CHANGES IN ARTERIAL STIFFNESS AND OTHER CARDIOVASCULAR RISK VARIABLES FOLLOWING SPECIFIC EXERCISE PROGRAMMES

A Thesis submitted for the degree of Doctor of Philosophy

By

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Abstract

Arterial stiffness is one of the major risk factors and markers of cardiovascular disease (CVD). An increase in the arterial stiffness is influenced by various factors such as age, lifestyle, genetics and the presence of other cardiovascular risks such as obesity and diabetes. Arterial stiffness is a consistent thread in this thesis. This thesis investigates the effects of exercise-based management programmes for CVD and risk factors with a focus on carotid-radial applanation tonometry which is a specific non-invasive technique for measuring arterial stiffness. Erectile dysfunction is a marker of CVD and is associated with endothelial dysfunction that leads to arterial stiffness. The effects of centre-based, supervised and exercise-based cardiac rehabilitation (CR) programmes were studied on the changes in arterial stiffness, erectile dysfunction and quality of life of patients with CVD. Despite the effectiveness of CR programmes, there is poor attendance at these programmes and unsupervised home-based, IT (information technology)-supported programmes could improve patient participation and cost effectiveness. Moreover, earlier identification of risks and appropriate management can reduce the incidence of CVD. There are no such programmes for early stages of CVD in practice, especially in developing countries such as India. A 12-week, IT-supported home-based exercise programme in India, for patients with metabolic syndrome was developed and studied. In general, arterial stiffness was improved in both centre-based and home-based exercise programmes. There were acute increases in arterial stiffness following exercise in healthy Caucasians and South Asians as well as people with metabolic syndrome. Carotid-radial pulse wave analysis could be a simple and reliable prognostic tool in exercise based rehabilitation programmes.

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Without the support, patience and guidance of the following people, it would not be possible to complete this thesis. I owe my deepest gratitude to all of them.

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Finally and most importantly, I thank my wife Ila, for her love, endured tolerance, encouragement, support and sacrifices throughout the period of this thesis, and I dedicate this thesis to her.

AUTHOR'S DECLARATION

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

J Radhakrishnan

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LIST OF ABBREVIATIONS

AIx	Augmentation index
AT	Anaerobic threshold
Aug P	Augmentation pressure
BMI	Body Mass Index
DBP	Diastolic blood pressure
ED	Erectile dysfunction
F_ECO_2	Fraction of expired carbon dioxide
F_EO_2	Fraction of expired oxygen
HR	Hear rate
ISWT	Incremental shuttle walk test
MAP	Mean arterial blood pressure
MET	Metabolic equivalent
MS	Metabolic syndrome
$P_{ET}CO_2$	End tidal carbon dioxide concentration
PP	Pulse pressure
PWV	Pulse wave velocity
RER	Respiratory exchange ratio

SBP	Systolic blood pressure
SEVR	Subendocardial viability ratio
STDP	Selective toluene disproportionation
VCO_2	Carbon dioxide production
V_E	Minute ventilation
VO_2	Oxygen consumption

GLOSSARY OF TERMS

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 lactate threshold). Postulated by some authors to be oxygen consumption above which anaerobic energy production substantially supplements aerobic energy production.

Borg scale: A scale, which is used for an individual to rate his/her perceived level of exertion during exercise.

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

Functional capacity: The maximal capacity of an individual to perform aerobic work is defined by the maximal oxygen consumption. It is expressed in metabolic equivalents (METs): One MET = 3.5 mL O_2. $kg^{-1}.min^{-1}$.

Incremental shuttle walk test: A progressive 10-metre shuttle walk test to measure functional capacity with audio beeps played from a pre-recorded CD to control the speed.

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

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 in to or being utilized from the body's stores. In the steady-state, oxygen uptake equals oxygen consumption.

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

Respiratory Exchange Ratio: Ratio between percentage of oxygen uptake and carbon dioxide release in breathing.

Tidal volume: The normal volume of air displaced between normal inspiration and expiration when extra effort is not applied.

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 variable in one context may be a parameter in another.

CHAPTER 1. INTRODUCTION

1.1. Context

Arterial stiffness is one of the major risk factors and markers of cardiovascular disease (CVD). It is defined as a reduction in arterial distensibility (Lacolley *et al*. 2009). It is caused by reversible or irreversible changes in both the structural and cellular components of arterial wall. A number of studies have established the association of arterial stiffness with coronary artery disease and myocardial ischaemia (Barenbrock *et al*. 1995; Cameron *et al*. 1996; Gatzka *et al*. 1998; Hirai *et al*. 1989; Kingwell *et al*. 2002; Leung *et al*. 2006; Lim *et al*. 2004; Triposkiadis *et al*. 1993; Waddell *et al*. 2001). Arterial stiffness is also identified as a marker of cardiovascular disease due to its relationship with many cardiovascular risk factors such as diabetes (Salomaa *et al*. 1995), hypertension (Payne *et al*. 2010), dyslipidaemia and metabolic syndrome (Scuteri *et al*. 2004). Arterial stiffness has also been found in the early stages of conditions such as insulin resistance (Sengstock *et al*. 2005) and glucose intolerance (Henry *et al*. 2003). Various invasive and non-invasive methods have been developed to measure arterial stiffness. This thesis focuses on the diagnostic and prognostic values of arterial stiffness variables measured from a specific non-invasive technique.

Erectile dysfunction is a marker of cardiovascular disease. It often occurs in association with or as a precursor of arterial stiffness in central and peripheral arteries. Earlier research work at Bucks New University, carried out by Hodges *et al* (2007), reported that 66% of men with CVD had erectile dysfunction and only half of them discussed the symptoms with a health professional. There was

an opportunity to develop the previous work on erectile dysfunction with advanced equipment. In this thesis, the relationship between severity of erectile dysfunction and non-invasive arterial stiffness was studied.

Cardiac rehabilitation is an established programme in the UK for patients with CVD or cardiovascular risks. The effects of centre-based cardiac rehabilitation on arterial stiffness and erectile dysfunction were studied in this thesis. Despite the fact that cardiac rehabilitation is proven as an effective intervention, the uptake of cardiac rehabilitation is poor (Dalal and Evans 2003). Various factors are responsible for this poor participation including limited places in the hospital-based or outpatient-department based rehabilitation units, distance & transport, low self-esteem, socioeconomic status and lack of education (Daly *et al*. 2002). Van Elderen-van Kemenade *et al* (1994) offered a health education and counselling programme for myocardial infarction patients during hospitalization and followed it up by telephone for twelve months. The programme improved their lifestyle during hospitalization and for the first two months after hospitalization. Many studies proved that home-based exercise programmes were as equally effective as supervised hospital or centre-based group exercise programmes (Dalal *et al*. 2010; Jolly *et al*. 2009; Jolly *et al*. 2007; King *et al*. 1991). This thesis has evaluated a home-based programme for people with cardiovascular risk.

Metabolic syndrome is a cluster of cardiovascular risks such as increased blood glucose, increased blood pressure, high triglycerides, low level of high-density lipoproteins and abdominal obesity (Grundy *et al*. 2004). In the current thesis, the effects of a home-based exercise programme incorporating IT (information

technology) support for people with metabolic syndrome were studied. The effects of this programme were assessed by observing the changes in arterial stiffness, associated cardiovascular risks and quality of life.

Earlier diagnosis and exercise-based rehabilitation programmes are well established in the developed western countries. However, those facilities are not generally available in the developing counties. It is important to undertake research and improve health care using alternative methods in those countries to minimize cardiovascular health risks. In this thesis, opportunities were provided to establish research collaborations in various health institutions in the UK and the developing countries. The Investigator, who has a physiotherapy background from India, had distinctive opportunities to progress as an exercise scientist with helping the people in South Asian countries as well as UK through the research work in this thesis. In addition, it was made possible to use the cutting-edge equipment in the developing countries for investigations on different ethnic groups. This thesis explored the prevalence of cardiac risks, clinical associations of arterial stiffness and early management of cardiac risks in the developing South Asian countries such as India and Nepal for the first time. The findings of the thesis could help to improve the health care in such countries and to develop further research.

1.2. Aims and Objectives for the Thesis

Over the years, non-invasive measurement of arterial stiffness using various methods such as oscillometry and tonometry has been developed. In this thesis, the measurements were taken using a SphygmoCor, one of the common systems in use, which records pulse waveforms from an arterial applanation

tonometer. It is a recently developed technology, which measures central aortic pressures calculated from peripheral arterial pressures (Smulyan *et al*. 2003; Yasmin and Brown 1999).

Firstly, this thesis aims to establish the reliability of the arterial stiffness estimates using the non-invasive and less intrusive applanation tonometry and its relationship with specific cardiovascular risk factors. Secondly, the thesis aims to establish the effects of a structured supervised exercise programme on arterial stiffness. Thirdly, the thesis aims to establish the effects of early management of cardiovascular risks in people with pre-existing metabolic syndrome, using an unsupervised, home-based exercise programme, enhanced with IT (information technology) support.

The objectives of the thesis were:

- To review the existing literature regarding arterial stiffness and determine future research directions
- To assess the reproducibility of non-invasive equipment on measuring the variables of arterial stiffness
- To establish the relationship between non-invasive arterial stiffness measurement and adiposity
- To establish the changes in arterial stiffness following acute exercises in different ethnic groups
- To establish the relationship between arterial stiffness and exercise capacity using simple and advanced techniques

- To establish the changes in arterial stiffness following acute and long-term exercise in patients with metabolic syndrome

- To review the existing literature regarding metabolic syndrome and its development, prevalence and current management

- To establish the prevalence of metabolic syndrome in the specific regions of South Asia such as Nepal

- To establish the relationship between non-invasive arterial stiffness measurement and other cardiovascular risks such as erectile dysfunction

- To review the existing literature regarding cardiac rehabilitation and erectile dysfunction

- To establish the effects of supervised exercise-based programmes such as cardiac rehabilitation on arterial stiffness and other cardiovascular risks

- To establish the effects of a non-supervised exercise programme on cardiovascular risk factors such as metabolic syndrome

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 consequences of this is that certain elements of the methodology are repeated in different chapters. To make this clear to the reader and to save unnecessary repeat reading, the section which use the same methodology have

been shown in a green font. The final chapter is a brief summary including recommendations, written according to the style of the British Medical Journal. This includes two sections: (1) what is known of the topic; and (2) what this study adds. This relates to each chapter of the thesis.

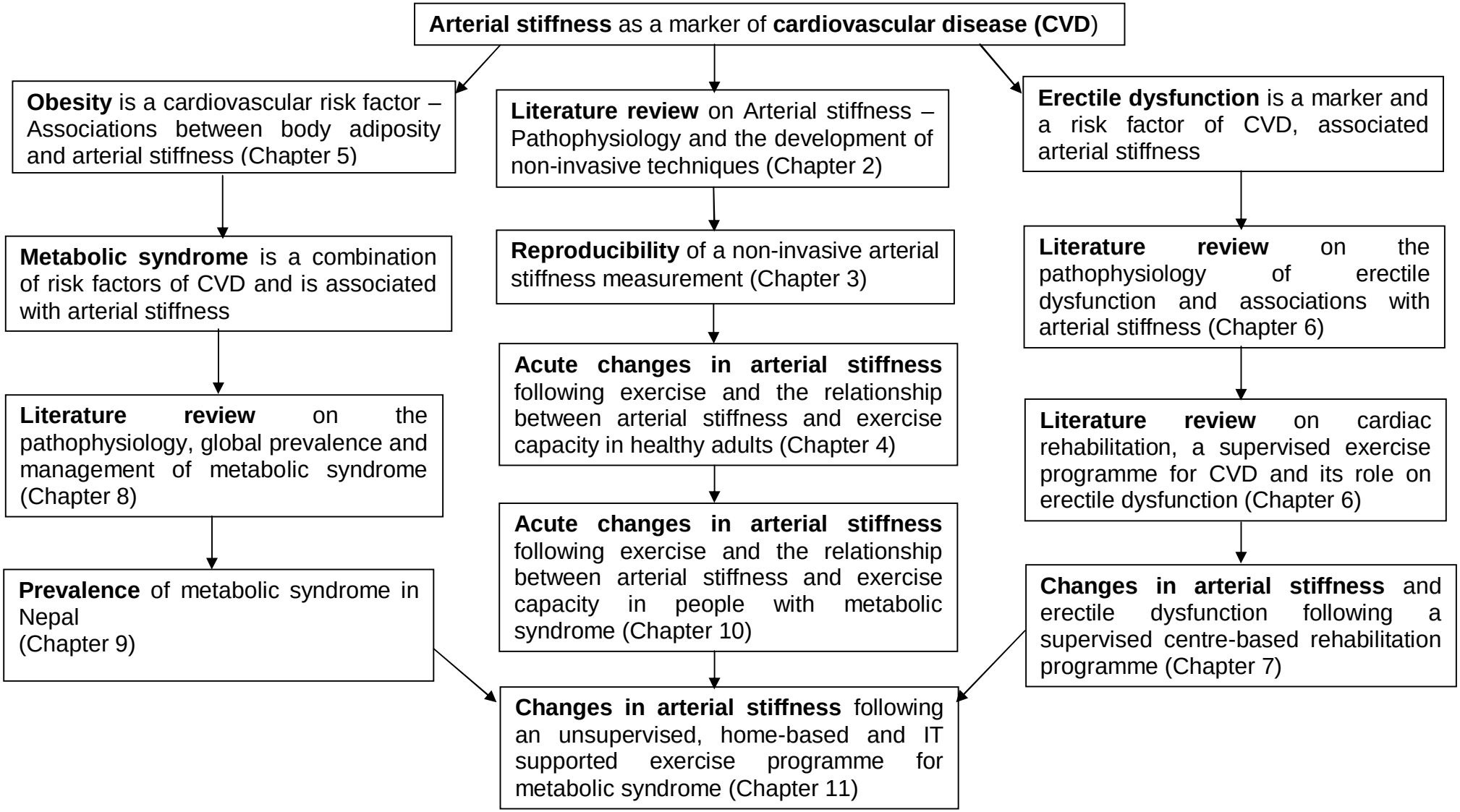

Figure 1.1 The structure of the thesis

Chapter Two is a review of available literature, which is related to the mechanism of arterial stiffness, development of non-invasive measurement techniques and clinical implications.

Chapter Three illustrates the immediate and 24 hour reproducibility of the non-invasive measurement technique on healthy adults.

Exercise capacity is related to arterial stiffness as cardiac output is determined by aortic compliance. Acute exercise results in immediate changes in arterial compliance by increasing vasodilatation. Exercise capacity varies with a number of factors such as ethnicity, lifestyle, presence of cardiovascular risk etc. **Chapter Four** demonstrates changes in non-invasive arterial stiffness immediately after a sub-maximal exercise. The non-invasive measurements are compared with exercise capacity measured by a standard metabolic analyser. Further, this chapter also compares the findings between two different ethnic groups living in the UK.

Young people with obesity have higher risk of arterial stiffness. Earlier diagnosis can help to reduce cardiac risk. **Chapter Five** demonstrates the relationship between non-invasive arterial stiffness measurements and adiposity, which is calculated from skinfold thickness in young Indian adults.

Erectile dysfunction is a marker of cardiovascular disease. **Chapter Six** is a review of available literature on the pathophysiology and relationship between erectile dysfunction and arterial stiffness and the role of cardiac rehabilitation programmes in treating erectile dysfunction.

Chapter Seven investigates the effects of supervised cardiac rehabilitation programmes on non-invasive arterial stiffness and erectile dysfunction in people with erectile dysfunction who had a cardiac event and were undergoing a cardiac rehabilitation programme in the UK.

Metabolic syndrome is a cluster of cardiovascular risks. **Chapter Eight** is a review on available literature, which is related to the development, pathophysiology, prevalence and management of metabolic syndrome.

Chapter Nine reports on the prevalence of metabolic syndrome in Nepal. This is the first study on the prevalence of metabolic syndrome in Nepal. This chapter observe the difference in the prevalence in the general population with different demographics and lifestyles.

Chapter Ten is a development of chapter four. It demonstrates the changes in non-invasive arterial stiffness immediately after exercise in people with metabolic syndrome.

As a modified development of the previous chapters, **Chapter Eleven** investigates whether a 12-week, IT-supported, home-based exercise programme has a specific effect on non-invasive arterial stiffness measurements and exercise capacity in people with metabolic syndrome in India.

Finally, **Chapter Twelve** provides a brief, integrated summary of the whole thesis.

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CHAPTER 2. ARTERIAL STIFFNESS – A LITERATURE REVIEW

Abstract

The aim of this chapter was to review existing literature, which has evaluated the mechanism of arterial stiffness and the methods of measuring arterial stiffness non-invasively. The association of arterial stiffness with coronary artery disease and myocardial ischaemia is well established. Arterial stiffness is a marker of cardiovascular disease and mortality. Several cardiovascular risks such as hypertension, diabetes, obesity, dyslipidaemia are also associated with the stiffness of arteries. A number of molecular, cellular and genetic causes underlie the mechanism of arterial stiffness with an associated increase in collagen fibres, a decrease in elastin fibres and endothelial dysfunction.

Systolic pulse wave is reflected backwards to the heart throughout the vascular system. In chronic vascular stiffening, there is an early or premature pulse wave reflection. Analysis of pulse wave has a long history. In the modern era, several invasive and non-invasive techniques have been developed. The non-invasive techniques are simple, portable, less time consuming and cost-effective. Tonometric, piezo-electronic and oscillometric techniques are commonly used and have established their clinical validity. Applanation tonometry is considered as a gold standard method. Many of the arterial stiffness variables such as pulse pressure, augmentation pressure, augmentation index and pulse wave velocity are established for individual predictive values for cardiovascular disease and mortality. The variables are of more prognostic value than diagnostic. More studies are needed to establish the clinical validity on various ethnic and clinical populations.

2.1. Arterial mechanics

2.1.1. Structure of an artery

Arteries are composed of three layers; (i) intima- the innermost layer which is a single layer of endothelial and connective tissues, (ii) media- the middle layer which is composed of elastic and smooth muscle tissue and (iii) adventitia- the outermost layer which is composed of fibrous connective tissue. These layers are embedded on each other by the extra cellular matrix (ECM) that is composed of collagen fibres, structural glycoproteins and proteoglycans (Fig 2.1 & 2.2) (Jacob 2003). The arteries have up to 40% of elastic fibres in the thoracic aorta and then decreasing gradually towards the periphery (Bader 1983). The collagen fibres are responsible for tensile strength and the elastin for elasticity (Jacob 2003).

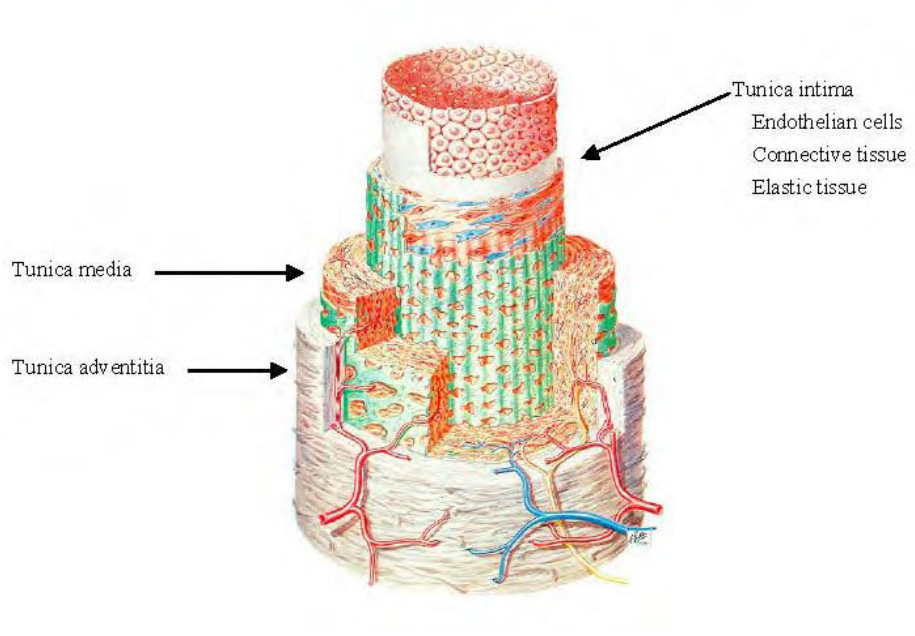


Figure 2.1 Structure of an artery
(Kangasniem and Opas 1997)

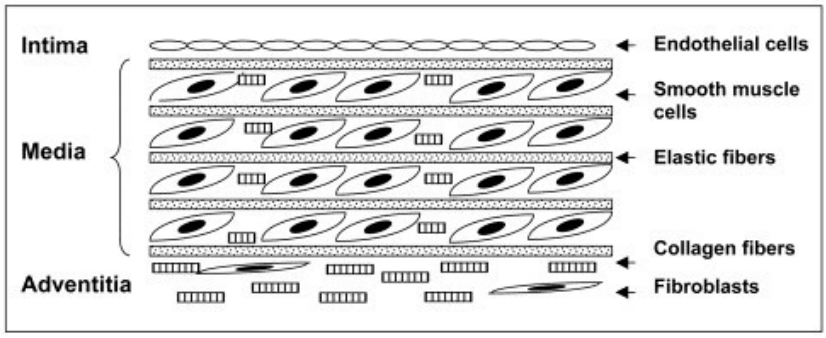


Figure 2.2 Layers of arterial wall
From Jacob (2003)

2.1.2. Mechanical properties of arteries

In the main, large arteries have conduit and cushion functions. The conduit function is to deliver blood to the organs of the body as per demand with minimal loss of perfusion pressure. The cushion function is to adjust and streamline the blood for a steady flow by smoothing the flow pulsations caused by the heart (O'Rourke 1982; O'Rourke 1995). The cushioning function of the artery is called by various generic terms such as arterial stiffness, distensibility and compliance (O'Rourke 1995).

Hales (1733) was the first to introduce the simplest model of the arterial system, which was later developed as the ‘Windkessel’ model. The model explains how the continuous blood flow is maintained in the aorta without being much affected by the pulsed pumping of the heart. Greenwald (2002) illustrated the Windkessel function with the mediaeval German fire compression chamber (Fig 2.3) showing how a continuous water flow in the fire hose is maintained with a pulsatile pump.

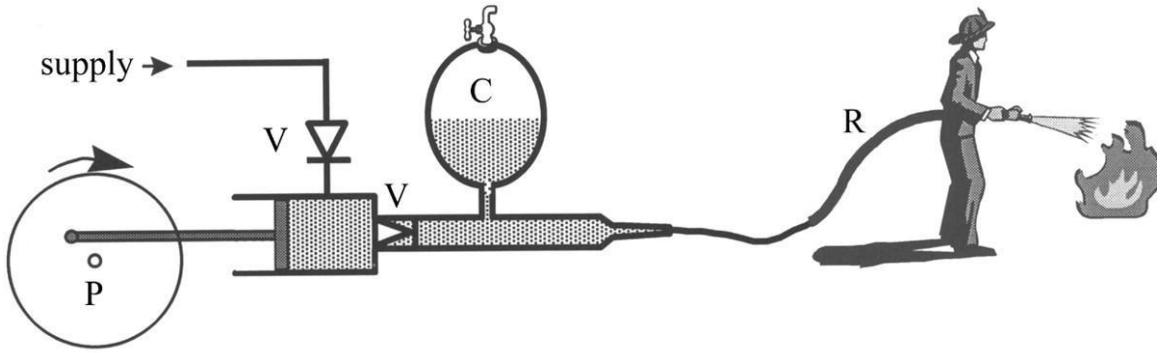


Figure 2.3 Diagrammatic representation of Windkessel function

A pulsatile pump (P) is connected to a reservoir capacitor (C) through two one-way valves (V) which supply to the capacitor. The capacitor is connected to a high resistance (R) tube. The capacitor pressure maintains the constant flow at the terminal end of the tube (Greenwald 2002).

Windkessel function in the heart is illustrated in Figure 2.4. The stoke volume is ejected from the left ventricle to the aorta during systole. Approximately 50% of the stoke volume is directly pushed to the peripheral circulation and the remaining 50% is stored in the aorta. During diastole, the aortic valve is closed and the remaining 50% is pushed to the peripheral circulation due to the recoiling of the aortic tissue (Belz 1995).

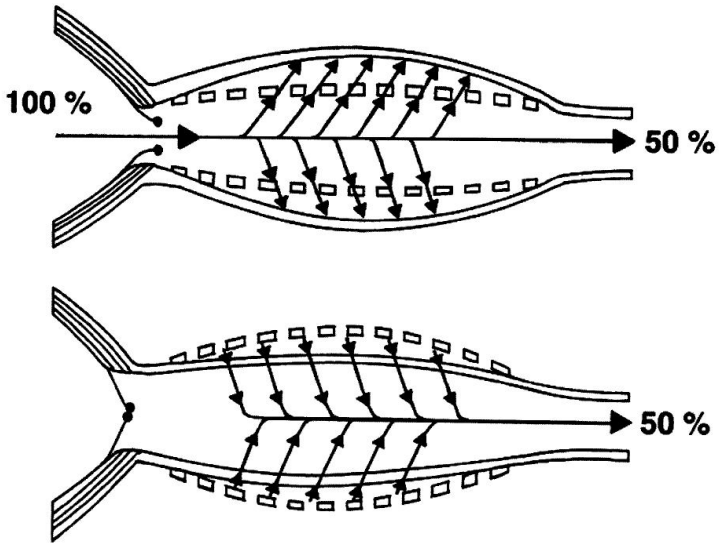


Figure 2.4 Windkessel function of the aorta
(Belz 1995)

However, the Windkessel model is a simple theory, which could not explain much of how the complex arterial system fits with elastic theories. Windkessel theory suggests that conduit and cushion functions are separate, where they are actually combined functions. Secondly, the model did not address the heterogeneous character of the arterial tree. For example, the pulse wave velocity increases towards the periphery, because the conduit and cushioning effects are lower and there is an increasing vascular resistance towards the periphery of the arterial tree (Laurent *et al*. 2006).

Stress is a force distributed on the internal or external surface of a body. Strain is described as a deformation of a body compared with its original form in response to the stress. Vascular structures are influenced by three types of stress: (i) longitudinal- change in length, (ii) circumferential and (iii) shear stress (Fig 2.5).

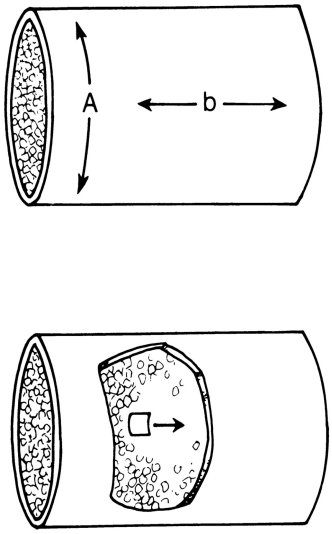


Figure 2.5 Schematic representation arterial wall stress

Circumferential (A) and longitudinal (b) stresses in the arterial wall (top) and shear stress at the vascular interface (bottom) (O'Rourke 1995)

Shear stress (rubbing and sliding) is a comprehensive stress that results in angular deformation, a displacement of two points in parallel planes in a direction parallel to those planes (Nichols *et al*. 2005). Concepts of elasticity are important in the understanding of the functions of arteries. A body is called elastic when deformation occurs after an applied stress and then it readopts its original shape after the stress is stopped. The response to stress differs between solid and liquid bodies. The liquid bodies will undergo viscous flow where the solid bodies do not. Some bodies such as arterial walls are called viscoelastic as they have combined qualities of solid and liquid. They respond to stress depending on the size and rate of the stressing force (Nichols *et al*. 2005).

Hooke's law states that the deformation produced by a stress is directly proportional to the deforming force or load applied (Encyclopædia-Britannica 2012). The body can reform to its original position until it reaches the elastic

limit. Beyond that yielding point, the body will break and undergo a permanent deformation. However, these theories apply to homogenous bodies. The arteries are complex structures with different elastic properties. They are composed of different proportions of elastin, collagen and muscle tissues, which are arranged in parallel and take different amounts of load (Bergel 1961; Wolinsky and Glagov 1964) . Arterial stiffness develops due to the reversible or irreversible deformations in the arterial wall.

2.2. Mechanism of arterial stiffness

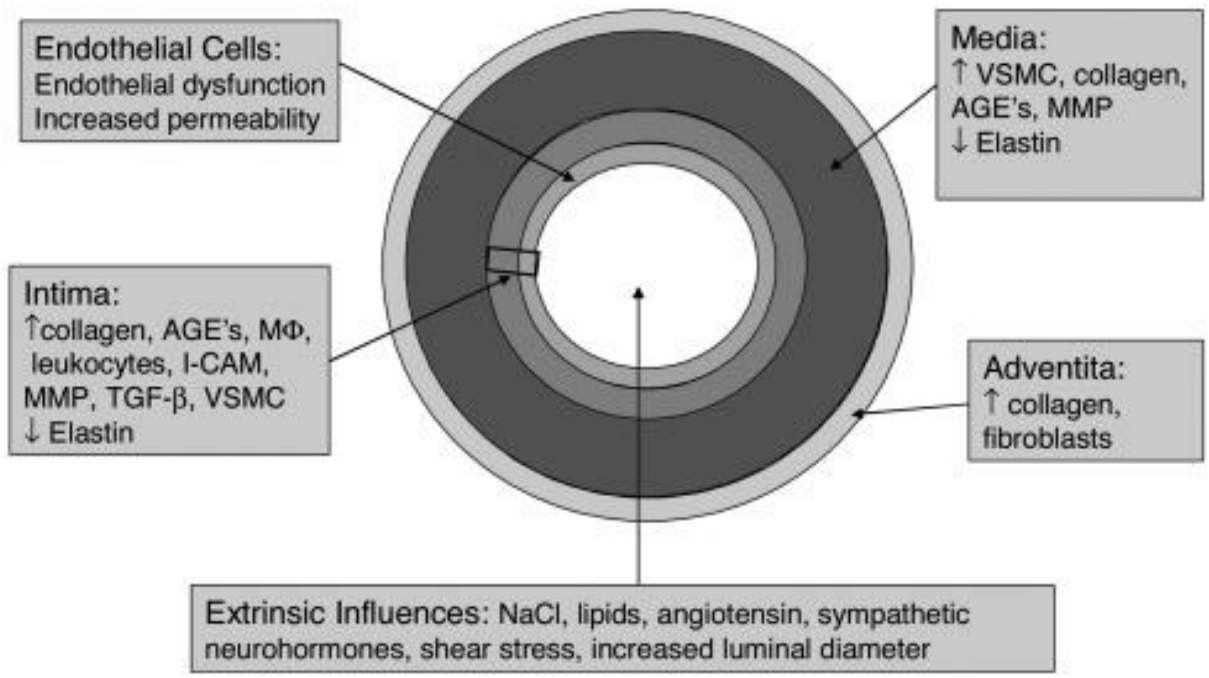
2.2.1. Definition of arterial stiffness

Arterial stiffness is defined as a reduction in arterial distensibility (Lacolley *et al*. 2009). There are number of molecular, cellular and genetic causes underlying the mechanism of arterial stiffness (Lacolley *et al*. 2009). The distensibility of the arteries is decreased if intra-luminal pressure is increased or when there is an increase in arterial stiffness due to aging or any pathological changes (Stratos *et al*. 1992).

