathoexcitation with vagal withdrawal. The resultant vasoconstriction and increased afterload cause further deterioration of left ventricular function, forming a vicious cycle (Piepoli et al., 1996). This results in further worsening of exercise tolerance, skeletal muscle myopathy, and may eventually lead to a progressive adverse effect on left ventricular remodelling (Piepoli et al., 1996).

Finally, exercise tolerance depends not only on the capacity of the cardiopulmonary system to deliver oxygen to the working muscles, but also on regional blood flow (e.g. the capacity of the vasculature to redistribute cardiac output to the muscles during exercise). In healthy normal adults, up to 85% of the total cardiac output is directed toward active skeletal muscle at high levels of exercise, with flow to leg muscles usually receiving the greatest increases in blood flow (Knight et al., 1992). Although some evidence suggests that muscle blood flow is reduced in proportion to the reduction in cardiac output in CHF patients (Yamabe et al., 1995), several studies have demonstrated the reduction in flow to the muscles during exercise occurs to a degree out of proportion to the reduction in cardiac output. Sullivan and Cobb (1992) reported that the percentage of cardiac output distributed to both lower extremities during maximal exercise was attenuated in patients with CHF when compared with healthy subjects (51% vs. 71%). Vascular resistance fails to decrease normally during exercise in patients with CHF, and flow to the nonexercising tissues may be

preferentially maintained at the expense of hypoperfusion in the exercising muscles (Sullivan et al., 1989; Wada et al., 1997).

10.2.2 Modes of Exercise Training and Their Effect on Clinical Outcomes, Exercise Performance and Cardiac Function in CHF Patients

Prior to the late 1980s, bed rest and restricted physical activity were recommended for all stages and forms of heart failure (Working Group Report, 2001). However, prolonged bed rest and physical inactivity can lead to skeletal muscle atrophy, pulmonary embolism, venous thrombosis, and a further reduction in exercise tolerance and exacerbation of symptoms (Working Group Report, 2001). The concept of exercise training in patients with CHF was initiated in the late 1980s. Coats et al. (1990), in the first randomized study of training patients with stable heart failure, showed that eight weeks of exercise training led to an increase in exercise capacity and to an improvement of the abnormal sympathovagal balance. Research over the past 20 years has expanded understanding and knowledge of the role of exercise training in patients with left ventricular dysfunction and heart failure. Over the time it has become clear that patients with CHF may benefit so much from exercise training that it has been recommended by a number of international scientific organizations such as American Heart Association and European Society of Cardiology (Pina et al., 2003; Working Group Report, 2001). It has been shown that exercise training is firstly safe in CHF patients (Smart and Marwick, 2004) and can improve peak oxygen consumption (Duscha, 2008; Pina et al., 2003; Working Group Report, 2001), muscle strength and mass (Braith and Beck, 2008), New York Heart Association Class (Hambrecht et al., 2000), quality of life (Belardinelli et al., 1999), but also reduces hospital admission and mortality rate (Piepoli et al., 2004). Different modalities of exercise may have different effects on cardiovascular function in CHF. Therefore, authors have been interested in the effects of different exercise modalities on clinical outcomes, exercise performance and cardiac function. Three modes of exercise in CHF patients have been utilized such as aerobic, resistance and combined.

10.2.2.1 Aerobic exercise training in CHF patients

Most of the studies which assessed the effect of exercise training in CHF patients utilized aerobic training modalities (e.g. walking, jogging, cycling, rowing, arm ergometer, step aerobic exercises, etc) (Coats, 2000, Duscha et al., 2008). The rationale for aerobic training in cardiac patients was originally premised on expectations for improved inotropic and chronotropic capacities (Duscha et al., 2008). Historically, aerobic exercise is implanted in cardiac rehabilitation programs in an attempt to resolve oxidative enzymatic abnormalities (Bylund et al., 1977) and thereby increase exercise tolerance (Braith et al., 2005).

Numerous systematic reviews and meta analyses showed that aerobic exercise training improves exercise tolerance and functional capacity in chronic heart failure patients (Coats et al., 2000; Duscha et al., 2008; Haykowsky et al., 2007; McKelvie, 2008; Pina et al., 2003; Smart and Marwick, 2004; Working Group Report 2001). In a meta-analysis of 14 trials (812 patients) performed by Haykowsky et al. (2007), an overall improvement in peak oxygen consumption of ~20% was reported. Moreover, aerobic training was associated with statistically significant increase in peak oxygen consumption of ~3 ml·kg⁻¹·min⁻¹ (from 9 randomized trials with 538 patients). In this meta-analysis, studies that utilized an aerobic training modality demonstrated these beneficial effects, whereas studies that used combined exercise modality did not. The authors suggested that this may be because of the heightened systolic and diastolic pressure loading that occurs with strength training (Cheetham et al., 2002; Keren et al., 1989; McKelvie et al., 1995).

The other systematic review of 57 studies that measured peak oxygen consumption directly (Smart and Marwick, 2004) suggests that the mean improvement was 16.8% (95% confidence interval: 13.7-17.9%). Authors however noted that studies of aerobic exercise training demonstrated a greater increment in peak oxygen consumption (16.5%) compared with studies that employed strength training alone (9.3%). However, this review suggests that the mean increment in peak oxygen consumption following aerobic exercise training only slightly exceeded the combined mode of exercise training (by 1.5%).

Several mechanisms that may occur in response to aerobic exercise training may contribute to significant increase in exercise tolerance in CHF patients. Firstly, aerobic exercise training increases capillary density, promotes the synthesis and release of nitric oxide, improves angiogenesis, vasodilation and endothelial function, reduces oxidative stress and peripheral vascular resistance, and increases metabolic capacity and musculoskeletal blood flow (Adamopoulos et al., 2003; Duscha et al., 2008; Wisloff et al., 2007). Secondly, aerobic exercise training in CHF patients is associated with lower blood lactate threshold and blood lactate concentration at standardized submaximal workload levels (Belardinelli et al., 1995), reduced depletion and more rapid resynthesis of phosphocreatine (Adamopoulos et al., 2003), and increased citrate synthases activity (Duscha et al., 2008). Following aerobic training, the mitochondrial total volume density is increased, mitochondrial enzymatic activity and skeletal muscles' oxidative capacity are enhanced (Belardinelli et al., 1995; Duscha et al., 2008; Piepoli et al., 1998). In addition, recent data suggest that aerobic training improves phase II O₂ kinetics, which is an indirect index of muscle oxidative capacity (Roditis et al., 2007). Also, some studies have shown a shift from IIb to IIa muscle fibre type (Duscha et al., 2008) and a modest increase in type I muscle fibres (Hambrecht et al., 1997).

Finally, most single centre exercise training studies of heart failure patients did not include end-points such as hospitalizations and survival. However, a European collaborative meta-analysis examined death from all causes in 805 patients data sets from 41 exercise training trials of heart failure (Piepoli et al., 2004). They found that exercise training significantly reduced both mortality and death plus hospital admission. Importantly, eight of nine trials included in their analysis incorporated aerobic exercise training. Now, a large, multicentre, randomized clinical trial (sponsored by the USA National Heart, Lung, and Blood Institute) has been undertaken to assess the effect of exercise training on the clinically relevant end-points of mortality, hospitalisation, and quality of life with heart failure: HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) (Whellan et al., 2007). Following baseline assessment to determine whether they can safely exercise, 3000 patients were randomized to either usual care or exercise training, the latter consisting of supervised facility-based aerobic (cycling or walking) exercise training sessions. After completing the supervised sessions, patients initiated,

and then transitioned to, solely home-based exercise. The followed-up period of up to 4 years has been proposed. A number of substudies were planned. The outcome of this study should have a profound effect on this issue.

Interval vs. steady-state (continuous) training. The rationale for developing interval training methods for cardiac patients was to apply more intense exercise stimuli on peripheral muscles than that obtained during steady-state training methods, but without inducing greater cardiovascular stress (Working Group Report, 2001). This is possible by using short bouts of work phases in repeated sequence followed by short recovery phases. Chronic heart failure patients with very low baseline aerobic capacity demonstrated an improvement in ventilatory threshold by 24% on average, and peak oxygen consumption by 20% after only three weeks of interval training (Meyer et al., 1996a). This finding is similar to that reported by other studies but after much longer training periods (8-24 weeks) using steady-state method (Belardinelli et al., 1995; Belardinelli et al., 1998; Coats et al., 1992; Hambrecht et al., 1995; Kavanagh et al., 1996; Keteyian et al., 1996). Although ejection fraction, mean arterial blood pressure and heart rate during interval training are similar to that seen in steady-state exercise, blood lactate is significantly higher during interval exercise, indicating a greater peripheral training stimulus (Meyer et al., 1998). Therefore, interval training allows more intense exercise stimuli on peripheral muscles with no greater left ventricular stress than when using a steady state training method (Working Group Report, 2001). A superior cardiovascular effect of aerobic interval training versus moderate continuous aerobic training in heart failure patients was shown recently by Wisloff et al. (2007). Patients were randomized to either moderate continuous training group (exercise intensity of 70% of peak heart rate) or aerobic interval training (95% of peak heart rate) three times per week for 12 weeks or to a control group. Peak oxygen consumption increased more with aerobic interval training than moderate continuous training (46% vs. 14%, $p < 0.001$), and was associated with reverse left ventricular remodelling (left ventricular end-diastolic and end-systolic volumes declined with aerobic interval training only, by 18% and 25%, respectively). The authors concluded that exercise intensity is an important factor for reversing left ventricular remodelling and improving aerobic capacity. Finally, that interval training leads to more pronounced improvement in central haemodynamics compared with continuous exercise has been shown by Necwatal et al. (2002). Effect

of exercise on central adaptation in CHF patients will be detailed below in section 10.2.3.

10.2.2.2 Resistance exercise training in CHF patients

Additionally to central and peripheral abnormalities described above, skeletal muscle atrophy may also contribute to the reduced exercise capacity in CHF patients (Williams et al., 2004). These patients also exhibit reduced muscle strength due at least partly to the significant muscle atrophy (Harrington and Coats, 1997). Conversely to aerobic exercise training, which has little influence on muscle mass (Meredith et al., 1989), resistance training is an exercise modality that has the most potential to increase muscle mass which appears to affect exercise capacity in CHF patients (Williams et al., 2004). Moreover, it has been reported that muscle strength, and specifically leg strength, is a parameter that independently predicts survival in patients with severe CHF (Hulsmann et al., 2004).

Resistance training has traditionally been discouraged due to concerns for furthering impairment of left ventricular function and adverse left ventricular remodelling caused by increased afterload and blood pressure during lifting phase (Braith and Beck, 2008). In reality, however, due to the low intensity at which patients with CHF perform resistance training, the haemodynamic responses do not exceed levels attained during standard treadmill testing (McKelvie et al., 1995) and adverse left ventricular remodelling after resistance training has not been demonstrated (Pu et al., 2001). Moreover, performance of the left ventricle during strength testing and resistance training has been assessed by echocardiography. Most studies agree that absolute haemodynamic responses (heart rate, systolic blood pressure, ejection fraction, cardiac output, left ventricular end-diastolic volume) are higher during treadmill testing than during strength testing or resistance training (at least up to 15 repetitions at up to 60% of one maximal repetition) (Delagardelle et al., 1999; Delagardelle et al., 2002; Karlsdottir et al., 2002; Levinger et al., 2005; McKelvie et al., 1995; Pu et al., 2001; Werber-Zion et al., 2004). Additionally, it has been shown that during rhythmic double leg press exercise (at loads of 60% and 80% maximum voluntary contraction using interval modes with 60 s work phases of 12 repetitions each and 120 s rest phases) CHF patients demonstrated increased left ventricular

stroke work index and decreased systematic vascular resistance, suggesting enhanced left ventricular function (Meyer et al., 1999). This might be due to a rhythmic sequence of submaximal isometric muscle contractions, which help to maintain venous return, reduce systemic vascular resistance, maintain blood flow, and meet muscle metabolic need (Working Group Report, 2001).

In CHF patients there is a global reduction of muscle mass, even in mild CHF patients, and further reduction in mass are associated with severity of disease (Mancini et al., 1992; Minotti et al., 1993). Decreased muscle mass could potentially explain the observed exercise intolerance in CHF and correlations studies have shown a link between muscle volume and exercise capacity in CHF patients (Harrington and Coats, 1997). However, there is evidence that muscle mass only partially influences endurance (Mancini et al., 1992) and strength (Minotti et al., 1993) in patients with CHF. Nonetheless, resistance training, as previously mentioned, has potential to increase muscle mass in CHF patients (Baith and Becks, 2008).

Resistance training independently improves both aerobic (oxidative) and anaerobic (glycolytic) performance of skeletal muscle (Braith et al., 2005). Six months of resistance training independently increased both citrate enzyme, a marker of oxidative (i.e. aerobic) Krebs's Cycle activity, and lactate dehydrogenase, a marker of glycolytic (i.e. anaerobic) activity (Braith et al., 2005). Additionally, it has been suggested that resistance training may influence changes in muscle morphology caused by the heart failure. This includes shift from glycolytic type II fibre toward oxidative type I fibre in patients who suffer skeletal muscle myopathy (Braith et al., 2005). Regarding cardiac function, it has been found that resistance training elicited improvements in left ventricular ejection fraction (LVEF) by 13% and 17.8% (Feiereisen et al., 2007; Levinger et al., 2005). Levinger et al. (2005) assessed the effects of eight weeks resistance training on the left ventricular structure and function in CHF patients. This study revealed that resistance training does not cause a reduction of left ventricular contractility function as measured by ejection fraction and fractional shortening. Compared with the control group, the resistance training group also elicited an increase in stroke volume by 13.1%, measured at rest.

Feiereisen et al. (2007) compared the efficacy of three training modalities on peak oxygen consumption in three groups of 15 patients with CHF. Patients underwent either resistance training, aerobic training, or combined aerobic plus resistance training during 40 sessions, three times weekly for 45 minutes. Surprising result of the study was that the three exercise modes were comparably effective in improving peak oxygen consumption (resistance group +16.7%, aerobic group +11.1%, and combined group +14.2%). Additionally, resistance training elicited significant improvements in peripheral muscle strength but aerobic training did not. The 16% increase in peak oxygen consumption is remarkable, since in healthy, sedentary individuals, resistance training increases peak oxygen consumption by only 3% (Tanaka and Swensen, 1998). This finding is in accordance with the literature, where others have shown that patients with CHF achieve 10-18% increases in peak oxygen consumption during resistance training and 15-20% after aerobic training (Meyer, 2006). A significant increase in peak oxygen consumption (14.5%) was observed after 12 weeks of training using weight collars in patients with CHF awaiting heart transplantation (Grosse et al., 2001). In contrast, others have reported no improvement in peak oxygen consumption despite lower oxygen consumption at submaximal workloads after 11-week resistance training in patients with moderate CHF (mean EF: 26%, NYHA class II-III) and significant improvement in exercise time (13%) (Pu et al., 2001) and maximal exercise capacity (10%) (Magnusson et al., 1996) in patients with CHF after 8 weeks of resistance training. Interestingly, one study reported that leg strength accounted for 81% of the variability in peak oxygen consumption among heart transplant recipients but only accounted for 42% of the variability in healthy age-matched controls (Braith et al., 1993). Thus, peak oxygen consumption in individuals with normal leg strength is likely to be restricted by cardiovascular reserve, whereas in patients with CHF myopathy phenotype of leg muscles may be a primary factor limiting aerobic power (Okita et al., 1998; Vescovo et al., 1998).