2.2.2. Structural changes

Arterial stiffness is caused by reversible or irreversible changes in both the structural and cellular components of the arterial wall. A schematic representation of these changes is illustrated in figure 2.6. In general, the mechanical aging characterised by degeneration increases the arterial stiffness. During aging and pathological conditions, imbalance in the structures of the arterial wall and remodelling of extra cellular matrix (ECM) occurs (Jacob 2003). A decrease in ECM is also found with aging (Cattell *et al*. 1996).

Metalloproteinases (MMP), collectively called matrixins, are a major part of collagenolytic enzymes. With age, the balance between MMP and their inhibitors is affected and it degrades ECM (Nagase and Woessner 1999; Visse and Nagase 2003). This results in a newly synthesized ECM (Jacob 2003) with damage in enzymatic cross-links in collagen as well as elastin fibres. This results in a decrease in elastin fibres and increase in collagen fibres (Gillessen *et al*. 1995). With the new combinations in the ECM, the vascular structures change with an increase in intima-media thickness (Jacob 2003).



AGE-Advanced Glycation End Product; MMP-Metalloproteinases; Mφ- Macrophages; VSMC- Vascular Smooth Muscle Cell; I-CAM- Intercellular Adhesion Molecule; TGF-β- Tumour Necrosis Factor-β; NaCl- Sodium Chloride

Figure 2.6 Schematic representation of changes in structures and function of an artery in the development of arterial stiffness

(Zieman *et al*. 2005)

Advanced glycation end products (AGEs) are strongly linked to the development of arterial stiffness in cardiovascular disease (Schram *et al*. 2005;

McNulty *et al*. 2007). They are forms of a wide range of carbohydrates that are produced from fragmentation of non-enzymatic protein glycation (Baynes 2001). An increased level of AGEs affects intra and extra cellular structure and function (Goldin *et al*. 2006). AGEs bind to specific cell receptors such as receptor for AGEs (RAGE) and produce cross-links (Schmidt *et al*. 1994). These cross-links form in collagen fibres and result in abnormal fibre distribution and an increase in stiffer collagen (Verzijl *et al*. 2000; Zieman *et al*. 2005). The cross-links also affects elastin which results in weak elastic matrix (Konova *et al*. 2004). Normally, specific AGEs receptors and anti-AGEs antibodies maintain the homeostasis, but in aging and pathological conditions, the homeostasis becomes inefficient (Konova *et al*. 2004). The RAGE-AGEs binding also affects stress signalling and induce inflammatory response (Yan *et al*. 1994). The influence of RAGE-AGEs bind on the structure of endothelium resulting in endothelial hyper-permeability which leads to an increased vascular leakage of protein and plasma fluid in the paracellular area (Goldin *et al*. 2006). This may be due to AGEs induced reduction in the endothelial isoform of nitric oxide synthase (eNOS) (Xu *et al*. 2003). The reduced availability of nitric oxide results in endothelial cell proliferation (O'Rourke and Hashimoto 2007), abnormal vascular remodelling and endothelial dysfunction (Rudic and Sessa 1999). These increase vascular smooth muscle cell tone, depress endothelial flow mediated dilation, and diminish response to vascular injury, affecting angiogenesis and promoting atherosclerotic plaque formation (Schmidt and Stern 2000; Stern *et al*. 2002; Wendt *et al*. 2002).

2.2.3. Genetic relations

Arterial stiffness, having a multifactorial nature, is linked to a number of genetic polymorphisms (Zieman *et al*. 2005). Lacolley *et al* (2009) state in a review that many candidate gene polymorphisms, that are responsible for arterial stiffness, have been identified. For example, a number of proteins were established to have links with arterial stiffness due to gene polymorphism such as angiotensin converting agent (ACE) (Cambien *et al*. 1994), angiotensin II type I receptor (Benetos *et al*. 1996), endothelin a and B receptor (Lajemi *et al*. 2001), collagen 1α (1) (Brull *et al*. 2001), fibrillin-1(Medley *et al*. 2002), AGF-1 (Schut *et al*. 2003), α –adducing (Balkestein *et al*. 2001), aldosterone synthase (Pojoga *et al*. 1998) and MMPs 3 and 9 (Medley *et al*. 2003; Medley *et al*. 2004). Mitchell *et al* (2005) carried out a genome wide scan on the Framingham study population, and found correlations with reflective wave amplitude, forward wave amplitude and mean arterial pressure. They established the arterial stiffness linkage with specific genetic loci on chromosomes 1,2,4,7,8,13 and 15.

2.2.4. Clinical implications of arterial stiffness

2.2.4.1. Atherosclerosis and arteriosclerosis

The cushioning functions of arteries are disturbed in diseased states such as atherosclerosis and arteriosclerosis. Atherosclerosis is a focal and occlusive disorder that primarily affects the intima. The conduit function is affected due to narrowing of a major artery and ischaemia to the distal organ or tissues (Fig 2.7). Arteriosclerosis is a diffuse and dilatory disorder and primarily affects the media. The cushioning function is affected due to the stiffening and dilation of

major arteries, which results in raised blood pressure and pulse pressure, and the disturbance of the load upstream to the heart (Fig 2.7) (O'Rourke 1995).

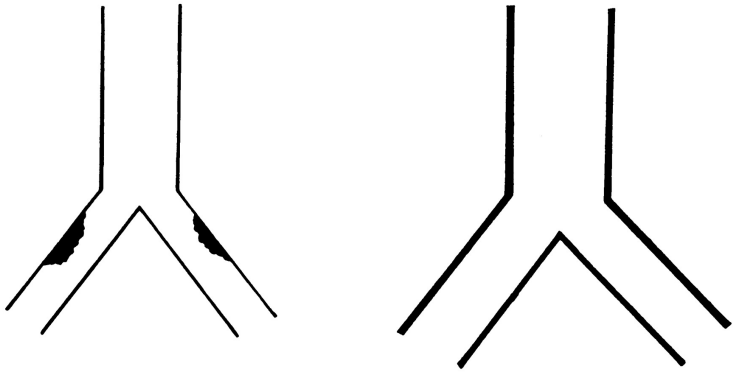


Figure 2.7 Atherosclerosis and arteriosclerosis:

Atherosclerosis (left) narrows the arteries due to localized patches on the intima and thus limiting the blood supply downstream. Arteriosclerosis (right) causes dilation and stiffening due to a generalized degeneration throughout large central arteries. It predominantly affects the cushioning function of the arteries and increases the load upstream

(O'Rourke 1995)

2.2.4.2. Aging and arterial stiffness

Stiffening of arteries is considered a normal process of aging. Comparing with any other cardiac risks, arterial stiffness increases more steadily with age (Mattace-Raso *et al*. 2006). However, the arterial stiffness in aging is characterised by a diffuse stiffening across the arterial tree i.e. arteriosclerosis rather than a stenotic and localised atherosclerosis (Vlachopoulos and O'Rourke 2000). The arteriosclerosis in aging is caused by changes in arterial media. The elastin fibres undergo thinning, splitting, fraying and fragmentation and there is an increase in collagen fibres and ground substance (Nicholls and O'Rourke 2005). These changes in the arteries are progressive throughout life (Nichols *et al*. 1985). Moreover, the arterial changes with aging that are found in various ethnic populations confirm that they are true age-related changes

(Schimmler 1965; Avolio *et al*. 1983; Avolio *et al*. 1985; Lanne *et al*. 1992; Sonesson *et al*. 1993). Most of these studies have confirmed the changes especially in the aorta and central arteries with little evidence on peripheral arteries. The peripheral arteries seem to be protected by smooth muscle and collagenous elements. Moreover the peripheral vessels do not expand to the extend which central arteries do (Boutouyrie *et al*. 1992). Normally, central arteries expand by 10% for each heartbeat and the peripheral arteries expand by 5% (Isnard *et al*. 1989; Benetos *et al*. 1991; Boutouyrie *et al*. 1992). O'Rourke (1995) compares the arterial distensibility with natural rubber which has similar characteristics to the arteries. Natural rubber fractures after 109 cycles of expansions in relation to central arteries' expansions whereas the central arteries reach such a state after about 25-30 years of life with a normal heart rate (Cadwell *et al*. 1940; Lindley 1974). The peripheral arteries need 3×109 cycles to achieve such damage, which is about 100 years of life (O'Rourke 1983; O'Rourke 1995).

2.2.4.3. Coronary artery disease and arterial stiffness

The association of arterial stiffness with coronary artery disease and myocardial ischaemia is established in many studies (Hirai *et al*. 1989; Triposkiadis *et al*. 1993; Barenbrock *et al*. 1995; Cameron *et al*. 1996; Gatzka *et al*. 1998; Waddell *et al*. 2001; Kingwell *et al*. 2002; Lim *et al*. 2004; Leung *et al*. 2006). Arterial stiffness is a predictor for cardiovascular disease (CVD) (Laurent *et al*. 2001; Boutouyrie *et al*. 2002) and is associated with cardiovascular and all cause mortality (Stork *et al*. 2004; Vlachopoulos *et al*. 2010). For example, increase in aortic pulse wave velocity (an index of arterial stiffness) by 1 m/s increases by

15% the chance of a cardiac event and all cause mortality (Vlachopoulos *et al*. 2010).

In chronic vascular stiffening, there is an early or premature pulse wave reflection. This increases the systolic pressure and afterload that leads to systolic hypertension and left ventricular hypertrophy (Kelly *et al*. 1992; Mattace-Raso *et al*. 2006). A reduced diastolic pressure increases the pulse pressure and reduces coronary arterial pressure and thus perfusion. There is a reduction in ejection fraction and an increase in oxygen demand. This increases the mismatch between demand and supply to the myocardial tissue (Nichols *et al*. 1990), resulting in ischaemia.

2.2.4.4. Cardiovascular disease and risk factors

The associations of arterial stiffness with cardiovascular disease such as hypertension (Arnett *et al*. 2000), diabetes (Mather and Lewanczuk 2004) and chronic kidney disease (Kimoto *et al*. 2006) are well established. The changes in arterial stiffness are observed in the initial stages of CVD risks such as glucose intolerance (Henry *et al*. 2003) and insulin resistance (Sengstock *et al*. 2005). The severity of arterial stiffness is proportional to the number of risk factors present, such in metabolic syndrome (Scuteri *et al*. 2004).

2.2.4.5. Other factors influencing arterial stiffness

As with every other cardiovascular diagnostic feature, arterial stiffness has racial and ethnic differences. For example, Hispanic and African people have higher arterial stiffness compared with Caucasians in young as well as in

increasing age (Heffernan *et al*. 2008; Markert *et al*. 2011). However, there is a lack of ethnic studies in specific cardiovascular risks in developing countries such as in south Asia.

Environmental factors also affect the haemodynamics and arterial stiffness variables. Low outdoor temperatures and high air pollution were identified as influencing factors of haemodynamics and arterial stiffness by reducing subendocardial viability ratio (Adamopoulos *et al*. 2010).

Dietary salt intake is shown to be influencing arterial stiffness. Excessive sodium chloride (NaCl) increases the levels of asymmetric dimethylarginine in the circulation, which is an endogenous nitric oxide synthase inhibitor. There is also an increase in angitension II and endogenous natriuretic sodium pump ligands. All these factors reduce the availability of nitric oxide and thus leads to endothelial dysfunction (Bagrov and Lakatta 2004).

Exercise showed positive effects on arterial stiffness. Exercise capacity and exercise training shows negative correlations with age-related changes in arterial stiffness (Black *et al*. 2009; Sindler *et al*. 2009; Walker *et al*. 2009). These studies claim that exercise increases the bioavailability of nitric oxide and thus reduces oxidative stress and endothelial dysfunction. Lifestyle modification as a management strategy claims significant improvement in arterial stiffness (Tanaka and Safar 2005; Aizawa *et al*. 2009).

2.3. Development of arterial pulse wave analysis

The use of measuring arterial pulses in the diagnosis of various health conditions were in practice in ancient Indian ayurvedic medicine and Chinese

medicine 2600 years ago (Ghasemzadeh and Zafari 2011). In Greek medicine, Herophilus (335-280 BC) compared the pulse rate with musical rhythm. He also developed a portable water clock or Clepsydra (Figure 2.8) which was capable of containing specific amount of water for natural heart beats for different ages (Ghasemzadeh and Zafari 2011).

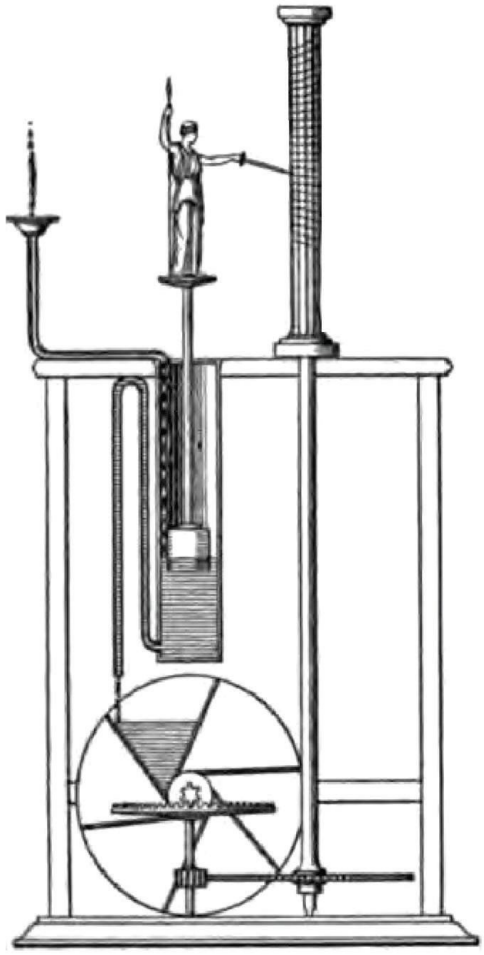


Figure 2.8 Clepsydra or Greek water clock– used by Herophilus for measuring pulse rate with different water levels according to age

(Ghasemzadeh and Zafari 2011)

In medieval medicine, Avicenna (981-1037 AD) established the importance of the quality of the pulse such as size of dilation, strength, duration, temperature, fullness, compressibility, equality and regularity (Ghasemzadeh and Zafari

2011). In more recent medicine, Santario Sanctorius (1561-1636 AD) invented a device ‘Pulsilogy’ following Galileo’s pendulum (Figure 2.9). Pulsilogy consisted of a scale of inches and a pendulum i.e. a cord with a movable weight. The weight was marked with a transverse line. The pendulum was moved downwards by increasing the rope-length until the speed of the pendulum matches the frequency of the pulse that was noted by the same physician’s finger. Then, the pulse rate was measured in inches by the length of the rope.

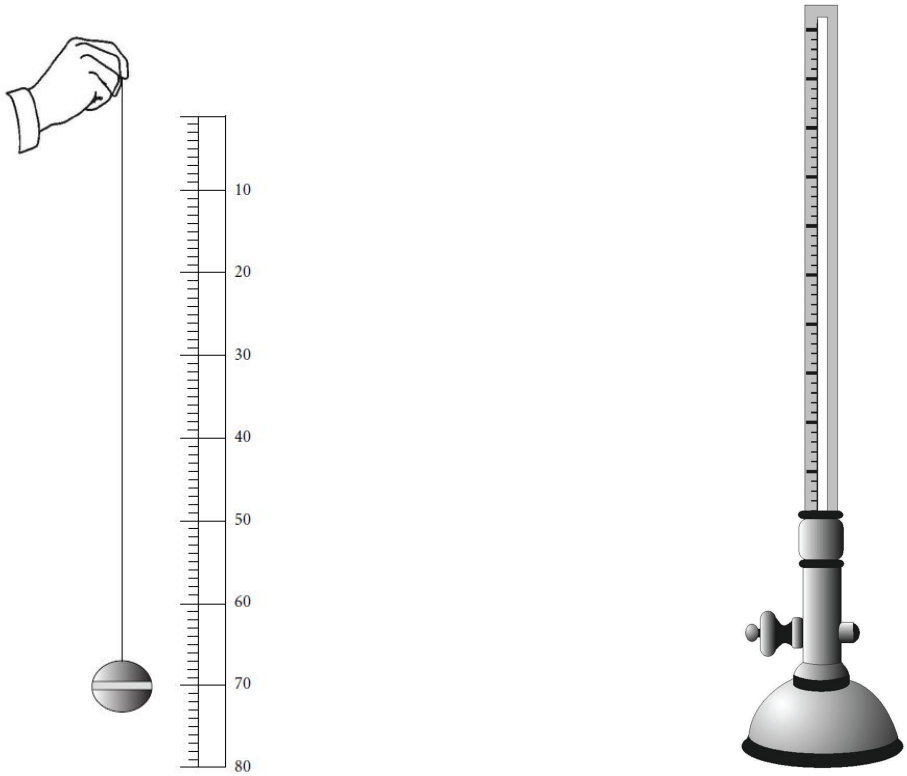


Figure 2.9 Pulsilogy of Sanctorius and Herrison’s sphygmometer

In the Pulsilogy of Sanctorius (Left) the speed of the pendulum was matched with the pulse rate and measured in inches. Herrison’s sphygmometer (Right) has a glass tube with mercury. The semiglobular steel ball was placed on a arterial site and the regularity, force and rhythm were monitored by the changes in mercury level (Ghasemzadeh and Zafari 2011).

John Flyer (1649-1734 AD) introduced the modern measurement of pulse rate continuously for 60 seconds. In the 19th century, Jules Herisson invented the

‘Sphygmometer’, which is composed of a graduated glass tube with mercury and a semicircular steel ball at one end (Figure 2.9). The steel ball was placed on the arterial site and the pulse rate and force was measured on the tube (Ghasemzadeh and Zafari 2011). In 1847, Carl Ludwig, a German physiologist invented the ‘Kymograph’, that was the first device to record haemodynamic variables (Figure 2.10).

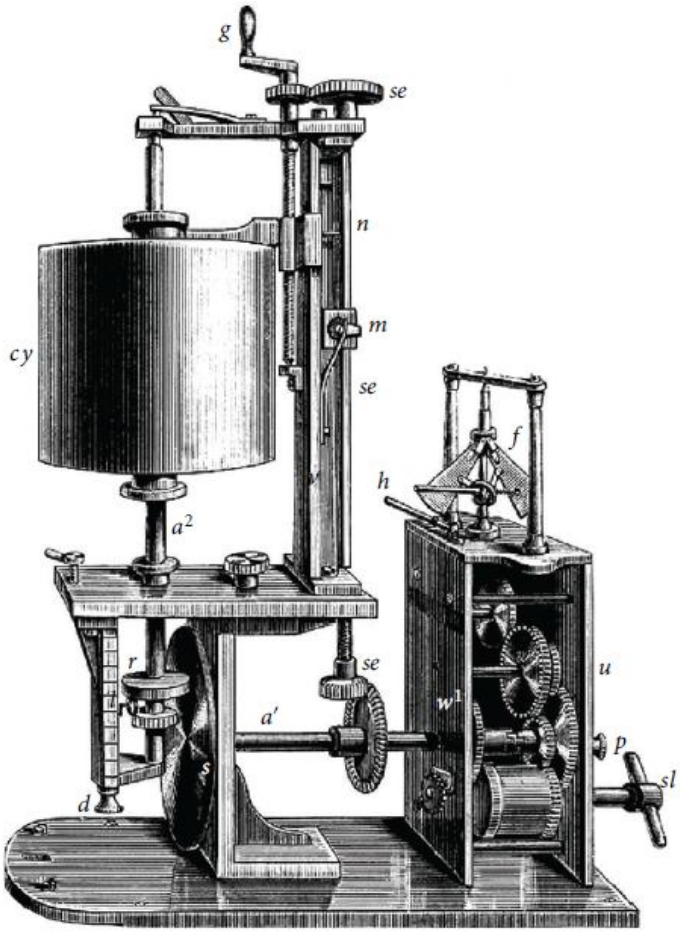


Figure 2.10 Ludwig’s kymograph (wave writer)
(Ghasemzadeh and Zafari 2011)

In 1855, Karl Vierordt designed the fist sphygmograph that can measure the pulse wave on the unbroken skin (Figure 2.11) (Lawrence 1978). Von Basch designed a sphygmomanometer in 1881 (Figure 2.12). Despite its complicated

appearance, it was also a simple model to measure the arterial pulse. Von Bosch's device was the first one to demonstrate pathological differences in pulse wave in clinical conditions such as atherosclerosis (Booth 1977).

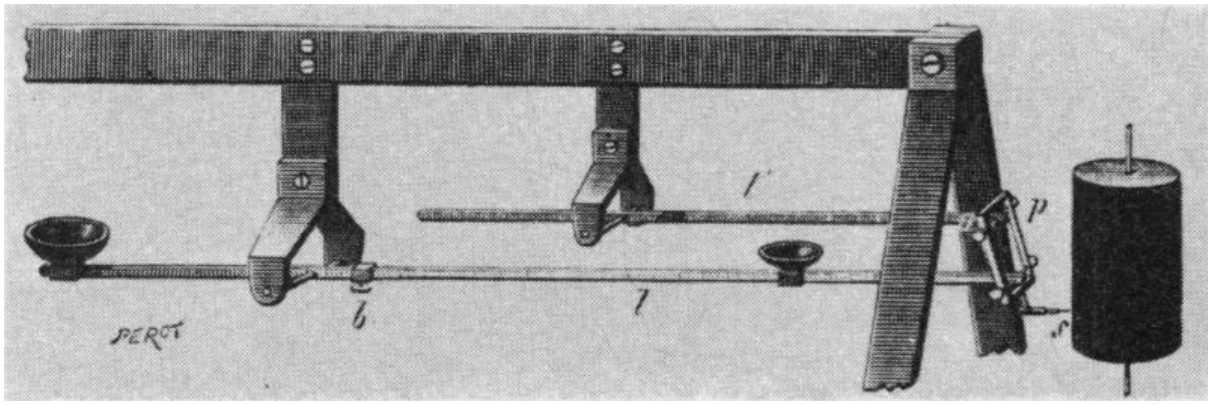


Figure 2.11 Vierordt's sphygmograph

It had a pad (b), which was placed on the radial artery at the wrist. It had a larger cup in which weights were added until a pulse wave was traced, and then weights were added in the smaller cup to adjust the quality of the pulse wave (Booth 1977)

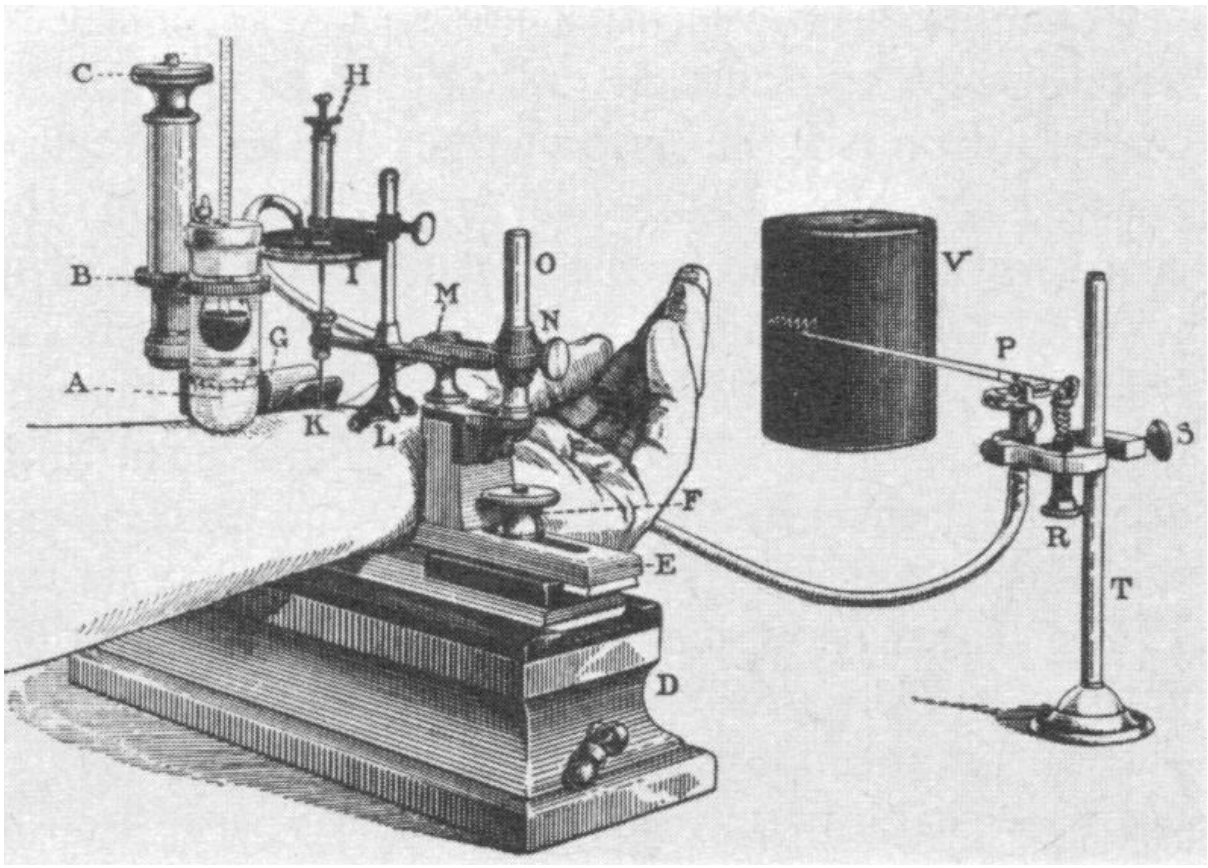


Figure 2.12 Von Basch's sphygmomanometer.

The wrist was placed on the stand and the India rubber cap (A) was placed on the radial artery. In that position, the arm was clamped between E and G. another pad (K) was also placed on the artery for the quality of the pulse wave recording by adjusting the screw H (Booth 1977)

In 1860, Etienne Marey (1830-1904), a French physiologist, modified the sphygmometer as ‘sphygmograph’. The sphygmograph was considered as the first convenient instrument to record a pulse wave graphically (Lawrence 1978). The equipment was applied on the wrist (Figure 2.13) and the pulse waveforms were recorded. Etienne Marey established the difference in pulse waveforms between elderly and younger adults (Ghasemzadeh and Zafari 2011). Marey’s sphygmograph was continuously studied and modified by many authors (Foster 1868; Garrod 1871) and differences in various clinical conditions were established. Later, Mahomed (1849-1884) revised the sphygmograph. By

adding a screw, the device was capable of measuring the pressure (Figure 2.14) (Ghasemzadeh and Zafari 2011).

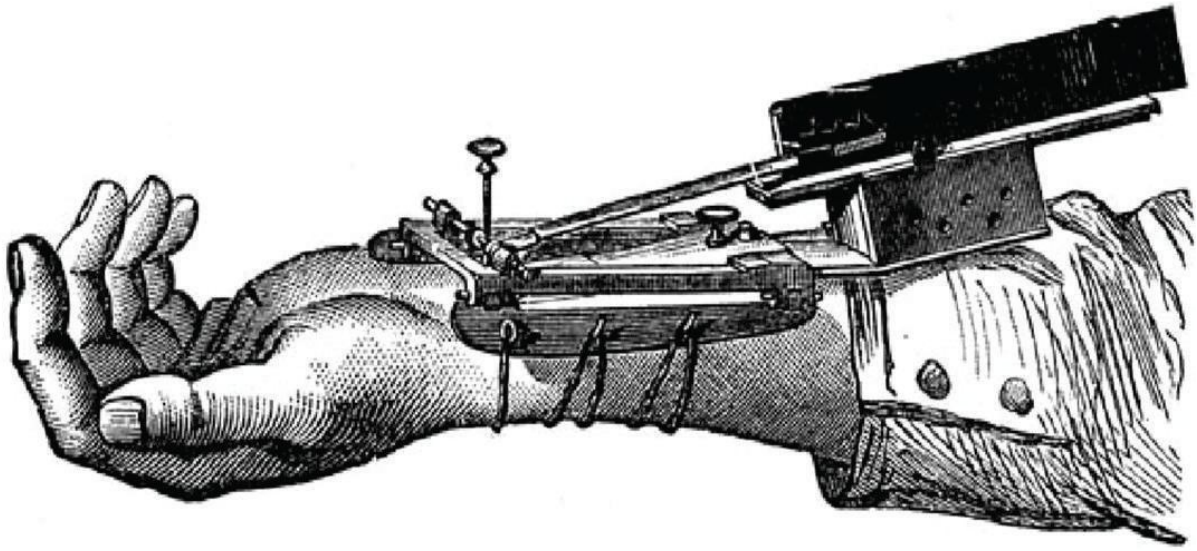


Figure 2.13 Marey's sphygmograph

The device was applied on the wrist and the screw was adjusted to elicit radial pulse. The device was able to record the pulse graphically (Ghasemzadeh and Zafari 2011).

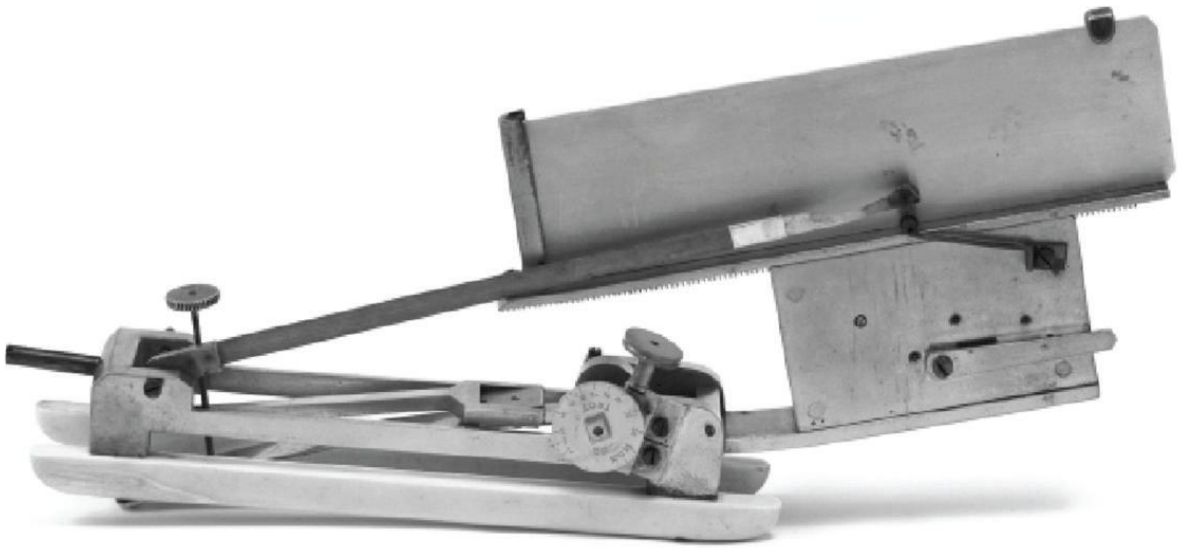


Figure 2.14 Mahomed's sphygmograph

This device was a revised form of Marey's sphygmograph with an added screw. It was capable of measuring the pressure needed to occlude the arterial wave along its graphical recordings of the arterial pulse wave dynamics (Ghasemzadeh and Zafari 2011).