10.2.2.3 Combined (aerobic plus resistance) exercise training in CHF patients

Although confounded by utilization of two exercise modes, comparative studies have shown that the combination of resistance and aerobic exercise training results in better adaptation of peak oxygen consumption than aerobic training alone. Maiorana et al. (2000) found increases in peak oxygen consumption of 13% following a 12-week

combined exercise training in CHF patients (mean EF: 26%, NYHA class I-III). Delagardelle et al. (1999) also used combined exercise training for 24 weeks in outpatients with CHF (mean EF: 36%, NYHA class II) and observed a 10% increase in peak oxygen consumption. In a follow-up study, the same authors randomized patients into either aerobic or combined exercise training (Delagardelle et al, 2002). Peak oxygen consumption was significantly increased during combination training (+7.8%) but remained unchanged (+0.2%) in the group that performed only cycling. Selig et al. (2004) reported a 21% improvement of peak oxygen consumption in a prospective, randomized study after three months of combined exercise training in CHF patients (mean EF: 27%, NYHA class II-III). It has been suggested that combined training improves both oxidative and glycolytic skeletal muscle capacity (Braith and Beck, 2008), increases the cross-sectional area of skeletal muscles (Belardinelli et al., 1995), and improves neuromuscular function, all leading to a significant increase in muscle strength and endurance (Braith and Beck, 2008; Williams et al., 2007).

10.2.3 Central Adaptation to Exercise Training in CHF patients

Since data about central adaptation to resistance training in CHF patients are limited, only adaptations to aerobic training will be described. In comparison with a great number of studies which assessed skeletal muscle adaptation to exercise training programmes, relatively few papers (eight) have studied the cardiac output response to aerobic training in CHF patients (Belardinelli et al., 1995; Belardinelli et al., 1996; Coats et al., 1992; Dubach et al., 1997; Hambrecht et al., 1995; Hambrecht et al., 2000; Necwatal et al., 2002; Sullivan et al., 1988). Small number of studies which evaluated central adaptation to exercise training is mainly due to methodological issues, as the gold standard for cardiac output measurement is right heart catheterization, an invasive procedure with possible risks for the patients. Since new, non-invasive, easy to use methods for measurement of cardiac output have become available over the last years (e.g. inert gas rebreathing, bio-reactance), the previous fact regarding methodological limitations should not be used as a strong argument for lack of central haemodynamic measurements in CHF patients. Nonetheless, the authors of the previously mentioned “muscle hypothesis” (Clark et al., 1996) concluded their work saying that measurement of central haemodynamics is not unimportant as in the

genesis of the heart failure “an initial cardiac abnormality is essential”.

Most of the above mentioned studies have demonstrated a significant increase of cardiac output at peak exercise with respect to pre-training values. As is well known, cardiac output is the product of heart rate and stroke volume. Therefore, the increase of cardiac output could be due to different combinations of heart rate and stroke volume relative changes, with significant increase only in stroke volume (Nechwatal et al., 2002), of heart rate only (Hambrecht et al., 1995), of both volume and heart rate (Coats et al., 1992), or with little, not significant increases of both resulting in a significant increase of their product (Dubach et al., 1997). It has also been shown that central adaptation to aerobic exercise training is possible in patients with severe heart failure (NYHA class III). Failure to demonstrate a significant improvement in peak cardiac output is often associated with a weaker study design (Belardinelli et al., 1995; Sullivan et al., 1988) and lower training intensities (Belardinelli et al., 1995).

Evidence available so far suggests there are only two meta-analyses which assessed the effect of exercise training on cardiac function in heart failure patients. Van Tol et al. (2006), using a meta-analysis, assessed the effects of exercise training on cardiac performance. From 35 randomized controlled trials, 24 used aerobic exercise programmes (either continuous or interval or both), eight used combined and only three resistance exercise programmes. The average training period lasted for 13 weeks with a mean duration of 50 minutes per session and an average frequency of four times per week. Results revealed that resting diastolic blood pressure and end-diastolic volume showed a significant improvement following exercise intervention, decreasing by 2.7% and 1.2%. A decrease in resting heart rate (by 2.6 beats·min⁻¹ or 3.3%) and an increase in resting cardiac output and LVEF by 6.4% (0.32 l·min⁻¹) and by 2.9% was not statistically significant. During maximal exercise, however, heart rate, systolic blood pressure and cardiac output increased significantly after exercise training by 2.5% (3.5 beats·min⁻¹), by 3.3% (5.4 mmHg) and by 21.1% (2.51 l·min⁻¹), respectively. A decrease in diastolic blood pressure of 3.2% (2.9 mmHg) was not significantly different and there were insufficient data to obtain results of the left ventricular ejection fraction during exercise. It should be noted that the above mentioned data have been collected during pre-beta-blockers era. Consequently, the effect of beta-blocking therapy on the cardiac output response to aerobic exercise has

not been well studied. However, some studies have demonstrated an improvement of peak oxygen consumption after aerobic training in CHF patients on beta-blockers similar to that of patients off these drugs (Curnier et al., 2001; Forissier et al., 2001). Given the above, and if one assumes that beta-blockers are not expected to significantly modify peripheral oxygen extraction, the linear relationship between relative changes in cardiac output and peak oxygen consumption should be preserved also in beta-blocked CHF patients (Mezzani et al., 2008). The only available study evaluating the cardiac output response to aerobic training in CHF patients on beta-blockers seems to confirm this hypothesis, at least in patients undergoing interval training sessions (Nechwatal et al., 2002).

The second meta-analysis, performed by Haykowsky et al. (2007), assessed the effect of exercise training on left ventricular remodelling on heart failure patients. Fourteen randomized trials were identified. Most (nine) incorporated aerobic training at intensity between 60% and 80% of baseline peak oxygen consumption for 20 to 60 minutes per session. Four trials examined the effect of combined strength and aerobic training, and one trial examined strength training alone. The length of the training programme varied between two and 12 months. The results from aerobic trials demonstrated that exercise training was associated with improvement in LVEF (~3%) whereas combined or resistance training did not show this improvement. Furthermore, whereas aerobic exercise training was associated with a significant decrease in end-diastolic and end-systolic volumes (by ~11 ml and ~13 ml), the effects of combined aerobic and strength training were inconclusive. The authors suggested that aerobic exercise training reverses ventricular remodelling in clinically stable heart failure patients. Moreover, it has been suggested that favourable changes in left ventricular volume and ejection fraction associated with aerobic training were supplementary to pharmacological benefits; that is they occurred despite the patients being prescribed medications with a proven anti-remodelling effect.

10.2.4 *Principles of Exercise Prescription in CHF Patients*

According to Myers (2008) exercise prescription essentially describes the process whereby a person's recommended regimen of physical activity is designed in a systematic and individualized manner. This implies specific strategies to optimize return to work or activities of daily living, reduction of risk factors for future cardiac events, and maximization of the patient's capacity to maintain an active lifestyle (Myers, 2008). Most patients with reduced left ventricular function who are clinically stable and have reduced exercise tolerance are candidates for exercise programmes (Pina te al., 2003; Working Group Report, 2001). Stability can be assured by the absence of recent changes in body weight, the absence of recent changes in symptoms, and control of comorbid conditions (Myers, 2008). It seems that, the benefits of exercise training are not dependent on the aetiology of CHF, or standard clinical measures such as baseline peak oxygen consumption or ejection fraction (Myers, 2000; Working Group Report, 2001). Absolute and relative contraindications to exercise specific to CHF patients are summarised in table 10.1.

The major principles of exercise prescription are mode (type), frequency, duration, and intensity of exercise. These principles apply to healthy but also to diseased populations. An exercise prescription must consider the patient's goals, health status, and availability of time in addition to practical consideration such as cost, availability of equipment and facilities. Additionally the overload, specificity and reversibility principles are key considerations in developing an effective exercise programme (Arena et al., 2008). The overload principle relates to the fact that the training stimulus must be greater than what the physiological systems (e.g. cardiovascular and skeletal muscle) are accustomed to, for positive change to occur. The specificity principle states that physiological improvements are unique to the mode of exercise performed. Lastly, the reversibility principle states that positive training adaptations are not maintained if an individual returns to a sedentary behaviour pattern of life style. There is no single programme that is the best for all patients or even one patient over the time. Therefore, the development of an appropriate exercise prescription to meet the individual patient's needs has a sound scientific foundation, but there is also an art to effective exercise programming (Myers, 2008).

Table 10.1 Relative and Absolute Contraindications to Exercise Training Among Patients with Stable CHF (Working Group Report, 2001)

Relative contraindications

1. ≥ 1.8 kg increase in body mass over previous 1-3 days
2. Concurrent continuous or intermittent dobutamine therapy
3. Decrease in systolic blood pressure with exercise
4. New York Heart Association Class IV
5. Complex ventricular arrhythmias at rest or appearing with exertion
6. Supine resting heart rate ≥ 100 beats min^{-1}
7. Preexisting comorbidities

Absolute contraindications

1. Progressive worsening of exercise tolerance or dyspnoea at rest or on exertion over previous 3-5 days
 2. Significant ischaemia at low work rates (< 2 METS, or ~ 50 W)
 3. Uncontrolled diabetes
 4. Acute systematic illness or fever
 5. Recent embolism
 6. Thrombophlebitis
 7. Active pericarditis or myocarditis
 8. Moderate or severe aortic stenosis
 9. Regurgitant valvular heart disease requiring surgery
 10. Myocardial infarction within previous three weeks
 11. New onset atrial fibrillation
-

The general frequency, duration and intensity recommendations for aerobic exercise in CHF patients are 3-5 days per week, 30-60 minute and 50-80% of maximal aerobic capacity (Myers, 2008; Pina et al., 2003). Previously it has been suggested that training intensity does not seem to influence the magnitude of the increase in exercise tolerance directly (Meyer et al., 1996). More recently, however, Wisloff et al. (2007) demonstrated that higher intensity interval training led to more functional improvement than that obtained with lower continuous type of training. The exercise intensity may be expressed as % of peak oxygen consumption, % of peak heart rate and a rate of perceived exertion. In terms of peak oxygen consumption, an intensity of 40-80% of peak oxygen consumption was applied successfully (Pina et al., 2003; Working Group Report, 2001). Since intensity and duration of exercise training are

closely interrelated in terms of training effect expected, low intensity can partly be compensated by the training sessions of longer duration, or higher frequency. In terms of using heart rate it has been suggested that exercise intensities of 60-80% heart rate reserve and 60-80 % of peak heart rate (Working Group Report, 2001) should be applied. It has been further suggested that exercise intensities ranging from 40-80% of peak oxygen consumption, are generally equivalent to 50-90% of the maximal heart rate (Pollock et al., 1998). However, heart rate-derived exercise intensities may be inaccurate in advanced CHF patients (Pina et al., 2003). In the current era of β -blockers, heart rate alone as a measure of intensity may not be practical, particularly in patients with atrial fibrillation (Schuchert, 2005). Therefore, the Borg scale of rate of perceived exertion (scores from 6 to 20) (Borg, 1970) can be quite useful in prescribing exercise intensity, especially in patients on β -blockers (Pina et al., 2003). Exercise intensities corresponding to a perceived exertion level between 12 and 14 (13 somewhat hard) have been shown to be well-tolerated and associated with favourable training responses in patients with CHF (Keteyian et al., 1996). In addition to aerobic exercise, interval training seems to be beneficial in CHF patients. This is the mode of exercise in which short bouts of work phases in repeated sequences are followed by short recovery phases. Work phases of 30 seconds and recovery phases of 60 seconds are useful, using an intensity of 50% of maximum short term exercise capacity for work phases. During the recovery phase patients may perform exercise at a lower intensity (Working Group Report, 2001). Although cycle ergometry is preferred for applying interval training, this method can also be performed on a treadmill, or even other devices which allow aerobic exercise (e.g. skiing machine, stepper). In this case, a practical way is to choose work and recovery phases of 60 seconds each (Working Group Report, 2001).

Regarding resistance exercise training in CHF patients, it has been usually performed in the form of circuit training (Braith and Beck, 2008). According to this method there are several working stations on which patients perform exercise followed by a resting period. Common exercises include leg press, knee extension, bicep curls, etc. To approximate the appropriate limb-specific weight load for resistance training, Williams et al. (2007) recommended determination of the maximum weight that can be used to complete 1-RM (one repetition maximum) for a given exercise. An initial intensity that corresponds to 30% to 40% of 1-RM for the upper body and 50% and

60% of 1-RM for the hips and legs is recommended (Williams et al., 2007). Recommendations for designing resistance training programmes for patients with CHF are summarized in Table 10.2 according to the available literature (Braith and Beck, 2008).

Each exercise session should include the warm-up period (10 to 15 minutes), followed by the main part of training (20 to 30 minutes) at the desired intensity. A cool-down period is also advised (Pina et al., 2003). Most studies used three to five times per week as the optimal training frequency. Although the first benefits of aerobic exercise in CHF patients are seen after just three weeks of the exercise programme (Meyer et al., 1996a), most of exercise programmes varied from eight to 24 weeks (Working Group Report, 2001).

Table 10.2 Recommendations for Designing Resistance Training Programs for Patients with CHF (Braith and Beck, 2008)

<i>Characteristic</i>	<i>NYHA class I</i>	<i>NYHA class II and III</i>
Frequency	2-3 days/week	1-2 days/week
Duration	10-30 min	15-20 min
Intensity	50-60% 1RM	40-50% 1RM
Contraction speed	6 s (3 concentric+3 eccentric)	6 s (3 concentric+3 eccentric)
Work: rest ratio (duration)	60 s or longer (1:2)	60 s or longer (1:2)
Number of exercise stations	4-9	3-4
Number of sets per station	2-3	1-2
Number of repetition per set	6-15	4-10
Involve muscle mass	Unilateral and/or bilateral	Unilateral and/or bilateral
Mode of training	Segmental training during the introductory phase (first months) whole body training rarely, when tolerated	Segmental training mainly, then whole body training when/if tolerated
Flexibility	Daily as tolerated	Daily as tolerated

NYHA, New York Heart Association; 1RM, 1 repetition maximum

Finally, the need for monitoring prescribed exercise programmes in CHF patients has not been systematically studied (Pina et al., 2003). The design of most studies ranged from monitored to supervised to home based exercise without supervision. It has been recommended that the setting should be one of direct monitoring and supervision, especially during initial training sessions (Haskell, 1994). A supervised programme allows for education, including advice on recognition of symptoms, nutrition guidelines, the disease process, and the importance of compliance (Haskell, 1994). Home training should follow this early supervised period, which may vary from patient to patient according to the level of deconditioning and disease stability (Pina et al., 2003).

10.2.5 *Rationale and Purposes of the Study*

As detailed above, both aerobic and resistance exercise programs may improve exercise capacity, represented by peak oxygen consumption and exercise duration, in patients with CHF. Additionally, it has been demonstrated that aerobic exercise training may even reverse left ventricular remodelling and improve cardiac function in heart failure patients (Haykowsky et al., 2007; van Tol et al., 2006).

The effect of exercise training on cardiac power output so far has only been evaluated in a few studies, none of which recruited patients with stable CHF. Marshal and colleagues (2001) assessed healthy middle-aged individuals and Hodges et al. (2008) patients with atherosclerotic disease. Furthermore, Wright et al. (2002) assessed the effect of exercise on cardiac function in patients following coronary bypass surgery, whereas Patwala et al. (2006) assessed whether exercise rehabilitation enhances the benefits of cardiac resynchronisation therapy. Finally, Carroll et al. (2007) evaluated the effect of lifestyle intervention on peak cardiac power output and reserve in premenopausal obese women.

Although a few studies evaluated the effect of aerobic exercise on peak cardiac output (Mezzani et al., 2008), it appears that a limited number of studies, if any, assessed the effect of resistance training on central hemodynamic measures such as cardiac output or cardiac power output. Therefore, the first purpose of the present study was to assess the effect of aerobic and resistance exercise programs on cardiac power output and

other central haemodynamic measures. Secondly, the study evaluated the effect of the two exercise programmes on peak oxygen consumption and selected cardio-respiratory variables obtained from gas exchange measurements.

10.2.6 *Research Hypotheses*

H_1 – There will be a non-significant effect of either aerobic or resistance exercise on resting haemodynamic or metabolic measurements.