In 1905 N C Korotkoff, a Russian surgeon reported the current technique of blood pressure measurement with a cuff and stethoscope on the brachial artery at the cubital fossa (Booth 1977). However, Mahomed (Mahomed 1987) interpreted arterial stiffness using pulse wave analysis long before the introduction of the sphygmomanometer. In the 20th century, the sphygmograph was modified to a digital measurement (Waller 1900; Baldwin 1929; Baldwin and Panzer 1946; Panzer *et al*. 1947; Herman 1978). The digitalised Mahomed's sphygmograph is one of the currently used techniques in the pulse wave measurements and analysis. There is another technique used currently which was introduced by a German Physician Otto Frank (1865-1944). Frank was the first one to derive mathematical formulae for the Windkessel function and to detect the pulse wave reflections (Frank 1926; Sagawa *et al*. 1990; Parker 2009). Following the controversies in the Windkessel model and the

development of new hydraulic and elastic theories, new propagation models were developed for the circulatory system by Frank (1920) and Bramwell and Hill (1922). Bramwell and Hill (1922) introduced the concept of pulse wave velocity. They modified the Moens–Korteweg equation by a series substitution.

Moens–Korteweg equation:

$CO = \sqrt{(Eh/2R\rho)}$

CO - Wave speed; E- Young's modulus in the circumferential direction:

h- Wall thickness; R- Radius; ρ- Density of fluid.

Moens–Korteweg equation with Bramwell and Hill's substitutions;

$CO = \sqrt{(V.\ \partial P/\ \rho.\ \partial V)}$

CO - Wave speed; V- Volume; ρ- Density of fluid;

∂P - Change in arterial pressure; ∂V- Change in arterial volume.

Cohn *et al* (1995) developed a circulatory model to examine pulse waves non-invasively. Pulse wave reflections and arterial compliance were measured using a tonometer and calibrated with an ocillometric method using a cuff on the opposite side. The results were not identical to invasive measurements. However, their results were able to confirm abnormalities in the pulse waves in CVD and the early detection of CVD. Otto Schmitt is one of the pioneers of electrical impedance theories and he constructed the first electrical impedance plethysmograph in the mid twentieth century (Valentinuzzi and Belalcazar

2006). What followed was enormous progress on pulse wave research (Ghasemzadeh and Zafari 2011).

2.3.1. Modern equipment

There are several advanced non-invasive techniques to measure local arterial stiffness such as arterial distensibility and pulse wave velocity. The change in arterial diameter is measured by relating change in area to the distending pressure. The most commonly used techniques are Doppler ultrasonography (Lehmann *et al*. 1993; Pannier *et al*. 2002; Kullo and Malik 2007; Jiang *et al*. 2008) magnetic resonance imaging (MRI) and computed tomography (CT) (Grotenhuis *et al*. 2009; Joly *et al*. 2009; Nelson *et al*. 2009; Ohayon *et al*. 2011). Despite having accurate measurements, these techniques have some disadvantages such as the need of expensive equipment and high level expertise to operate the equipment (Stoner *et al*. 2012). Comparatively, there are many automated, less expensive types of equipment available using non-invasive pulse wave analysis. They are simple to assess, need comparatively low expertise and time to operate, are portable and cost effective (Stoner *et al*. 2012).

Asmar *et al* (1995) validated new automatic equipment that used a pressure sensitive transducer measurement on pulse wave velocity for the first time. They established significant accuracy and reproducibility of the measurements. These findings initiated the development of many automated devices (Stoner *et al*. 2012) such as: (1) Complior (Artech Medical, Pantin, France), (2) SphygmoCor (Atcor Medical, Sydney), and (3) Arteriograph (Tensiomed,

Budapest, Hungary). A list of commonly used automated devices is given in the table 2.1.

Table 2.1 Commercially available automated equipment for pulse wave analysis

Device	Type	Relevant supporting research
Complior	Peizo-electronic	(Baulmann *et al*. 2008; Jatoi *et al*. 2009)
SphygmoCor	Tonometric	(Millasseau *et al*. 2002; Hope *et al*. 2008; Jatoi *et al*. 2009; Wassertheurer *et al*. 2010; Kracht *et al*. 2011)
PulsePen	Tonometric	(Salvi *et al*. 2010; Palombo *et al*. 2011)
ARCSolver	Oscillometric	(Wassertheurer *et al*. 2010; Weber *et al*. 2011)
Arteriograph	Oscillometric	(Horvath *et al*. 2010; Nemes *et al*. 2010; Gavaller *et al*. 2011; Nemes *et al*. 2011; Rezai *et al*. 2011; Gaszner *et al*. 2012)
Omron	Oscillometric	(Rezai *et al*. 2011; Seibert *et al*. 2011)
PulseCore	Oscillometric	(Lowe *et al*. 2009; Climie *et al*. 2012)
Vicorder	Oscillometric	(Hickson *et al*. 2009; van Leeuwen-Segarceanu *et al*. 2010; Kracht *et al*. 2011)
PulseTrace	Photoplethysmographic	(Chowienczyk *et al*. 1999; Millasseau *et al*. 2000; Millasseau *et al*. 2002; Padilla *et al*. 2009)

2.3.1.1. Oscillometric devices

Oscillometric devices such as Arteriograph and Vicorder (Figure 2.15) use a unique technique. A high fidelity pressure sensor is used which is connected to a conventional blood pressure cuff. The blood pressure is measured using an oscillometric method and then the cuff pressure is applied about 35mmHg in excess of the measured systolic blood pressure. Then, the pulse wave reflections are recorded by detecting the oscillations in the pressure. The measurement is digitalised using a three level algorithm and pulse wave

velocity is calculated from the pulse wave return time (Rajzer *et al*. 2008; Jatoi *et al*. 2009; Wassertheurer *et al*. 2010).

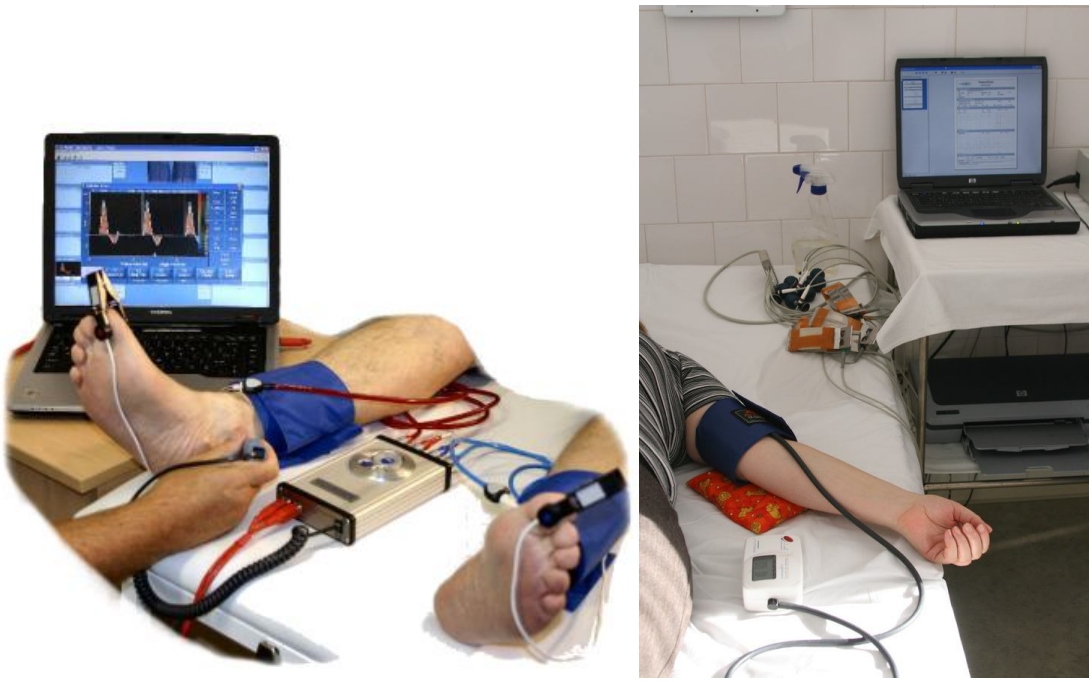


Figure 2.15 Oscillometric devices: The Vicorder (Left) and Arteriograph (Right)

2.3.1.2. Piezo-electronic device

Complior (Figure 2.16) uses mechano-transducers which are directly applied on the skin at the arterial sites and measurements taken simultaneously from different arterial sites: carotid-brachial, carotid-femoral and femoral-dorsalis pedis (Asmar *et al*. 1995). It measures the pulse wave velocity by calculating the beat-to-beat time delay between the two ends of an arterial pulse. A correlation algorithm is performed within the equipment for this calculation.

Figure 2.16 The Complior- A piezo-electronic system

2.3.1.3. Tonometric device

SphygmoCor (Figure 2.17) uses the applanation tonometry with a high-fidelity tonometer (Miller®). Applanation tonometry is considered as a 'Gold Standard' method in non-invasive pulse wave analysis (O'Rourke *et al*. 2001). The tonometer has a coplanar sensor that is placed on the site of local artery and a mild pressure applied to flatten the arterial wall. The pulse waves are calculated and displayed on a personal computer using specific internal software with a generalised transfer function. Pulse wave velocity is calculated using foot to foot method by consecutive measurements at arterial sites. It is derived by calculating the time between the R waves of ECG, which is measured simultaneously. The quality of measurement can be monitored using the operator index calculation. The central pressures are calibrated from peripherally measured blood pressure. Generally, carotid-femoral pulse wave velocity was used in most of the epidemiological studies. It is claimed as a standard method as femoral artery is a direct branch of aorta, which can give

accurate propagation. However, it is difficult to access the femoral artery and/or measure accurately in few clinical conditions such as metabolic syndrome, obesity, diabetes and peripheral arterial disease (Van Bortel *et al*. 2002). The carotid-radial method is recommended in such conditions and the transfer function is better in upper limb arteries using SphygmoCor (Van Bortel *et al*. 2002). Usually brachial artery pressure is used instead of radial artery when carotid-radial pulse waves are analysed. This is considered a disadvantage as it can cause errors (Verbeke *et al*. 2005). However, O'Rourke claims that the difference between brachial and radial pressure is negligible. More studies are needed to establish the validity of carotid-radial pulse wave analysis which is a less intrusive technique.

Figure 2.17 The SphygmoCor – A tonometric system

A number of studies tried to establish reference values for the measurements used in applanation tonometry. Wojciechowska *et al* (2006) established reference values of pulse pressure and augmentation index for a limited European population. The reference values for pulse wave velocity are available for Americans (Elias *et al*. 2011), Chinese (Li *et al*. 2008; Wang *et al*. 2009) elderly Caucasians (Alecu *et al*. 2008) and Africans (Shiburi *et al*. 2006).

Khoshdel *et al* (2006) carried out a meta analysis to find age specific reference values for pulse wave velocity in Caucasians. However, so far there are no generalized reference values available for all the arterial stiffness variables using applanation tonometry. Further, there is a lack of research on populations in developing countries such as in South Asia. Applanation tonometry has been used in epidemiological and interventional studies for its established prognostic value (Shiburi *et al*. 2006; DeLoach and Townsend 2008; Rajzer *et al*. 2008). Nonetheless, Medical Services Assessment Committee (MSAC 2006) reports that its diagnostic value is limited due to the lack of generalised data.

2.4. The parameters of pulse wave reflections in applanation tonometry

2.4.1. Pulse wave

During systole, after the blood is ejected into the systemic circulation, the intravascular pressure undergoes a small change. The wave motion through which the change of pressure is transmitted toward the periphery is known as pulse wave. A small part of forward travelling pulse wave is reflected backwards to the heart at every branching artery throughout the vascular system. The forward and reflected waves summate and produce wave deflections (Dart and Kingwell 2001). Many of the arterial stiffness variables such as pulse pressure, augmentation pressure, augmentation index and pulse wave velocity are established for individual predictive values for cardiovascular disease and mortality (Laurent *et al*. 2006). There are a number of definitions and formulae to calculate arterial stiffness, which can be derived from the change in pressure and size. The indices of arterial stiffness are listed in table 2.2. A normal pulse wave and the variables are illustrated in fig 2.18.

Table 2.2 Indices of arterial stiffness

Elastic modulus	The pressure step required for (theoretical) 100% stretch from resting diameter at fixed vessel length (ΔP · D)/ΔD (mm Hg)
Arterial distensibility	Relative diameter (or area) change for a pressure increment; the inverse of elastic modulus ΔD/(ΔP · D) (mm Hg-1)
Arterial compliance	Absolute diameter (or area) change for a given pressure step at fixed vessel length ΔD/ΔP (cm/mm Hg) (or cm2/mm Hg)
Volume elastic modulus	Pressure step required for (theoretical) 100% increase in volume ΔP/(ΔV/V) (mm Hg)=ΔP/(ΔD/D) (mm Hg) (where there is no change in length)
Young's modulus	Elastic modulus per unit area; the pressure step per square centimeter required for (theoretical) 100% stretch from resting length ΔP · D/(ΔD · h) (mm Hg/cm)
Pulse Pressure	The difference between systolic and diastolic pressure Ps-Pd (mmHg)
Pulse wave velocity	Speed of travel of the pulse along an arterial segment Distance/Δt (m/s)
Characteristic impedance	Relationship between pressure change and flow velocity in the absence of wave reflections ΔP/Δv [(mm Hg/cm)/s]
Augmentation Pressure	Contribution of arterial pressure wave reflection to systolic arterial pressure (Difference between first and second systolic shoulders in a pulse wave)
Stiffness index	Ratio of logarithm (systolic/diastolic pressures) to (relative change in diameter) $\beta = \frac{In(P_s/P_d}{(D_s - D_d)/D_d\ (nondimensional)}$
Augmentation index	Difference between the second and first systolic peaks as a percentage of pulse pressure (Ps-Pi) / (Ps-Pd)
Capacitive compliance	Relationship between pressure fall and volume fall in the arterial tree during the exponential component of diastolic pressure decay ΔV/ΔP (cm3/mm Hg)
Oscillatory compliance	Relationship between oscillating pressure change and oscillating volume change around the exponential pressure decay during diastole ΔV/ΔP (cm3/mm Hg)
Ejection Duration	Duration of systole calculated from the arterial pulse wave
Subendocardial Viability Ratio	Ratio between systolic and diastolic area in arterial pulse wave and it is related to the energy supply of the heart SEVR = Tension Time index/ Diastolic Pressure time index

P - pressure; D- diameter; V- volume; h- wall thickness; t- time; v- flow velocity; s- systolic; d- diastolic; Pi-wave reflection; (Murgo *et al*. 1980; Hirai *et al*. 1989; McVeigh *et al*. 1991; O'Rourke 1995)

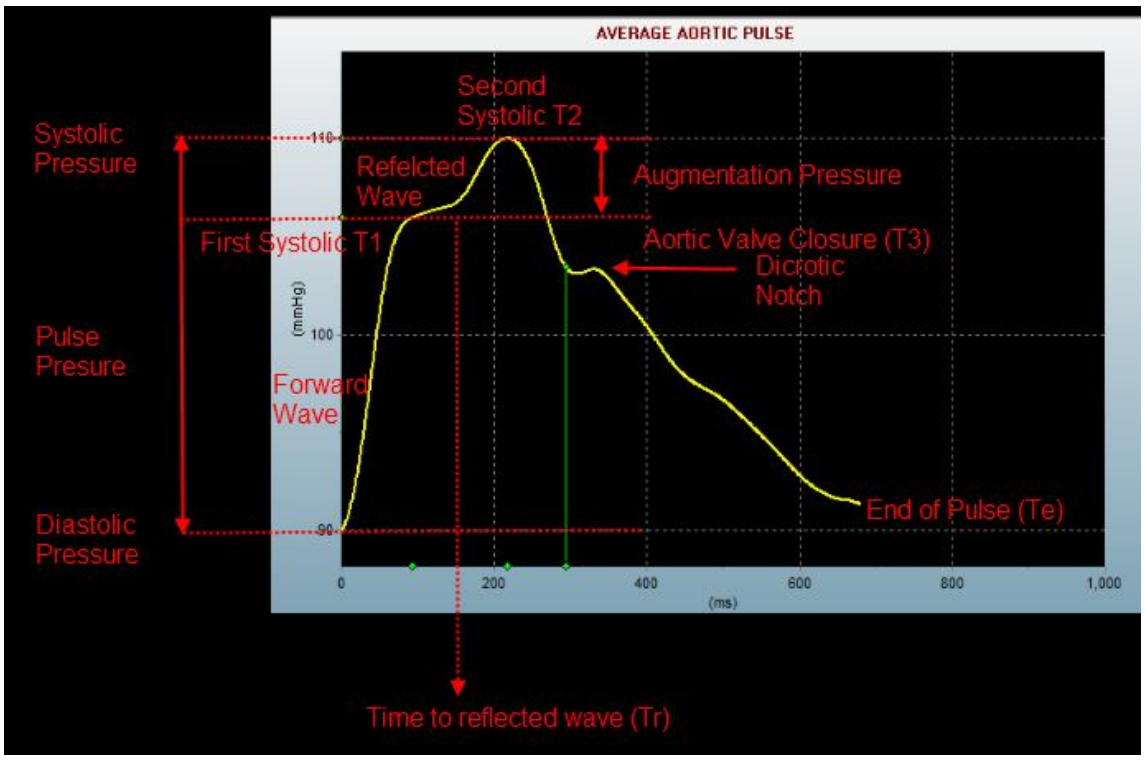


Figure 2.18 Structure of an arterial pulse wave.

A average aortic pulse wave obtained from a SphygmoCor and adopted from Stoner *et al* (2012)

2.4.2. Pulse wave velocity (PWV)

When the heart contracts it generates a pulse or energy wave that travels through the circulation. The speed of travel of this pulse wave is termed as pulse wave velocity. In other words, it is an estimation of the velocity of the propagation of the forward and backward pressure between two points of the arterial tree (Lacolley *et al*. 2009). Pulse wave velocity is considered a gold standard for any diagnostic technique in measuring arterial stiffness (Laurent *et al*. 2006) and it has established clinical implications (Accetto *et al*. 2007) . A schematic representation of changes in pulse wave velocity with arterial stiffness is illustrated in Fig 2.19.

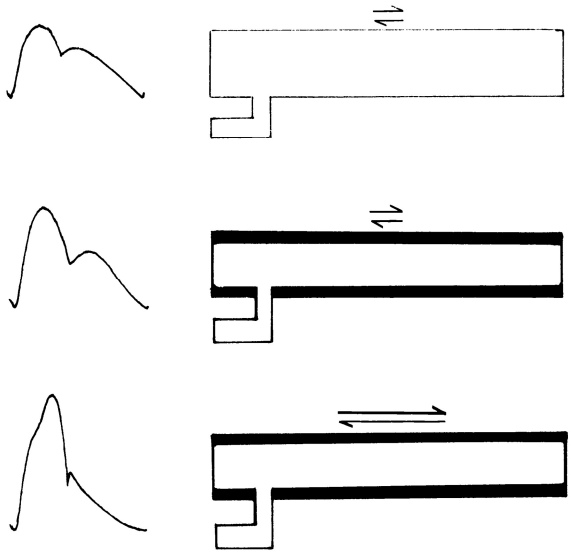


Figure 2.19 Schematic representation of changes in arterial pulse wave velocity with arterial distensibility

Top: Distensibility and pulse wave velocity in a young healthy artery – Moderate amplitude and contour of pressure wave. Middle: Decreased distensibility but normal pulse wave velocity in an aging and nearly healthy artery- pressure wave with slightly increased amplitude. Bottom: Decreased distensibility with increased pulse wave velocity in an aged and unhealthy artery- Pressure wave with increased amplitude. (O'Rourke MF 1987).

Pulse wave velocity is most commonly measured using foot to foot algorithm. In SphygmoCor, a sequence of pulse waves are recorded from two different sites e.g. radial and carotid arteries (Fig 2.20). The pulse waves are synchoronised with electrocardiogram (ECG) and an average pulse wave derived for each site with a time difference between the pulse waves. An intersecting tangent algorithm is used to identify the foot of each pulse wave. Then the foot to foot distance is calculated (Δt) (Fig. 2.21). The distance between arterial sites were manually measured on the skin (D). Then the pulse wave velocity is calculated as D/Δt in the SphygomoCor.

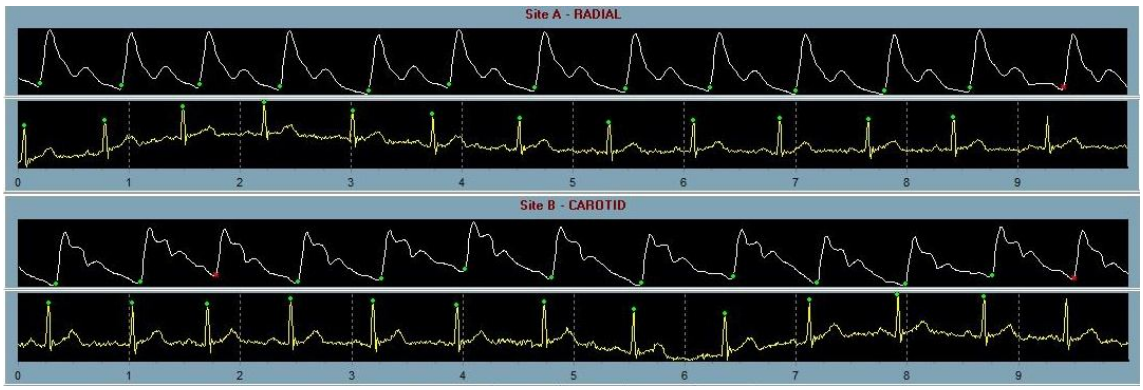


Figure 2.20 A sequence of pulse waves, captured from radial (top) and carotid (Bottom) arteries that are sycronised with ECG in Sphygmocor

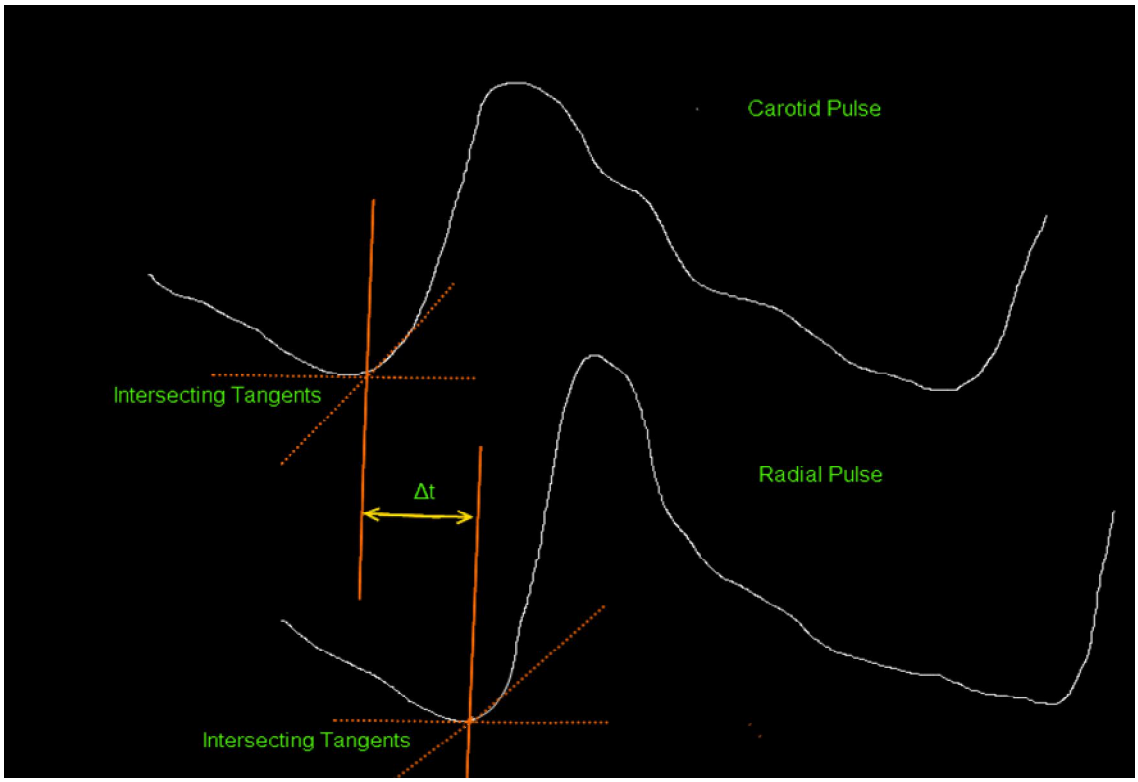


Figure 2.21 A schematic diagram for calculating pulse wave velocity using intersecting tangent method in SphygmoCor

The pulses waves are matched with ECG and intersecting tangents are derived from the foot of the each pulse wave. The time difference between the pulse waves from different arterial sites was calculated. Adopted from Millasseau (2005)

2.4.3. Augmentation pressure

The ejection of blood from the ventricle into the aorta generates an aortic pressure pulse. In many cases, the timing of the peak pressure does not coincide with the timing of peak flow, such that peak pressure may occur later. In this event, there is usually a systolic shoulder on the ascending limb pressure curve, which coincides with peak flow, then a rise in pressure to the systolic peak. The increase in the pressure is defined as augmentation pressure. When there is an increased peripheral vascular resistance and arterial stiffness, there is also an increase in premature pressure wave reflections. The accumulation of these premature reflections increases augmentation pressure and thus aortic systolic pressure (Wassertheurer *et al*. 2010).

2.4.4. Augmentation index (AIx)

The amount of augmentation pressure is quantified in terms of the relative change over the whole pulse. It is the percent ratio of augmentation pressure to the aortic pulse pressure (Wassertheurer *et al*. 2010). That is, once the early systolic shoulder and the peak (T1) or the late systolic shoulder (T2) is identified, the absolute augmentation is calculated (T2-T1). Then the augmentation index is defined. SphygmoCor calculates AIx in two ways: (1) AIx = change in pressure/T1 (2) AIx = pulse pressure/T1. Augmentation index is considered as a key tool to reflect endothelial function. This was confirmed by significant reduction in AIx after the administration of a β2 agonist endothelium dependant vasodilator, for example salbutamol (Chowienczyk *et al*. 1999; Hayward *et al*. 2002; Wilkinson *et al*. 2002). These studies claim that β2 agonist

induces the release of nitric oxide, which is responsible for smooth muscle relaxation. Thus, it reduces the reflection of arterial pulse and AIx.

2.4.5. Pulse pressure (PP)

Pulse pressure is the systolic pressure minus the diastolic pressure. Theoretically, the systemic pulse pressure can be conceptualized as being proportional to stroke volume and inversely proportional to the compliance of the aorta. It has a strong association with mean arterial pressure (Redelinghuys *et al*. 2010). Pulse pressure shows significant haemodynamic changes with advancing age and conditions such as hypertension (Mitchell 2006).

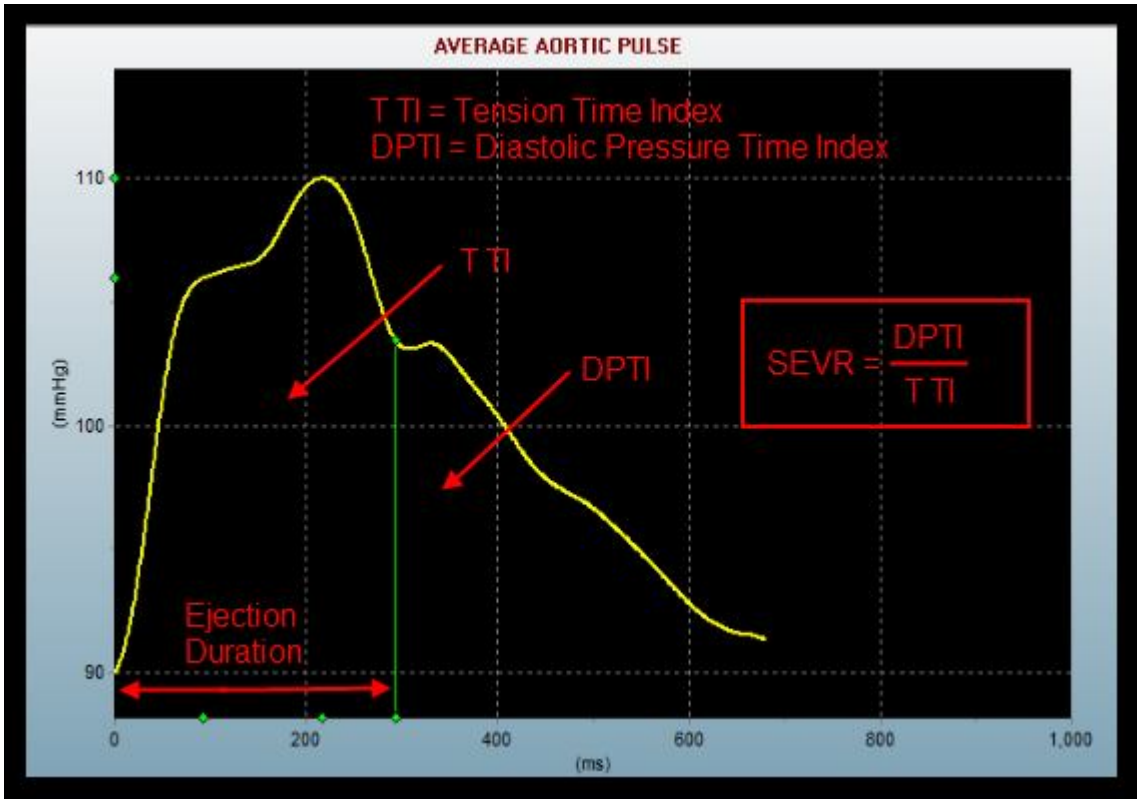
2.4.6. Ejection duration

Ejection duration is usually measured by detecting the beginning of the pulse and the closure of the aortic valve, using the incisura as a marker of the second heart sound. The duration of ventricular ejection is measured in applanation tonometry despite the absence of a sharp incisura. The transfer function derives the corresponding point and calculates systolic time (Fig 2.22). However, ejection duration that is derived from applanation tonometry is less frequently studied and the validity of this measurement is not completely established.

2.4.7. Subendocardial viability ratio

The ratio of energy supply and the demand of the heart is termed as subendocardial viability ratio (SEVR). By transferring the ejection duration, the area under the systolic (Tension Time Index) and diastolic (Diastolic Pressure Time Index) part of the curve can be calculated (Fig 2.22). Systolic area is

associated with the work of the heart and oxygen consumption. Diastolic area is associated with the pressure and time for coronary perfusion. Thus, they are related to energy supply of the heart. This variable is also less frequently studied and its validity needs to be established on healthy as well as clinical conditions.



2.22 A schematic diagram for calculation of ejection duration and subendocardial viability ratio (SEVR) in SphygmoCor

2.5. Conclusions

Various molecular, cellular and genetic causes are responsible for the structural changes in arteries and arterial stiffness. Arterial stiffness has a strong association with CVD and is a marker of CVD. Arterial stiffness increases with age irrespective of the presence of other cardiac risk factors. Pulse wave analysis in the measurement of arterial stiffness has a long history. Applanation tonometry is a recently developed non-invasive technique for pulse wave analysis. Simple, reliable and portable equipments are commercially available for non-invasive applanation tonometry. Variables such as pulse wave velocity, augmentation pressure and augmentation index are established as reliable indices of non-invasive arterial stiffness measurements. More research is necessary for establishing generalised reference values for applanation tonometry and to establish the efficiency of less intrusive non-invasive techniques such as carotid-radial pulse wave analysis.

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CHAPTER 3. REPRODUCIBILITY OF ARTERIAL STIFFNESS MEASUREMENTS FROM NON-INVASIVE PULSE WAVE ANALYSIS

Abstract

Background: Non-invasive pulse wave analysis is a non-intrusive method to measure central arterial stiffness. Reproducibility of this method has been studied less frequently. The current study has been designed to test the reproducibility of the various pulse wave analysis variables in different time durations. **Methods**: In total, 181 young adult Indian students (mean age 22.0 ± 2.2) participated and arterial stiffness was measured using a SphygmoCor system. The variables include pulse wave velocity (PWV), pulse pressure (PP), augmentation pressure (Aug. P), augmentation index (AIx), heart rate corrected augmentation index (AIx@HR75), subendocardial viability ratio (SEVR) and ejection duration. The participants were measured consecutively twice and once again after 24 hours duration. **Results**: There was perfect reproducibility between the measurements taken consecutively on the first day (ICC= 9-10). The reproducibility was less 24 hours later. Pulse wave velocity and augmentation index @75%HR showed strong agreement. Augmentation pressure, aortic pulse pressure and augmentation index showed moderate agreement. There was a fair agreement in the measures of SEVR, ejection duration, aortic systolic pressure, aortic diastolic pressure and mean pressure. **Conclusion**: In healthy people, the variables of pulse wave analysis are highly reproducible when re-measured immediately. However, the reproducibility reduces with time. These reproducibility values are important and should be considered when designing interventional studies.

3.1. Introduction

Central aortic pressures have an important clinical value in cardiovascular risk assessment. Techniques for non-invasive measurement of central aortic pulse and arterial stiffness, using peripheral pulse wave analysis have been developed recently. The SphygmoCor is one of them. It is a computerized and portable device to assess pulse waveforms and one of the common systems in use to measure arterial stiffness (Yasmin and Brown 1999). It uses an arterial applanation tonometer for recording pressure waveforms that includes pulse pressure (PP) and augmentation index (AIx). In addition, pulse wave velocity (PWV) is measured from the foot of the carotid waveform to that of the radial waveform using sequential recordings referenced to the electrocardiogram (ECG). The advantage of this technique is the ease of performing applanation tonometry at the artery sites. ECG recordings are also used during SphygmoCor measurements for synchronization of carotid and radial pulse wave times.

The validity of non-invasive pulse wave analysis has been proven with invasive measurements in previous studies (Chen *et al*. 1997). The reproducibility of the SphygmoCor has been studied mostly on measurements, which were taken consecutively. Only a few studies have addressed the measurements, which were taken over a longer time (Frimodt-Moller *et al*. 2008; Papaioannou *et al*. 2007). Wilkinson *et al* (1998) studied the reproducibility of consecutive measurements of pulse wave velocity and augmentation index on a mixed population aged 20-72 years. Filipovsky *et al* (2000) assessed intra-rater reproducibility of SphygmoCor on healthy people aged 19-53. The duration between the measurements was not clear in their study. There is a paucity of

studies, showing reproducibility of pulse wave measurements both consecutively and over a longer period.

The current study assesses the reproducibility of the arterial stiffness measures from a SphygmoCor, consecutively as well as after 24 hours on a specific young adult age group. To the investigators' knowledge, this is the first study conducted on young Indian adults.

3.1.1. Objectives

To assess the repeatability of SphygmoCor measurements on the arterial stiffness variables: augmentation pressure, augmentation index, pulse wave velocity, pulse pressure, subendocardial viability ratio, ejection duration and augmentation index@75 and mean pressures.

3.1.2. Hypothesis

The measurements of arterial stiffness variables using a SphygmoCor will show a non-significant difference on consecutive measures as well as over a 24 hour period.

3.2. Methods

3.2.1. Subjects

After obtaining ethical approval, the students from Father Muller Medical College, Mangalore, India volunteered to participate in the study. In total 181 students, aged 19-27 were recruited. None of them had a history of any cardiovascular conditions or any other serious disease. They were measured

for arterial stiffness twice consequently within five minutes and once again the next day. On the days of testing, none of them had any remarkable change in their everyday activities such as excessive physical activities, use of any medications or alcohol, which might alter their physical conditions.

3.2.2. Arterial stiffness measurement

Participants were asked not to smoke for three hours before the study. Measurements were performed while subjects were in a quiet environment after at least 10 min of supine rest. Local blood pressures were assessed using a conventional measurement of the ipsilateral brachial artery blood pressure according to the recommendations of the European Society of Hypertension (O'Brien *et al*. 2003) using a validated oscillometric device (BP-300, Kernel Intl Ltd). The mean of three brachial blood pressure values was used for the auto-calibration in the measurement of arterial stiffness. Arterial stiffness was assessed with a SphygmoCor system (SCOR-PVx, Version 8.0, Atcor Medical Private Ltd, USA). The SphygmoCor is one of the recently developed computerized portable and simple to use devices to assess pulse waveforms and one of the common systems in use for measuring arterial stiffness. It uses an arterial applanation tonometer for recording pressure waveforms that includes pulse wave velocity (PWV), pulse pressure (PP), augmentation pressure (Aug. P), augmentation index (AIx), augmentation index corrected for heart rate at 75 bpm (AIx@HR75), subendocardial viability ratio (SEVR) and ejection duration. An electrocardiogram (ECG) recording during measurements is used for synchronization of carotid and radial pulse wave times and heart rate.

The measurements were taken under optimal conditions for applanation as advocated by Rietzschel *et al*. (2001). The flat tonometer's end was placed on the arterial site with a small amount of pressure that was applied perpendicular to the artery, so that arterial wall was flattened and the tangential forces were minimized. The difference in the pressure waveforms due to the applied pressure on the tonometer was calibrated in the SphygmoCor with the manually measured brachial artery pressures, obtained using ocillometric devices. The waveforms were displayed on the personal computer screen. A 10-second of stable waveforms with a satisfactory quality were captured and fed into the SphygmoCor system. An averaged pulse waveform was derived from the recording using the integral software. A validated general transfer function was used and aortic pressure waveform was derived. A computer algorithm, comparable to invasive techniques, was used to derive augmentation index (AIx) from the ascending aortic waveform, It is "the height of the second systolic peak above the wave foot divided by the height of the first systolic peak above the wave foot expressed as a percentage" (Rietzschel *et al*. 2001)**.** Brachial artery pulse pressure was derived from the difference between systolic and diastolic blood pressure. Aortic PP was assessed from radial artery waveforms applying a radial-to-aorta transfer function and carotid artery waveforms applying a carotid-to-aorta transfer function (Rietzschel *et al*. 2001).

Pulse wave velocity (PWV) is measured from sequential recording of ipsilateral carotid and radial waveforms. A foot to foot comparison of these two waveforms was used. The time delay was derived with a reference of simultaneous ECG recording and gating the peak of R waves (Oliver and Webb 2003). The waveforms' travelling distance was measured from a common point

‘suprasternal notch’ using a tape measure. For the distal pulse, it was measured between suprasternal notch and the radial artery location. For the proximal pulse, it was measured between suprasternal notch and carotid pulse location. The difference between the proximal and distal pulse distances was calculated automatically as a travelling distance in the SphgmoCor. PWV was calculated as the ‘distance:transit time ratio’ and is expressed as metres per second**.** All reported data are mean values of three consecutive high-quality recordings. Care was taken to place the transducers over the same point of the arteries and the same distance was used.

Measurements were taken twice consecutivelywithin 10 minutes and once again at the same time on the next day i.e after 24 hours.

3.2.3. Statistical analysis

The statistical analysis was carried out using SPSS (Version 18.0). The data were checked for univariate and multivariate outliers using standard Z-distribution cut-offs and Mahalanobis distance tests respectively. A Kolmogorov-Smirnov test was used to assess the normality of distribution. A paired t-test was used to test the difference between the measurements at Day-1 test-I, Day-1 test II and Day-2 test. Intra class correlation coefficient (ICC) was calculated for each variable to test the repeatability. Bland-Altman plots were drawn for first and second day measurements of each variable to assess the reliability further. The significance level was set to $p<0.05$ for all statistical tests used.

3.3. Results

In total, 57 males and 124 females aged 19-28 (mean age 22.0 ± 2.2), were measured on day-1 and four males and 34 females on day-2. The physical characteristics of the participants were: mean height 162.3 ± 11.0 cm, weight was 58.8 ± 10.9 kg and the mean body mass index (BMI) 22.1 ± 2.2 kg/m^2. Their blood pressure was 113.8 ± 11.3 mmHg systolic and 76.6 ± 9.1 mmHg diastolic. The means and standard deviations of each variable from test- I & II on day-1 and the test on Day-2 are listed in table 3.1. The test-I on Day-1 was considered as a baseline measure and compared with the other two measurements. There were no significant differences between the consecutive measurements taken on Day-1. There were significant differences between Day-1 measurements and Day-2 measurements only on heart rate, ejection duration and SEVR.

Table 3.1 Paired t-test results for the arterial stiffness measurements

	Day 1- Test- I (n=181)		Day 1- Test-II (n=181)		Day-2- Test (n=38)		Paired t Test Significance (p)	
	Mean	±SD	Mean	±SD	Mean	±SD	Day 1- Test 1 vs. Day 1- Test 2	Day 1- Test 1 vs. Day 2- Test
PWV (m/s)	7.98	±1.03	7.96	±1.17	7.65	±1.33	NS	NS
Aug P (mmHg)	3.37	±3.00	3.35	±3.16	3.48	±2.41	NS	NS
Aug Index	13.17	±9.43	13.38	±9.99	15.19	±8.83	NS	NS
Aug Index@75HR	13.21	±10.24	13.51	±10.59	14.51	±8.59	NS	NS
Aortic PP (mmHg)	24.64	±6.05	24.88	±7.26	23.31	±5.17	NS	NS
Aortic SP (mmHg)	102.40	±9.72	102.53	±10.00	99.76	±8.57	NS	NS
Aortic DP (mmHg)	77.78	±8.85	77.68	±9.11	76.47	±7.94	NS	NS
Mean P (mmHg)	89.57	±8.85	89.61	±8.99	87.73	±7.75	NS	NS
Ejection Duration (ms)	39.95	±4.77	39.76	±5.24	39.48	±4.24	NS	*
SEVR	136.46	±28.03	137.18	±30.01	139.51	±24.25	NS	*
HR (bpm)	75.06	±10.38	74.76	±11.22	77.11	±8.96	NS	**

**Significant at p< 0.01 *Significant at p<0.05 NS- Not significant

(PWV- Pulse Wave Velocity; P-Pressure,SP- Systolic Pressure; DP- Diastolic Pressure; SEVR– Subendocardial Viability Ratio; Aug – Augmentation; HR- Heart rate)

The agreement between the measurements are listed in table. 3.2. The intra class correlations coefficients show strong agreements between test I and II on Day-1. The Day-2 measurements have lesser agreements compared with the agreements between the two measurements taken on Day-1. The values of ICC range from -1 to +1 in which -1 indicates perfect disagreement, 0 indicates random agreement and +1 indicates perfect agreement. ICC values are designated as follows: 0-0.2 indicates poor agreement: 0.3-0.4 indicates fair agreement; 0.5-0.6 indicates moderate agreement; 0.7-0.8

indicates strong agreement; and >0.8 indicates almost perfect agreement (Rietzschel *et al*. 2001). According to this approach, the current results show perfect agreements between the measurements taken consecutively on Day-1. Heart rate showed an almost perfect agreement after 24 hrs. Pulse wave velocity and augmentation index @75%HR showed a strong agreement. Augmentation pressure, aortic pulse pressure and augmentation index showed moderate agreement. There was a fair agreement in the measures of SEVR, ejection duration, aortic systolic pressure, aortic diastolic pressure and mean pressure.

Table 3.2 Intra class correlations between arterial stiffness tests

	Day 1- Test 1 vs. Day 1-Test 2 (n=181)			Day 1- Test 1 vs. Day 2- Test (n=38)		
	ICC	F value	Sig (p)	ICC	F value	Sig (p)
PWV (m/s)	0.902	19.322	**	0.724	6.248	**
Aug P (mmHg)	0.972	71.466	**	0.629	4.396	**
Aug Index	0.961	49.646	**	0.58	3.767	**
Aug Index @75HR	0.967	59.924	**	0.652	4.739	**
Aortic PP (mmHg)	0.952	40.894	**	0.45	2.635	**
Aortic SP (mmHg)	0.990	204.478	**	0.313	1.913	*
Aortic DP (mmHg)	0.993	275.5	**	0.421	2.453	**
Mean P (mmHg)	0.992	255.806	**	0.338	2.023	*
Ejection Duration (ms)	0.949	38.228	**	0.328	1.977	*
SEVR	0.96	49.087	**	0.321	1.946	*
HR (ppm)	0.964	54.92	**	0.94	32.239	**

**Significant at p< 0.01 *Significant at p<0.05

(PWV- Pulse Wave Velocity, P-Pressure, SP- Systolic Pressure, DP- Diastolic Pressure, SEVR– Subendocardial Viability Ratio, Aug – Augmentation, HR- Heart Rate)

The Bland-Altman plots (Fig 3.1 and Fig 3.2) show some examples of the further agreement between the arterial stiffness variables measured on the two different occasions. Complete Bland-Altman plots with gender comparison are given in the appendix 3.1. From the plot, the degree of agreement is observed by the percentage of points that fall within ± 2SD from the mean and the variation is observed by the points that fell out of ± 2SD from the mean. Less than a 10% variation has been observed in all the variables on both consecutive as well as after 24 hours duration.

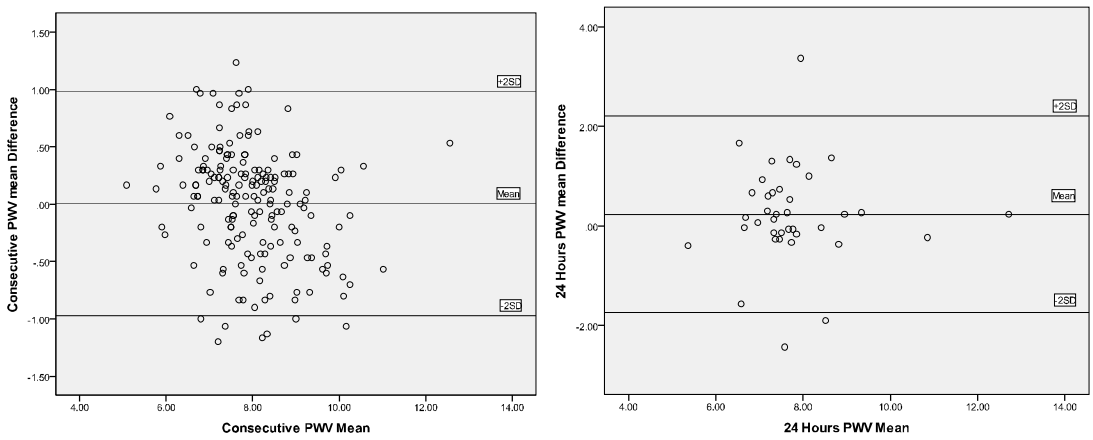

Figure 3.1 Bland - Altman limits of agreement in pulse wave velocity - Consecutive (left) and 24 hours difference (Right)

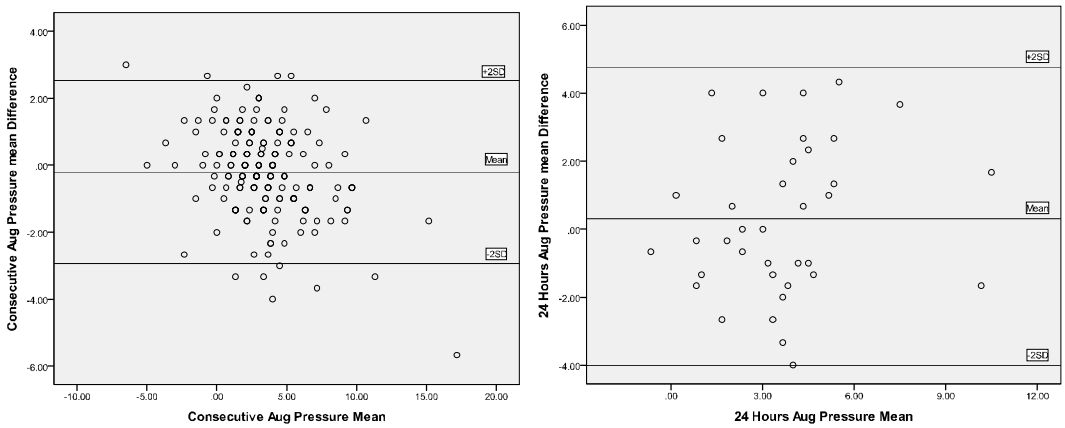

Figure 3.2 Bland - Altman limits of agreement in augmentation pressure - Consecutive (left) and 24 hours difference (Right)

3.4. Discussion

3.4.1. Statistical clarification

More than one method was used to analyse the reproducibility of the variables. Papaioannou *et al* (Portney and Watkins 1993) state that there is no simple method to describe all the important areas of reproducibility. Filipovsky *et al* (2007) have used a Spearman correlation test. Pearson or Spearman correlation coefficient is an inappropriate method as it could be used only to assess the linear relationships, not the concordance (Filipovsky *et al*. 2000). Intraclass correlation (ICC) seems to be a better option, because in ICC, the

data are centred and scaled using a pooled mean and standard deviation, whereas in Pearson correlation, each variable is centred and scaled by its own mean and standard deviation (Kramer and Feinstein 1981). Coefficient of variation is another method of testing reproducibility, however it is considered as less satisfactory and misleading (Scheffé 1999). The Bland-Altman plot is a standard statistical method to see the agreement between two measurements (Bland and Altman 1986). The Bland-Altman plot illustrates a qualitative report on the limits of agreement between any two measurements. Most of the previous studies have used this method (Bland and Altman 1986). It can be seen that although there is a fair degree of consistency between the results from different statistical methods, they do provide slightly different outcomes. In the case of heart rate, for example, the results from Day-1 to Day-2 appear less reliable using t-test compared with ICC.

3.4.2. Factors influencing reproducibility

To the investigators' knowledge, very few studies have studied the reproducibility of radial pulse wave analysis. A number of authors (Filipovsky *et al*. 2000; Frimodt-Moller *et al*. 2008; Siebenhofer *et al*. 1999; Wilkinson *et al*. 1998) studied the intra-rater and inter-rater reliability of pulse wave analysis using the SphygmoCor system. They found augmentation index as a reliable parameter of pulse wave analysis and found central aortic pressures and peripheral pressures to be less reliable. The variability of peripheral pressures was found to be high in their study. However, the central pressures are automatically calibrated to the peripheral pressures by the SphygmoCor system. In their study, although the measurements were taken on two different

visits, the time difference between the measurements was not clear. As the cardiovascular function has been shown to be influenced by circadian rhythm (Scheer *et al*. 2010), the peripheral and central pressures might have altered at different times of day. Moreover, the circadian rhythm itself could be altered due to various factors such as working hours, behavioural disturbances, sleep and social life etc (Harrington 2001). Changes in heart rate were also found to influence central pressures (Williams and Lacy 2009). Papaioannou *et al* (2007) found significant changes in heart rate hour-to-hour measurements using the SphygmoCor. However, there were no changes between week-to-week measurements at the same time of the day. In the current study, the t-test showed a significant change in the heart rate after 24 hours. However, the intra class correlations showed perfect reproducibility. In contrast to these studies, Avest *et al* (2005) found no influence of circadian rhythm on the measurement taken at 9.00 hours and 14.00 hours. They strongly suggest that food intake could be the only factor, which affects the sympathetic function and haemodynamics of the pulse wave.

Wilkinson *et al* (1998) studied the reproducibility of pulse wave velocity and augmentation index from two different studies. They found that both variables were highly reproducible with pulse wave velocity being less reproducible than augmentation index. However, the current results show that both the variables have perfect agreements on consecutive measurements and pulse wave velocity had a better reproducibility over a 24 hour period compared with augmentation index. Similarly, all the variables showed high reproducibility in the current study on consecutive measurement and lower reproducibility after 24 hours. Papaioannou *et al* (2007) also found similar results. They studied

hour-to-hour and week-to-week reproducibility of augmentation index, heart rate corrected augmentation index and the arrival time of reflected waves in the central aorta (pulse wave velocity) using the SphygmoCor. They also found higher reproducibility on hour-to-hour measurements and lesser reproducibility on week-to-week measurements. As they suggest, these findings are clinically important for the interventional studies. The correct design of studies, such as sample size and expected differences, could reduce the effects of the reproducibility errors in interventional studies which repeated measurements over a longer duration.

3.4.3. Reproducibility on healthy vs. clinical conditions

Frimodt-Moller (2008) studied the intra-rater and inter-rater reproducibility of pulse wave analysis on a limited number of 19 patients with chronic kidney disease and found high reproducibility with day-to-day measurements. Savage *et al* (2002) also found a high reproducibility on 188 patients with chronic renal failure (intra-observer difference of 0 ± 4% and inter-observer difference of 0 ± 3% and –1 ± 9% for augmentation index). Papaioannou *et al* (2004) found a high reproducibility of pulse wave analysis on patients with low blood pressures due to cardiogenic shock and who had received a stent for recent myocardial infarction (intra-observer difference was 0.10 ± 5.82% for aortic augmentation index and 0.14 ± 1.2% for reflection time index). Wilkinson *et al* (1998) also studied a mixed clinical group (eight hypertensives and six hypercholesterolaemics) and similarly found a high reproducibility (inter-observer difference was 0.23 ± 0.66% and intra-observer difference was 0.49 ± 0.93% for augmentation index). Studies on healthy subjects have also used

similar sample size and reproducibility on inter-rater measurements and time-to-time measurements. Filipovsky *et al* (2000) studied 88 healthy subjects measured by different raters (inter-observer differences was 0.4 ± 6.4 % for augmentation index, between visits 1 ± 0.9%). Papaioannou *et al* (2007) studied 22 healthy subjects on various occasions (hour-to-hour differences coefficient of variation = -7.1 ± 165% and ICC = 0.86 ±0.11, week-to-week differences coefficient of variation = 290.9 ± 466.6%, ICC = 0.72 ± 0.19). However, the reproducibility of pulse wave analysis was lower with time in healthy populations compared with studies on clinical population. It may be due to the lack of control on factors influencing haemodynamic changes such as age, physical activities and food intake.

3.5. Conclusions

In a healthy Indian population, the variables of pulse wave analysis are highly reproducible. The reproducibility slightly reduces with time. These reproducibility values are important and should be considered when designing interventional studies to reduce errors. More studies are needed to investigate reproducibility on people with clinical conditions, so that the results can be treated with confidence.

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CHAPTER 4. ACUTE CHANGES IN ARTERIAL STIFFNESS FOLLOWING EXERCISE IN HEALTHY CAUCASIANS AND SOUTH ASIANS

Abstract

Introduction: Arterial stiffness and exercise capacity are independent predictors of cardiovascular diseases. This study aims to find the acute changes in arterial stiffness using applanation tonometry following sub-maximal exercise in Caucasians and South Asians. This study also aims to establish the relationship between exercise capacity and arterial stiffness. **Methods**: In total, 69 participants including 32 Caucasians and 37 South Asians were assessed for arterial stiffness non-invasively using SpygmoCor (SCOR-PVx, Version 8.0, Atcor Medical Private Ltd, USA) before and after an exercise test using the Bruce protocol on a treadmill and by measuring aerobic capacity using a metabolic analyser (Medical Graphics, Cardio Control, Minnesota, USA). **Results**: Significant increases in arterial stiffness variables were observed including augmentation pressure, subendocardial viability ratio, ejection duration, pulse pressure, augmentation index and mean arterial pressure following exercise in both ethnic groups ($P<0.05$). There were no significant differences in these increases between the ethnic groups ($p>0.05$). There was no change in pulse wave velocity ($p>0.05$). Exercise capacity was inversely related to arterial stiffness ($P<0.05$). **Conclusion**: There are no differences in arterial stiffness at the baseline and following acute exercise between Caucasians and South Asians. There was significant increase in arterial stiffness following exercise in both groups. Exercise capacity is inversely related to arterial stiffness. The results suggest that non invasive arterial stiffness could be used as a tool to measure acute changes following exercise.

4.1. Introduction

4.1.1. Arterial stiffness

Changes in arterial distensibility occur with aging and arterial stiffness increases. These biophysical signs are elevated in cardiovascular conditions such as diabetes and hypertension (Boutouyrie *et al*. 2002; Cruickshank *et al*. 2002). Measurement of central aortic pressures has an important clinical value in the early diagnosis of cardiovascular risk. Central aortic pressures are often different from peripheral pressures and they have more diagnostic value than peripheral pressures because they are pathophysiologically more relevant (Smulyan *et al*. 2003). Recently a 'Generalized Transfer Function' (GTF) technique has been developed and widely used to measure the central aortic pressures non-invasively using peripheral pulse wave analysis. Different types of equipment are available on the market to measure arterial stiffness using pulse wave analysis non-invasively. There are some differences between the measured values from those different systems (Millasseau *et al*. 2005), yet non-invasive measurements provide important diagnostic and prognostic values. Studies show that non invasive assessment of pulse wave and arterial stiffness can be an independent predictor for cardiovascular mortality in healthy people (Benetos *et al*. 1997; Willum-Hansen *et al*. 2006).

The SphygmoCor is one of the recently developed, computerized, portable and simple to use devices to assess pulse waveforms, and one of the common systems in use for measuring arterial stiffness (Yasmin *et al*., 1999). It uses an arterial applanation tonometer for recording pressure waveforms. The advantage of this technique is the ease of performing applanation tonometry at

the artery sites. Arterial stiffness varies with age, sex and ethnicity (Hlaing *et al*. 2006; Heffernan *et al*. 2008). However, the non-invasive arterial stiffness measures are less frequently studied and reference values are not established for South Asian populations such as in India.

4.1.2. Exercise capacity

Measurement of exercise capacity using metabolic analysers is a standard method to predict or diagnose cardiovascular disease. Exercise capacity is inversely related to arterial stiffness in healthy people as well as those with cardiovascular conditions (Vaitkevicius *et al*. 1993; Kingwell 2002). For example pulse wave velocity, one of the arterial stiffness variables derived from pulse wave analysis, has been shown to have an inverse correlation with exercise capacity in people with coronary artery disease (Enko *et al*. 2008).

Ethnic differences in exercise capacity have been observed and well established (Wyndham *et al*. 1963). However, the ethnic differences in the relationship between exercise capacity and arterial stiffness have been studied infrequently, especially between Caucasians and South Asians. The changes in arterial distensibility immediately following exercise may have important clinical importance. However, these are scarcely reported using maximum oxygen uptake (VO_2) and non-invasive carotid-radial pulse wave analysis.

The current study was carried out to explore the acute changes in arterial stiffness using applanation tonometry following a sub-maximal exercise in Caucasians and South Asians. This study also aims to find the relationships between exercise capacity and arterial stiffness.

4.1.3. Hypotheses

H1 - There will be significant changes in arterial stiffness immediately after sub- maximal exercise.

H2 - There will be significant relationships between exercise capacity variables using metabolic analysis and arterial stiffness variables using pulse wave analysis.

H3 - There will be a significant difference between Caucasians and South Asians in exercise capacity and changes in arterial stiffness following acute exercise.

4.2. Methods

4.2.1. Subjects

Following institutional ethical approval, the study was advertised to staff and students at Bucks New University through posters on notice boards and through emails. Sixty nine volunteers aged 20-63 (mean 33.09 ± 11.94) participated. Healthy Caucasians (37) and South Asians (32) were included. Subjects were excluded who had known cardiovascular conditions and any orthopaedic conditions which could limit exercise testing on treadmill.

4.2.2. Procedures and protocol

Participants who showed interest were given a detailed information sheet with the entire requirement to be undertaken before the study. Participants were asked (i) not to smoke or have caffeinated drinks for three hours before the

study, (ii) not to drink alcohol or participate in unusually heavy activity for a day before the test. They were also advised not to take heavy meals immediately before the test. Upon arrival at the Research Lab, Bucks New University, Uxbridge, the participants were measured for weight using a floor scale (Seca model 761, Vogel ad Halke, Germany) and height using a free standing stadiometer (Leicester Height Measure, Invicta Plastics, Oadby, Leicester, UK). The treadmill exercise testing was explained to the participants and a familiarisation session on treadmill walking was performed if necessary. They then sat in a chair and rested for 10 min. During this time they completed a Physical Activity Readiness Questionnaire (PARQ), a detailed demographic information sheet and the consent forms.

4.2.2.1. Measurement of arterial stiffness

The procedures for measuring arterial stiffness are given in detail in Chapter 3.2.2. The measurements were repeated within 5-10 min after completing a submaximal exercise testing.