H_2 – There will be a significant improvement in maximal cardiac pumping capability following aerobic, but not following resistance exercise program.

H_3 – There will be a significant improvement in peak oxygen consumption and selected cardio-respiratory variables following both, aerobic and resistance exercise program.

10.3 Methods

10.3.1 *Study Design*

The study was originally proposed to be a prospective, randomized trial to assess the effect of two different 12-week exercise programmes (aerobic and resistance) on cardiac power output and selected cardio-respiratory variables. The present study was part of the clinical trial “Cardiac power output, heart rate variability and heart rate recovery in response to exercise training in heart failure patients” approved by the Hounslow and Hillingdon NHS Research Ethics Committee in March 2007. Originally proposed number of patients was 72 (36 to perform exercise: 18 aerobic and 18 resistance patients, and 36 to be control).

The sample size was calculated for each key variable (cardiac power output, heart rate variability and heart rate recovery). Sufficient sample size that provides high power of the study for cardiac power output was half of the above mentioned number (detailed below in 10.3.4). However, from the aspect of heart rate variability sample size of 72 was needed.

The project commenced in July 2007 and finished at the end of December 2008. The initial list of patients available to take part in the study included six patients only. The control group has been postponed due to concerns expressed by the panel member of the above mentioned Ethics Committee. They stressed that every patient should be offered to take part in exercise programme. According to them, control group may include those patients who do not want to exercise, or due to some other reasons (e.g. work commitments) are not able to participate in an exercise programme.

After six months, the researchers realized that the number of patients already recruited and involved in cardiac rehabilitation was dramatically below that expected and originally proposed. Following consultation with the principal investigator (DAB) and cardiologist (RGM), it was decided to do a cross-over study in order to increase the number in each group. This was approved by the above mentioned Ethics Committee. In order to ensure more patients, there was an attempt to recruit patients from other local hospitals (Wexham Park Hospital, Wycombe General Hospital). Due to travel costs and time issues, certain contacted patients (N=7) were not able to undertake the exercise programme, nor used as controls.

Not all patients recruited were able to complete the cross-over study design, mostly due to time issues. Therefore, the originally proposed prospective, randomized trial, study was changed to a prospective, treatment only randomized, semi cross-over design. A proper randomization into aerobic or resistance group, with a computerized random numbers table, was undertaken only on the first six patients available at the beginning of the project and before baseline tests were performed. As this was “rolling programme” each new available patient was allocated into the aerobic or resistance group consequently. This was the only way to ensure the same number of patients in each group.

In this study design each patient was tested twice before starting the exercise programme and following 12 weeks of exercise training. Two baseline cardiopulmonary exercise tests were undertaken to ensure the reliability of measurements (Chapter 9). The average of two measurements was taken as the baseline. All patients who underwent the cross-over design had a 12-week “non-exercising” period. Before and after the “non-exercising” period patients performed a

cardiopulmonary exercise test.

10.3.2 *Patients*

The study group consisted of 16 stable chronic heart failure patients (13 men, 3 women; mean±SD age 64±10 years) randomized into aerobic (N=8) or resistance group (N=8). Patients' demographic and clinical characteristics and medications are presented in table 10.3, according to the report by Dr RGM. Medications were not altered during the study. Inclusion criteria were reduced left ventricular ejection fraction (<40%) as assessed by echocardiography, and New York Heart Association (NYHA) class I and II. Additionally, all patients had to be in a clinically stable condition and on the same dose of optimal drug therapy for at least two months before entry in to the study. Exclusion criteria were exercise-induced myocardial ischaemia or uncontrolled arrhythmias, valvular heart disease, congestive heart failure, uncontrolled hypertension (resting systolic blood pressure above 160 mmHg, and/or resting diastolic blood pressure above 105 mmHg), peripheral vascular disease, chronic obstructive pulmonary disease and orthopaedic or other condition precluding regular participation in exercise sessions. All patients gave informed written consent before enrolment in the study.

Table 10.3 Study Patients' Demographic and Clinical Characteristics and Medications

	Aerobic Group (N=8)	Resistance Group (N=8)	Group difference p-value
Age (yrs)	65±12	63±10	0.64
Weight (kg)	74±15	78±18	0.54
Height (cm)	171±11	172±12	0.98
BMI (kg/m ²)	25±4	26±5	0.36
BSA (m ²)	1.86±0.25	1.91±0.26	0.66
LVEF (%)	31±6	28±5	0.69
NYHA I/II	4/4	3/5	
Men/Women	5/3	6/2	
<i>Aetiology:</i>			
IHD	1	2	
DCM	7	6	
<i>Medication:</i>			
	N of patients	N of patients	
ACE inhibitors	5	6	
β-blockers	6	7	
Diuretics	4	2	
ARBs	2	1	
Digoxin	3	2	
Antiarrhythmics	3	5	
Aspirin	2	5	
Warfarin	2	1	
Spironolactone	1	1	

BMI-body mass index, BSA-body surface area, LVEF-left ventricular ejection fraction, NYHA-New York Heart Association, IHD-ischaemic heart disease, DCM-dilated cardiomyopathy, ARBs-angiotensin II receptors blockers.

10.3.3 *Testing Procedure and Exercise Programme*

The testing procedure is detailed in the previous Chapter of this thesis, section 9.2.3. Briefly, each patient undertook two baseline cardiopulmonary exercise tests (modified Bruce protocol) one week apart. Metabolic and ECG data were recorded from the CardioO₂ metabolic analyser (Medical Graphics Corporation, Minnesota, USA) at rest and throughout the exercise test. Cardiac output was measured at rest and at peak exercise using the inert gas rebreathing methodology (Innocor, Innovision, Denmark). Blood pressure was also measured at rest, during and at peak exercise. The mean value of two exercise tests for all analyzed variables was taken as a baseline value in

the current study.

The exercise training programmes, both aerobic and resistance, included five sessions per week for a period of 12 weeks. One session was undertaken in Hillingdon Hospital Cardiac Rehabilitation Unit and this was a supervised exercise session which occurred every Monday during a 12-week exercise program. Additional four exercise sessions were performed at home (home based exercise) according to instructions provided by researchers (see below). Patients were asked to complete a daily exercise diary which was analysed every Monday just before a supervised exercise session. Before each supervised exercise session “pre-exercise” assessment was undertaken (e.g. measurement of blood pressure, health status, medication, home exercises adherence, etc.) Each supervised exercise session lasted between 50 and 60 minutes. This included a warm-up period (10-15 minutes), the main part of the training – aerobic or resistance exercise (25-35 minutes) and a cool-down period and stretching (10-15 minutes), with a further 15 minute post exercise monitoring period. The first session for each participant was a learning session where the correct technique and exercise intensities were demonstrated. For those participants who were severely de-conditioned, initial exercise intensity was set at approximately 40-50% of peak oxygen consumption, with a Rating of Perceived Exertion (Borg Scale) set at 11 – 12. An interval approach was used to ensure periods of active recovery which allowed the participant to exercise for longer. Participants who had a greater baseline peak oxygen consumption were encouraged to exercise approximately 60-80% of peak oxygen consumption, with a Rating of Perceived Exertion set between 11 – 13. The exercise prescription were progressed individually, as conditioning took place, with the emphasis placed on duration before intensity.

10.3.3.1 Aerobic exercise programme

The circuit aerobic training consisted of two circuits, each including seven cardiovascular stations (e.g. treadmill, bike I, cross-trainer (ski-machine), backward lunges, bike II, step-ups, and mini-trampoline). The work – rest ratio intervals started as 1:1 (60 seconds of exercise followed by 60 seconds of active recovery), with further change in ratio to 1.5:1 as conditioning took place. Active recovery was performed off the exercise station and included low intensity exercise (e.g. marching on spot).

Exercise intensity was between 40 and 50% or between 60 and 80% of maximal aerobic capacity, depending on initial peak oxygen consumption. In most of the patients this was equivalent to the Borg scale of between 11 – 12 and 12 – 13, as indicated during the baseline tests. The level of exercise intensity (rate of perceived exertion) was monitored on each exercise stations at 30 and 60 seconds by the use of the Borg scale, and periodic adjustments of exercise intensity were made according to individual exercise-capacity progression.

Home based aerobic exercise training (four days per week) essentially included a brisk walk taking between 20 and 40 minutes with a rate of perceived exertion of 11 to 13 (Borg scale). The first few weeks of exercise training duration were shorter (e.g. 20 minutes) with further increases in duration according to individual exercise-capacity progression. Each training session could be broken down into 15 or 10 minute segments if necessary in order to keep the required intensity level.

10.3.3.2 Resistance exercise programme

Resistance exercises included the use of body weight exercise, various strength of therabands, light hand and leg weights. Specifically, circuit resistance training consisted of two circuits, each included six exercise stations (e.g. biceps curls, calf raises, wall chest press, leg extension, lateral raises and hamstring curls). The principle of work – rest ratio intervals were the same as in the aerobic group. Active recovery was performed off the exercise station and included low intensity exercise (e.g. marching on spot). The exercise intensity targeted 12 to 15 repetitions per exercise station with sufficient weight that the patient score results were between 11 and 13 on the Borg scale. Exercise progressions were introduced gradually either by increasing the intensity (weight) or the number of sets for a given intensity. The level of exercise intensity was monitored at the end of each exercise, and periodic adjustments of exercise intensity were made according to individual exercise-capacity progression.

Home based resistance exercise (four sessions per week) of 30 minutes consisted of warm up and stretch (five to six minutes) followed by resistance exercises mentioned above with a work-rest ratio 1:1 (60 seconds of exercise followed by 60 seconds of

active recovery).

10.3.4 Study Power, Calculations and Statistical Analysis

The present study proposed to assess cardiac power output (CPO) before and after a 12 week exercise intervention period in patients with stable chronic heart failure. Sample size was calculated *a priori* (Faul et al., 2007) for a two-sided test where alpha and beta were 0.05 and 0.8, respectively. Due to the nature of cardiac power output measurements values, the majority effects that are observed are small and ranged from 0.34 (Wright et al., 2002) to 0.87 W (Patwala et al., 2006). This study proposed high statistical power (0.8 or more). Patwala et al. (2006) assessed CPO in a group of cardiac patients before and after exercise intervention (N = 14). In the exercise group, CPO increased from 2.46 (0.23) W to 3.33 (0.26) W. Calculated effect size for pre/post CPO in rehab group was 3.54 (high effect size). The power of the study was high (Beta = 1). Based on this study it seems that 10 subjects per exercise group will provide a high power of the study (0.92).

The cardiac power output was calculated from the product of cardiac output and mean arterial pressure using the following equation (Cooke et al., 1998): $CPO = (\dot{Q}_T \times MAP) \times K$, where CPO is cardiac power output in Watts (W), \dot{Q}_T is cardiac output in $l \cdot min^{-1}$, MAP is mean arterial pressure in mm Hg and K is the conversion factor (2.22×10^{-3}). The physiological cardiac reserve is equal to the difference in between peak CPO and baseline resting CPO (Cooke et al., 1998). The mean arterial pressure was calculated as $DBP + 0.412 \times (SBP - DBP)$, where SBP is systolic blood pressure and DBP is diastolic blood pressure (Meaney et al., 2000). Systematic vascular resistance to blood flow (SVR) at peak exercise was estimated as MAP/\dot{Q}_T and as per convention multiplied by a factor of 80 to convert units to $dyn \cdot s^{-1} \cdot cm^{-5}$. Peak exercise arteriovenous O_2 content difference ($a-\bar{v} O_2 dif.$), expressed as vol.%, was calculated as $(\dot{V}O_{2 peak}/\dot{Q}_T peak) \times 100$.

All statistical analysis was carried out using SPSS version 13.0 (SPSS inc. Chicago, Illinois, USA). Prior to statistical analysis, data were checked for univariate and multivariate outliers using standard Z-distribution cut-offs and Mahalanobis distance

tests respectively. Normality of distribution was assessed using a Kolmogorov-Smirnov test. The difference between the groups at baseline level was identified using independent *t*-tests or Mann Whitney U test, as appropriate. Furthermore, a repeated measures analysis of variance was constructed to analyse the effect of primary interest by time (pre and post) for each group and was also used to examine the effect of treatment (aerobic and resistance) over time (pre and post) between the two group. Where significant main effect (group or time) were identified, paired or unpaired *t*-tests as appropriate, were used to locate the specific effects (Williams et al., 2007). A *p* value of less than 0.05 was designated to indicate statistical significance. If significant change was found before and after exercise intervention in peak cardiac output, peak oxygen consumption and peak arteriovenous O₂ content difference, than Pearson's moment of correlation was used to assess the relationship between exercise-induced-changes in the aforementioned variables. All data are presented as means \pm SD unless otherwise indicated. As this was not fully crossed-over study design (only three and two patients crossed-over from one to the other group), recommended procedure for cross-over study design by Hills and Armitage (1979) has not been used due to insufficient number of patients in each group (two and three). These data are graphically presented.

10.4 Results

10.4.1 Pre Training Comparison

All 16 patients completed the exercise programme and five patients took part in the cross-over design following a 12-week “non-exercising” period. Three patients from the resistance training group crossed over to the aerobic training group following a “non-exercising” period of 12-weeks. Similarly, two patients from aerobic exercise group crossed over to resistance exercise training group following a “non-exercising” period. This increased the number of patients in each group; the aerobic group consisted of 11 (three female), whereas the resistance group consisted of 10 (two female) patients. During the exercise programme patients remained in a clinically stable condition without changing their medication. Overall attendance at the exercise sessions was very good, and patients from both aerobic and resistance exercise group performed ~90% of planned exercise sessions.

No significant differences were found pre training between the groups for age and body anthropometry (Table 10.3). Additionally, no significant difference between aerobic and resistance exercise group was found for any haemodynamic or metabolic variables measured at rest or at peak exercise, respectively (Table 10.4).

Table 10.4 Baseline Resting and Peak Exercise Haemodynamic and Metabolic Measurements

	Sitting at rest			Peak exercise		
	Aerobic (N=11)	Resistance (N=10)	$p^{\#}$ value	Aerobic (N=11)	Resistance (N=10)	$p^{\#}$ value
<i>Haemodynamics</i>						
CPO (W)	0.74±0.21	0.77±0.25	0.50	2.56±1.78	2.58±0.82	0.39
HR (beats·min ⁻¹)	60±9	63±11	0.51	125±25	123±28	0.58
\dot{Q}_T (l·min ⁻¹)	3.7±1.1	3.8±1.1	0.81	11.1±6.7	10.9±4.1	0.27
SV (ml·beat ⁻¹)	63.2±19.1	60.4±15.3	0.71	89.6±51.5	88.2±29	0.48
DBP (mm Hg)	73±8	72±9	0.18	71±11	76.7±11.2	0.22
SBP (mm Hg)	116±15	117±12	0.44	146±25	147±22	0.86
MAP (mm Hg)	91±10	92±7	0.23	102±15	106±14	0.55
CR (W)	-	-	-	1.82±1.22	1.78±0.43	0.26
<i>Metabolics</i>						
$\dot{V}O_2$ (ml·min ⁻¹)	285±79	331±106	0.26	1778±861	1726±610	0.87
$\dot{V}O_2$ (ml·kg ⁻¹ ·min ⁻¹)	3.9±0.7	4.2±1.0	0.50	23.3±6.5	22.2±5.3	0.63
$\dot{V}C_2$ (ml·min ⁻¹)	210±69	258±85	0.17	1879±902	1822±651	0.79
RER	0.73±0.10	0.78±0.11	0.27	1.06±0.1	1.07±0.1	0.56
\dot{V}_E (l·min ⁻¹)	10.2±2.3	11.8±3.1	0.48	42.4±12.1	41.9±7.5	0.91
a- \bar{v} O ₂ dif, vol. %	-	-	-	15.5±2.8	15.6±2.9	0.31
AT (ml·kg ⁻¹ ·min ⁻¹)	-	-	-	14.2±3.9	13.1±2.2	0.41
Exercise time (s)	-	-	-	687±279	743±104	0.54

CPO-cardiac power output, CR-cardiac reserve, HR-heart rate, \dot{Q}_T -cardiac output, SV-stroke volume, DBP-diastolic blood pressure, SBP-systolic blood pressure, MAP-mean arterial blood pressure, $\dot{V}O_2$ -oxygen consumption, $\dot{V}C_2$ -carbon dioxide production, RER-respiratory exchange ratio, \dot{V}_E -minute ventilation, AT-anaerobic threshold.