4.2.2.2. Measurement of exercise capacity

After arterial stiffness measurement, ECG electrodes and leads were connected to the participants according to the instruction manual and the participants were connected to the metabolic analyzer (Medical Graphics, Cardio Control, Minnesota, USA) via a disposable pneumotach and facemask. Resting measurements were taken for five minutes for oxygen consumption (VO_2), carbon dioxide production (VCO_2) and minute ventilation (V_E). Then, the participants performed a Bruce protocol (Bruce *et al*. 1973) on treadmill with the

continuous breath-by-breath measurement of respiratory gases. The protocol consists of seven stages having three min each. It starts with 2.7 kmph with 10% gradient. The speed increased by 1.3 kmph every stage until the treadmill reaches 18% grade and 8 kmph. After this, the speed is increased by 1.8 kmph at every stage. All the participants were instructed to walk or run as long as they could endure. Handrail support was discouraged, however hand rail (on the front) support was allowed if necessary to maintain balance. Blood pressure was measured at the last minute of each stage of the Bruce protocol. The ACSM guidelines were followed for any early termination of exercise testing (ACSM 2000). The criteria are as follows:

- Onset of angina or angina like symptoms
- Significant drop (20 mmHg) in systolic blood pressure or a failure of the systolic blood pressure to rise with an increase in exercise intensity
- Excessive rise in blood pressure: systolic >260 mmHg or diastolic pressure >115 mmHg
- Signs of poor perfusion: light headedness, confusion, ataxia, pallor, cyanosis, nausea or cold and clammy skin
- Failure of heart rate to increase with increased exercise intensity
- Noticeable change in heart rhythm
- Subject requests to stop
- Physical or verbal manifestations of severe fatigue

- Failure of testing equipment

The exercise was stopped on achieving of 90% of the maximum heart rate or if the participant was not able to continue. The subjective feeling of high intensity work was monitored using the Borg scale. A printed scale was placed in front of the participant at a reachable distance to point to the exact levels. The exercise was normally stopped when reaching 17 on the Borg scale; however some participants were allowed to exercise up to 19 on Borg scale if they were willing to continue. The participants were asked every minute of the test “are you feeling ok?” and before the end of each stage “are you ok to continue for the next stage?”. The participants responded for the questions with thumb signals. At the termination of test, the subjects undertook active recovery and the ECG and gas exchange were monitored and measured for five minutes. The arterial stiffness measurements were taken immediately and always within 5-10 min after exercise testing.

4.2.3. Statistical analysis

All statistical analysis was carried out using SPSS version 18.0 (IBM Corporation, New York, USA). Normality of distribution was assessed using a Kolmogorov-Smirnov test. Levene’s test was used to confirm the homogeneity of the variances. Difference between ethnicity, gender and age were assessed using analysis of covariance (ANCOVA). Paired t test was used to compare the changes in arterial stiffness before and after exercise in each group. An independent t test was used to compare the difference between groups before the exercise and after the exercise separately. The correlations between

exercise capacity variables and arterial stiffness variables were performed using a Pearson's correlations test. A 'p' value of < 0.05 (95% confidence interval) was considered as statistical significance for all the statistical tests.

4.3. Results

4.3.1. Demography

The participants' demographic details are given in table 4.1. There was a significant difference in age between the ethnic groups (p=0.001), but not in BMI (p=0.87). To reduce the age related effects on the results, statistical analysis was carried out with the data controlled for age up to 40 years.

Table 4.1 Demographic details of the participants

Characteristics	Caucasian n=37	Asian n=32	Male	Female
Age (years) (Mean ± SD)	39.0 ± 13.2	26.2 ± 4.4	33.0± 12.9	33.2± 11.2
Height (cm) (Mean ± SD)	170.1± 10.1	167.1± 7.1	174.8± 7.6	162.8± 5.5
Weight (kg) (Mean ± SD)	74.4±15.8	64.4± 11.0	76.1± 11.9	63.6± 14.4
Body Mass Index (Mean ± SD)	25.6± 0.7	26.1±16.1	27.6± 15.3	24.1± 4.7

Physical activity was higher in South Asians with 65.7% of South Asians and 42.8% of Caucasians regularly involved in physical activities of more than 30 min at least three days a week.

4.3.2. Ethnic differences

The ethnic differences in metabolic measures during sub-maximal exercise are listed in table 4.2 at $VO_{2\ max}$ and table 4.3 at the time of anaerobic threshold (AT). There were significant differences between the groups at $VO_{2\ max}$ for

VCO_2, respiratory rate (RR), tidal Volume (V_t), expiratory volume (V_E), breathing reserve (BR), VO_2/HR and at AT for RR and V_E.

There was no difference in maximal treadmill exercise time between the groups. $VCO_{2\ peak}$ was significantly lower in the South Asian group. After controlling the data for age, there were significant differences in the exercise capacity values. After controlling the data for age the significance increased including $VO_{2\ Peak}$ with South Asians now having a lower aerobic capacity (table4.4)

Table 4.2 Difference in exercise variables between groups

Variables	Group	Mean ± SD	Sig
Exercise Time (min)	Caucasian	13.8 ± 2.5	NS
	South Asian	13.9 ± 2.5	
$VO_{2\ Peak}$ $mL.kg^{-1}.min^{-1}$	Caucasian	28.71 ± 6.24	NS
	South Asian	26.66 ± 5.41	
$VCO_{2\ Peak}$ $mL.kg^{-1}.min^{-1}$	Caucasian	22.85 ±7.98	**
	South Asian	17.54 ±5.57	
RER	Caucasian	1.06 ± 0.11	NS
	South Asian	1.03 ± 0.09	
METs	Caucasian	8.15 ± 1.78	NS
	South Asian	7.50 ± 1.66	
RR (br/min)	Caucasian	31.88 ± 5.96	*
	South Asian	36.00 ± 6.54	
V_t BTPS (L)	Caucasian	1.90 ± 0.61	**
	South Asian	1.31 ± 0.29	
V_E BTPS (L/min)	Caucasian	59.73 ±19.42	**
	South Asian	46.36 ± 13.64	
BR (%)	Caucasian	57.35 ± 9.71	**
	South Asian	67.71 ± 8.23	
V_E/VO_2	Caucasian	27.85 ± 2.88	NS
	South Asian	28.03 ± 3.69	
V_E/VCO_2	Caucasian	26.42 ± 2.59	NS
	South Asian	27.13 ± 3.35	
VO_2/HR	Caucasian	13.55 ± 3.97	**
	South Asian	10.03 ± 3.17	
$P_{ET}O_2$ (kpa)	Caucasian	13.81 ± 0.60	NS
	South Asian	13.75 ± 0.80	
$P_{ET}CO_2$ (kpa)	Caucasian	5.52 ± 0.57	NS
	South Asian	5.56 ± 0.67	
BORG RPE	Caucasian	14.88 ± 2.56	NS
	South Asian	13.89 ± 3.86	

n= 37 Caucasians and 32 South Asians, NS – No significance
*Statistically significant at p<0.05 **Statistically significant at p<0.01

VO_2- oxygen uptake, VCO_2- carbon dioxide production, RER- respiratory exchange ratio, METs- metabolic equivalents, V_t- ,tidal volume V_E- minute ventilation, BTPS- body temperature and pressure saturated , BR- breathing reserve, HR- heart rate, $P_{ET}O_2$- end tidal oxygen tension, $P_{ET}CO_2$- end tidal carbon dioxide tension, RPE- rate of perceived exertion

Table 4.3 Difference between groups in exercise gas changes at anaerobic threshold

Variables	Group	Mean ± SD	Sig
Speed at $VO_{2\ max}$ (kmph)	Caucasian	2.70 ± 0.85	NS
	South Asian	2.33 ± 0.64	
Speed at AT (kmph)	Caucasian	3.52 ± 1.06	NS
	South Asian	3.51 ± 0.78	
VO2 at AT $mL.kg^{-1}.min^{-1}$	Caucasian	16.26 ± 3.78	NS
	South Asian	14.32 ± 3.53	
RER at AT	Caucasian	0.86 ± 0.05	NS
	South Asian	0.87 ± 0.09	
METs at AT	Caucasian	4.45 ± 1.35	NS
	South Asian	4.09 ± 1.02	
RR at AT (br/min)	Caucasian	20.73 ± 4.86	**
	South Asian	24.84 ± 6.61	
V_E at AT (L/min)	Caucasian	26.20 ± 8.23	*
	South Asian	21.97 ± 4.97	

n= 37 Caucasians and 32 South Asians, NS – No significance
*Statistically significant at p<0.05 **Statistically significant at p<0.01

AT – anaerobic threshold, VO_2- oxygen uptake, RER- respiratory exchange ratio, METs- metabolic equivalents, RR- respiratory rate, V_E- minute ventilation

The differences in arterial stiffness variabl es between the groups are listed table 4.5. There was no significant difference between the groups before exercise except in aortic pulse pressure, aortic systolic pressure and pulse wave velocity. After controlling the data for age there was no change in the significance in the resting values (table 4.6).

The acute changes in arterial stiffness in relation to ethnicity, gender and age are illustrated in table 4.7. The ANCOVA analysis did not show any significant influences of these factors on the changes in arterial stiffness except mean pressure with ethnicity.

Table 4.4 Difference in exercise variables between groups for reduced data for age

Variables	Group	Mean	±SD	Sig	Variables	Mean	±SD	Sig
Exercise Time (min)	Caucasian	14.56	±2.30	NS	VO_2/HR	12.64	±3.05	*
	South Asian	14.02	±2.38			10.03	±3.17	
VO_2 Peak ($mL.kg^{-1}.min^{-1}$)	Caucasian	30.43	±5.12	*	$P_{ET}O_2$ (kpa)	13.86	±0.66	NS
	South Asian	26.87	±5.38			13.74	±0.82	
VCO_2 Peak ($mL.kg^{-1}.min^{-1}$)	Caucasian	24.61	±7.23	**	$P_{ET}CO_2$ (kpa)	5.71	±0.47	NS
	South Asian	17.54	±5.66			5.58	±0.67	
RER	Caucasian	1.11	±0.10	*	BORG RPE	15.06	±2.56	NS
	South Asian	1.03	±0.09			13.76	±3.84	
METs	Caucasian	8.69	±1.45	*	Speed at $VO_{2\ max}$ (KMPH)	2.69	±0.83	NS
	South Asian	7.55	±1.66			2.33	±0.65	
RR (br/min)	Caucasian	33.25	±5.80	NS	Speed at AT (KMPH)	3.99	±1.10	NS
	South Asian	36.10	±6.62			3.57	±0.72	
V_t (L)	Caucasian	1.92	±0.69	**	VO_2 at AT ($mL.kg^{-1}.min^{-1}$)	16.96	±4.22	*
	South Asian	1.30	±0.29			14.53	±3.38	
V_E (L/min)	Caucasian	61.84	±16.81	**	RER at AT	0.85	±0.05	NS
	South Asian	46.09	±13.78			0.87	±0.09	
BR (%)	Caucasian	59.62	±9.11	**	METs at AT	4.48	±1.69	NS
	South Asian	67.83	±8.34			4.15	±0.97	
V_E/VO_2	Caucasian	27.94	±3.26	NS	RR at AT (br/min)	19.88	±4.04	**
	South Asian	27.87	±3.64			24.77	±6.71	
V_E/VCO_2	Caucasian	25.25	±2.32	NS	V_E at AT (L/min)	24.61	±8.97	NS
	South Asian	27.00	±3.33			22.06	±5.02	

(n= 17 Caucasians, 30 South Asians) NS – No significance *Significant at $p<0.05$ **Significant at $p<0.01$

VO_2- oxygen uptake, VCO_2- carbon dioxide production, RER- respiratory exchange ratio, METs- metabolic equivalents, V_t- ,tidal volume V_E- minute ventilation, BTPS- body temperature and pressure saturated , BR- breathing reserve, HR- heart rate, $P_{ET}O_2$- end tidal oxygen tension, $P_{ET}CO_2$- end tidal carbon dioxide tension, RPE- rate of perceived exertion, AT – anaerobic threshold, RR- respiratory rate

Table 4.5 Difference in arterial stiffness before exercise

Variables	Group	Mean ±SD	Sig
Pulse Wave Velocity (m/s)	Caucasian	8.37 ± 1.50	*
	South Asian	7.72 ± 1.03	
Aug Pressure (mmHg)	Caucasian	4.00 ± 4.62	NS
	South Asian	2.08 ± 3.07	
Aug Index	Caucasian	11.56 ± 14.30	NS
	South Asian	8.03 ± 10.78	
Aortic Pulse Pressure (mmHg)	Caucasian	31.55 ± 7.40	**
	South Asian	26.05 ± 4.47	
Aortic Systolic Pressure (mmHg)	Caucasian	109.70 ± 14.26	*
	South Asian	102.25 ± 9.53	
Aortic Diastolic Pressure (mmHg)	Caucasian	78.14 ± 10.61	NS
	South Asian	76.10 ± 8.23	
Mean Pressure (mmHg)	Caucasian	92.38 ± 12.44	NS
	South Asian	88.60 ± 9.03	
Ejection Duration (ms)	Caucasian	37.06 ± 9.30	NS
	South Asian	36.66 ± 5.19	
SEVR	Caucasian	156.72 ± 45.86	NS
	South Asian	158.26 ± 34.47	
HR (bpm)	Caucasian	69.48 ± 17.13	NS
	South Asian	70.92 ± 12.01	

NS – No significance, *Significant at $p<0.05$ **Significant at $p<0.01$

(n= 36 Caucasians, 32 South Asians), SEVR – Subendocardial Viability Ratio, Aug – Augmentation, HR- Heart Rate

Table 4.6 Difference in baseline arterial stiffness values at rest between groups, for data controlled for age

Variables	Group	Mean ± SD	Sig
Pulse Wave Velocity (m/s)	Caucasian	7.99 ±1.30	NS
	South Asian	7.71 ±1.04	
Aug Pressure (mmHg)	Caucasian	1.91 ±3.98	NS
	South Asian	2.01 ±3.09	
Augmentation Index	Caucasian	7.53 ±13.98	NS
	South Asian	9.41 ±10.75	
Augmentation Index@75HR	Caucasian	5.04 ±14.47	NS
	South Asian	7.86 ±10.92	
Aortic Pulse Pressure (mmHg)	Caucasian	27.29 ±5.54	NS
	South Asian	25.68 ±4.04	
Aortic Systolic Pressure (mmHg)	Caucasian	102.62 ±11.20	NS
	South Asian	102.02 ±9.60	
Aortic Diastolic Pressure (mmHg)	Caucasian	75.39 ±9.11	NS
	South Asian	76.24 ±8.33	
Mean Pressure (mmHg)	Caucasian	87.68 ±10.29	NS
	South Asian	88.58 ±9.18	
Ejection Duration (ms)	Caucasian	38.16 ±9.51	NS
	South Asian	36.93 ±5.04	
Subendocardial Viability Ratio	Caucasian	151.56 ±49.93	NS
	South Asian	156.08 ±32.71	
Heart Rate (bpm)	Caucasian	72.95 ±15.85	NS
	South Asian	71.49 ±11.76	

NS – No significance (n= 17 Caucasians, 30 South Asians)

Table 4.7 Significance in Analysis of Covariance in arterial stiffness variables

Variables	Ethnicity	Gender	Gender within Ethnicity	Age within Ethnicity
Pulse Wave Velocity	NS	NS	NS	NS
Aug Pressure	NS	NS	NS	NS
Aug Index	NS	NS	NS	NS
Pulse pressure	NS	NS	NS	NS
Mean Pressure	*	NS	NS	NS
Ejection Duration	NS	NS	NS	NS
SEVR	NS	NS	NS	NS

NS – No significance *Statistically significant at $p<0.05$

SEVR – Subendocardial Viability Ratio, Aug – Augmentation, HR- Heart Rate

4.3.3. Acute changes following exercise

Table 4.8 lists the changes in arterial stiffness variables before and after exercise within Caucasian and South Asian groups. Most of the variables (15/20) had significant changes following exercise in both the groups. The only non-significant changes were in pulse wave velocity in both groups, in augmentation index in Caucasians, and in augmentation pressure and aortic pulse pressure in South Asians.

Table 4.8 Changes in arterial stiffness after exercise in Caucasians and South Asians

		Caucasians			South Asians		
		Mean ± SD		Sig	Mean ± SD		Sig
Pulse Wave Velocity (m/s)	Before Exercise	8.32	±1.38	NS	7.72	±1.06	NS
	After Exercise	8.46	±1.24		7.98	±0.91	
Aug Pressure (mmHg)	Before Exercise	3.90	±4.81	*	1.89	±3.10	NS
	After Exercise	6.22	±6.29		3.13	±3.74	
Aug Index	Before Exercise	15.45	±14.26	NS	10.03	±10.98	*
	After Exercise	12.81	±13.05		4.48	±11.93	
Aortic PP (mmHg)	Before Exercise	32.23	±6.77	**	26.20	±4.62	NS
	After Exercise	38.34	±10.98		28.70	±7.70	
Aortic SP (mmHg)	Before Exercise	110.39	±13.92	**	102.00	±9.90	**
	After Exercise	123.80	±16.28		111.20	±11.80	
Aortic DP(mmHg)	Before Exercise	78.15	±10.89	**	75.68	±8.30	**
	After Exercise	85.55	±10.52		82.51	±7.41	
Mean P (mmHg)	Before Exercise	92.83	±12.50	**	88.22	±9.26	**
	After Exercise	103.24	±12.51		95.94	±8.75	
Ejection Duration (ms)	Before Exercise	36.80	±7.63	**	36.36	±5.22	**
	After Exercise	42.55	±4.89		43.40	±3.61	
SEVR	Before Exercise	155.29	±39.26	**	160.52	±34.70	**
	After Exercise	116.35	±23.74		114.71	±20.59	
HR (bpm)	Before Exercise	69.26	±15.69	**	70.02	±11.81	**
	After Exercise	80.20	±11.80		87.75	±10.16	

NS – No significance *Significant at p<0.05 **Significant at p<0.01

Caucasians (n=32) and South Asians (n=29)

SEVR – Subendocardial Viability Ratio, Aug – Augmentation, HR- Heart Rate, SP- Systolic Pressure, DP- Diastolic Pressure

4.3.4. Relationship between variables

There was a significant inverse relationship between exercise capacity variables and arterial stiffness variables in both Caucasians and South Asians (Table 4.9 & 4.10). The patterns of relationship between $VO_{2\ peak}$ and augmentation pressure before and after exercise for both groups are exemplified in figures 4.1- 4.4. More figures on the relationship between $VO_{2\ peak}$ and arterial stiffness variables are given in appendix.2.

Table 4.9 Relationship between the variables of exercise capacity and arterial stiffness among Caucasians at peak value (correlation coefficeints)

Variables	$VO_{2\ Peak}$ ($L.kg^{-1}.min^{-1}$)	$VCO_{2\ Peak}$ ($L.kg^{-1}.min^{-1}$)	METs	V_t L	V_E L/min
Pulse Wave Velocity (m/s)	0.01	0.09	0.03	0.12	0.10
Augmentation Pressure (mmHg)	-0.41*	-0.17	-0.37**	0.04	-0.08
Augmentation Index	-0.35*	-0.06	-0.30*	0.17	0.04
Aortic Pulse pressure mmHg	0.00	0.20	-0.03	0.39**	0.26*
Ejection Duration (ms)	-0.19	-0.34*	-0.18	-0.37**	-0.31*
SEVR	0.18	0.37**	0.19	0.42**	0.34*

n=37 NS – No significance *Significant at p<0.05 **Significant at p<0.01

Table 4.10 Relationship between the variables of exercise capacity and arterial stiffness among South Asians

Variables	$VO_{2\ Peak}$ ($L.kg^{-1}.min^{-1}$)	$VCO_{2\ Peak}$ ($L.kg^{-1}.min^{-1}$)	METs	V_t L	V_E L/min
Pulse Wave Velocity (m/s)	.213	.281	.254	.059	.144
Augmentation Pressure (mmHg)	-.261	-.221	-.240	-.135	-.100
Augmentation Index	-.294	-.183	-.227	.007	-.001
Aortic Pulse Pressure (mmHg)	-.050	-.018	-.171	.112	.013
Ejection Duration (ms)	-.106	-.268	-.120	-.457*	-.216
SEVR	.055	.270	.109	.462*	.243

n=32 NS – No significance *Significant at p<0.05 **Significant at p<0.01

SEVR – Subendocardial Viability Ratio, Aug – Augmentation

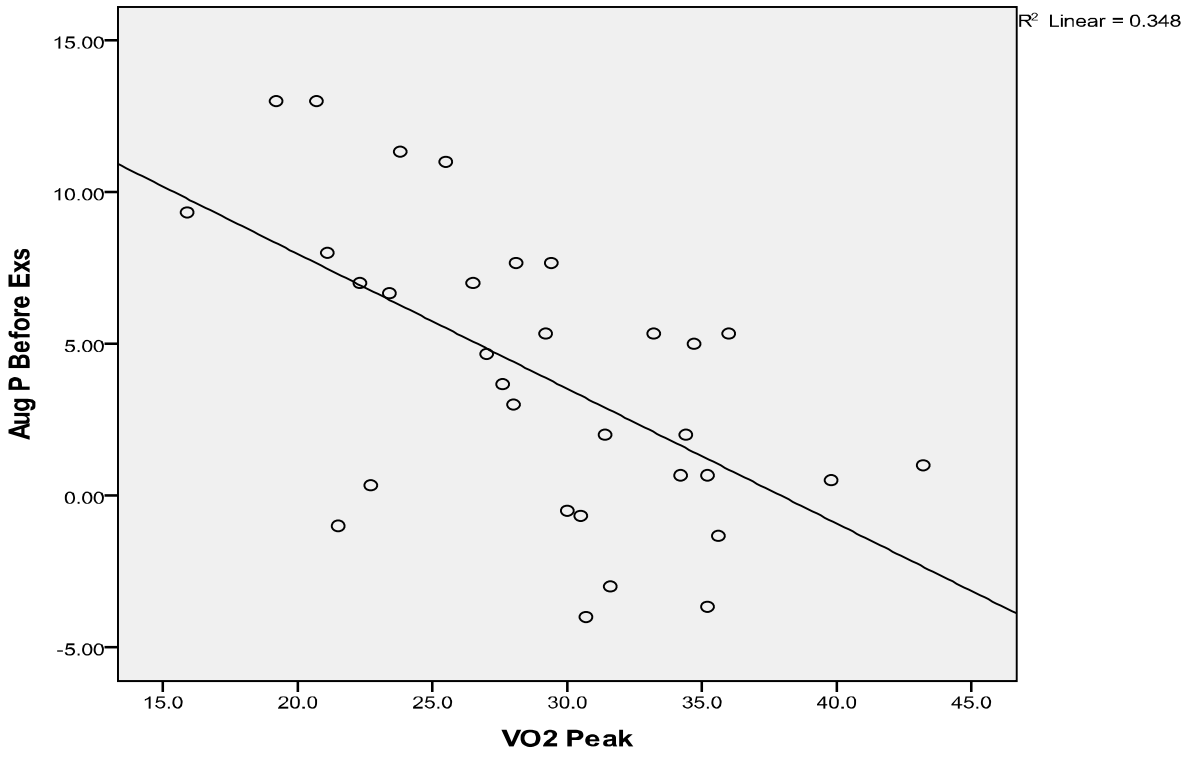

Figure 4.1 $VO_{2\ peak}$ vs. Augmentation pressure before exercise in Caucasians

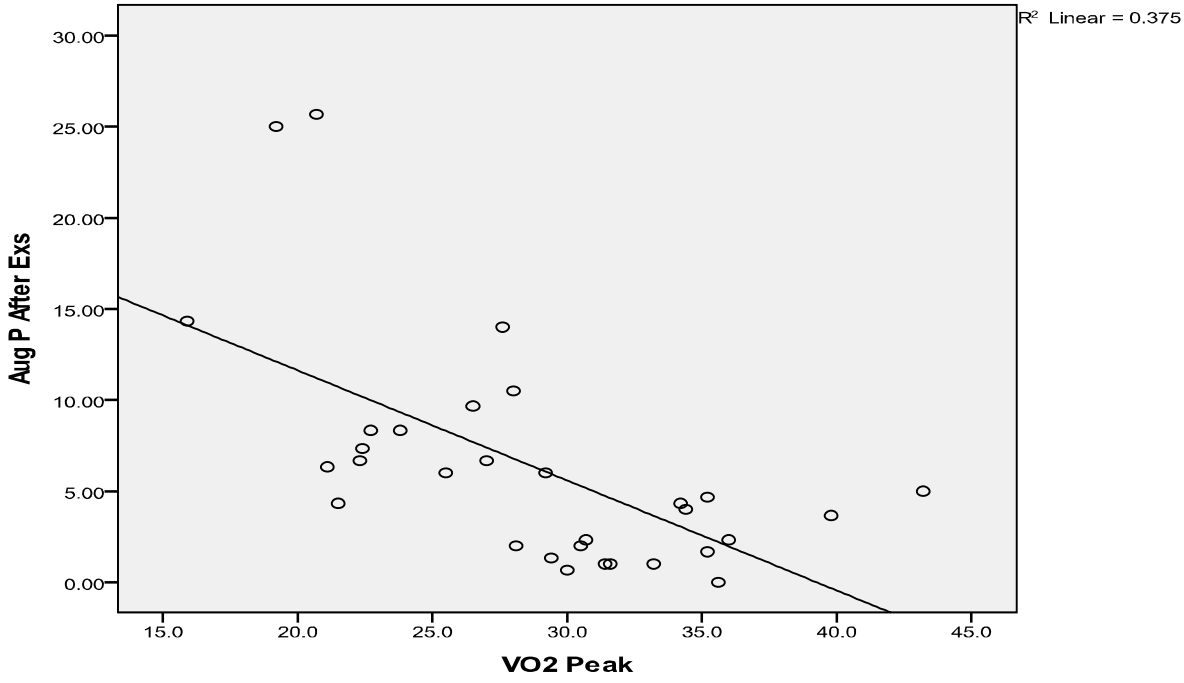

Figure 4.2 $VO_{2\ Peak}$ vs. Augmentation pressure after exercise in Caucasians

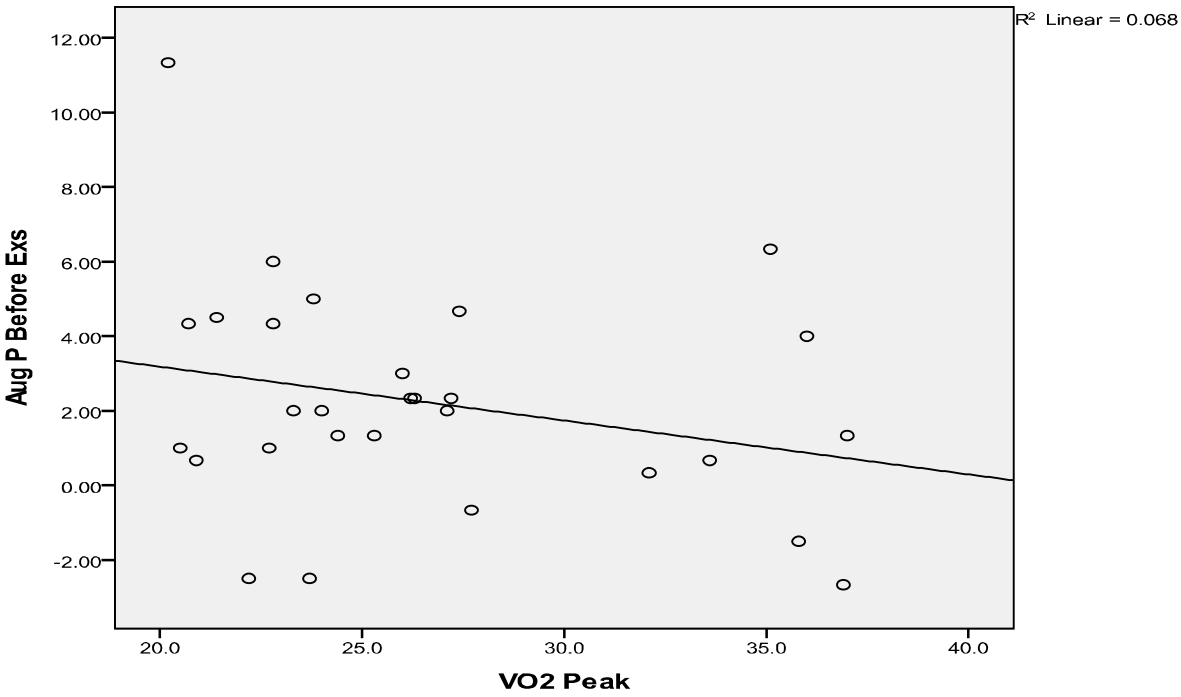

Figure 4.3 $VO_{2\ peak}$ vs. Augmentation pressure after exercise in South Asians

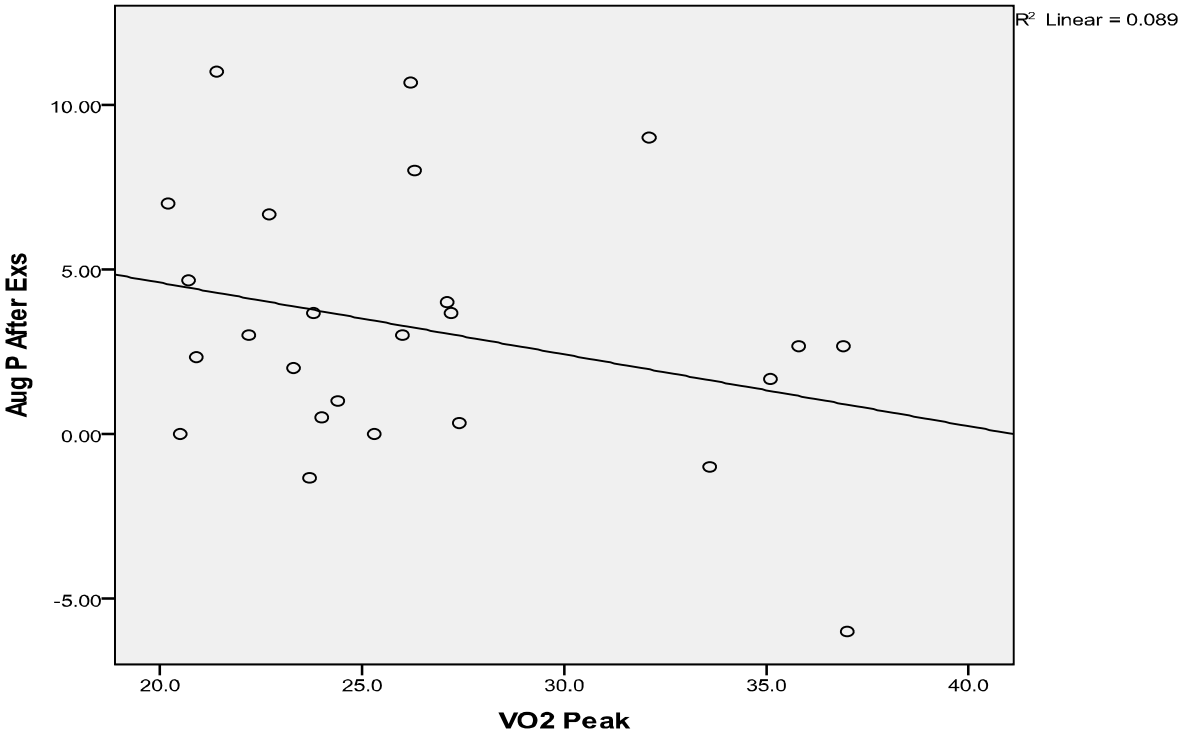

Figure 4.4 $VO_{2\ peak}$ vs. Augmentation pressure after exercise in South Asians

4.4. Discussion

Pulse wave analysis using generalized transfer function with applanation tonometry is used in many studies to determine central blood pressures non-invasively at rest and exercise (Naka *et al*. 2003; Munir *et al*. 2008; Dawson *et al*. 2009; Campbell *et al*. 2011). The accuracy of the transfer function is debatable. Sharman *et al* (2006) found that the values obtained from the measurements from the non-invasive technique are reliable and similar to invasive techniques. Hickson *et al* (2009) claim that the peripheral waveforms approximate the central waveforms in various age groups. However, it was also claimed that the accuracy of this technique altered with the inaccuracy of the brachial pressure measured using oscillometric devices (Smulyan *et al*. 2003; Zuo *et al*. 2010). In the current study, extra care was taken to measure oscillometric brachial pressures. SphygmoCor measurements were taken with precision, considering the same side and site of the radial and carotid arteries and the position of the participants. This is the first to study the changes in arterial stiffness and its relationship with cardiac exercise capacity within two ethnic groups, Caucasians and South Asians.

4.4.1. Changes in arterial stiffness

Most of the arterial stiffness variables showed an increase following acute exercise. The increase in arterial stiffness may be due to an increase in blood viscosity immediately following the exercise. Blood viscosity is inversely proportional to arterial distensibility (Kingwell *et al*. 1997). Naka *et al* (2003) studied the changes in pulse wave velocity along with plasma viscosity and found that there was an increase in pulse wave velocity (~35%) three min after

exercise, then a decline in pulse wave velocity lower than baseline (~6%) after 10 min and further lowered (~10%) after 60 min. Plasma viscosity also increased three min after exercise and resumed to normal after 20 min. They suggest that the immediate increase in pulse wave velocity may be influenced by reduced vascular distensibility by neurohumoral and endothelial influence on vascular tone. Dulai *et a*l (2011) studied changes in arterial stiffness three, 15 and 30 minutes after moderate intensity exercise. They found a significant increase in pulse wave velocity after three minutes and a complete recovery in 15 minutes. In contrast to these findings, pulse wave velocity did not change significantly after exercise in the current study. It was not possible to take arterial stiffness measures immediately after the completion of exercise as the participants were still connected to the metabolic analyser to monitor recovery for any adverse changes. The current measurements were taken 5-10 min after exercise where the pulse wave velocity could have been shown substantial recovery. However, Munir *et al* (2008) found pulse wave velocity unchanged up to an hour after exercise, though there was a reduction in augmentation Index. Their results are similar to the current findings.

Augmentation index is a reflection of aortic pulse wave and it is influenced by wave velocity. Thus, it is a measure of arterial stiffness. Dawson *et al* (2009) define augmentation index as a representation of the difference in amplitude between incident and reflected pulse wave as a percentage of pulse pressure. They found significant increase in mean arterial pressure and augmentation index with increasing workload. However, in the current study, augmentation index reduced after exercise which is not clear. Similar to the current results, Sharman *et al* (2006) observed an increase in pulse pressure, mean arterial

pressure and a decrease in SEVR after exercise. In contrast, the ejection duration increased after exercise in the current study, the reason for which is not clear.

High mean pressure during exercise is associated with decreased endothelial function (Gonzales *et al*. 2011). This may be due to the oxidation stress produced by the increase in oxygen uptake during acute exercise (Harris *et al*. 2008)

There was no significant difference between Caucasians and South Asians on arterial stiffness variables at rest (table 4.4). In previous studies, the South Asians seem to have more endothelial dysfunction than the Caucasians. Murphy *et al* (2007) studied the resistance vessel endothelial function by forearm blood flow (FBF) and the number of circulating endothelial progenitor cells (EPC) which are responsible for nitric oxide production and endothelial repair. They found lower levels of EPC and FBF in South Asians compared with Caucasians. This may be the reason for the higher pulse wave velocity in South Asians in the current study. However, South Asians had comparatively lower aortic systolic pressure and pulse pressure. These variables need to be investigated more to validate these differences.

4.4.2. Exercise capacity and its relationship with arterial stiffness

There was a significant difference in exercise capacity between groups. The Caucasians had a higher exercise capacity in the age controlled results. The differences may not be due to variations in height or weight as there was no significant difference in body mass index between the groups. The difference in

the exercise capacity may be due to nutritional and socio-cultural factors (Swaminathan *et al*. 1997), but this would need to be studied specifically to confirm such speculations. There was also a significant difference in VO_2/HR. The VO_2 and HR increase linearly with exercise intensity and the relationship between them is important for the assessment and prescription of exercise (ACSM 2000; Skinner *et al*. 2003). Studies show that comparatively low levels of physical activity were observed in South Asians living in the UK (Fischbacher *et al*. 2004). However, the South Asian participants in the current study reported higher levels of physical activity in terms of duration, but the intensity of physical activities was not defined.

The current study finds that arterial stiffness has an inverse relationship with exercise capacity. In Caucasians, augmentation pressure and augmentation index had significant inverse relationship with VO_2. These agree with the findings of previous studies (Vaitkevicius *et al*. 1993; Kingwell 2002). In South Asians, there was also an inverse relationship between these variables but it was not found be statistically significant in the current study. Binder *et al* (2006) also found a similar inverse relation between $VO_{2\ max}$ and augmentation index. Kingswell (2002) suggested that people with high resting aortic pulse pressure might experience higher aortic pulse pressure at maximal exercise. This was corroborated in the current study (table 4.4).

4.4.3. Limitations

Due to the lack of availability of the participants, it was not possible to take serial measurement of arterial stiffness. The SphygmoCor technique does not allow measurement during exercise on the treadmill. A greater number of

participants would improve the power of the results and allow for matched subgroup analysis. One of the major limitations was the age difference between the groups. The ANCOVA results could have been strengthened if there were a greater number of age matched participants. Previous studies suggest that there are variations in the immediate change in arterial stiffness between the exercising limb and the other regions of the body (Sugawara *et al*. 2003). It would require more studies to clarify the regional differences in arterial stiffness due to acute exercise. In the current study, it was not possible to measure the arterial stiffness immediately at the end of exercise session due to metabolic monitoring and no further measurements were carried out after 10 minutes due to unavailability of the participants. More sequential measurements for a longer duration could be more informative in the arterial stiffness changes following acute exercise.

4.5. Conclusions

There are no differences in arterial stiffness variables at rest between Caucasians and South Asians. There was significant increase in central aortic pressures and reduction in augmentation index within 5-10 min following acute exercise in both groups. However, there was no difference in these increases due to ethnicity, gender or age. There were differences between these ethnic groups in exercise capacity and gas exchange variables during sub-maximal exercise. This may be due to the difference in adhering to a healthy lifestyle and needs to be investigated. There were strong inverse correlations between exercise capacity and arterial stiffness. Non-invasive carotid-radial arterial stiffness measurements could be used in exercise-based interventional studies. The findings of this study advance the understanding of the clinical evaluation in

difference ethnic groups who are in higher risk. More studies need to be carried out on clinical populations with cardiovascular risks to enable appropriate preventive measures. Larger scale studies need to establish the validity of the individual variables of arterial stiffness using applanation tonometry.

4.6. References

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CHAPTER 5. RELATIONSHIP BETWEEN BODY ADIPOSITY AND ARTERIAL STIFFNESS IN YOUNG INDIAN ADULTS

Abstract

Background: Obesity is one of the major cardiovascular risk factors and is linked with arterial stiffness. This study has been undertaken to establish the relationship between regional adiposity and arterial stiffness using simple non-invasive techniques. **Methods**: In total, 181 young Asian-Indian adults aged 18-28 years (mean age 21.9 ± 2.2) were measured for adiposity and arterial stiffness. Total body fat percentage was derived from skinfold thickness of various body sites. Body mass index (BMI) and waist-hip-ratio (WHR) were also measured. Arterial stiffness was measured using a SphygmoCor with a carotid-radial pulse wave analysis technique **Results**: Significant gender differences were observed on anthropometric variables including skinfold thickness ($p<0.05$) and all the arterial stiffness variables ($p<0.05$) except pulse wave velocity. Systolic pressure, augmentation pressure, augmentation index, augmentation index at 75% heart rate, aortic systolic pressure had statistically significant correlations with all three adiposity variables ($p<0.05$). Significant correlations were found in a higher number of variables in the females. Physical activity had negative correlations with arterial stiffness and adiposity variables ($p<0.05$). **Conclusion**: Arterial stiffness measured by carotid radial pulse wave analysis is strongly related to adiposity measured from skinfold thickness in females. Females had higher arterial stiffness and adiposity compared with men. These findings could be helpful in future research using non-invasive arterial stiffness measurements.

5.1. Introduction

5.1.1. Obesity prevalence

Obesity is one of the important risk factors for diabetes and other cardiovascular disease. The World Health Organisation has declared that ischaemic heart disease will be ranked first and diabetes will move from 11th place to sixth place for the global burden of diseases and mortality by 2030 (2006). In 2005, it was estimated that 33% of the world's adult population were overweight or obese. Further it is projected that there will be up to 57% overweight or obesity levels by 2030 (Kelly *et al*. 2008). Obesity prevalence is observed in developed as well as developing counties such as India. In India, it is projected that there will be an increase of the prevalence of overweight or obesity from 16.9% (as in 2005) to 32.8% by 2030 (Kelly *et al*. 2008). In India, obesity was observed even in school age pre-adolescents and adolescents in both males and females. There was higher a prevalence in high socio-economic children and females (Chhatwal *et al*. 2004).

5.1.2. Arterial stiffness and obesity

Arterial stiffness is one of the key tools in the measurement of cardiovascular risk. Many studies have confirmed the relationship between arterial stiffness and adiposity in different age groups (Acree *et al*. 2007; Ferreira *et al*. 2004; Sakuragi *et al*. 2009; Whincup *et al*. 2005). A strong relationship between adiposity and arterial distensibility using ultrasound imaging was found in British adolescents (Whincup *et al*. 2005). In addition to adiposity, physical fitness and lifestyle also influence arterial stiffness (Sakuragi *et al*. 2009). Physical activities have a strong correlation with the incidence of obesity in adolescents and young

adults (Kemper *et al*. 1999). Body mass index is a standard method of assessing overall obesity. Skinfold thickness and waist/hip circumferences are used to measure adiposity in specific parts of the human body. Acree *et al* (2007) found obesity was associated with decrease in large and small artery compliance. In their study, large arterial compliance had significant correlations with the skinfold thickness and small arterial compliance with the waist/hip circumferences and the ratios. Total adiposity and truncal subcutaneous fat accumulation at the age of adolescence had positive correlations with the carotid intima-media thickness at the age of 36 in a longitudinal study (Ferreira *et al*. 2004). Juonala *et al*. (2005) also found childhood obesity was related to the development of carotid stiffness in adulthood. Interestingly, Zebekakis *et al* (2005) found that carotid distensibility decreased with higher BMI. They state that the arterial stiffness was modulated with age i.e. the negative effects of obesity on arterial stiffness were higher in younger age groups. They also suggest studying whether obesity in young adults has a higher risk of arterial stiffness and cardiovascular disease. It could help to find the potential of preventing obesity at younger age (Zebekakis *et al*. 2005) . Most of the studies using non-invasive pulse wave analysis have measured carotid-femoral pulse wave velocity. The current study aims to use and establish the importance of carotid radial pulse wave velocity, which is less intrusive.

To the investigators' knowledge, no study has been carried out to find the relationship between adiposity and arterial stiffness in young and healthy Indian adults. The current study aims to study the relationship between adiposity using skinfold thickness and arterial stiffness using pulse wave analysis in young Indian adults.

5.1.3. Hypothesis

In young healthy Indian adults:

H1 - There will be a significant positive relationship between body fat percentage measured by skinfold thickness and arterial stiffness measured by a non-invasive pulse wave analysis.

H2 - There will be significant differences between males and females in the above said relationship.

H3 – There will be a significant relationship between abdominal obesity and arterial stiffness.

5.2. Methods

The participants were same as in chapter 3 who were aged 18-28 years (mean age 21.9 ± 2.2) were recruited and 181 participants volunteered for the study.

5.2.1. Skinfold thickness

The skinfold thickness was measured using a Harpenden skinfold calliper (Quality Measurement Limited, UK). Measurements were taken according to the manufacturer's guidelines.

Measurement was taken on healthy, undamaged and uninfected dry skin. The participants were instructed to keep the muscles relaxed during the test. All the measurements were taken on the right side of the body. An exception was made in case of a deformity in the right limb. The skinfold site was marked using a water-soluble ink marker. A tape measure was used to find the accurate

mid-points. Each skinfold was firmly grasped by the thumb and index finger, using the pads at the tip of the thumb and finger. Then skinfold was gently pulled away from the body; the calliper was placed with its dial facing up; perpendicular to the true double fold of skin thickness; on the site marked the calliper was applied at approximately 1cm below the finger and thumb. While maintaining the grasp of the skinfold, the calliper was allowed to release so that full tension was placed on the skinfold. After the grip was fully released for one to two seconds, the dial was read to the nearest 0.50mm. Two measurements were taken at each site and averaged. The measurements were repeated if the two measurements varied by more than 1 mm. The skinfold measurement was taken from seven sites as follows. Chest measurements were taken only on male participants.

Site 1 Biceps - The anterior surface of the biceps midway between the anterior fold and the antecubital fossa.

Site 2 Triceps - A vertical fold on the posterior midline of the upper arm, over the triceps muscle, halfway between the acromion process (bony process on top of the shoulder) and olecranon process (bony process on elbow). The elbow should be extended and the arm relaxed.

Site 3 Subscapular - The fold is taken on the diagonal line coming from the vertebral border to between 1 and 2cm from the inferior angle of the scapula. (A diagonal fold about 1 to 2cm below the point of the shoulder blade and 1-2cm toward the arm).

Site 4 Supra-iliac - A diagonal fold above the crest of the ilium at the spot where an imaginary line would come down from the anterior auxiliary line, just above the hipbone and 2-3cm forward.

Site 5 Chest (Juxta-nipples) - A diagonal fold taken one half of the distance between the anterior auxiliary line and the nipple. (The anterior auxiliary line is the crease where the top of the arm, when hanging down, meets the chest).

Site 6 Abdominal - The vertical fold taken at the lateral distance of approximately 2cm from the umbilicus (2cm to the side of the umbilicus).

Site 7 Thigh - A vertical fold on the anterior aspect of the thigh, midway between the hip and knee joints (on the front of the thigh halfway between the hip joint, where the leg bends when the knee is lifted, and the middle of the knee cap). The leg should be straight and relaxed.

The body fat percentage was calculated using the linear regression equations of Durnin & Wormersley and Siri's equation (Durnin and Womersley 1974) (Table 5.1). The four skinfolds that includes biceps, triceps, subscapular and supra-illiac were used in this equation.

Body density = C [M (log 10 sum of all four skinfolds)]

(C, M = Constant values)

Table 5.1 Body density constants

MALE	17-19 YEARS	20-29 YEARS	30-39 YEARS	40-49 YEARS	50+ YEARS
C	1.162	11631	1.1422	1.162	1.1715
M	0.063	0.0632	0.0544	0.07	0.0779
FEMALE	17-19 YEARS	20-29 YEARS	30-39YEARS	40-49 YEARS	50+ YEARS
C	1.1549	1.1599	1.1423	1.1333	1.1339
M	0.0678	0.0717	0.0632	0.0612	0.0645

The Siri's equation fat percentage = [(4.95/Body Density) -4.5] x100

5.2.2. Arterial stiffness measurement

The procedures for measuring arterial stiffness are given in detail in Chapter 3.2.2.

5.2.3. Calculations and statistical analysis

Abdominal obesity was determined using the International Federation of Diabetes's guidelines (waist circumference ≥ 90 cm in men and ≥80 cm in women).

Data were analysed using a software package, SPSS 18 (IBM Limited, USA). A Kolmogorov-Smirnov test was applied to test the normality of the data. A Pearson correlation test was used to analyse the relationship between the adiposity and arterial stiffness variables. The meaningfulness of the correlation coefficient was evaluated by calculating the coefficient of determination (r^2). An

independent t test was used to find the difference in the measured values between males and females. Statistical significance was indicated if $p<0.05$.

5.3. Results

5.3.1. Gender Differences

In total, 124 females and 57 males participated. The physical characteristics of the participants were (Mean ± SD): Height (cm) -162.3±11.0, Weight (kg) - 58.8±10.9 and Body Mass Index - 22.1±3.0 kg/m^2. More than half of the participants engaged in no physical activity. The duration of their physical activity per day was categorized as follows; >60 min-15.4%, 30-60 min -15.4%, < 30 min - 9.4% and none - 59.1%.

The differences in the variables between males and females are listed in table 5.2. There were significant differences in height and weight between males and females, but there was no difference in their body mass index. There were significant differences in the anthropometric variables between males and females except abdomen skinfold thickness. Abdominal obesity was found in 11.9% males and 15.9% females. There were significant differences in all the arterial stiffness variables except pulse wave velocity. This was especially the case for females, who had a two-fold higher augmentation index than the males.

Table 5.2 Differences in arterial stiffness variables and skin fold thickness between sexes

Variables	Sex	Mean ± SD		Sig	Variables	Sex	Mean ± SD		Sig
Height (cm)	Male	169.5	±14.9	**	SEVR	Male	158.26	±26.1	**
	Female	159.0	±6.3			Female	126.36	±22.7	
Weight (kg)	Male	66.9	±10.4	**	BP (mmHg)	Male	Systolic 121.1±9.9		**
	Female	55.1	±9.0			Female	Systolic 110.5±0.9		
BMI (kg/m2)	Male	22.7	±2.6	NS	HR (bpm)	Male	69.05	±8.9	**
	Female	21.8	±3.1			Female	77.85	±9.8	
Fat %	Male	20.89	±4.5	**	Waist (cm)	Male	80.4	±8.1	**
	Female	31.31	±3.8			Female	72.1	±8.2	
PWV (m/s)	Male	8.00	±1.1	NS	Hip (cm)	Male	95.3	±7.4	*
	Female	7.96	±1.0			Female	92.15	±6.4	
Aug P (mmHg)	Male	1.23	±2.4	**	Waist/Hip	Male	0.84	±0.1	**
	Female	4.36	±2.8			Female	0.77	±0.1	
Aug Index	Male	7.34	±8.3	**	SFT Chest (mm)	Male	13.99	±6.2	
	Female	15.88	±8.7			Female	Not measured		
Aug Index @75	Male	4.54	±8.5	**	SFT Biceps (mm)	Male	9.77	±10.5	**
	Female	17.23	±8.3			Female	16.84	±8.8	
Aortic PP (mmHg)	Male	26.09	±5.3	*	SFT Triceps (mm)	Male	14.30	±4.8	**
	Female	23.98	±6.3			Female	20.73	±9.4	
Aortic SP (mmHg)	Male	107.20	±8.2	**	SFT Thigh (mm)	Male	22.79	±8.8	**
	Female	100.17	±9.6			Female	34.57	±8.0	
Aortic DP (mmHg)	Male	81.13	±7.7	**	SFT Sub Scapular (mm)	Male	17.18	±7.2	*
	Female	76.23	±8.9			Female	14.77	±4.8	
Mean P (mmHg)	Male	93.38	±7.7	**	SFT Abdomen (mm)	Male	26.34	±10.7	NS
	Female	87.80	±8.8			Female	26.29	±5.9	
Ejection Duration (msec)	Male	36.26	±3.7	**	SFT Iliac Crest (mm)	Male	21.47	±9.9	*
	Female	41.66	±4.2			Female	18.70	±5.9	

**Significant at p< 0.01 *Significant at p<0.05 NS- Not significant

(BMI- Body Mass Index, PWV – Pulse Wave Velocity, SP- Systolic Pressure, DP- Diastolic Pressure, SEVR– Subendocardial Viability Ratio, HR- Heart Rate, Aug – Augmentation, SFT – Skinfold Thickness, mm – Millimetres, cm - Centimetres)

5.3.2. Relationships

The relationship between the adiposity and arterial stiffness variables are listed in table 5.3. Systolic pressure, augmentation pressure, augmentation index, augmentation index at 75% heart rate, aortic systolic pressure had statistically significant correlations with all three adiposity variables. There was no significant relationship found between fat percentage and body mass index with gender combined (table 5.3), but a significant relationship was established when the data were analysed separately (Table 5.4). Augmentation index had a significant negative correlation with height (r = -0.329, p= 0.0001).

Table 5.3 Relationship between arterial stiffness measures and body fat percentage (correlations coefficients)

Variables	Fat Percentage	Body Mass Index	Waist Hip Ratio
Pulse Wave Velocity	.042	.025	.021
Aug Pressure	.306**	.224**	.325**
Aug Index	.210*	.264**	.274**
Aug Index @75	.413**	.217**	.340**
Aortic PP	.274**	.046	.055
Aortic Systolic Pressure	.256**	.294**	.269**
Aortic Diastolic Pressure	.095	.349**	.270**
Mean Pressure	.167	.333**	.271**
Ejection Duration	.540**	.058	.203*
SEVR	-.514**	-.031	.173
Systolic Pressure	.330**	.309**	.309**
Diastolic Pressure	.104	.345**	.276**
Heart Rate	.461**	.048	.152

**Significant at p< 0.01 *Significant at p<0.05

(SP- Systolic Pressure, DP- Diastolic Pressure, SEVR– Subendocardial Viability Ratio, Aug - Augmentation)

There were no significant correlations between fat percentage derived from skinfold thickness and any of the arterial stiffness variables in males. Mean pressure and aortic systolic pressure had a significant correlation with waist hip ratio (WHR). The females' adiposity variables had significant correlations with a greater number of arterial stiffness variables, including augmentation pressure, augmentation index and mean pressure.

Table 5.4 Relationship between arterial stiffness variables and fat percentage in both sexes (correlation coefficients)

Variables	Male			Female		
	Fat Percentage	Body Mass Index	WHR	Fat Percentage	Body Mass Index	WHR
Fat Percentage		.607**	.327*		.556**	.250*
Body Mass Index			.183			.382**
Pulse Wave Velocity	.160	.154	.054	.106	.100	.036
Augmentation Pressure	.001	.083	.241	.279**	.214*	.284**
Aug Index	.159	.222	.001	.320**	.231*	.165
AugIndex@75	.011	.092	.239	.264	.202	.254*
Aortic Pulse Pressure	.088	.001	.182	.183	.094	.227*
Aortic SP	.019	.153	.349*	.168	.302**	.014
Aortic DP	.025	.147	.251	.315**	.389**	.135
Mean Pressure	.019	.158	.341*	.254*	.361**	.069
Ejection Duration	.216	.203	.364*	.193	.140	.090
SEVR	-.191	-.208	-.427**	-.148	-.089	.119
SP	.002	.202	.352*	.178	.308**	-.013
DP	.023	.154	.234	.320**	.378**	.144
Heart Rate	.291*	.206	.432**	.156	.081	.114

**Significant at p< 0.01 *Significant at p<0.05

(SP- Systolic Pressure, DP- Diastolic Pressure, SEVR– Subendocardial Viability Ratio, Aug - Augmentation)

The participants who had higher physical activity scores had significantly less fat percentage. However, the BMI had non-significant correlations and WHR had a positive correlation with physical activity (table 5.5). Most of the arterial stiffness variables had negative correlations with physical activity (table 5.5).

Table 5.5 Relationship of physical activity with arterial stiffness and adiposity variables

Pulse Wave Velocity	Aug Index	Aug Pressure	SEVR	Heart Rate	Ejection Duration	Aortic Pulse Pressure
0.123	-0.306**	-0.375**	0.336**	-0.309**	-0.335**	0.126
Aug Index @75	Aortic SP	Aortic DP	Mean Pressure	BMI	Fat Percentage	WHR
-0.438**	0.242**	0.183*	0.211	0.093	-0.502**	0.207*

Correlation coefficients **Significant at p< 0.01 *Significant at p<0.05

(SEVR– Subendocardial Viability Ratio, Aug – Augmentation, BMI- Body Mass Index, WHR- Waist Hip Ratio)

5.4. Discussion

5.4.1. Influence of gender and physical characteristics

Any discussion of correlation must take into account the contribution to the total variance. This study showed a number of significant correlations within the range of 0.3-0.5. it is recognised that the contribution to the total variance is low (9-25%), still leaving a large unaccounted variance. The following discussion recognise this limitation.

The results show a strong relationship between adiposity derived from skinfold thickness and arterial stiffness derived from a less invasive carotid-radial pulse wave analysis. These results are similar to previous studies, which used similar and alternative methods. De Jongh *et al* (2006) studied the relationship between visceral adiposity using magnetic resonance imaging, skinfold

thickness and post occlusive skin capillary recruitment using a vascular microscope. They found that vascular recruitment was inversely related to inflammation score, visceral adiposity and truncal/extremities skinfold thickness. Whincup *et al* (2005) studied the relationship between adiposity and arterial distensibility in adolescents. They measured the arterial distensibility using ultrasound and body fat using skinfold thickness, similar to the current study. They found a significant relationship between them in both sexes. There was a lower arterial distensibility in females in their study. Similarly, the females in the current study had higher arterial stiffness that includes ejection duration, pulse pressure and augmentation index. In agreement with these results, Yasmin and Brown (1999) also found higher augmentation index in females using a similar radial pulse wave analysis. These findings clearly show a need to have separate reference values for males and female. Yasmin and Brown (1999) also found a similar negative correlation between augmentation index and height. It confirms that there could be an earlier reflection of pulse waves in shorter people, which results in a lower augmentation index. It is also important to note that females also had a higher fat percentage as estimated by the measurement of the individual skinfold thickness of the biceps, triceps and thigh. The current study showed significant relationships between obesity (BMI and WHR) and arterial stiffness similar to Whincup *et al*'s (2005) study. However, the relationships were more significant in a number of variables in females (Table 5.4). This may be due to the higher number of female participants. Nevertheless, the females had lower BMI compared with males yet their fat percentage was significantly higher. Several studies have found that Asians have higher fat percentage and in general, females have higher fat percentage

compared with their body mass index (Deurenberg-Yap *et al*. 2000; Wang *et al*. 1994). It was suggested that it might be due to the difference in body type such as trunk/leg length in different ethnics and lifestyle factors (Deurenberg-Yap *et al*. 2000; Dudeja *et al*. 2001; Novotny *et al*. 2006; Wang *et al*. 1994). Thus, in the current study, the higher fat percentage may be the reason for the significant correlations found between more arterial stiffness variables and fat percentage in females. These findings suggest that fat percentage measured by skinfold thickness has more clinical importance than simple BMI measurements.

5.4.2. Relationship between adiposity, insulin resistance/hyperinsulinaemia and arterial stiffness

A possible mechanism for the positive relationship between adiposity and arterial stiffness is the increase in insulin resistance due to adiposity (Garg 2004; Ross *et al*. 2002). Banerji *et al* (1999) found a strong correlation between insulin resistance and total body fat as well as regional and subcutaneous fat in Asian Indians. They state that visceral fat increases with total body fat and this results in increased insulin resistance. Urakawa *et al* (2003) observed a direct correlation between adiposity and oxidative stress. They state that adiposity increases the release of reactive oxygen species from leukocytes and thus increases the oxidative stress and leads to an increase in insulin resistance. Insulin resistance results in hyperinsulinaemia. Hyperinsulineamia leads to many following physiological reactions: (1) sodium retention due to increased sodium absorption in the renal circulation (DeFronzo *et al*. 1976; ter Maaten *et al*. 1999) (2) Previous studies have found that body fat is associated with over activity of autonomic nervous system especially sympathetic system at rest

(Chen *et al*. 2008; Scherrer *et al*. 1994). Hyperinsulinaemia is the main mechanism that triggers sympathetic activity (Vollenweider *et al*. 1993). This results in an increase in resting heart rate and blood pressure (Baba *et al*. 2007). The positive relationship between heart rate, systolic blood pressure and fat percentage in the current results (table 5.4) confirms these findings. (3) Hyperinsulinaemia increases the mitogenic activities that lead to vascular smooth muscle proliferation, increased collagen synthesis in the vascular wall and vascular hypertrophy (DeFronzo and Ferrannini 1991; Draznin 2011; Zimlichman *et al*. 1995). In addition, adiponectin, a protein derived from adipocyte, act as a modulator for vascular smooth muscle proliferation (Arita *et al*. 2002). An increase in other inflammatory adipocytokines such as tumor necrosis factor-α, interlekin-6, leptin, plasminogen activator inhibitor-1, angiotensinogen, resistin and C-reactive protein (CRP) also have negative impacts on vascular structure (Lau *et al*. 2005). All these mechanisms ultimately affect the endothelium dependant vasodilatation and increase vascular stiffness (DeFronzo and Ferrannini 1991; Kotchen 1999).

Leptin was not measured in this study. Leptin is a protein, which regulates adiposity and increases in concentration when body fat percentage increases (Considine *et al*. 1996). Leptin is also found to be an important factor that increases sympathetic activity (Haynes *et al*. 1997). Singhal *et al* (2002) studied the relationship between leptin, body fat mass and arterial distensibility. They found the arterial distensibility had a negative relationship with leptin concentration in blood and body fat mass derived from skinfold thickness. This negative relationship was irrespective of other inflammatory markers such as C-reactive protein, insulin and lipids.

Pulse wave velocity had significant positive relationship with body adiposity variables in many previous studies. Sutton-Tyrrell *et al* (2001) found a strong relationship between visceral adiposity measured by computed tomography and pulse wave velocity measure using Doppler flow signals on 2488 older adults with a mean age of 74 years. However, they found a weak correlation between pulse wave velocity and the subcutaneous fat (p=0.026). Wildman *et al* (Wildman *et al*. 2003) also found a strong positive relationship between Doppler measures carotid-femoral pulse wave velocity and BMI. However, the current study results did not show any significant relationship of pulse wave velocity with any adiposity variables. Carotid-radial pulse wave velocity may therefore not be an early indicator of arterial stiffness in young Indian adults. This needs to be studied more to be confirmed.