$p^{\#}$ value – group difference.

10.4.2 Effect of Exercise Training on Resting Haemodynamic and Metabolic Measurements

Repeated measures analysis of variance showed that there were no significant reductions in body weight following either aerobic or resistance exercise. Repeated measures analysis of variance revealed that there was non-significant difference between the two groups over the time (test for interaction, $p>0.05$) for all variables measured at rest. Resting cardiac power output, cardiac output, heart rate and stroke volume were not significantly different before and after either aerobic or resistance exercise training ($p>0.05$). Resting arterial blood pressure and metabolic measurements did not change significantly as a result of the aerobic or resistance exercise, as shown in Table 10.5.

Table 10.5 Pre (Baseline)– and Post (End Point)– Exercise Intervention Resting Haemodynamic and Metabolic Measurements

	Aerobic Group (N=11)			Resistance Group (N=10)		
	Baseline	End Point	%	Baseline	End Point	%
<i>Haemodynamics</i>						
CPO (W)	0.74±0.21	0.75±0.28	1.1	0.77±0.25	0.75±0.25	-2.2
HR (beats·min ⁻¹)	60±9	61±8	1.2	63±11	65±12	2.9
\dot{Q}_T (l·min ⁻¹)	3.7±1.1	3.9±1.3	4.8	3.7±1.1	3.8±0.9	3.8
SV (ml·beat ⁻¹)	63.4±19.1	64.1±26.8	1.3	60.2±15.3	58.9±14.3	-3.1
DBP (mm Hg)	73±8	71±8	-4.9	72±9	70±11	-2.6
SBP (mm Hg)	114±15	111±11	-3.1	117±12	114±16	-2.1
MAP (mm Hg)	91±10	87±8	-4.6	92±7	88±13	-3.9
<i>Metabolics</i>						
$\dot{V}O_2$ (ml·min ⁻¹)	285±79	329±129	7.6	331±106	313±135	-5.8
$\dot{V}O_2$ (ml·kg ⁻¹ ·min ⁻¹)	3.9±0.7	4.4±1.0	7.7	4.2±1.0	3.9±1.0	-7.5
$\dot{V}C_2$ (ml·min ⁻¹)	210±69	241±112	15.1	258±85	252±117	-3.2
RER	0.73±0.10	0.75±0.13	5.3	0.78±0.11	0.80±0.10	2.1
\dot{V}_E (ml·min ⁻¹)	10.2±2	11.04±4.0	7.6	11.8±3.1	10.4±4.6	11.9

%-percentage change from baseline, CPO-cardiac power output, HR-heart rate, \dot{Q}_T -cardiac output, SV-stroke volume, DBP-diastolic blood pressure, SBP-systolic blood pressure, MAP-mean arterial blood pressure, $\dot{V}O_2$ -oxygen consumption, $\dot{V}C_2$ -carbon dioxide production, RER-respiratory exchange ratio, \dot{V}_E -minute ventilation.

10.4.3 *Effect of Exercise Training on Peak Exercise Haemodynamic and Metabolic Measurements*

Table 10.6 shows the effect of aerobic and resistance exercise programs on peak haemodynamic and metabolic variables. Peak cardiac power output increased by 6.2% following aerobic exercise, whereas following resistance training remained unchanged. Peak cardiac output significantly increased in the aerobic group (by $0.8 \text{ l}\cdot\text{min}^{-1}$, $p<0.05$) but not in resistance exercise group. This increase in peak cardiac output following aerobic exercise was associated with an increase in peak stroke volume by ~6%. No significant change, however, was identified in any of the measured haemodynamic variables following resistance exercise training (Table 10.6). Post training cardiac output and stroke volume of the aerobic group was significantly higher compared with the resistance exercise group (11.9 vs. $10.8 \text{ l}\cdot\text{min}^{-1}$, and 94.9 vs. $86.9 \text{ ml}\cdot\text{beat}^{-1}$, $p<0.05$), respectively. Similarly, systematic vascular resistance following aerobic exercise was significantly lower compared with that following resistance exercise (684 vs. $806 \text{ dyn}\cdot\text{s}^{-1}\cdot\text{cm}^{-5}$).

Following aerobic exercise training, peak oxygen consumption and anaerobic threshold increased significantly from baseline values by 7.1% and 7.8%. No significant increase for the same variables was found following resistance training. An increase in anaerobic threshold following aerobic exercise was significantly higher than that following resistance exercise ($p<0.05$). Exercise time increased significantly following both aerobic and resistance exercise training, as were peak minute ventilation, carbon dioxide production and respiratory exchange ratio (Table 10.6).

Table 10.6 Pre (Baseline)– and Post (End Point)– Exercise Intervention Peak Exercise Haemodynamic and Metabolic Measurements

	Aerobic Group (N=11)			Resistance Group (N=10)		
	Baseline	End Point	%	Baseline	End Point	%
<i>Haemodynamics</i>						
CPO (W)	2.56±1.78	2.72±1.61	6.2	2.58±0.82	2.59±0.62	0.8
CR (W)	1.82±1.22	1.98±1.12	5.9	1.80±0.43	1.81±0.51	0.6
HR (beats·min ⁻¹)	125±25	126±22	0.9	123±28	125±27	1.6
\dot{Q}_T (l·min ⁻¹)	11.1±6.7	11.9±6.4*	7.1	10.9±4.1	10.8±2.2 [†]	-0.8
SV (ml·beat ⁻¹)	89.6±51.8	94.9±53.8*	6.1	88.2±29.4	86.9±28.2 [†]	-1.7
DBP (mm Hg)	71±11	72±10	1.2	76±11	76±14	-0.7
SBP (mm Hg)	146±25	147±27	0.3	147±22	152±23	2.3
MAP (mm Hg)	102±15	103±16	0.6	106±14	108±18	1.1
SVR (dyn·s ⁻¹ ·cm ⁻⁵)	742±231	684±212*	-8.2	771±179	806±186 [†]	3.8
<i>Metabolics</i>						
$\dot{V}O_2$ (ml·min ⁻¹)	1778±861	1889±896**	5.7	1726±610	1796±537	4.6
$\dot{V}O_2$ (ml·kg ⁻¹ ·min ⁻¹)	23.3±6.5	25.1±6.7*	7.1	22.2±5.3	23.2±3.6	4.9
$\dot{V}C_2$ (ml·min ⁻¹)	1879±902	2132±1049**	11.8	1822±651	1988±630*	8.8
RER	1.06±0.10	1.13±0.10**	6.4	1.07±0.10	1.12±0.11*	4.7
\dot{V}_E (ml·min ⁻¹)	42.4±12.1	60.8±26.2**	29.4	41.9±7.5	62.3±18.4**	32.1
a- \bar{v} O ₂ dif, vol.%	15.5±2.8	15.6±2.8	0.7	15.6±2.9	15.9±3.0	1.2
AT (ml·kg ⁻¹ ·min ⁻¹)	14.2±3.9	15.5±4.5**	7.8	13.1±2.2	14.0±2.7 [†]	5.8
Exercise time (s)	721±279	803±260**	10.4	743±104	799±100*	6.9

%-percentage change from baseline, CPO-cardiac power output, CR-cardiac reserve, HR-heart rate, \dot{Q}_T -cardiac output, SV-stroke volume, DBP-diastolic blood pressure, SBP-systolic blood pressure, MAP-mean arterial blood pressure, SVR-systemic vascular resistance, $\dot{V}O_2$ -oxygen consumption, $\dot{V}C_2$ -carbon dioxide production, RER-respiratory exchange ratio, \dot{V}_E -minute ventilation, a- \bar{v} O₂dif-arteriovenous O₂ difference, AT-anaerobic threshold.

*Denotes p<0.05 vs. baseline

**Denotes p<0.01 vs. baseline

[†]Denotes p<0.05 vs. aerobic (post-exercise)

A high positive correlation was found between changes in peak cardiac output and changes in peak oxygen consumption following aerobic exercise training ($r=0.82$, $p<0.01$).

It is important to emphasize that statistical analysis for key exercise variables (e.g. cardiac power output, cardiac output, mean arterial pressure, peak oxygen consumption and anaerobic threshold), in addition to one described before, was also performed with groups consisted of eight patients. Analysis of variance revealed that results were not differed from those when groups consisted of 11 and 10 patients (when two/three patients performed the opposite exercise programme following a 12 week “non-exercising” period).

10.4.4 Cross-Over Study Design Results

As previously mentioned, the main reason for asking patients to take part in the “cross-over” design was to increase number of patients in each exercise group. Only two patients from the aerobic exercise group took part in the “cross-over” design. Since they completed the aerobic exercise programme, they were allowed a 12-week “non-exercising” period, following which they performed a baseline exercise test. Consequently, they were enrolled into resistance exercise group for a 12-week exercise programme followed by cardiopulmonary exercise test.

Figure 10.1 illustrates changes in key variables (peak cardiac power output, peak oxygen consumption, anaerobic threshold and peak cardiac output) over the time in two male patients (mean age, 65 yrs; weight, 77 kg; height, 178 cm; NYHA class, I-II).

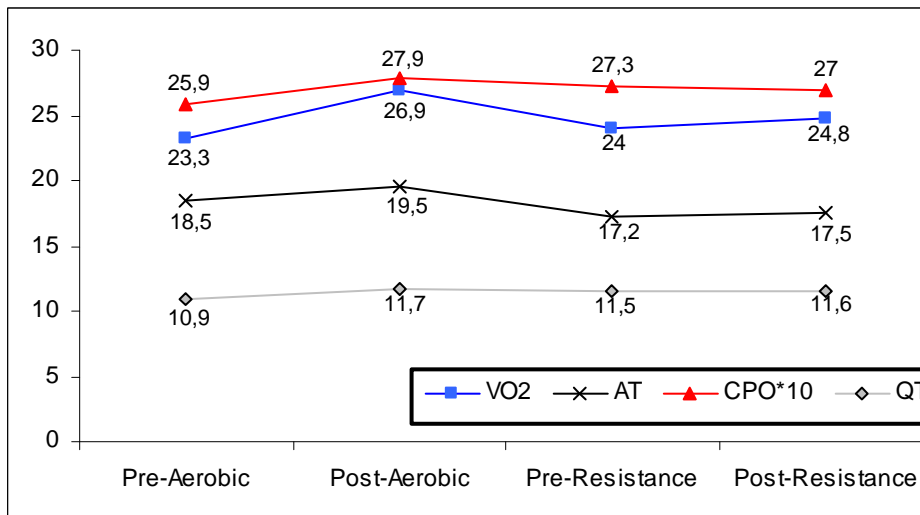


Figure 10-1 Changes in key variables (peak oxygen consumption, $\dot{V}O_2$; anaerobic threshold, AT; peak cardiac power output, CPO; and peak cardiac output, \dot{Q}_T) following aerobic and resistance exercise programmes separated by a 12-week “non-exercising” period (N=2).

Figure 10.2 shows mean results for three patients (mean age, 69 yrs; weight, 74 kg; height, 172 cm; NYHA class, II) who firstly performed resistance exercise followed by a 12-week “non-exercising” period and aerobic exercise.

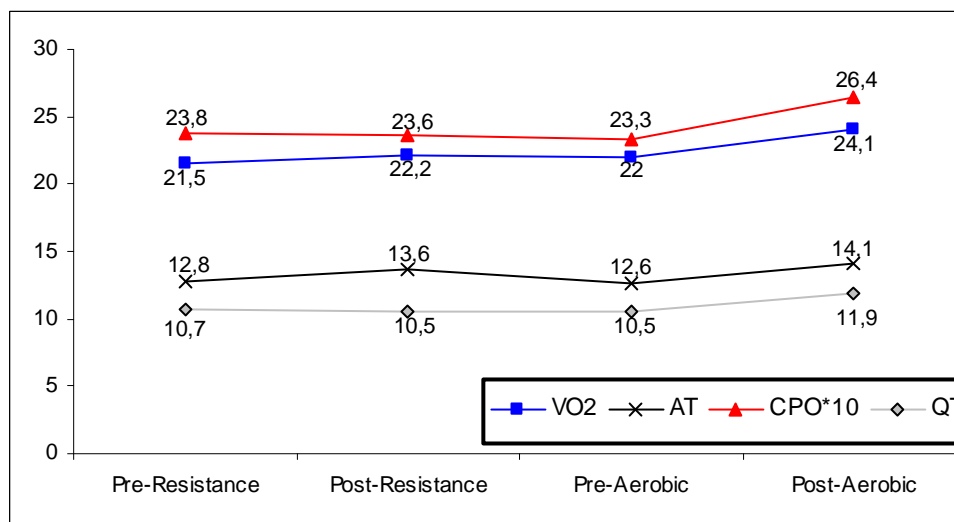


Figure 10-2 Changes in key variables (peak oxygen consumption, $\dot{V}O_2$; anaerobic threshold, AT; peak cardiac power output, CPO; and peak cardiac output, \dot{Q}_T) following resistance and aerobic exercise programmes separated by a 12-week “non-exercising” period (N=3).

10.5 Discussion

The present study describes changes that occur in central haemodynamic and selected cardio-respiratory variables in response to different, clinically relevant modalities of exercise. The main finding of this study suggests that aerobic exercise training was generally associated with positive changes in central haemodynamic and metabolic variables, whereas resistance exercise training had little effect on the same variables.

10.5.1 *The Effect of Aerobic Exercise Training on Cardiac Power Output and Selected Cardio-Respiratory Variables*

A limited number of studies has assessed the effect of an aerobic exercise programme on cardiac power output in heart failure patients. This should not be surprising as only a few investigations measured cardiac output at peak exercise before and after an exercise intervention in heart failure patients (Mezzani et al., 2008).

It has been demonstrated that aerobic exercise training of eight weeks (cycling five days per week with an intensity of 75-80% of the $\dot{V}O_2$ max for 20 minutes) resulted in an increase of 16% in peak cardiac power output, 21% in cardiac reserve, and 11% in stroke volume in healthy middle-aged volunteers (Marshall et al., 2001). It has also been shown that even a low intensity, short-term (six weeks) aerobic exercise programme led to an improvement in overall cardiac function in ischaemic cardiac patients following coronary artery bypass graft surgery (Wright et al., 2002). Peak cardiac power output and cardiac reserve increased significantly by 10% and 12%. This was mostly due to increase in cardiac output by 0.9 l min^{-1} . Patwala et al. (2006) assessed the effect of aerobic exercise (three times per week treadmill walking up to 20 minutes and cycling of 10 minutes) on cardiac power output in patients three and six months following cardiac resynchronization therapy. Results showed that peak cardiac power output increased more in patients who participated in exercise programme than those who were in the control group. The present study also indicates that aerobic exercise training had a positive effect on overall cardiac function in patients with stable chronic heart failure. This is demonstrated by an increase in peak cardiac power output and cardiac reserve by 6.2%, and 5.9%. Most of these changes

in cardiac power output are associated with changes in flow-generating capacity of the heart (cardiac output). On average, peak cardiac output increased by $0.8 \text{ l}\cdot\text{min}^{-1}$ following aerobic exercise training.

The finding of the present study that aerobic exercise training increases peak cardiac output is consistent with previous studies (Coats et al., 1992; Hambrecht et al., 1995; Hambrecht et al., 2000; Sullivan et al., 1988). This increase in cardiac output found in the present study is mainly due to increase in stroke volume, whereas heart rate remained almost unchanged.