5.4.3. Physical activity

The negative correlations between physical activity and fat percentage have been demonstrated in previous studies. Sakuragi *et al* (2009) found a negative relationship between cardiac fitness and arterial stiffness (using carotid-femoral pulse wave analysis) as well as adiposity. However, there was no correlation between physical activity and BMI in the current study. Controversially, there was positive correlation between physical activity and WHR. This may be due to the differences in the other lifestyle factors among the participants. Thus, skinfold thickness may be a more valid method to measure body fat. However, it is also important to consider the factors other than physical activity that influence obesity such as ethnicity, parental obesity, dietary pattern and

sedentary behaviours such as watching television (Gordon-Larsen *et al*. 2002; Maffeis *et al*. 1998; Salmon *et al*. 2000)

To the investigators' knowledge, this is the first study in India to establish the relationship between adiposity and non-invasive brachial-radial arterial stiffness. The agreement between the current findings and previous studies confirms that the non-invasive arterial stiffness could be a marker for cardiovascular risks in young adults. The increase in the prevalence of obesity is seen in all the age groups and continuously developing globally. The current findings could be helpful for future studies and for developing diagnostic and preventive measures for cardiovascular risk at younger age groups.

5.4.4. Limitations

A larger number of participants could improve the significance of the results. It was not possible to control the dietary pattern and physical activities in the participants and they had a wide range of these values. Measurement of blood lipids and inflammatory biomarkers such as leptin and C-reactive protein would have improved the correlations of arterial stiffness. It was not possible in this study due to limited availability of funds.

5.5. Conclusions

Arterial stiffness measured by carotid radial pulse wave analysis is strongly related to adiposity measured from skinfold thickness in young South Asian females. There are gender differences in arterial stiffness variables derived from pulse wave analysis. More controlled studies are necessary to improve the

quality of the results using this less intrusive technique, the carotid-radial pulse wave analysis.

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CHAPTER 6. REVIEW OF LITERATURE- ERECTILE DYSFUNCTION AND CARDIAC REHABILITATION

Abstract

Erectile dysfunction (ED) is identified as one of the markers of coronary artery disease (CAD) and is highly prevalent and increasing all over the world. There are strong physiological and pathophysiological relationships between cardiovascular and erectile functions. The prevalence of ED increases with age and is mainly caused by endothelial dysfunction that develops arterial stiffness. The treatment for ED is based on the level of cardiovascular risk. Medical therapy is available and oral phosphodiestrase-5 is one of the successful drugs in treating ED with a vascular cause. In addition to medical therapy, invasive therapies such as Intra-cavernosal/urethral injection therapy or vacuum/constrictive devices can be used.

Modern cardiac rehabilitation/secondary prevention programmes (CR) are recognized as integral to the comprehensive care of patients with cardiovascular disease. CR programmes are known for reducing all cause mortality, hospital readmissions and recurrence of cardic events. Restoring complete sexual functions is one of the major goals for CR programmes. However, this part is not undertaken very often. The regular exercise in CR can reduce the cardiac work required for sexual activity. The cardiac rehabilitation programmes in the UK are infrequently studied for their effects on sexual functions. The improvement in the exercise capacity and its relationship with arterial stiffness and erectile functions need to be studied to establish effective treatment options.

6.1. Erectile dysfunction

Erectile dysfunction (ED) is defined as an inability to attain or maintain erection sufficient for satisfactory sexual performance [National Institute of Health Consensus Development Programme (NIHCDP 1992) & The National Health and Social Life Survey (1992) (Laumann *et al*. 1999)]. These programmes addressed erectile dysfunction as the leading complaint and primary source of the patients attending sex clinics. Generally ED has a multifactorial pathophysiology that includes arterial, neurogenic, hormonal, cavernosal, iatrogenic and psychogenic aspects (Billups 2005b). This chapter discusses erectile function, its relationship with cardiovascular pathology and management.

6.1.1. Erection and the heart

There is a strong physiological and pathophysiological relationship between the heart and penis. Rajfer *et al* (2004) describe the penis as a specialised extension of the vascular system. Both heart and penis are midline structures having an intimate relationship with the peripheral vascular system. Vascular smooth muscles at the corpora of the penis have two cylinders of a syncytium, which look similar to myocardium. They both are regulated by the parasympathetic system, specifically the non-adrenergic, non-cholinergic system that uses nitric oxide as its neurotransmitter (Rajfer 2004). The regulation of blood flow through the peripheral vascular system is mainly influenced by the endothelium. This includes the cavernous arteries, which supply blood to the penis. This regulation is achieved by changing the arterial diameter, mainly by releasing endothelial derived nitric oxide (NO).

6.1.2. Erection physiology

The penis is a richly vascularised organ (Billups 2005a), which consists of two corpus cavernosae and a ventral corpus spongiosum that surrounds the urethra. These are expandable tissues, composed of a meshwork of endothelium lined, interconnected smooth muscle cells (Bivalacqua *et al*. 2003). They are expanded with an influx of blood in the penile chambers. The dorsal and cavernosal artery supplies the corpus cavernosae. The venous blood returns in the subtunincal venular plexus, the deep dorsal vein and others. It needs a simultaneous action of psychological, hormonal, vascular and neurological agents to optimize male sexual function (Schwarz and Rodriguez 2005). However, erection is considered primarily a vascular function. Following sexual stimulation the NO pathway is activated and NO is released in the penile smooth muscle from i) enzyme endothelial nitric oxide synthase (eNOS) from endothelial cells lining the cavernosal smooth muscle cells and resistance helican arteries in response to sheer stress, ii) agonist induced activation by acetylcholine release from cholinergic nerves and iii) neuronal NOS (nNOS) activity in non adrenergic non cholinergic (NANC) neurons. NO diffuses to the adjacent smooth muscle cells and activates guanylyl cyclise. This converts guanosine triphosphate into a second messenger, cyclic guanosine monophosphate (cGMP) and induces substantial intracellular cGMP (Schwarz and Rodriguez 2005). It results in smooth muscle relaxation and increased blood flow in the penile arteries. The cGMP induced trabecular smooth muscle relaxation facilitates the engorgement of the sinusoidal spaces, lengthening and

enlargement of the penis and compression of subtunical venules (Billups 2005b). Eventually it results in complete occlusion of penile venous outflow and trapping of blood within the corpus cavernosae. It leads to the stasis of more blood in the penis and a harder erection. Erection is enhanced by various factors like vasodilatation due to nitric acid, radiation of blood flow from the internal pudental artery into penile chambers, physical senses and psychogenic factors. Importantly, the continuous activation and production of eNOS maintains the tumescence phase of penile erection (Bivalacqua *et al*. 2003; Billups 2005b; Billups 2005a; Schwarz and Rodriguez 2005).

6.1.3. Prevalence of erectile dysfunction

Erectile dysfunction is highly prevalent worldwide. It was estimated that 100 million men were affected world wide by 1993 (NIHCDH 1993) and 140 million by 2006 [The second Princeton Consensus (Jackson 2006)]. Further it is expected that this condition will more than double in the next 25 years, ultimately affecting more than 330 million men worldwide (Goldstein 2000).

A number of studies have been carried out and the prevalence of ED has been stated in various populations. An estimation of the prevalence is presented in fig 6.2 (Goldstein 2000). A community based multidisciplinary study on Massachusetts males showed that the combined prevalence of minimal, moderate and complete erectile dysfunction. There were 52% of men with ED in the age group of 40 to 70. Moreover the prevalence of complete erectile dysfunction tripled from 5 to 15% between ages 40 and 70 (Feldman *et al*. 1994).

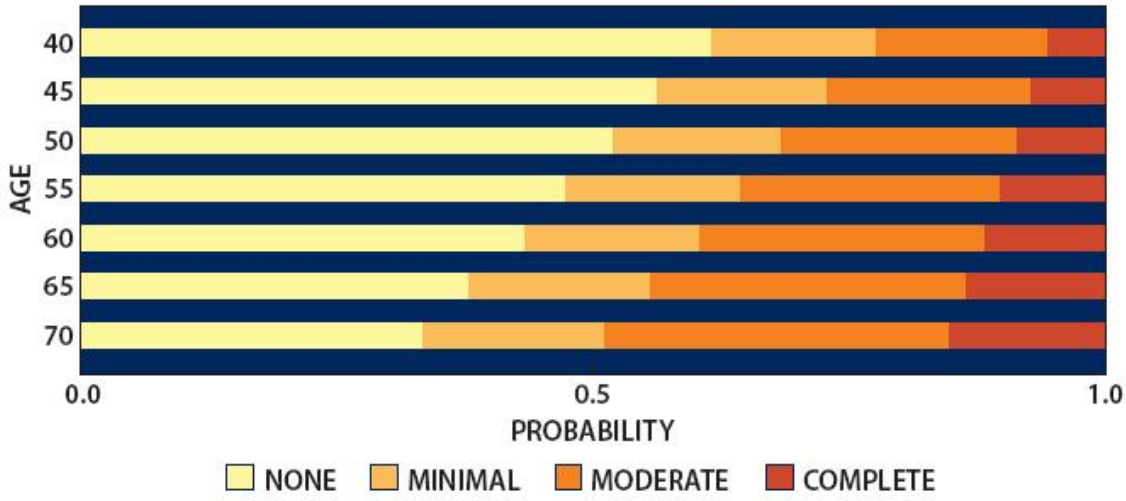

Figure 6.1 Impact of age on erectile dysfucntion

Age shows a strong impact on erectile dysfunction (1.0 = 100% probability). Goldstein (2000) estimated in his study that ED affects about 40% of men over age 40 and up to 70% of men over 70 years old (Scientific American, 2000).

Laumann *et al* (1999) analysed the data of 1410 men aged between 18 to 59 years from the National Health and Social Life Survey in the United States. They found that the prevalence of sexual dysfunction was 31% in men and the ages 52-59 years were likely to experience ED more than three times greater in comparison to men aged 18-29 years. Bacon *et al* (2003) reviewed observational studies and found a strong relationship between erectile dysfunction and aging. They carried out the largest study to date which observed 31,742 various health professional men between 53 and 90 years. They found that the relative risk for erectile dysfunction increased up to 10-fold with age, regardless of health status or previous erectile function. There was 32% prevalence of ED among men older than 50 years of age. The co-morbid conditions increased the absolute risk for erectile dysfunction, approximately 10% higher at all ages for co-morbid men compared with healthy men. Lewis *et al* (2004) reviewed 24 studies undertaken from 1993 to 2003 around the world

and listed the prevalence of ED. The prevalence of ED was 1-9 % for those below 40 years, 2-30% for those aged 40-59 years, 20-40% for those aged 60-69 years and 50-75% for those aged above 70 years. Gazzaruso *et al* (2004) found in their study that ED had increased fourfold in men aged 70 years compared with the men aged less than 50 years. These findings clearly show that age has strong associations with the prevalence of ED. The estimated prevalence of ED has a considerable variation because of various populations studied and the definition and methods used (Rosen *et al*. 1999).

6.1.4. ED and coronary artery diseases (CAD)

According to 'the global burden of disease study', ischemic heart disease was the fifth most common cause of disability in 1990 worldwide and by the year 2020, it is expected to be the leading cause of global disability (Murray *et al*. 1994; Lopez and Murray 1998; MacLean and Chockalingam 1999). The latest statistics shows that in the UK, heart and circulatory disease is the biggest killer and it claims 200,000 lives every year. Every year 146,000 people suffer a heart attack and every 6 min someone dies from a heart attack. There are 1.4 million people over 35 years in the UK who have survived a heart attack and there are 970,000 men among them [British Heart Foundation (BHF 2008)].

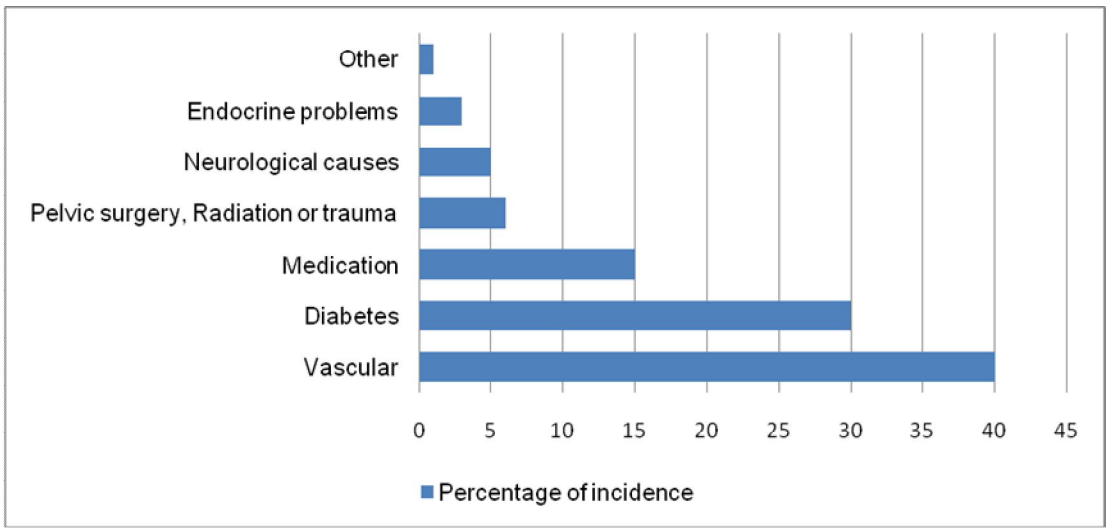

Figure 6.2 The range of causes of erectile dysfunction

Though ED is associated with various causes, mainly it is a vascular condition. The figure shows the various causes of ED and their percentage of incidence (Goldstein 2000).

It has been widely accepted that ED is primarily caused by underlying vascular diseases especially atherosclerosis (Billups 2005b). The range of causes and percentage of incidence is shown in fig.6.2 .Vascular ED and coronary artery diseases share common risk factors such as a sedentary life style, obesity, heavy drinking, recreational drug use, high plasma cholesterol and triglycerides levels and smoking (Barrett-Connor 2005; Burnett 2006). These risk factors damage the endothelium and it affects the coronary arteries as well as the arteries throughout the body inclusive of the corpus cavernosum of the penis (Kaya *et al*. 2006).

ED is strongly associated with micro albuminuria, which suggests that there is a strong link between ED, CAD and endothelial dysfunction (Gazzaruso *et al*. 2004). Greenstein *et al* (1997) studied the relationship between the severity of coronary artery disease and erectile function on men who underwent an angiogram for cardiac disease. They evaluated the severity of the CAD by the number of occluded arteries, the level of anginal syndrome and whether or not

the patient had experienced an MI. The results showed that severity of the cardiac disease had worsened the erectile dysfunction. The associated risks like age, diabetes and hypertension also had further negative effects on the quality of an erection.

6.1.5. Pathophysiology of ED with vascular cause

For decades, the reduction in sexual function has been considered as a part of the natural aging process, it really involves a number of disease processes leading to abnormal erectile function with age (Bivalacqua *et al*. 2003). The ageing penile vascular artery undergoes characteristic changes involving the arterial and vascular beds. It includes endothelial dysfunction. Billups (2005b) strongly suggests to consider endothelial dysfunction as a central aetiological factor in systemic and peripheral vascular disease.

6.1.5.1. Endothelial dysfunction

Vascular endothelium serves as a barrier for the arterial and venous blood. It also plays a pivotal role in modulating vascular tone and blood flow as the response to humoral, neural and mechanical stimuli. These stimuli also play a role in the regulation of inflammation, platelet aggregation, vascular smooth muscle proliferation and thrombosis (Bivalacqua *et al*. 2003).

Endothelial dysfunction is defined as a functional deterioration of endothelium characterized by vasospasm, vasoconstriction, alteration in coagulation mechanisms and fibrinolysis, and increased vascular proliferation (Kaya *et al*. 2006). The primary underlying mechanisms are elevated vasoconstrictor tone

and decreased endothelial and neurogenic endothelial relaxation of the penile vascular artery. These are considered to be due to the reduced NO biosynthesis and reduced enzyme activity of eNOS in the aged penile vasculature. There is also a lack of substrate or co factors for eNOS. There is an alteration in intra cellular signalling such that eNOS is not appropriately activated or uncoupled or accelerated degradation of NO by reactine oxygen species (ROS). Oxidation stress in particular, the reaction of NO and a superoxide anion is an important pathogenic element in the development of endothelial dysfunction in vascular diseases such as diabetes mellitus (DM), hypertension, atherosclerosis and hypercholesterolaemia. These vascular disorders are highly prevalent in patients with ED and have been identified as independent risk factors for ED in large population based studies (Bivalacqua *et al*. 2003). The prevalence of ED in DM is three times higher in men, occurs at an earlier age and increase with disease duration (De Tejada *et al*. 2005). The enhancement of oxygen free radicals including advanced glycosylatin end products (AGE) in diabetes impairs the endothelium dependent relaxation in the aorta and corpus cavernosae. There is a diminished effect of released NO. In diabetes, there is a significant reduction of endothelial dependant vascular relaxation in the penile resistant arteries which is mediated by the endothelium derived hyperpolarizing factor (EDHF) (De Tejada *et al*. 2005). The changes in the neural integrity of the cavernosal nerve and pelvic plexus also play a role in the overall reduction of endothelial cell function (Bivalacqua *et al*. 2003).

6.1.5.2. Drug induced ED

A medical treatment or examination that unintentionally results in an illness as a complication is called an iatrogenic cause. There are iatrogenic causes of ED from some common drugs used to treat cardiac diseases. In fact, drugs are one of the major causes of ED in up to 25% of patients attending an ED clinic (Eardley and Sethia, 2003). Some antihypertensive drugs, like diuretics and β blockers are highly associated with ED. Collectively, an antihypertensive agent that reduces the systemic pressure results in a reduction in pelvic pressure gradient. Eventually it worsens the vascular function and exacerbates erectile dysfunction (De Tejada *et al*. 2005; Burnett 2006). A list of drugs and their effects on sexual function are given in table 6.1.

Table 6.1 Drugs that may cause ED

Drug Group	Types of drug group	Iatrogenic cause
Anti hypertensives	Diuretics	ED
	Beta blockers	ED
	Centrally acting agents	ED, loss of libido, ejaculatory disfunction
	Ganglion blockers	ED
	Alpha blockers	Retrograde ejaculation and priapism
Major tranquilizer	Thioridazine	ejaculatory disfunction
	Phenothiazines	ED, loss of libido, ejaculatory disfunction and priapism
	Butyrophenones	ED and painful ejaculation
Endocrine Drugs	Steroidal anti-androgens	ED and loss of libido
	LHRH analogues	ED and loss of libido
	Oestrogens	ED and loss of libido
Anti cholinergics	Atropine, Propantheline	ED
Others	Cimetidine	ED and loss of libido
	Digoxin	ED
	Metoclopramide	ED and loss of libido
	Pheytoin, carbamazepine	ED and loss of libido

(Eardley and Sethia 2003)

6.1.6. ED as a predictor of CAD

It has been found that endothelial dysfunction precedes the development of atherosclerotic changes in the arteries. The small vessels of the penis are very sensitive to functional and structural changes (Kaya *et al*. 2006) and they are more prone to develop atherosclerotic occlusion compared with the larger vessels of the other parts of the body (Kirby *et al*. 2001).

Recent studies demonstrated that damage to the penile vascular beds occurs earlier than systemic vascular illness. Sixty seven percent of patients, having CAD with ED reported that symptoms of ED began before CAD symptoms in a mean time interval of at least three years. The severity of ED correlates with the severity of CAD and thus may be a useful indicator CAD (Kaya *et al*. 2006).

In the presence of ED with other cardiovascular risk factors, the prevalence of coronary artery diseases is higher. Gazzaruso *et al* (2004) found a strong and independent association between ED and silent CAD. They studied diabetic men with and without ED and found that ED was the most efficient predictor of coronary vascular disease. The presence of ED was as high as eight fold in the patients with silent CAD compared with the others. Even the uncomplicated diabetic patients, with no silent CAD, also had a similar presence of ED.

Bluementals *et al* (2003) studied 25,650 males with and without ED. They found ED as a marker for peripheral vascular disease and the risk became more pronounced with increase in age. Hodges *et al* (2007) found in their study population that 43% of healthy subjects had ED. Sixty six percent of subjects had ED prior to CVD and 79% of subjects had ED after CVD.

C-reactive protein (CRP) is a marker for endothelial function. Billups *et al*., (2003) studied the relationship between C-reactive protein and cardiovascular risks in men with ED but not clinically established coronary artery disease. They found that CRP was significantly associated with increase in severity of ED. Inman *et al* (2009) studied biennially 1400 community dwelling men who had regular sex partners and without known CAD for the presence of ED. The results showed that the younger men (50-59 years) with ED had marked increase in the risk of future cardiac events than the older men (60-69 years). In older men, ED appears to be of little prognostic importance.

6.1.7. ED and Quality of Life (QoL)

QoL is defined as "individuals' perception of their position in life in the context of the culture and value systems in which they live in relation to their goals, expectations, standards and concerns". It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships and their relationships to salient features of their environment (WHO 1996). The relevance of its dimensions on a person's life depends on how the individual perceives them (Mallis *et al*. 2006).

Sexual dysfunction is an important component of a patient's QoL and subjective wellbeing. Studies have shown that ED has a significant negative effect on QoL of not only the person with ED but also his partner and family (Mallis *et al*. 2006). Men with ED showed lower satisfaction with sexual life as well as their overall life compared with healthy individuals. In addition, severity of ED had a stronger negative effect on patients' satisfaction with sexual life (Mallis *et al*.

2006). Litwin *et al* (1998) studied the effect of ED on health related QOL using the SF-36 questionnaire. The results showed that the emotional domains were associated with more profound impairment than physical domains. Many other studies also accepted that ED affects the psychological aspects of the patient more. Laumann *et al* (1999) stated that ED affects individuals' mood and interpersonal functioning. Hatzichristtou *et al* (2005) stated that the association of ED and CAD was mediated by the psychological impact of both disorders. It commonly leads to a depressive status and clinical depression.

6.1.8. Management of ED

The second Princeton Consensus (Kostis *et al*. 2005) divided patients with ED according to their level of cardiac risks.

Low risk:

- Asymptomatic, less than three cardiovascular risk factors
- Controlled hypertension
- Mild, stable angina pectoris
- Post revascularisation
- Post myocardial infarction (MI) (≥6 to 8 weeks)
- Mild vascular disease
- Left ventricular dysfunction class I (New York Heart Association) NYHA

High risk:

- Unstable or refractory angina
- Uncontrolled hypertension
- Congestive heart failure (NYHA class III or IV)
- Recent MI (≤2 weeks)
- High-risk arrhythmia
- Obstructive hypertrophic cardiomyopathy
- Moderate to severe valvular disease

Intermediate risk factors:

- Asymptomatic, >3 risk factors
- Moderate, stable angina pectoris
- History of MI (≥ 2 weeks, ≤ 6 weeks)
- Left ventricular dysfunction (or) congestive cardiac failure
- (NYHA class II)
- Non-cardiac sequel of atherosclerotic disease

Further, the consensus has derived an algorithm for risk stratification and patient management in three steps.

Step 1: Sexual function should be assessed at the initial level of cardiovascular evaluation. Based on the initial evaluation, the patients are assigned a level of risk following specialised tests if necessary.

Step 2: Low risk patients may safely engage in sexual activity with or without treatment for ED. High risk patients should be stabilised by specific cardiovascular interventions before engaging in sexual activity is considered, or specific interventions of ED is recommended. The patients should be regularly followed up and reassessed.

Step 3: The patients with ED should be routinely evaluated for cardiovascular risks. The patients should be discussed on monitoring, evaluating and improving the risk and subclinical cardiovascular disease risks

Various treatment options are available for erectile dysfunction. The second international consultation on erectile dysfunction (Wyllie 2003) recommends letting the patient decide the most appropriate treatment.

6.1.8.1. Medical therapy

Reversible conditions that cause erectile dysfunction are considered for medical therapy (NIHCDP 1992). Amongst oral therapy, phosphodiesterase-5 (PDE) inhibitors have been proven effective in the treatment of ED with minimal or no side effects for people with cardiac disease. The cyclic guanosine monophosphate (cGMP) enzyme levels are regulated by cGMP specific phasphodiestrase. The inhibitors of these enzymes increase cGMP concentrations at the level of the endothelium. It enhances the smooth muscle

relaxation and the inflow of arterial blood into the corpus cavernosum. Sildenefil was the first oral phosphodiestrase-5 (PDE-5) inhibitor for the treatment of men with ED. Originally it was developed and studied as an anti-anginal agent. Very positive clinical results on erectile function were due to the effects on cGMP levels and increased intracavernosal smooth muscle relaxation. Sildenefil is the most thoroughly studied PDE-5 agent in the class and has been proven safe for men with cardiovascular risk. It has been successful even in patients taking diuretics and beta-blockers. However, a pre evaluation is necessary for any additional risk such as the use of nitrates (Billups 2005a; Shigemura *et al*. 2006). A marked hypotension results from the usage of nitrates and sildenafil also has a hypotensive effect (Mahmud *et al*. 2001). Vardanafil is a highly selective PDE-5 inhibitor, which has been another effective oral treatment for ED. Vardanafil increased the ischemic threshold during exercise and increased the ability to undergo exercise for a longer period. This increased exercise tolerance level was more than the normal required level to complete sexual activity (Thadani *et al*. 2002). The alpha-adrenergic receptor antagonist also facilitates erection when administered orally. These alpha-blockers antagonize the activity of nor-epinephrine and attenuate the contractile response opposing the NO mediated smooth muscle relaxation. An important fundamental issue in these orally administered PDE-5 inhibitors is that the efficacy of these agents depends on the associated sexual stimulation (Lue and Lee 2000).

If a trial of oral therapy fails, then it is usual to proceed to invasive therapies. Intra-cavernosal and intra-urethral injection therapy are available such as papavarine hydrochloride and alpha-adrenergic receptor antagonist. These agents are effective in increasing the intra cavernosal blood flow and activation

of veno-occlusive mechanism (Lue and Lee 2000). These are successful for many patients and careful consideration for contraindication and effectiveness with individuals is recommended. Alternatively, vacuum/constrictive devices are effective at generating and maintaining an erection with low incidence of side effects. However, there is a significant rate of patient drop out for many reasons including a lack of spontaneity between partners, general discomfort and impaired ejaculation. There are surgical treatments also available. Patients with venous leakage have been treated effectively with venous legation surgery. There are three forms of penile prosthesis available, which could be used when other forms of therapy failed or were refused by the patients. They are semi rigid, malleable and inflatable. Their effectiveness, complication and acceptability vary and the main problems identified are mechanical failure requiring reoperation and infection (NIHCDP 1992). Many of the patients are reluctant to take any further specific treatment of ED due to several reasons such as advanced age, organic and psychological diseases, problems in the relationships, lack of information and the fear of complications (Maroto-Montero *et al*. 2008).

A multidisciplinary approach may be of great benefit in defining the problem and arriving at a solution (NIHCDP 1992). Cardiac rehabilitation (CR) is one such programme that is a well established for cardiovascular risk patients.

6.2. Cardiac Rehabilitation (CR)

Among surviving patients after a myocardial infarction (MI), only a quarter of them experience improvements, another quarter experience deterioration and the remaining half experience no change in their life (Thompson and Bowman

1998). A structured care for chronic cardiac disease management can improve the outcome for people with risk factors (Dalal *et al*. 2004). CR programmes were developed in 1960 as an exercise-based therapeutic management. Despite the effectiveness of them, the evaluations of the programme required attention to various components other than exercise (Jones and West 1995). Balady *et al* (2007) suggest cardiac rehabilitation programmes do not consist of exercise training alone, but they are actually a multifaceted and multidisciplinary approach to overall cardiovascular risk reduction. The National Service Framework for Coronary Heart Disease (NSF 2000) recognized CR as an effective multidisciplinary approach with a combination of exercise, medical, psychological and educational interventions (Lau-Walker 2004).

Modern cardiac rehabilitation/secondary prevention programmes are recognized as integral to the comprehensive care of patients with cardiovascular disease (Balady *et al*. 2007). The World Health Organization defines CR as “the sum of activities required to influence favourably the underlying cause of the disease as well as the best possible physical, mental and social conditions, so that they may, by their own efforts preserve or resume when lost, as normal a place as possible in the community” (Coats *et al*. 1995). According to the American Heart Association, the core components of cardiac rehabilitation/secondary prevention programmes are patient assessment, nutritional counselling, blood pressure management, lipid management, diabetes management, tobacco cessation, psychosocial management, physical activity counselling, and exercise training (Balady *et al*. 2007).

The target groups for CR are acute coronary syndromes, post revascularizations, stable angina, chronic heart failure, cardiac transplantations, valve surgeries, congenital heart diseases, implanted cardioverter defibrillators (Coats *et al*. 1995; Thow 2006)

6.2.1. Phase of cardiac rehabilitation

In the UK, cardiac rehabilitation is divided into four phases, progressing from the acute hospital admission stage to long-term maintenance of lifestyle changes, as follows (Thow 2006):

- Phase I – in-patient period or after a 'step change' in cardiac condition
- Phase II – early post-discharge
- Phase III – supervised out-patient programme including structured exercise
- Phase IV – long-term maintenance of exercise and other lifestyle changes

The British Association of Cardiac Rehabilitation (BACR) and Scottish Intercollegiate Guidelines Network (SIGN) have published guidelines for cardiac rehabilitation programmes (Coats *et al*. 1995; SIGN 2002).

Phase I

It is the first stage of the patient's cardiac rehabilitation pathway. It either starts as an in-patient stage, or after a 'step change' in the patient's cardiac condition.

These step changes include myocardial infarction, onset of angina, any emergency hospital admission for coronary heart disease, cardiac surgery or angioplasty and/or stent, and first diagnosis of heart failure. Patients with any age are included and there is no specific exclusion to phase I. The participants are visited in the coronary care unit or ward by the CR team members. The partner or family are also included in this phase. Reassurance, information/education, mobilization and discharge planning are included in the phase I.

The education component adhering to adult education principles including:

- Relevance (tailored to patients' knowledge, beliefs and circumstances)
- Feedback (informed regarding progress with learning or change)
- Individualisation (tailored to personal needs)
- Facilitation (provided with means to take action and/or reduce barriers)
- Reinforcement (reward for progress).

Phase I CR includes educational advice regarding:

- Risk factors (modifiable and non-modifiable)
- Living with CHD
- Anatomy and physiology of the heart
- Clinical management of CHD

- Cardio-protective diet
- Sensible alcohol use
- The benefits of exercise
- Cardiac misconceptions
- Return to driving, employment and hobbies
- Holiday advice
- Medications
- Psychological aspects of CHD and stress management
- Sexual activity
- Sleep

To achieve these needs, an individual assessment is carried out by considering the patients personal requirements and risk factors. The assessment includes family/personal history, risk factor assessment, prognostic evaluation, risk stratification, psychosocial status, socio-economic status, vocational/leisure activities. Then, a tailored plan is produced for every individual to achieve the above goals. On average, the patients stay 5-7 days in the hospital, but that varies with the diagnosis and the treatment. On discharge, patients are offered the following as an integral part of acute care:

- Assessment of physical, psychological and social needs for future CR

- Negotiation of a written individual plan for meeting these needs
- Prescription of effective medication, and education about its use, benefits and side effects
- Involvement of relevant informal carer(s)
- Provision of information about cardiac support groups
- Provision of locally relevant, written information about CR

(Coats *et al*. 1995; SIGN 2002)

The BACR guidelines (Coats *et al*. 1995) recommend that patients receive a programme of graduated mobilisation and exercises, so that by discharge time the patient is ambulant, able to climb stairs and attend to his or her own activities of daily living.