Sullivan et al. (1988) assessed the effect of four to six months aerobic exercise training in 12 patients with stable CHF. Patients exercised (cycling, walking, jogging, stair climbing) approximately four hours per week at heart rate corresponding to 75% of peak oxygen consumption. Exercise training resulted in a 10% and 23% increase in maximal cardiac output and peak oxygen consumption (from 8.9 to $9.9 \text{ l}\cdot\text{min}^{-1}$, and from 16.8 to $20.6 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$). Left ventricular ejection fraction, end-diastolic and end-systolic volume were unchanged, whereas peak stroke volume tended to increase. Coats et al. (1992) evaluated the effect of eight weeks exercise training (cycling 20 minutes, five days per week, with intensity between 60 to 80% of $\dot{V}\text{O}_2$ peak) in 17 male patients with stable moderate to severe CHF. Training significantly increased peak cardiac output and peak oxygen consumption (from 6.3 to $7.1 \text{ l}\cdot\text{min}^{-1}$ and 13.9 to $16.5 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$), whereas non significant change was found before and after training in peak mean arterial pressure. Further, Hambrecht et al. (1995) determined hemodynamic and functional response to six months aerobic exercise training (daily cycling for approximately 40 minutes at 70% of $\dot{V}\text{O}_2$ peak) in 12 patients with CHF. After training, patients demonstrated a significant increase in cardiac output, peak oxygen consumption and oxygen consumption at anaerobic threshold by 19%, 23% and 31%. No significant difference before and after training was found for mean arterial blood pressure either at rest or at peak exercise, whereas peak heart rate increased significantly after training (from 163 to $172 \text{ beats}\cdot\text{min}^{-1}$ or 3%).

In a subsequent study, Hambrecht et al. (2000) evaluated the effects of six months aerobic exercise training (daily cycling at heart rate corresponding to 70% of

$\dot{V}O_2$ peak for 20 minutes). In contrast with previous and present studies, Hambrecht and colleagues found an increase in resting cardiac output by $0.3 \text{ l}\cdot\text{min}^{-1}$ which was associated with an increase in stroke volume by $\sim 18\%$. As in the present study, Hambrecht et al. (2000) did not find significant changes in mean arterial pressure at rest nor at peak exercise following exercise intervention compared with baseline values. Furthermore in a study by Hambrecht and colleagues, peak exercise cardiac output and stroke volume increased by $\sim 16\%$ and $\sim 13\%$, respectively, whereas in the present study by 7.1% and 6.1% . Similarly with the present study, they reported a significant reduction in systematic vascular resistance following aerobic training, suggesting training-induced afterload modifications. As suggested by Hambrecht et al. (1998), these changes are likely to be due to a corrective effect of aerobic training on the endothelial dysfunction typical in CHF. In addition, Hambrecht and associates (2000) demonstrated significant increase in peak oxygen consumption and anaerobic threshold from 18.2 to $23 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ and from 10.4 to $13.8 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ following a six-month aerobic training.

It seems that more functional improvement is associated with an exercise training programme of greater intensity and duration as suggested by Rees et al. (2004). That low intensity aerobic exercise training has little effect on haemodynamic measures has been demonstrated by Belardinelli et al. (1995). Eighteen patients with mild CHF underwent a low intensity (40% of $\dot{V}O_2$ peak) training programme (cycling) three times per week for eight weeks. $\dot{V}O_2$ peak and anaerobic threshold increased by 17% (from 16.1 to $18.9 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) and 20% compared with baseline in the training, but not in the control group. Cardiac output at rest, submaximal exercise or at peak exercise was not significantly different before and after exercise training. Interestingly, from skeletal muscle biopsy, Belardinelli et al. (1995) found that there was an increase in volume density of mitochondria, and subsequently high correlation was found between changes in peak oxygen uptake and in volume density of mitochondria ($r=0.77$) and between changes in lactate threshold and volume density of mitochondria ($r=0.81$). Peripheral changes in response to aerobic exercise training have been detailed in section 10.2.2.1 of this Chapter.

In contrast to Belardinelli et al. (1995), Dubach et al. (1997) evaluated the effects of a

two month high intensity aerobic exercise training (four sessions per week of 40 minutes cycling at 70% and 80% of $\dot{V}O_2$ peak in addition to every day two hours walking). In this, as in the present study, resting cardiac output was not significantly changed before and after training. Similarly, nor arterial pressure either at rest or peak exercise. Peak cardiac output, however, increased significantly by 12% (from 12 to 13.7 l·min⁻¹). Also, $\dot{V}O_2$ peak increased by 23 % after one month of exercise, and by an additional 6% after two months.

Based on studies of Belardinelli et al. (1995) and Dubach et al. (1997), but also considering those previously mentioned in this section, it may be argued that only aerobic exercise training of higher intensity (e.g. >70% of $\dot{V}O_2$ peak) will enhance cardiac function and improvement in maximal cardiac output. The present study also intended that patients perform a higher intensity exercise as indicated on the Borg scale between 12 and 13. This Rate of Perceived Exertion was expected to demonstrate an exercise intensity of 60% to 80% of $\dot{V}O_2$ peak, as shown during the baseline exercise test. Therefore an increase in peak cardiac output by 0.8 l·min⁻¹ is not unexpected.

It should be noted that most of the above cited studies which evaluated the effect of exercise on cardiac output were performed in pre-beta-blockers era. In Hambrecht and colleagues' study (2000) only eight percents of patients were on β -blockade therapy, whereas in the present study 75% of patients in the aerobic group used β -blockers. Currently, only one more study evaluated cardiac output response to exercise following an aerobic exercise intervention in patients on β -blockers (Nachwatel et al., 2002). Specifically, they assessed the effect of short-term (three weeks) interval versus continuous aerobic exercise on metabolic and haemodynamic data. Although both modalities had similar positive effects on $\dot{V}O_2$ peak and anaerobic threshold, continuous short-term exercise had no impact on cardiac index. In contrast, after interval training, cardiac index increased significantly by 9%. These studies, therefore, demonstrate that aerobic exercise training may improve peak cardiac output in patients on β -blockers as in patients without this medication. Interestingly, the present study suggests that most of the improvement in peak cardiac output is due to an increase in stroke volume, whereas peak heart rate before and after aerobic

exercise training remained unchanged.

Consistent with the above cited studies, the present study also demonstrates that aerobic exercise training significantly increased $\dot{V}O_2$ peak. The percentage difference before and after training of 7.1% ($1.8 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) is, however, lower than previously reported. Most studies observed an improvement in $\dot{V}O_2$ peak, ranging from 10% to 30% (Rees et al., 2004) or $\sim 3 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ (Haykowsky et al., 2007). It should be noted, however, that patients in the present study had a higher baseline $\dot{V}O_2$ peak values ($23.3 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) compared with patients in most of the previous studies ($<20 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$), suggesting better overall functional capacity of the patients before starting the aerobic exercise programme. This is likely to explain smaller percentage improvement in $\dot{V}O_2$ peak between the present and previous studies. Similarly, anaerobic threshold was also significantly higher compared with baseline value in aerobic group, but also compared with the resistance exercise group.

Theoretically, the underlying mechanisms responsible for the increase in $\dot{V}O_2$ peak can be divided into mechanisms responsible for improvement in cardiac output and factors that improve oxygen extraction (arteriovenous O_2 content difference). The latter has not significantly changed following aerobic training. The change in maximal cardiac output was highly correlated with the change in peak oxygen consumption, suggesting that central haemodynamic adaptations contribute to improved exercise performance after aerobic exercise training in the present study. A similar finding to this was also observed by Hambrecht et al. (1995) following aerobic exercise intervention.

The findings of the present study further suggest that maximal cardiac pumping capability (peak cardiac power output) and peak cardiac pumping reserve (cardiac reserve), both improved by $\sim 6\%$ following aerobic exercise training. Peak mean arterial pressure remained unchanged, as was peak heart rate, and therefore, slight improvement in overall cardiac function is likely to be explained by an improvement in stroke volume. From literature available, it seems that there are several mechanisms which may possibly explain improvement in stroke volume. Stroke volume is calculated from the following formulae (Mezzani et al., (2008): $SV=[LVEDV \times$

LVEF X (1-MRF)], where SV is stroke volume, LVEDV is left-ventricular end-diastolic volume, LVEF is left ventricular ejection fraction, and MRF is mitral regurgitant fraction.

The meta-analysis mentioned previously, which assessed the effect of exercise training on cardiac performance (van Tol et al., 2006), demonstrated a small but significant improvement in resting LVEDV (mean decrease of 3.1 ml) and resting diastolic blood pressure (mean decrease of 2.7 mm Hg) after aerobic training (mean duration 13±8 weeks) in CHF patients. Also, Haykowsky et al. (2007) in another meta-analysis, reported that aerobic exercise training reverses left ventricular remodelling in clinically stable CHF patients. It has been found that aerobic exercise training significantly improved ejection fraction by 3%, and decreased end-diastolic and end-systolic volumes by ~11% and ~13%, respectively. Moreover, Haykowsky et al. (2007) suggested that favourable changes in left ventricular volumes and ejection fraction associated with aerobic training were supplementary to pharmacological benefits (e.g. they occurred despite patients being prescribed medications with a proven antiremodeling effect). The mechanisms for such antiremodelling effects are not entirely understood. However, Haykowsky suggested that it may be due to the reduction in vasoconstrictive neurohormones or a decline in haemodynamic loading.

Braith et al. (1999) reported that aerobic training reduces resting plasma angiotensin II, aldosterone, vasopressin, atrial natriuretic peptide, brain natriuretic peptide, epinephrine, and norepinephrine levels. Coats et al. (1992) also reported that short-term aerobic training is associated with a decrease in sympathetic tone and a concomitant increase in vagal activity in stable CHF patients. Haykowsky et al. (2007) argued that improved sympathovagal balance, coupled with a decline in vasoconstrictive neurohormones, is associated with a reduction in vascular load that may attenuate left ventricular remodelling. Indeed, Hambrecht et al. (1995, 2000) have shown that the reduction in resting left ventricular end-diastolic volume and increase in peak exercise stroke volume that occurred with aerobic training were related to the decline in resting and peak exercise systemic vascular resistance (Hambrecht et al., 1995). Additionally, Belardinelli et al. (1996,1998) demonstrated that aerobic training improves myocardial contractility and diastolic filling in heart failure patients. In patients with dilated cardiomyopathy of ischaemic origin, aerobic

training may improve blood flow supply to left ventricular areas of hibernating myocardium ultimately leading to some degree of recovery of regional contractility and regression of unfavourable remodelling (Gianuzzi et al., 2003). Improvement of endothelial function, regression of coronary atherosclerosis, collateral formation, and increased vasculogenesis have all been proposed as mechanisms favouring training-induced increase in myocardial perfusion both in normal and patients with coronary artery disease (Linke et al., 2006; Nakamura et al., 2002). Aerobic training is associated with an improvement of left ventricular diastolic filling by an increase of diastolic filling time and increased relaxation velocity in CHF patients (Belardinelli et al., 1996). Mechanisms used to explain training-induced enhancement of diastolic function in CHF are increased calcium uptake by the sarcoplasmic reticulum (Moore et al., 1995), an improved perfusion of myocardium (Linke et al., 2006), more efficient myocardial bioenergetics (Ventura-Clapier et al., 2007), and reduction of left ventricular diastolic asynchrony (Belardinelli et al., 1996).

The present study demonstrates that training-induced afterload modifications at peak effort in patients with CHF (e.g. peripheral vascular resistance decreased by $\sim 60 \text{ dyn}\cdot\text{s}^{-1}\cdot\text{cm}^{-5}$). Similar finding was reported previously by Dubach et al. (1997) and Hambrecht et al. (2000). These adaptations are likely to be due to the possible corrective effect of aerobic training on endothelial dysfunction typical of CHF (Hambrecht et al., 1998).

Finally, besides the increases in peak cardiac output and peak oxygen consumption, there was a $\sim 7\%$ statistically significant increase in anaerobic threshold, $\sim 12\%$ in peak carbon dioxide production, $\sim 10\%$ in maximal exercise time and, $\sim 30\%$ in maximal minute ventilation, respectively. These findings are similar to those by Hambrecht et al. (2000), and they are also reported elsewhere (Pina et al., 2003; Working Report Group, 2000). Several mechanisms that may occur in response to aerobic exercise training may contribute to significant increase in exercise tolerance and anaerobic threshold in CHF patients. Firstly, aerobic exercise training increases capillary density, promotes the synthesis and release of nitric oxide, improves angiogenesis, vasodilation and endothelial function, reduces oxidative stress and peripheral vascular resistance, and increases metabolic capacity and musculoskeletal blood flow (Adamopoulos et al., 2003; Duscha et al., 2008; Wisloff et al., 2007). Secondly,

aerobic exercise training in CHF patients is associated with lower blood lactate threshold and blood lactate concentration at standardized submaximal workload levels (Belardinelli et al., 1995), reduced depletion and more rapid resynthesis of phosphocreatine (Adamopoulos et al., 2003), and increased citrate synthase activity (Duscha et al., 2008). Following aerobic training, the mitochondrial total volume density is increased, mitochondrial enzymatic activity and skeletal muscles' oxidative capacity are enhanced (Belardinelli et al., 1995; Duscha et al., 2008; Piepoli et al., 1998). In addition, it has been suggested that aerobic training improves phase II O₂ kinetics, which is an indirect index of muscle oxidative capacity (Roditis et al., 2007). Also, some studies have shown a shift from IIb to IIa muscle fibre type (Duscha et al., 2008) and a modest increase in type I muscle fibres (Hambrecht et al., 1997). Although the present study was not proposed to evaluate any of the above mentioned underlying mechanisms which may be responsible for positive changes in metabolic variables, there is no reason why some of these changes could occur in the studied cohort of patients.

To summarize this section, it is clear that aerobic exercise training as utilised in the present study is associated with improvement in key haemodynamic and exercise tolerance variables such as cardiac output, oxygen consumption, anaerobic threshold and exercise duration.

10.5.2 The Effect of Resistance Exercise Training on Cardiac Power Output and Selected Cardio-Respiratory Variables

The findings of the present study clearly suggest that resistance exercise training did not have significant effect on any of the central haemodynamic variables measured at rest or at peak exercise, nor on peak oxygen consumption and anaerobic threshold. There was, however, a significant increase in carbon dioxide production, minute ventilation and exercise duration following resistance exercise training.

Two decades ago, a study by Elkayam and colleagues (1985) raised a fear that isometric exercise significantly deteriorates cardiac performance in some patients with advanced chronic heart failure. They reported that during isometric exercise systematic vascular resistance increases while cardiac index and stroke volume index

decreases. The findings of this study caused a great concern regarding the suitability of resistance training for chronic heart failure patients. The protocol in their study however, examined the patients response to 5-7 minutes of isometric exercise at 30% of maximal voluntary contraction (Elkayam et al., 1985) which today is not recommended for any population (Pollock et al., 2000). It has been suggested that during a lower intensity of resistance exercise, the haemodynamic responses do not exceed levels attained during standard treadmill test (McKelvie et al., 1995), and adverse left ventricular remodelling after resistance training has not been demonstrated (Pu et al., 2001).

Exercise intolerance in CHF patients may partially be explained by a reduction of muscle mass and strength of skeletal muscles (Harrington and Coats, 1997). Therefore, it has been suggested that in contrast to aerobic, resistance exercise training has potential to increase muscle mass and subsequently enhance exercise performance (Baith and Becks, 2008). Moreover, Williams and associates (2007) argued that effects of resistance training in heart failure appear to be directed at improving skeletal muscle ultrastructural abnormalities and/or neuromuscular function rather than simply increasing muscle mass.

Conversely to a number of studies which evaluated the effect of aerobic exercise in CHF patients, a few investigations evaluated the effect of resistance exercise training on functional improvement in CHF patients. Two studies only (Levinger et al., 2005; Feiereisen et al., 2007) assessed central haemodynamics, although measured at rest. Levinger et al. (2005) assessed the effect of eight weeks resistance training on the left ventricular structure and function in patients with CHF (baseline $\dot{V}O_2$ peak of 14.4 ml·kg⁻¹·min⁻¹). Patients performed three sessions per week which included nine different exercises for the major muscle groups. Initial intensity corresponded to 40-60% of maximal strength (one set of 15 to 20 repetitions). The intensity was gradually increased during the eight-week programme by increasing the weight and reducing the number of repetitions. Results revealed that ejection fraction and stroke volume at rest increased significantly by ~13% in comparison with baseline value, respectively. Non-significant differences were found in end-diastolic and end-systolic volume before and after training. The authors concluded that the resistance training was a suitable method of training in patients with CHF since it does not cause a reduction of

left ventricular contractility function or enhance myocardial deterioration. Furthermore, Feiereisen et al. (2007) reported that resistance exercise training improved LVEF, and decreased left ventricular end-diastolic and end-systolic volumes, indicating for the first time that resistance exercise training may have an antiremodelling effect. Authors believed that exercise training could potentially add to the effect of medication by inducing endothelium-dependent vasodilation, reducing peripheral vascular resistance and afterload and resulting in a further increase in LVEF. The present study, however, did not show significant difference in systematic vascular resistance nor in diastolic blood pressure, suggesting that resistance training did not enhance afterload of the left ventricle.

It should be noted that apart from resting echocardiography, Levinger and associates (2005) as well as Feiereisen et al. (2007) were not able to demonstrate any measure of cardiac performance during exercise or at peak exercise. It is well documented that no association exists between resting and peak exercise measures of cardiac performance (Pina et al., 2003). The present study suggests that resistance exercise training did not significantly increase any central haemodynamic measure either at rest or at peak exercise. In these cited studies, most of the patients were on β -blockers; patients had considerably different levels of peak oxygen consumption at baseline level (14.6 and 15.6 vs. 22.3 ml·kg⁻¹·min⁻¹ in the present study). This may indicate that patients who possess better functional capacity at baseline level are unlikely to benefit from resistance exercise training, at least using the methodology as in the present study. Nonetheless, in the already mentioned meta-analysis, Haykowsky et al. (2007) suggested that the favourable effect of aerobic exercise training on left ventricular remodelling has not been shown in those studies which combined aerobic or resistance modes of exercise. This may be because of the heightened systolic and diastolic pressure loading that occur with strength training (Cheetham et al., 2002; McKelvie et al., 1995). These studies also suggested that strength-training-mediated increase in left ventricular wall stress, coupled with the impaired contractile and preload reserve could explain why stroke volume and ejection fraction do not increase when heart failure patients perform this type of exercise (Cheetham et al., 2002; McKelvie et al., 1995).

The effect of resistance training on peak oxygen consumption has been better

documented than its effect on central haemodynamic measures. Some studies demonstrated improvement in maximal oxygen consumption, whereas some studies reported no changes in peak oxygen consumption before and after training. Feiereisen et al. (2007) compared the efficacy of three training modalities on peak oxygen consumption in three groups of 15 patients with CHF. Patients underwent either resistance training, aerobic training, or a combination of aerobic plus resistance training during 40 sessions, three times weekly for 45 minutes. Surprising result of the study was that the three exercise modes were comparably effective in improving peak oxygen consumption (resistance group +16.7%, aerobic group +11.1%, and combined group +14.2%). Additionally, resistance training elicited significant improvements in peripheral muscle strength but aerobic training did not. The 16% increase in peak oxygen consumption is remarkable, since in healthy, sedentary individuals, resistance training increases peak oxygen consumption by only 3% (Tanaka and Swensen, 1998). This finding is in accordance with the literature, where others have shown that patients with CHF achieve 10-18% increases in peak oxygen consumption during resistance training and 15-20% after aerobic training (Meyer, 2006). A significant increase in peak oxygen consumption (14.5%) was observed after 12 weeks of training using weight collars in patients with CHF awaiting heart transplantation (Grosse et al., 2001).

In contrast, the present study and others have reported no improvement in peak oxygen consumption. Pu et al. 2001 did not find significant changes in $\dot{V}O_2$ peak after an 11-week resistance training in patients with moderate CHF (mean EF: 26%, NYHA class II-III) but reported a significant improvement in exercise time (by 13%). Similarly, Magnusson et al. (1996) demonstrated significant improvement in maximal exercise capacity (by 10%) in patients with CHF after eight weeks of resistance training but did not report any changes in $\dot{V}O_2$ peak. The present study also suggests that resistance training improved exercise duration in addition to peak minute ventilation and peak carbon dioxide production but not peak oxygen consumption or anaerobic threshold. This improvement in exercise capacity may be due to a number of peripheral factors, including possible increase in muscle strength, endurance, type I fibre area, and oxidative enzyme capacity as suggested by Pu et al. (2001). They also demonstrated no changes in any resting central haemodynamic factors or $\dot{V}O_2$ peak

following resistance exercise training.

The resistance training as used in the present study did not alter any measured central haemodynamic variable, not also variables of aerobic capacity such as peak oxygen consumption and anaerobic threshold.

10.5.3 *“Cross-Over” Results*

Graphically presented results for the few patients who participated in a “cross-over” design, supported the major finding of this study that improved cardiac function and peak oxygen consumption was associated with aerobic but not with the resistance exercise training. .

More specifically, Figure 10.1 demonstrated that the aerobic exercise programme led to more functional improvement than the resistance exercise programme. It also showed that during a 12-week “non-exercise” period there is a decline in all variables. It should be, however, noted that this decline is more pronounced in metabolic variables such as oxygen consumption and anaerobic threshold, than that in central haemodynamic measures such as cardiac power output or cardiac output. In other words, it seems that improvement in cardiac function following aerobic exercise is more preserved during the “non-exercising” period compared with peak oxygen consumption or anaerobic threshold. Figure 10.1 also suggests that the resistance exercise programme performed in the present study had little effect on either central haemodynamic or metabolic variables. The resistance exercise training used in the present study had little effect on metabolic and haemodynamic data as illustrated in Figure 10.2.

It is recognised that this section is based on a very small sample and its inclusion is largely illustrative and cannot be extrapolated to a larger population.

10.5.4 Study Limitations

The present study has several limitations. Firstly, apart from the small sample size, there was a lack of the control group originally proposed. Although all efforts were made to overcome this early recognized limitation (e.g. contacting other hospitals in the area) the study has finished with no control group. It should be, however, noted that most studies which observed an improvement in haemodynamic and functional capacity of patients assigned into an exercise intervention group, did not find the same improvement in a control group (Belardinelli et al., 1995; Dubach et al., 1997; Hambrecht et al., 1995; Hambrecht et al., 2000). Secondly, this was not full cross-over trial as it was intended after the study commenced. This is associated with the fact that only a few patients were able to participate in the cross-over design for a variety of reasons (e.g. work commitments, travel), as well as the fact that this study had its own time framework due to the approaching deadline for submission of this thesis. Finally, the present study may have limitations from a methodological point of view. It is recognised that insertion of the Innocor respiratory valve unit into the CardioO₂ metabolic analyser's pneumotach is not ideal as it may reduce the patient's concentration at peak exercise, as well as introduce a small resistance to breathing from a bacterial filter. Although the rebreathing procedure lasts for only a few seconds it may cause additional discomfort to the patient, particularly when the patient was asked to control his rebreathing frequency, and hold the breath for a second. However, the use of both systems, the Innocor for cardiac output measurement and CardioO₂ for metabolic and ECG recordings, was necessary due the following two reasons. Firstly, the Innocor systems measures heart rate by pulse oxymetry. The use of this methodology is limited during cardiopulmonary exercise test when there is excessive motion (e.g. fast treadmill walking). Additionally, metabolic data, particularly $\dot{V}C_{O_2}$, measured by the Innocor were significantly different from those obtained from the CardioO₂ system (Chapter 2). Secondly, as previously mentioned this clinical trial was a group project, in which one of the researchers particularly looked at heart rate recovery and O₂ kinetics matched with heart rate. As the latter could not be performed accurately with the Innocor system alone, it was decided to use both systems.

10.6 Clinical Implications and Conclusions

It has been well documented that patients with CHF may benefit from exercise training. Different modalities of exercise such as aerobic, resistance or combined may improve functional capacity of CHF patients, particularly peak oxygen consumption, anaerobic threshold and exercise duration. Over the years, researchers have demonstrated that a variety of central and peripheral adaptations occur in response to exercise training that are responsible for improvement in functional capacity in these patients.

The most frequently reported variables used to assess the effect of an exercise intervention in CHF patients are those obtained from a cardiopulmonary exercise test procedure with gas exchange measurements (e.g. peak oxygen consumption). It seems that even an exercise programme of only three weeks is sufficient to demonstrate significant improvement in this variable, possibly by exercise-induced alteration within the skeletal muscle.

Unlike metabolic and structural adaptations induced by exercise training, changes in central haemodynamic measurements, particularly cardiac output and cardiac power output, have been evaluated by a limited number of studies. This is mainly due to methodological issues surrounding cardiac output measurements, particularly during or at peak exercise. Nonetheless, several studies have demonstrated positive effect of exercise training on cardiac function.

The primary indication of heart failure is cardiac dysfunction. It is recognised that “in the genesis of the heart failure, an initial cardiac abnormality is essential”. Therefore, most other interventions in heart failure patients (e.g. drugs, surgery) have been introduced to enhance cardiac function. Therefore a legitimate question to ask is whether the first aim of exercise intervention in patients with chronic heart failure should be to improve cardiac or skeletal muscle function?

The primary aim of each exercise intervention in CHF patients should be improvement in overall cardiac function as its deterioration is the primary cause of the disease. In order to achieve this goal it seems that a more scientific approach to

exercise training prescription (intensity, duration, mode of exercise, proper training periodization, etc.) as well as “super-sophisticated” equipment for cardiac output measurement at rest and during all levels of exercise, are needed. Such a “more-scientific” approach may enhance the peripheral adaptations at the same time and possibly before improvements in cardiac function.

The current study assessed the effect of aerobic and resistance exercise training on, firstly overall cardiac function, represented by cardiac power output, but also on selected cardio-respiratory variables. The present study suggests that resistance exercise training did not induce any significant changes in either central or peripheral determinants of exercise performance in patients with mild CHF. Although the resistance training has been shown to improve some of the skeletal muscle characteristics, based on this but also on the previous studies, it is reasonable to suggest that its effect on power generating capacity of the heart is limited.

In conclusion aerobic, in contrast with resistance exercise training, increases maximal flow-generating capacity of the heart and delays anaerobic metabolism during sub maximal exercise in patients with stable chronic heart failure. Improved peak oxygen consumption following aerobic exercise training is closely associated to an exercise-induced increase in cardiac output.

10.7 References

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CHAPTER 11: SUMMARY AND CONCLUSIONS

Instead of summarising this thesis in the conventional continuous prose style, it was recommended to follow the model used in the British Medical Journal and others. This was to summarise each chapter in the form of brief bullet points relating to what is known on the topic and what the research adds to the topic. The result is a ‘tighter’ set of ‘take home messages’ which provides an executive summary. It is hoped that this approach will provide the required impact to conclude the work.

CHAPTER 2: LACK OF AGREEMENT BETWEEN GAS EXCHANGE VARIABLES MEASURED BY TWO METABOLIC SYSTEMS

WHAT IS ALREADY KNOWN

- The use of automated metabolic gas analysis systems has become common in cardiopulmonary exercise testing throughout the world
- CardioO₂ (Medical Graphics Corporation, Minnesota, USA) metabolic analyser is a valid and reliable instrument for gas exchange measurements
- Recently introduced Innocor (Innovision, Denmark) metabolic system has no published data on its performance for measuring gas exchange variables

WHAT THIS CHAPTER ADDS

- Data are now available on gas exchange variables for the Innocor system
- Limits of agreement between gas exchange variables measured by the CardioO₂ and Innocor appear to be wide and unacceptable
- The Innocor and the CardioO₂ metabolic systems cannot be used interchangeably, as to do so could affect the diagnosis of an individual patient

CHAPTER 3: COMPARISON OF CARDIAC OUTPUT DETERMINED BY DIFFERENT REBREATHING METHODS AT REST AND AT PEAK EXERCISE

WHAT IS ALREADY KNOWN

- The non-invasive determination of cardiac output is of value in human physiology, especially clinical cardiology
- Popular rebreathing methods today are the carbon dioxide rebreathing methods and the inert gas rebreathing method

WHAT THIS CHAPTER ADDS

- The inert gas rebreathing method seems to be more valid than the exponential and equilibrium CO₂ methods for measuring cardiac output at rest
- At peak exercise the exponential and inert gas rebreathing methods produced similar results and showed acceptable limits of agreement
- The exponential and inert gas rebreathing methods may be used interchangeable at peak exercise.

CHAPTER 4: CARDIAC POWER OUTPUT IN HEALTHY AND DISEASED POPULATIONS – A LITERATURE REVIEW

WHAT IS ALREADY KNOWN

- Cardiac power output is a unique central haemodynamic measure which accounts for both pressure- and flow-generating capacities of the heart
- Cardiac power output is an indicator of overall cardiac function and strong predictor of prognosis in patients with heart failure
- A limited number of studies have evaluated cardiac power output in healthy and in diseased populations

WHAT THIS CHAPTER ADDS

- The relationship between peak cardiac power output and a number of cardio-respiratory variables in healthy and heart failure patients has not been identified
- Cardiac power output has not been evaluated in patients implanted with a left ventricular assist device
- The effect on cardiac power output of different modalities of exercise programme has not been assessed

CHAPTER 5: RELATIONSHIP BETWEEN PEAK CARDIAC POWER OUTPUT AND SELECTED CARDIO-RESPIRATORY VARIABLES IN HEALTHY ADULTS

WHAT IS ALREADY KNOWN

- Peak cardiac power output is highly correlated with peak oxygen consumption and circulatory power in healthy adults
- The strength of the relationship between peak cardiac power output and other routinely measured cardio-respiratory variables in healthy subjects is unknown

WHAT THIS CHAPTER ADDS

- Peak cardiac power output is modestly related to anaerobic threshold, carbon dioxide production, oxygen pulse and minute ventilation
- These variables explained between 22% and 41% of the variance in peak cardiac power output in healthy adults
- Central haemodynamic measures such as peak cardiac output and peak stroke volume, but not peak heart rate, are strong predictors of peak cardiac power output

CHAPTER 6: COMPARISON OF CARDIAC POWER OUTPUT AND EXERCISE PERFORMANCE IN PATIENTS WITH LEFT VENTRICULAR ASSIST DEVICES, EXPLANTED (RECOVERED) PATIENTS AND THOSE WITH SEVERE HEART FAILURE

WHAT IS ALREADY KNOWN

- The use of a left ventricular assist device (LVAD) with specific pharmacologic therapy may restore cardiac function to a level that the device may be explanted
- Some patients implanted with a left ventricular assist device demonstrate better exercise performance than patients with severe heart failure

WHAT THIS CHAPTER ADDS

- Cardiac power output differentiates well during cardiac restoration using LVADs and emphasizes the benefits of this therapy
- Cardiac power output and exercise performance are significantly higher in patients implanted with a LVAD than those with severe heart failure
- LVAD explanted (recovered) patients demonstrated higher cardiac power output values and exercise performance than those with severe heart failure and LVAD implanted patients

CHAPTER 7: RESTING AND EXERCISE HAEMODYNAMIC AND METABOLIC RESPONSES TO ACUTE REDUCTION OF LVAD SUPPORT: ASSESSMENT OF MYOCARDIAL RECOVERY

WHAT IS ALREADY KNOWN

- Myocardial recovery occurs after LVAD implantation
- Performing a cardiopulmonary exercise test in patients with an LVAD when the device functions at reduced performance is safe and allows non-invasive assessment of myocardial recovery

WHAT THIS CHAPTER ADDS

- As a consequence of acute reduction of LVAD support there is a decrease in cardiac pumping capability at rest and particularly at peak exercise
- A decrease at rest and at peak exercise, expressed in percentages, was higher in central haemodynamics, particularly in cardiac power output, than in the conventionally measured oxygen consumption
- Cardiac power output seems to be more sensitive to acute reduction of LVAD support than oxygen consumption.

CHAPTER 8: RELATIONSHIP BETWEEN PEAK CARDIAC PUMPING CAPACITY AND EXERCISE-DERIVED PROGNOSTIC INDICATORS IN PATIENTS WITH SEVERE HEART FAILURE AND THOSE IMPLANTED AND EXPLANTED WITH A LEFT VENTRICULAR ASSIST DEVICE

WHAT IS ALREADY KNOWN

- Several exercise-derived variables have been shown to be strong predictors of prognosis in chronic heart failure
- Peak oxygen consumption does not necessarily reflect cardiac function /dysfunction in patients with severe heart failure

WHAT THIS CHAPTER ADDS

- The strength of the relationship between direct and indirect indicators of cardiac pumping capacity is weaker in patients with severe heart failure and those implanted with an LVAD, compared with LVAD explanted patients
- This justifies the need for assessment of maximal cardiac pumping capability directly by measuring cardiac power output rather than using other surrogates of cardiac function

CHAPTER 9: REPRODUCIBILITY OF CARDIAC POWER OUTPUT AND SELECTED CARDIO-RESPIRATORY EXERCISE TEST VARIABLES IN PATIENTS WITH STABLE CHRONIC HEART FAILURE

WHAT IS ALREADY KNOWN

- Commonly measured cardio-respiratory variables such as peak oxygen consumption, anaerobic threshold, carbon dioxide production, minute ventilation and respiratory exchange ratio demonstrate good reproducibility in patients with chronic heart failure

WHAT THIS CHAPTER ADDS

- Measurement of central haemodynamic variables and particularly cardiac power output is more relevant in the evaluation of the severity of cardiac dysfunction in heart failure patients than any other metabolic or ventilatory variable
- Cardiac output and cardiac power output, as direct indicators of cardiac function, had lower coefficients of variation than any of the commonly reported gas exchange variables at rest, but also at peak exercise, demonstrating a high degree of reproducibility

CHAPTER 10: THE EFFECT OF AEROBIC VERSUS RESISTANCE EXERCISE TRAINING ON CARDIAC POWER OUTPUT AND SELECTED CARDIO-RESPIRATORY VARIABLES IN PATIENTS WITH STABLE CHRONIC HEART FAILURE

WHAT IS ALREADY KNOWN

- Exercise training in heart failure patients may improve exercise tolerance, functional capacity, quality of life, and also may reduce hospital admission and mortality rate
- Both aerobic and resistance exercise training may improve exercise tolerance in patients with chronic heart failure

WHAT THIS CHAPTER ADDS

- In contrast with resistance training, aerobic exercise training increases maximal flow-generating capacity of the heart and delays anaerobic metabolism during submaximal exercise in patients with stable chronic heart failure
- Improvement in peak oxygen consumption following aerobic exercise training is closely associated with an exercise-induced increase in cardiac output in patients with stable chronic heart failure

INTEGRATED CONCLUSIONS FROM THIS THESIS

- Gas exchange variables obtained from different metabolic analysers should be considered with caution
- The inert gas rebreathing method for cardiac output measurement has the capacity to evaluate cardiac output at rest and at peak exercise more precisely than CO₂ rebreathing methods
- Cardiac power output should be assessed as a priority compared with other cardio-respiratory variables in the evaluation of cardiac function/dysfunction due to: 1) its capacity to demonstrate both pressure- and flow-generating capacities of the heart, 2) its strong prognostic value, and 3) its excellent reproducibility
- Peak oxygen consumption, together with other commonly reported cardio-respiratory variables does not necessarily reflect cardiac function /dysfunction, particularly in severe heart failure and LVAD patients
- Cardiac power output, and particularly peak cardiac power output differentiates well during cardiac restoration using left ventricular assist devices and therefore can be used in management of LVAD patients
- In contrast with resistance training, aerobic exercise training improves maximal flow-generating capacity of the heart and consequently improves peak cardiac power output

RECOMMENDATIONS FOR FUTURE RESEARCH

- Weber et al. (1982) proposed a functional classification of heart failure patients in four stages based on the peak oxygen consumption and oxygen consumption at anaerobic threshold. Future research should investigate the possibility of providing a functional classification table of heart failure patients based on peak cardiac power output, as a more appropriate measure of cardiac function/dysfunction than peak oxygen consumption.
- Future ‘reduced LVAD support’ studies in larger cohorts of patients are required to find out the “cut-off” value of peak cardiac power output which may indicate sufficient myocardial recovery for the device to be explanted
- Investigations are required to assess whether an exercise programme soon after LVAD implantation may enhance cardiac function and exercise capacity and consequently accelerate the recovery protocol in LVAD patients
- Future research is needed to optimise the exercise programme which will target an improvement in cardiac function in heart failure patients as a priority. Key components of exercise programme such as exercise intensity, duration, mode of the exercise and training periodization should be carefully considered

APPENDIX I: STAGE BY STAGE RESPIRATORY DATA

Table I.1 Differences in measured gas exchange variables at the end of stage one of Bruce protocol between Innocor and Cardio₂ (N=15) – Paired samples t-test (t)

Gas exchange variables	Innocor mean \pm SD	Cardio ₂ mean \pm SD	t	p	Cronbach's Alpha
FeO ₂ (%)	16.40 \pm 1.36	17.23 \pm 0.35*	-2.39	0.03	0.16
FeCO ₂ (%)	2.95 \pm 0.71	3.70 \pm 0.35**	-4.01	0.00	0.20
$\dot{V}O_2$ (ml·kg ⁻¹ ·min ⁻¹)	15.19 \pm 2.42	15.36 \pm 2.53	-1.80	0.09	0.99
$\dot{V}O_2$ (l·min ⁻¹)	1.03 \pm 0.33	1.10 \pm 0.29	-1.87	0.08	0.94
\dot{V}_E (l·min ⁻¹)	23.09 \pm 5.80	22.97 \pm 5.01	0.12	0.91	0.84
$\dot{V}C_{O_2}$ (l·min ⁻¹)	0.67 \pm 0.17	0.85 \pm 0.20**	-6.64	0.00	0.91
$\frac{\dot{V}O_2}{\dot{V}_E}$ RER	0.67 \pm 0.09	0.78 \pm 0.07**	-4.29	0.00	0.35

* Indicates the Innocor result is significantly (p<0.05) different from the Cardio₂ system

** Indicates the Innocor result is significantly (p<0.01) different from the Cardio₂ system

Table I.2 Differences in measured gas exchange variables at the end of stage two of Bruce protocol between Innocor and Cardio₂ (N=15) – Paired samples t-test

Gas exchange variables	Innocor mean \pm SD	Cardio ₂ mean \pm SD	t	p	Cronbach's Alpha
FeO ₂ (%)	16.74 \pm 0.65	16.94 \pm 0.34	-1.46	0.17	0.64
FeCO ₂ (%)	3.18 \pm 0.42	3.99 \pm 0.34**	-9.50	0.00	0.77
$\dot{V}O_2$ (ml·kg ⁻¹ ·min ⁻¹)	20.7 \pm 3.77	21.13 \pm 3.35	-0.58	0.57	0.80
$\dot{V}O_2$ (l·min ⁻¹)	1.49 \pm 0.43	1.50 \pm 0.35	-0.29	0.78	0.93
\dot{V}_E (l·min ⁻¹)	35.25 \pm 7.33	32.71 \pm 7.04	1.95	0.07	0.86
$\dot{V}C_{O_2}$ (l·min ⁻¹)	1.13 \pm 0.31	1.31 \pm 0.31**	-4.15	0.00	0.92
$\frac{\dot{V}O_2}{\dot{V}_E}$ RER	0.77 \pm 0.8	0.88 \pm 0.12*	-3.35	0.01	0.22

* Indicates the Innocor result is significantly (p<0.05) different from the Cardio₂ system

** Indicates the Innocor result is significantly (p<0.01) different from the Cardio₂ system

Table I.3 Differences in measured gas exchange variables at the end of stage three of Bruce protocol between Innocor and CardioO₂ (N=15) – Paired samples t-test (t) and Wilcoxon signed rank test (z)

Gas exchange variables	Innocor mean \pm SD	CardioO ₂ mean \pm SD	t (z)	p	Cronbach's Alpha
FeO ₂ (%)	16.82 \pm 0.71	16.73 \pm 0.35	0.72	0.48	0.77
FeCO ₂ (%)	3.65 \pm 0.73	4.14 \pm 0.25*	-2.69	0.02	0.26
$\dot{V}O_2$ (ml·kg ⁻¹ ·min ⁻¹)	28.81 \pm 4.41	29.08 \pm 4.21	-0.36	0.72	0.87
$\dot{V}O_2$ (l·min ⁻¹)	2.06 \pm 0.51	2.05 \pm 0.39	0.17	0.87	0.95
\dot{V}_E (l·min ⁻¹)	49.98 \pm 8.84	48.98 \pm 9.30	1.04	0.32	0.96
$\dot{V}C_{O_2}$ (l·min ⁻¹)	1.85 \pm 0.63	2.04 \pm 0.43*	-2.56 (z)	0.01	0.84
$\frac{\dot{V}O_2}{\dot{V}_E}$ RER	0.91 \pm 0.3	0.99 \pm 0.09*	-2.56 (z)	0.01	0.61

* Indicates the Innocor result is significantly (p<0.05) different from the CardioO₂ system

Table I.4 Differences in measured gas exchange variables at the end of stage four of Bruce protocol between Innocor and CardioO₂ (N=12) – Paired samples t-test

Gas exchange variables	Innocor mean \pm SD	CardioO ₂ mean \pm SD	t	p	Cronbach's Alpha
FeO ₂ (%)	17.16 \pm 0.39	17.12 \pm 0.43	0.51	0.62	0.90
FeCO ₂ (%)	3.45 \pm 0.70	4.04 \pm 0.25*	-3.14	0.01	0.35
$\dot{V}O_2$ (ml·kg ⁻¹ ·min ⁻¹)	35.4 \pm 6.08	34.15 \pm 5.0	1.14	0.28	0.86
$\dot{V}O_2$ (l·min ⁻¹)	2.67 \pm 0.75	2.54 \pm 0.63	1.46	0.17	0.95
\dot{V}_E (l·min ⁻¹)	68.19 \pm 18.93	67.74 \pm 19.52	0.31	0.76	0.98
$\dot{V}C_{O_2}$ (l·min ⁻¹)	2.37 \pm 0.84	2.75 \pm 0.83**	-3.25	0.00	0.94
$\frac{\dot{V}O_2}{\dot{V}_E}$ RER	0.91 \pm 0.6	1.07 \pm 0.10**	-6.25	0.00	0.58

* Indicates the Innocor result is significantly (p<0.05) different from the CardioO₂ system

** Indicates the Innocor result is significantly (p<0.01) different from the CardioO₂ system

APPENDIX II: INNOCOR AND CARDIO₂ DESCRIPTION

II.1 Innocor Description

II.1.1 Measurement of airflow

The in/expiration flow is measured by a pressure difference pneumotach, returning a voltage related to the actual flow (Innovision, 2005). The relationship is nonlinear in nature and therefore a multi stroke calibration is performed to obtain a linear relation. The manufacturer suggested that the calibration is performed according to computerized determination of pneumotachometer characteristics described by Yeh et al. (1982). The result of the calibration is a set of calibration factors (sticks) equally spaced along the complete voltage range of the pneumotach sensor. The resulting flow is found as: $\text{Flow}_{\text{stick}} = (\text{X}-\text{offset}) * F_{\text{stick}}(\text{X})$, where X is value from pneumotach sensor, offset is offset value of the pneumotach sensor (value at zero flow), and F_{stick} is a function to calculate stick related to value X (Innovision, 2005). The set of sticks reflects the characteristics of the specific pneumotach and valve, and is assumed valid until some hardware is exchanged. However, the actual gain on the system varies over time and therefore the following formula is used: $\text{Flow} = G(\text{X}) * \text{Flow}_{\text{stick}}$, where G(X) is a function to return separate linear gain factors for in- and expired air, while X is a value from pneumotach sensor. The flow signal is always searched backwards for breaths, and therefore the steps for detecting a breath are: 1) find the expiration end point, 2) find the expiration start point (the inspiration end point), and 3) find the inspiration start point (the end point of the preceding expiration). Detailed analysis of these steps can be obtained from the manufactures.

II.1.2 Gas sampling system

The gas sampling is taken at the mouthpiece on the RVU. The gas moves through a Nafion Tube, which equilibrates the gas to the environment with respect to humidity. A Nafion sampling tube ensures equilibrium of the water vapour pressure of the sampled gas with that of the ambient air. Further, the gas passes a filter, which protects the analysers from dust and small particles. Next the gas passes the Oxigraf, where the oxygen level is analysed, and the photo acoustic gas analyser (PGA), where the other gas components are analysed. The PGA contains a flow regulator, which

controls the flow to approximately $120 \text{ l}\cdot\text{min}^{-1}$. The gas passes an attenuator and finally the pump before the gas leaves the outlet placed on the back of the Innocor. The purpose of the attenuator is to damp the pulsation from the pump.

II.1.3 Innocor principle of carbon dioxide measurement

It is well known that among the gas species of interest in physiological examinations all except monoatomic gases, noble gases, nitrogen and oxygen absorb specific wavelengths of light in the infrared (IR) spectrum by intermolecular bindings. Therefore in acoustic gas measurement for medical applications, Photo Acoustic Spectroscopy (PAS) is used to determine all concentrations except for oxygen. When the gas is subjected to intermittent infrared (IR) light of different gas-dependent, acoustic signals are produced and detected by a microphone.

Absorption of light means absorption of energy and causes a heating of the gases/vapour and thereby a rise in pressure. By pulsation of the energy applied to the gas, the rise in pressure will be intermittent, thus causing a pressure fluctuation. By choosing the pulsation frequency in the audible range, the pressure fluctuation becomes an acoustic signal, and it is possible to pick up the signal using a microphone. In terms of rise time and ambient noise suppression, a high pulsation frequency is desirable, but when choosing the pulsation frequency it has to be taken into consideration, that a high frequency results in a short time for energy to have its effect on the gas. This in turn means that a small signal is generated and that the sensitivity will be limited. With an appropriate pulsation frequency, the amplitude of the signal is equivalent to the amount (concentration) of molecules in the measuring chamber.

Light from an IR-source is reflected from gold-plated elliptic mirror towards a window in a measuring chamber. Before it enters the measuring chamber it passes individual optical filters. Each optical filter allows only a specific wavelength of light to pass through, and different wavelengths of light correspond to the IR-absorption spectra of gases/vapours, the system is designed to measure. The IR-light beams differing in both pulsating frequency and wavelength enter the measuring chamber through a window and excite the different gases they are optimized for by the optical

filters. Due to absorption of energy the gas will expand in the chamber at frequencies equal to the pulsating frequencies of the IR-light beams. The periodic expansions of the gas/vapour are within audible range (approx. 150-350 Hz) and a single highly sensitive microphone picks up the signals (Innovision, 2005). Finally the different pressure signals are distinguished electronically.

II.1.4 Innocor principle of oxygen measurement

The oxygen analyser is the Oxigraf O₂ sensor model X1004/X2004 from Oxigraf Inc. US. The patented Oxigraf sensor uses laser diode absorption spectroscopy in the visible spectrum, similar to the absorption method used to measure carbon dioxide in the infrared spectrum. However, oxygen absorption is in a region of the visible spectrum (760 nm) where there is no interference or absorption by other ventilation gases. Also the emission line width of the laser and the absorption line width of O₂ are very narrow, less than 0.01 nm, compared with perhaps 100 nm for the CO₂ absorption band at atmospheric pressure (Innovision, 2005). The spectrally pure laser is thermally tuned precisely to the oxygen absorption line. As the oxygen concentration increases, the light intensity is attenuated. The photo detector response varies linearly with the oxygen concentration.

II.2 Cardiac O₂ Description

II.2.1 Gas volume measurement

Measurement of airflow breath-by-breath during human ventilation has been accomplished historically with pneumotachometers with precision reported to be $\pm 3-4$ % (Porszasz et al., 1994). These authors introduced a new technique for measuring flow during breathing based on the principle of the differential pressure between two symmetrically disposed pitot tubes. Pitot tubes measure the pressure of gas flowing against a series of small tubes mounted at 90° to the direction of the gas flow. The pressures are dependant upon the density of the gas and the square of its velocity. The design involves a non-linear relationship between pressure differences and airflow, which is confounded by sensitivity to changes in gas density produced by changing gas composition. Commercial pitot tubes are very light, robust and cheap. Their linearity and sensitivity to changing compositions of expired and inspired gases

requires sophisticated software correction to linearise their output. The software correction is based on the measured gas (O_2 and CO_2) concentrations and is implemented in the data acquisition program of the system.

Conversion of the pressure measurement of the flow meter into airflow is accomplished in the software by the use of a shape table containing several points spanning a wide range of flows. This is then multiplied by a correction factor determined during calibration. The correction factor is calculated as the mean of five correction factors generated for five strokes of a calibrated syringe of known volume that are performed at different flow rates. This spans a physiological spectrum of flows. This procedure reduces any variability that may exist between flow meters. The integrated airflow measured by the pitot tube flow meter to obtain tidal ventilation proved to be reproducible and accurate to within 2% during exercise studies as suggested by Porszasz et al. (1994).

II.2.2 Gas concentration measurements

Different strategies have been used to measure gas concentrations necessary for breath-by-breath analysis (Hodges, 2004). Roca et al. (1997) suggested using an analyser capable of measuring all relevant gases, or using separate analysers for each gas species. The essential requirement for the gas analyser is to be accurate and able to give a quick response. Roca et al. indicated two separate components for analyser response. The first is transport delay time (time required for the gas to traverse the distance from the sampling site to the analyser which is usually from 0.2 to 0.5s. The second component is analyser response which represents the kinetics of response to change in gas composition introduced to the analyser. The analyser response often takes the form of an exponential or sigmoid response to a stepwise change gas composition.

II.2.3 $CardiO_2$ principle of carbon dioxide measurement

The $CardiO_2$ metabolic analyser uses an infrared carbon dioxide analyser, which relies on the fact that carbon dioxide absorbs infrared radiation. Dual beams of infrared radiation are sent through a reference cell and a parallel sample cell containing the test gas at constant flow. A mechanical system interrupts the two beams as they reach the

signal in the detector, providing an oscillating signal. The magnitude of the oscillations is proportional to the differences in the concentrations of the reference and test gas. Infrared carbon dioxide analysers are considered to be accurate and robust for most cardiovascular measurements, although care is needed to prevent contamination of the sample chamber by fluids (Macfarlane, 2001).

II.2.4 Cardio₂ principle of oxygen measurement

The Cardio₂ system uses a zirconia fuel cell. This is an electrochemical galvanic cell consisting of calcium stabilised zirconium oxide electrolyte with porous platinum electrodes (Mcfarlane, 2001). At its operating temperature (750-850°C) the electrolyte acts as a semi-permeable membrane that is selective for oxygen ions. The output voltage follows the Nernst equation, which is based on the logarithm of the partial pressure of oxygen in the sample and reference gas (Macfarlane, 2001). These analysers have the benefit of requiring little maintenance and of being both stable and accurate. Zirconia fuel cells are very fast responding (<100 ms) and require relatively high sample flow rates (Macfarlane, 2001).

APPENDIX III

Table III.1 Individual and mean values of cardiac output determined by the three by rebreathing methods

Subject	EXP I (l·min ⁻¹)	EXP II (l·min ⁻¹)	EQU I (l·min ⁻¹)	EQU II (l·min ⁻¹)	IGR I (l·min ⁻¹)	IGR II (l·min ⁻¹)	Mean of two measurements		
							EXP (l·min ⁻¹)	EQU (l·min ⁻¹)	IGR (l·min ⁻¹)
1	9.1	8.6	5.0	5.2	4.2	4.5	8.9	5.1	4.4
2	10.2	10.0	7.1	6.5	4.7	4.8	10.1	6.8	4.8
3	12.1	12.9	9.0	9.2	5.2	5.1	12.5	9.1	5.2
4	10.4	10.0	6.2	6.9	4.8	5.4	10.2	6.6	5.1
5	14.2	13.0	9.6	9.0	4.6	4.9	13.6	9.3	4.8
6	13.6	16.4	6.1	5.5	4.5	6.1	15.0	5.8	5.3
7	10.5	9.8	5.3	5.1	4.7	4.3	10.2	5.2	4.5
8	9.2	8.8	7.0	6.9	5.6	5.5	9.0	6.7	5.6
9	12.8	11.8	6.4	6.1	6.0	5.7	12.3	6.3	5.9
10	15.3	15.1	6.3	6.0	4.0	4.0	15.2	6.2	4.0
11	7.0	6.7	5.0	5.1	4.2	4.8	6.9	5.1	4.5
12	9.2	9.3	7.1	6.8	5.5	6.2	9.3	7.0	5.9
13	10.4	9.9	5.8	5.3	5.9	5.5	10.2	5.6	5.7
14	15.6	14.9	9.4	9.1	6.4	6.2	15.3	9.3	6.3
15	8.7	12.2	7.0	6.7	6.1	5.9	10.5	6.9	6.0
16	10.5	11.8	5.2	4.5	4.0	3.8	11.2	4.9	3.9
17	6.0	5.8	5.5	5.8	4.2	4.5	5.9	5.7	4.5
Mean±SD	10.9±2.7	11±2.9	6.7±1.5	6.5±1.5	5±0.8	5.1±0.9	10.9±2.8	6.6±1.5*	5.1±0.7*
Min	6	5.8	5	4.5	4	3.8	5.8	4.5	3.9
Max	15.6	16.4	9.6	9.2	6.4	6.2	15.1	9.1	6.3
Range	9.6	10.6	4.6	4.7	2.4	2.4	9.3	4.6	2.4

Table III.2 Individual and mean peak \dot{Q}_T values measured by the exponential and inert gas rebreathing methods

\dot{Q}_T (lmin ⁻¹)			
Subject	IGR	EXP	Mean Difference
1	18.6	18.7	-0.1
2	21.3	20.6	0.7
3	20	19.9	0.1
4	19.8	20.1	-0.3
5	28.7	28.3	0.4
6	14.5	14.3	0.2
7	14.3	14.1	0.2
8	22.4	22.6	-0.2
9	21.3	20.7	0.6
10	14.8	14.9	-0.1
11	21.9	21.5	0.4
12	20.8	20.9	-0.1
Mean±SD	19.87±4.05	19.72±3.97[#]	0.15
Min	14.3	14.1	-0.3
Max	28.7	28.3	0.7
Range	14.4	14.2	1

IGR – inert gas rebreathing method; EXP – exponential rebreathing method; [#] - indicates p value (p = 0.136).

APPENDIX IV: Pharmacological therapy in heart failure

Evidence for drugs use and its effect on heart failure are described below according to ACC/AHA Guideline (2005) and the ESC Task Force (2005).

1. *Angiotensin-converting enzyme inhibitors (ACE-inhibitors, ACEi)* are recommended as first line therapy in all patients with heart failure, with or without symptoms, who have reduced LVEF (<40-45%). It is not clear whether the effects of ACEi can be explained by solely by the suppression of angiotensin II production, because ACE inhibition not only interferes with the rennin-angiotensin system but also enhances the action of kinins and augmented kinin-mediated prostaglandin production. Systematic reviews of randomised controlled trials comparing ACE inhibitor to placebo have found that ACE inhibitor therapy in patients with heart failure due to left ventricular systolic dysfunction increases life expectancy. The effect is more marked in patients with more severe left ventricular systolic impairment, or more severe symptoms, although there is benefit for all NYHA classes. ACE inhibitor therapy also reduces the risk of hospitalisation. The symptoms of heart failure in patients with chronic heart failure due to left ventricular systolic dysfunction improve on therapy with an ACE inhibitor. There is some evidence from a randomised controlled trial that quality of life improves with ACE inhibitor therapy in heart failure patients. High doses of ACE inhibitors lower blood pressure more than lower doses but do not necessary confer greater benefit in terms of improving symptoms or life expectancy. Exercise performance has not consistently been shown to improve with ACE inhibitor therapy for all patients with heart failure due to left ventricular systolic dysfunction. Although ACE inhibitors improve functional status of patients with heart failure in general, small benefits in exercise capacity occur.

2. *Diuretics* are essential for symptomatic treatment when fluid overload is present and manifest as pulmonary congestion or peripheral oedema. The ultimate goal of diuretic treatment is to eliminate clinical evidence of fluid retention, such as jugular venous pressure elevation and peripheral oedema. Diuretics interfere with the sodium retention of heart failure by inhibiting the reabsorption of sodium or chloride at specific sites in the renal tubules. Bumetanide, furosemide, and torsemide act at the loop of

Henle (thus, they are called loop diuretics) whereas, thiazides, metolazone, and potassium-sparing agents (e.g. spironolactone) act in the distal portion of the tubule. These two classes of diuretics differ in their pharmacological actions. The loop diuretics increase sodium excretion up to 20% to 25% of the filtered load of sodium, enhance free water clearance, and maintain their efficacy unless renal function is severely impaired. In contrast, the thiazide diuretics increase the fractional excretion of sodium to only 5% to 10% in the filtered load, tend to decrease free water clearance, and lose their effectiveness in patients with impaired renal function. Therefore the loop diuretics have emerged as the preferred diuretic agents for use in most patients with heart failure. Thiazide diuretics may be preferred in hypertensive heart failure patients, with mild fluid retention because they confer more persistent antihypertensive effects. Potassium-sparing diuretics (e.g. amiloride, triamterene) should only be used if hypokalaemia persists despite ACE-inhibition, or in severe heart failure despite the combination ACE-inhibition and low-dose spironolactone. In short-term studies, diuretics have led to a reduction in jugular venous pressure, pulmonary congestion, peripheral oedema, and body weight, all of which were observed within days of initiation of therapy. In intermediate-term studies, diuretics have been shown to improve cardiac function, symptoms (dyspnoea), and exercise performance in patients with heart failure.

3. *Beta-adrenergic receptor blockers (β -blockers)* act principally to inhibit the adverse effects of the sympathetic nervous system in patients with heart failure, and these effects overcome their well-known negative inotropic effects. Whereas cardiac adrenergic drive initially supports the performance of the failing heart, long-term activation of the sympathetic nervous system exerts deleterious effects that can be antagonized by the use of β -blockers. Sympathetic activation can increase ventricular volumes and pressure by causing peripheral vasoconstriction and by impairing sodium excretion by the kidneys. Norepinephrin can also induce cardiac hypertrophy but restrict the ability of the coronary arteries to supply blood to thickened ventricular wall, leading to myocardial ischaemia. Activation of the sympathetic nervous system can also provoke arrhythmias by increasing the automaticity of cardiac cells, increasing triggered activity of the heart, and promoting the development of hypokalaemia. Norepinephrin can also increase heart rate and potentiate the activity and actions of other neurohormonal systems. Finally, by stimulating growth and

oxidative stress in terminally differentiated cells, norepinephrine can trigger programmed cell death or apoptosis. Beta-blocking agents are recommended for the treatment of all patients (in NYHA class II-IV) with stable, mild, moderate, and severe heart failure from ischaemic or non-ischaemic cardiomyopathies and reduced LVEF on standard treatment, including diuretics and ACE-inhibitors. Beta-blocking therapy reduces hospitalization, improves the functional class and leads to less worsening of heart failure. This beneficial effect has been consistently observed in subgroups of different age, gender, functional class, LVEF, and ischaemic or non-ischaemic aetiology. Beta-blockers are the only heart failure drugs that cause a significant improvement in LVEF, which occurs both in patients with ischaemic or non-ischaemic aetiology of heart failure. However, the improved left ventricular systolic function does not constantly result in a better exercise capacity probably because of the negative chronotropic effects of beta-blockers. There is evidence to show that long-term beta-blocker therapy increases exercise time but not peak oxygen consumption, and reduces peak carbon dioxide production (Witte et al., 2005, *European Journal of Heart Failure*, 7: 612-617).

4. *Aldosterone antagonists.* Although short-term therapy with ACEi can lower circulating levels of aldosterone, such suppression may not be sustained during long-term treatment. The lack of long-term suppression may be important because the aldosterone exerts adverse effects on the structure and function of the heart, independently of and in addition to the deleterious effects produced by angiotensin II. It is understood that aldosterone has an important role in the pathophysiology of heart failure. It promotes vascular and myocardial fibrosis, potassium and magnesium depletion, sympathetic activation, parasympathetic inhibition, and baroreceptor dysfunction. Aldosterone antagonists (e.g. spironolactone, eplerenone) are recommended in addition to ACEi, β -blockers, and diuretics in advanced heart failure (NYHA III-IV) to improve survival and morbidity irrespective of aetiology. The use of spironolactone (25 mg daily for six months) in 30 stable chronic heart failure patients had a positive effect on gas diffusion and exercise capacity (peak oxygen consumption) (Agostoni et al. 2005, *European Heart Journal*, 26: 159-164).

5. *Angiotensin II receptor antagonists (ARBs)* can be used as an alternative to ACE-inhibition in symptomatic patients intolerant to ACE inhibitors to improve morbidity

and mortality. ARBs and ACE inhibitors seem to have similar efficacy in chronic heart failure on mortality and morbidity. ARBs can be considered in combination with ACE inhibitors in patients who remain symptomatic. Addition of ARBs as well as ACE inhibitors improves morbidity and mortality, reduces hospitalization and improves signs/symptoms of heart failure and quality of life.

6. *Digitalis glycosides* (e.g. *digoxin*) exert their effects in patients with heart failure by virtue of their ability to inhibit sodium-potassium ($\text{Na}^+\text{-K}^+$) adenosine triphosphatase (ATPase). Inhibition of this enzyme in cardiac cells results in an increase in the contractile state of the heart. Increased intracellular sodium promotes sodium-calcium exchange, leading to a rise in the intracellular calcium concentration. This results in improved isolated myocyte contractile performance (increased shortening velocity) and overall left ventricular systolic function. For many decades, the benefits of digitalis in heart failure were ascribed exclusively to this positive inotropic action. However, recent evidence suggests that the benefits of digitalis may be related in part to enzyme inhibition in noncardiac tissue. Inhibition of $\text{Na}^+\text{-K}^+$ ATPase in vagal afferent fibers acts to sensitize cardiac baroreceptors, which in turn reduces sympathetic outflow from the central nervous system. In addition, by inhibiting $\text{Na}^+\text{-K}^+$ ATPase in the kidney, digitalis reduces the renal tubular reabsorption of sodium; the resulting increase in the delivery of sodium to the distal tubules leads to the suppression of rennin secretion from the kidneys. These observations have led to the hypothesis that digitalis acts in heart failure primarily by attenuating the activation of neurohormonal systems and not as a positive inotropic drug. The treatments with digoxin for one to three months can improve symptoms, quality of life, and exercise tolerance in patients with mild to moderate heart failure regardless of the cause of heart failure or concomitant therapy (with or without ACE inhibitors). In a long-term trial that enrolled patients who primarily had class II or III symptoms, treatment with digoxin for two to five years had no effect on mortality but modestly reduced the combined risk of death and hospitalization. Digoxin may prevent deterioration in maximal exercise performance for patients with heart failure due to left ventricular systolic function, and withdrawal may lead to deterioration in maximal, but not submaximal, exercise performance.