Phase II

This is the initial post-discharge stage and is of low intensity. After discharge, the patient may feel isolated, insecure, and anxious. Access to appropriate health care professionals is important in this period. With an involvement of primary care, the CR team may give care through phone or by home visits, depending on the available service. The modification of risk factors start at this stage and the goals set for phase I start to be realised (Thow 2006).

Phase III

Phase III is a well recognised, hospital based, outpatient education programme including structured exercise training sessions. Structured community programmes are also delivered safely and successfully. The risk factor modification and education are continued as established in phase I and II. The tailored approach for every individual is continued with monitoring and reassessing the identified risk factors and lifestyle. A multi-factorial risk factor modification as appropriate to each patient is emphasised. The outcomes are continuously reviewed, audited and modified appropriately. The involvements of partner/family/friends are important also in this phase. The patients are examined for risk stratification prior to exercise classes. Generally group exercises with aerobic circuit interval training are found effective and used in the CR programmes in the UK (SIGN 2002). Resistance exercises are also used depending on the patients' fitness and improvement. Patients are taught home-based exercises and self-monitoring skills to continue the rehabilitation at home. Every exercise training session consists of a warm-up, an aerobic conditioning phase and a cool-down period. It is important that the exercise programmes is tailored for each patient's needs and circumstances to encourage adherence to exercise (Thow 2006).

Phase IV

Phase IV focuses on the long-term goals of risk factor modification, with long-term follow-up in primary care. These are important for the sustained benefits achieved from the previous phases (SIGN 2002). It is an informal stage of CR

and primary health care teams take care of the individual goals that are set in the previous phases, outside the hospital setting (Coats *et al*. 1995). Patients are informed of the exact nature of the follow-up systems available. Patients are encouraged, on a formal or informal basis, to continue and progress appropriate physical activities. It is to ensure that the patients have appreciated their exercise abilities and learnt appropriate self monitoring techniques (Thow 2006).

6.2.2. Benefits of cardiac rehabilitation

There is an increasing appreciation of the value of a rehabilitation programme in helping patients back to normal or near normal life after a cardiac event (Song and Lee 2001). After myocardial infarction, approximately one-third of the patients undergoing cardiac rehabilitation have regained their quality of life in 100 days. Cardiac rehabilitation programmes reduces the readmissions to hospital and recurrence of cardiac events (Thompson and Bowman 1998).

6.2.2.1. Effects of exercise in cardiac rehabilitation

There have been several studies that revealed the physiological effects of exercise within cardiac rehabilitation. CR improves haemostasis, endothelial function and arterial blood pressure in patients with CAD (Lee *et al*. 2006). Exercise training has been shown to modify the sympathovagal control of the heart towards an increase in parasympathetic tone. It is considered that the rise in heart rate during exercise is related to the combination of parasympathetic withdrawal and sympathetic activation. The fall in heart rate immediately after exercise might result from reactivation of the parasympathetic nervous system.

Increased vagal activity, on the other hand, is associated with reduced risk of death from cardiac-related causes (Tiukinhoy *et al*. 2003). Dalal *et al* (2004) also stated that exercise-based cardiac rehabilitation after myocardial infarction has been shown to reduce all cause mortality. Moreover, findings from the previous meta-analysis show that rehabilitation with exercise after MI significantly reduced the total and cardiac mortality at various follow up durations from one to three years (Thompson and Bowman 1998).

6.2.2.1.1. Duration of CR

Different durations have been observed in various CR programmes. Hevey *et al* (2003) conducted a study to evaluate the effectiveness of a 4-week multifactorial CR programme compared with a standard 10-week CR programme on quality of life and exercise capacity. He found that exercise capacity, general health and quality of life dimensions (e.g., energy, pain, emotional well-being, social wellbeing, and general health) were significantly improved, irrespective of the duration of the cardiac rehabilitation programmes. Systematic reviews have suggested that longer programmes are associated with better outcomes. However, shorter programmes may still represent a valuable CR service option.

6.2.2.1.2. Age and CR

Marchionni *et al* (2003) found that the extent of the improvement by cardiac rehabilitation was independent of age. They studied the effects of a cardiac rehabilitation programme on different age groups varying from 45 to above 75 years. They found that the total work capacity and the health related quality of

life improved in all the age groups. They also compared the hospital based CR with home-based CR and found both of them similarly effective in the short term. Rajeski *et al* (2002) studied the effects of CR in elderly patients. They compared the effects of two different approaches to cardiac rehabilitation on performance-related and self-reported measures of physical function on three months of treatment. The interventions compared were a group-mediated cognitive-behavioural intervention for physical activity and a traditional exercise therapy programme. Overall, both treatment groups experienced statistically significant improvements in performance-related and self-reported physical function. However, the organized physical activity, coupled with group-mediated cognitive behavioural counselling achieved a better short-term benefit in older patients with lower physical function and the greatest risk for subsequent morbidity and mortality.

Lavie and Milani (2000) compared the effects of CR in the elderly with young people and demonstrated the disparate effects on improvements in aerobic exercise capacity and QoL. They found that the elderly had significant improvements with relatively smaller improvements in measures of aerobic exercise capacity including estimated metabolic equivalents, anaerobic threshold and peak VO_2. However, they had greater improvements in both total function scores and QoL scores after cardiac rehabilitation programmes, compared with younger patients.

6.2.2.2. Effects of cardiac rehabilitation on sexual function

The peripheral effects are improvement in muscle structure and function. These central and peripheral effects together improve the functional capacity and quality of life (Mustata *et al*. 2004). The energy expenditure in men for sexual activity that includes stimulation and orgasm is 2-METs (metabolic equivalents) for woman-on-top coitus and 3.5-METs for men-on-top coitus. There are significant individual variations that range from 2-METs to 5.4-METs. This energy expenditure is equivalent to the intensity of walking a kilometre in 15 minutes or to climbing up a flight of stairs in 10 seconds. Based on these, a functional capacity of 6-METs attained on exercise stress testing provides sufficient margin of safety (Sainz *et al*. 2004). Exercise training in cardiac rehabilitation could achieve this required functional capacity for sexual intercourse. Mickley *et al* (2000) also suggest that the improvement in the physical activity and self confidence following cardiac rehabilitation could help the patients to resume sexual activity. The performance of an exercise test at the time of discharge should be mandatory for risk stratification. The patients who can manage a work capacity of at least 100 watt without evidence of myocardial ischaemia or arrhythmia may take part in an active sexual life without concerns. Muller *et al* (1996) suggest that physicians should strongly encourage patients with known coronary artery disease to participate in a CR programme and perform regular exercise. Such exercise can reduce the cardiac work required for sexual activity and reduce the risk of triggering the onset of an MI.

Successful risk factor modification and the maintenance of a healthy lifestyle with regular physical activities is a lifelong process (Balady *et al*. 2007). Chronic heart diseases are attributable to unhealthy life styles and the psychological effect of coping with and recovering fully from myocardial infarction is great. Lifestyles have received increasing attention because many health conditions and premature deaths are preventable through modification in lifestyles (Song and Lee 2001). As a part of a Massachusetts male aging study, Derby *et al* (2000) studied 593 men without ED at baseline and followed them up for 8.8 years. They found the lowest risk for ED was among individuals who had a sedentary lifestyle at baseline and then became physically active during the course of the study. The highest risk for ED was among men who were sedentary at both the baseline visit and at follow-up. It was also found that physical activity, increased physical activity, leanness, moderate alcohol consumption and not smoking were associated with decreased risk of ED (Bacon *et al*. 2003).

6.2.2.3. Quality of life and sexual function

Sexual problems are widespread and adversely affect mood, well-being and interpersonal function. It is an important component of quality of life in cardiac patients (Tuniz *et al*. 2004). Improvement in the quality of life (QoL) is one of the potential major goals of CR programmes. These programmes not only aim to increase the life span but also try to help the patients to live better. Song and Lee (2001) examined the relationship between exercise and a healthy lifestyle by focusing on the role of motivation as an intervening factor. They examined the effects of a 12-week exercise programme on the motivation and

performance of a healthy lifestyle among persons who were recovering from coronary artery disease and confirmed that motivational variables were modifiable. The findings of the study partially support the positive effects of a 12-week exercise programme on the performance of a healthy lifestyle. It significantly supported the effects on motivation after controlling for income, education, and pre-test scores. Thus, when developing health promotion programmes for initiating and maintaining a healthy lifestyle, the relative importance of different motivational variables should be considered. To the investigators' knowledge, there have been no studies carried out to see changes in erectile dysfunction related quality of life in cardiac rehabilitation.

6.2.2.4. Family and Cardiac Rehabilitation

Comprehensive cardiac rehabilitation programmes tend to provide a range of services to support family members. Possibly the most compelling reason for cardiac rehabilitation is the prospect of improving health-related quality of life, not only for the patient, but also for the family (Thompson and Bowman 1998). The cardiologists and the team members could help almost all the patients in enhancing emotional well being and overall quality of life including sexual function as there are only a few patients have specific cardiac reasons that limit their sexual activity (Taylor 1999).

Sexual activity that was affected by a myocardial infarction can be a source of anxiety and fear. There is usually a temporary reduction in sexual activity and satisfaction but a substantial minority seem to experience a long-term deleterious effect on their sexual relationship. The reduction in sexual activity

and consequent dissatisfaction is mostly as a consequence of the spouses' or the patients' fear of a recurrent myocardial infarction. The relative risk of an MI in the two hours following sexual activity is 0.9% in patients with prior cardiac disease. Regular exercise can reduce and possibly eliminate the small risk of recurrence of MI associated with sexual activity. The annual risk of MI due to sexual activity is very low compared with the other potential risks such as anger and exertion. The frequency of sexual activity is less than the frequency of the other risks in patients with MI (Muller *et al*. 1996).

Gunzler *et al* (2007) found a significantly decreased partnership quality in patients with sexual dysfunction in cardiac rehabilitation programme. Concern about the return to sexual activity and the impact of the illness upon spouse and other members are some of the major issues that need discussion and counselling (Song and Lee 2001). Restoring normal sexual function is one of the primary goals of cardiac rehabilitation. Hood and Robertson (2004) state that cardiac rehabilitation programmes are ideally placed to enquire about symptoms of ED and to initiate treatment. Tuniz *et al* (2004) suggest that it is extremely important to face the problem of resuming the sexual activity systematically within the cardiac rehabilitation programme, with educational sessions, individual or couple conversations and with the aid of information pamphlets.

Very few studies have been carried out with a focus on sexual function in patients with cardiac rehabilitation. Klein *et al* (2007) added a sexual therapy that included patient education, cognitive restructuring, emotional support, guided imaginary and specific medication with regular cardiac rehabilitation in

Israel. The sexual therapy patients improved more than controls in quality of sexual function in (Klein *et al*. 2007) terms of libido, confidence to attain erection, satisfaction with sexual relationship, frequency of erection and enjoyment of sex. The sexual therapy patients were highly satisfied with cardiac rehabilitation and sexual therapy. The study group suggest that sexual therapy should be an integral part of cardiac rehabilitation. Maroto-Mantero *et al* (2008) studied the effects of cardiac rehabilitation on erectile dysfunction in Spain. They found a majority of participants refused any specific treatment for ED for various reasons such as advancing age, partnership problems and the fear of complication. They suggest that it is essential for the health care professionals to provide sufficient and good quality information to patients. They found excellent results when the patients are specifically treated with PDE-5 inhibitors, when there was no contraindication. However, none of the studies examined the diagnostic or prognostic values of arterial stiffness of the patients undergoing cardiac rehabilitation.

6.2.3. Uptake and participation

The participation was influenced by the provider, patient's choice, accountability, accessibility, improved health and protection/security. The patients' likelihood to participate in CR and undertake exercise were influenced by the following themes; improve health, feel better, enjoy being active, self motivation, companionship, setting/surroundings, habit and get back to previous activities. Though a great number of people suffer from cardiac events, only few survivors are offered comprehensive cardiac rehabilitation (Dalal *et al*. 2004). A significant number of that minority of patients who attend CR fail to complete it

(Turner *et al*. 2002). More research is needed to minimize these limitation and to establish more convenient alternate programmes.

6.3. Conclusions

Erectile dysfunction has strong associations with arterial stiffness and is a marker of cardiovascular disease. Regular exercise can reduce the cardiac work required for sexual activity and improve erectile dysfunction. Further medical therapy and invasive interventions are also available. Cardiac rehabilitation is an effective exercise-based programme for the reduction of cardiovascular risk. Restoring sexual function is also an important goal of cardiac rehabilitation. However, the effects of cardiac rehabilitation on sexual functions are infrequently studied in the UK. The improvement in the exercise capacity and its relationship with arterial stiffness and erectile functions need to be studied to establish effective treatment options.

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CHAPTER 7. CHANGES IN ERECTILE DYSFUNCTION AND ARTERIAL STIFFNESS FOLLOWING CARDIAC REHABILITATION

Abstract

Background: Modern cardiac rehabilitation (CR) programmes provide comprehensive care for patients with CVD. Resuming sexual function is one of its goals yet is often omitted. This study establishes the effects of CR on erectile dysfunction (ED) and arterial stiffness. **Methods**: 157 men with CVD, undergoing phase III CR participated and 61 of them completed all phases of the study. Before and after CR, they were assessed for arterial stiffness using carotid-radial applanation tonometry and completed four questionnaires: (i) a full medical history including erectile function details, (ii) the 5-item international index of erectile function questionnaire (IIEF-5), (iii) the erectile dysfunction related quality of life questionnaire (ED-EQOL), (iv) the erection hardness scale (EHS). **Results**: 63% of the participants had ED based on their IIEF- 5 scores. There was significant improvement in arterial stiffness following CR ($p<0.05$). Those who had mild erectile dysfunction before CR had a significant improvement in IIEF score ($p<0.05$) and those who had moderate to severe ED showed no significant change ($p>0.05$). There was no significant improvement on EHS and ED-QoL following CR ($p>0.05$). Those participants, who were treated medically for ED, had significant improvement in IIEF, erection hardness score and ED-QOL ($p<0.05$) **Conclusion**: CR programmes are effective in improving cardiovascular risk by reducing arterial stiffness. In general, the CR programmes do not improve erectile function to a clinically satisfactory level unless the condition is treated medically. Specific attention and motivation is needed for patients with ED in CR to utilize the available treatment options.

7.1. Introduction

7.1.1. Pathology of erectile dysfunction

Endothelial dysfunction is the central etiologic factor for systemic and peripheral cardiac disease (Billups 2005). It is defined as a functional deterioration of endothelium characterized by vasospasm, vasoconstriction, alteration in coagulation mechanisms and fibrinolysis and increased vascular proliferation (Kaya *et al*. 2006). These are considered to be due to the reduced NO release in the vascular system. It has been found that endothelial dysfunction precedes the development of atherosclerotic lesions. The small vessels of the penis are very sensitive to functional and structural changes (Kaya *et al*. 2006) and they are more susceptible to atherosclerotic occlusion than the larger vessels of the heart and limbs (Kirby *et al*. 2001). So the ED is now considered as a marker of cardiovascular diseases and the arterial stiffness plays a major role in the development of ED and cardiovascular disease.

7.1.2. Management of ED and cardiac rehabilitation

The second Princeton Consensus (Jackson 2006) divides patients with ED according to their cardiac condition as low risk, high risk and intermediate risk. The intermediate and low risk patients may safely engage in sex with or without treatment. The high-risk patients should be treated and their cardiovascular system should be stabilized before the resumption of sexual activity. Treatment for ED also recommended for them. Various treatment techniques are available for ED. Among them, the PDE-5 inhibitors are widely used and successful in treating the vascular ED.

Modern cardiac rehabilitation (CR) programmes are recognized as integral to the comprehensive care of patients with cardiovascular disease. The programmes aim to resume the best possible physical, mental and social function of cardiac patients. Resuming the sexual function is also one of the goals of CR. However, it is often omitted. The current study has been carried out to see the effects of cardiac rehabilitation exclusively on sexual function and sex related quality of life in relation to arterial stiffness.

7.1.3. Research Hypotheses

H1 – There will be significant improvement in erectile function and arterial stiffness following phase III cardiac rehabilitation in participants with erectile dysfunction

H2 – There will be a significant improvement in erectile function related quality of life (ED-QOL) following phase III cardiac rehabilitation in participants with erectile dysfunction

7.2. Methods

7.2.1. Recruitment of subjects

Following national ethics committee's approval, all the cardiac rehabilitation programmes in the list available from British Heart Foundation, were contacted through telephone and emails. Meetings were arranged with interested cardiac rehabilitation teams and 16 programmes offered to be involved. The project was approved by their research and development departments once all the requirements were fulfilled.

7.2.2. Subjects

The study involved 157 participants undergoing phase III cardiac rehabilitation who had at least one of the following conditions: myocardial infarction (MI), transient ischemic attack, attended rapid chest pain clinic, angina or a positive diagnosis for cardiovascular disease (e.g. cardiac failure). The predominant condition was MI, which presented in 78% of the participants. Individuals were excluded from the study if they had conditions affecting the brain, spinal cord, or pelvic nerves (e.g. multiple sclerosis, multi system atrophy, spinal cord injury and tumours), conditions affecting the cauda equine such as prolapsed intervertebral disc or tumours), disease to the asympathetic nerves within the pelvis that affecting the functions of prostate, seminal vesicle, external genitalia and blood vessels of pelvic organs received extensive surgery to the pelvis or abdomen chronic renal failure, hyperprolactinaemia, hypergonadism and hypogonadism.

7.2.3. Study Design

The study involved both the two stage (pre and post) CR longitudinal design and a cross sectional correlational analysis of measures at each stage.

7.2.4. Organizational procedure

Each participant was contacted on the pre-assessment day before starting the phase III cardiac rehabilitation. Participants were given a coded invitation pack that contained an invitation letter from the cardiac rehabilitation programme, a invitation letter from Buckinghamshire New University, a patient information sheet, three informed consent forms, a leaflet providing information on Medical

Research & Governance, a patient education booklet ‘Sex and the heart’ from Pfizer Ltd and four questionnaires: erectile dysfunction details; International Index of erectile function – 5 (IIEF-5); Erectile dysfunction related effects on quality of life (ED-EQOL); erection hardness scale (EHS) and a prepaid envelope. The questionnaires were completed privately by self-administration and returned to the Research Centre at Buckinghamshire New University. The participants were measured for arterial stiffness using a SphygmoCor as detailed below. The participants were reassessed on the post assessment day after completing cardiac rehabilitation and measured for arterial stiffness. They were given a pack of three questionnaires IIEF-5, ED-EQOL, EHS and following completion they were returned in a prepaid envelope.

7.2.4.1. Questionnaires

7.2.4.1.1. International index of erectile function – 5

IIEF has been adopted as the ‘gold standard’ treatment outcome measure for clinical trials in ED, regardless of the type of treatment intervention or study population under investigation. Since its introduction in 1997, more than 50 clinical trials have been conducted using this instrument with a broad range of treatment agents. It is approved by national institute of health (Rosen *et al*., 2002). The IIEF-5 questionnaire is an abbreviated form of the original IIEF. Four items were selected from the erectile domain portion of the IIEF-15 plus the item addressing sexual satisfaction (Hodges *et al*. 2007). The IIEF-5 fulfils the need for a simple patient administered diagnostic tool of ED for easy use in clinical settings. It could aid in decreasing the incorrect diagnosis of ED and

decreasing the number of undiagnosed cases worldwide. It provides accurate and reliable information as a quantitative index of ED severity. Many studies have used this short version of IIEF and reported that sensitivity and specificity of the questionnaire were high (Rosen *et al*. 1999). It consists of five questions and in each of them, patients make a self evaluation on a scale ranging from zero to five points. The sum of the scores of each question in the IIEF-5 was calculated and the degree of erectile dysfunction was derived as complete (≤ 4), severe (5-7), moderate (8-11), mild to moderate (12-16) mild (17-21) or none (22-25).

7.2.4.1.2. Erectile dysfunction related effects on quality of life (ED-QOL)

The ED-EQOL questionnaire is a robust instrument measuring the impact of ED on quality of life (QoL). It is simple to use and fulfils the usual psychometric properties of reliability, validity and responsiveness (MacDonagh *et al*. 2004).

The latest version ED-EQOL has 15 questions and each question has five possible responses scored from 0 to 4. The sum of the scores was calculated from the 15 questions. A score of less than 15 was considered that the individuals' QoL was not or only mildly affected by ED. A score of 15 to 29 indicated that QoL was moderately affected and a score of above 30 was considered that the individual is severely affected.

7.2.4.1.3. Erection hardness score

Erection hardness score (EHS) is a single item scale and a patient-reported outcome for scoring erection hardness on a scale ranging from one to four. EHS

demonstrates a high reliability and is highly responsive to treatment (Mulhall *et al*. 2007). It shows a close correspondence with the erectile function (IIEF) and ED related psychosocial factors in men (Cappelleri *et al*. 2009). The relationship between EHS and other erectile function questionnaires are strong and it is recommended for clinical practice (Goldstein *et al*. 2008).

The participants, who reported that they had used specific medicines for ED, were asked to complete two sets of the questionnaires according to their experience with and without the medications.

7.2.4.2. Arterial stiffness using SphygmoCor

The procedures for measuring arterial stiffness are given in detail in Chapter 3.2.2.

7.2.5. Statistical analysis

Statistical analysis was undertaken using the statistical software, SPSS for windows (version 14.0). Paired-samples t test was used to compare the results pre and post cardiac rehabilitation. The Pearson correlation test was used to find the relationship between erectile function scores and the SphygmoCor measurements. The scores and age were recorded to find the prevalence and severity of ED and the changes in the variables following CR in different sub groups.

7.3. Results

In total, all the male patients who were attending the cardiac rehabilitation programmes in 16 various hospitals were invited to participate in the study regardless of their sexual function. In total, 157 patients volunteered to participate in the study. Among them 130 participants underwent baseline SphygmoCor measurements and 61 completed post intervention measurements. Initially 114 participants filled the baseline questionnaires and nearly half of them completed post intervention questionnaires (Table 7.3). The participants' physical characteristics were as follows (Mean ± SD): age- 60.8 ± 11.0 years, height- 174.1 ± 7.5 cm, weight 84.8 ± 15.5 kg and body mass index- 27.9 ± 0.5. There were 9.5% current smokers and 14.6% ex-smokers. Fifty one percent of them were alcohol drinkers and >90% of them were within the recommended limit for a normal adult. The participants' cardiovascular comorbidities are listed in Table.7.1. About 40% of participants had more than one comorbid medical conditions, cardiovascular procedures or surgeries.

Table 7.1 Comorbid cardiovascular conditions of the participants

Comorbid conditions	% in total participants (n= 105)	% in participants with ED (n= 66)
Diabetic	13.5	20.7
Angioplasty	39	44.8
CABG	28.4	34.5
Stent	41.9	44.8
Thrombolysis	6.8	13.8
Symtomatic Angina	29.7	41.4
PVD	0	0

(CABG- Coronary artery bypass surgery, PVD- Peripheral vascular disease)

The medications administered to the participants with cardiac diseases are listed in Table 7.2. Beta blockers and ACE inhibitors were administered to a high number of participants. This could be a definite cause for the high number of ED prevalence in the study group.

Table 7.2 Drug administration in the participants

Drugs	% in total subjects (n=105)	% in Subjects with ED (n=66)
Aspirin	93.1	67.4
Beta Blockers	77.8	86.2
ACE Inhibitors	65.3	65.5
Calcium Channel Blockers	18.1	17.2
Alpha Blockers	1.4	0
Angiotension Receptor Antagonist	6.9	10.3
Diuretics	8.3	6.9
Nitrates	12.5	10.3
Potassium Channel Blockers	2.8	6.9
Chlestrol Lowering agents	90.3	93.1
PDE Inhibitors	4.2	6.9

7.3.1. Erectile dysfunction

Sixty three percent of the participants who were undergoing cardiac rehabilitation had ED based on their IIEF- 5 scores. They were divided in to five categories according to the severity of ED as complete (≤ 4), severe (5-7), moderate (8-11), mild to moderate (12-16) mild (17-21) or none (22-25) (Fig 7.1).

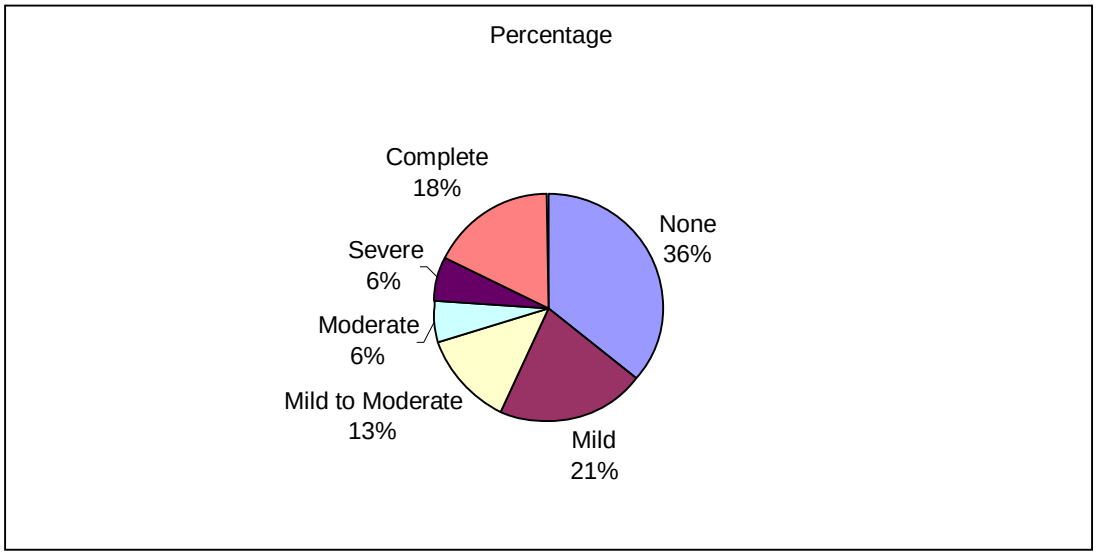

Figure 7.1 Severity of erectile dysfunction in the participants

The duration of ED varied from one month to 20 years with a mean of 3.6 years. There was a strong positive correlation between ED duration and the severity of ED ($p<0.05$).

Age had a strong positive correlation with the IIEF scores ($P<0.01$). Age also had a strong positive correlation with the severity of ED ($p<0.01$) and the participants above 70 years had an increased prevalence of ED and it was twice as severe as the other age groups.

7.3.1.1. International Index of Erectile dysfunction 5

In general, there was no significant change between the baseline measures (pre CR) and the final measure (post CR) for any of the domains of the IIEF scores in all the patients with ED (Table 7.3). Those who had mild erectile dysfunction before CR had a statistically significant improvement in IIEF score (19.43 ± 1.28 to 20.93 ± 1.33 $p<0.05$). However, this improvement did not

change the category of their ED severity. There was no significant change in IIEF-5 scores in participants who had mild to moderate, moderate or severe ED.

Table 7.3 Changes in erectile function questionnaires following CR

Questionnaires	Pre CR ± SD	Post CR ± SD	Significance
IIEF-5 Score (n=61)	14.83 ± 8.47	15.23 ± 9.1	Non-significant
ED-QOL Score (n=34)	15.93 ± 17.58	13.93 ±16.33	Non-significant
EH Score1 (n=59)	2.65 ± 1.14	2.72 ±1.28	Non-significant

7.3.1.2. Erectile function related effects on Quality of Life

Among the participants who had ED, 48.6% were considered as they were mildly or not affected in their erectile dysfunction related quality of life (ED-QoL score <15). There were 25.7% of moderately affected (ED-QoL score 15 to 30) and 22.9 % severely affected participants (ED-QoL score >30). The improvement in the ED-QoL following CR was not statistically significant. There was no significant correlation between ED-Qol score, IIEF score, IIEF score based severity of ED and age ($p>0.05$)

7.3.1.3. Erection Hardness Score

Though there was a mild improvement in the participants in EHS score, it was not statistically significant. However there was a strong positive correlation between IIEF and EHS scores at baseline (pre CR) as well as post CR ($p<0.001$).

7.3.2. Medication for ED in CR

7.3.2.1. PDE-5 Inhibitors

There were only four participants who used sildenafil citrate during the CR and there was a statistically significant change in erectile function. They could achieve normal erectile function (IIEF score >21, EHS score ≥ 3) every time they used sildenafil citrate.

7.3.3. Pulse wave reflections

Over half of the arterial stiffness measures were reduced following CR with all others showing a non-significant change (Table 7.4 and fig 7.3). There was a significant reduction in peripheral and aortic systolic pressure. Though there was no significant change in diastolic pressure and mean arterial pressure, there was a significant reduction in aortic pulse pressure. The augmentation pressure was significantly reduced after CR as was the augmentation index and augmentation index at 75%. The pulse wave velocity was significantly reduced. There was no significant change in subendocardial viability ratio, ejection duration and heart rate. The changes in the pulse wave reflections were visible in the shape of pulse wave following CR. A sample from a participants pre and post intervention pulse wave shapes are illustrated in Fig 7.4. The peak of late systolic peak and the augmentation pressure were markedly reduced. There was a significant negative correlation between IIEF scores and pulse wave velocity and pulse pressure (Table 7.5). There was also a negative correlation between erection hardness scores and pulse wave velocity.

Table 7.4 The pulse wave analysis results following CR

Variables	All participants (n=61)			Participants with ED (n=25)		
	Pre CR	Post CR	Significance	Pre CR	Post CR	Significance
Pulse wave velocity (m/s)	7.32 ± 1.40	6.35 ± 0.96	*	7.56 ±1.37	6.69 ±1.26	*
Augmentation pressure (mmHg)	6.81 ± 5.24	3.22 ± 6.38	*	7.92 ±5.04	6.28 ±5.22	NS
Augmentation Index	24.64 ± 12.00	13.33 ± 20.23	*	22.36 ±11.38	18.96 ±14.67	NS
Augmentation Index@75	19.56 ± 10.78	9.22 ± 20.50	*	16.46 ±8.77	16.58 ±12.59	NS
Aortic pulse pressure (mmHg)	34.47 ± 9.50	29.03 ± 7.81	*	33.36 ±9.10	28.76 ±7.86	*
Aortic systolic pressure (mmHg)	116.00 ± 11.38	111.44 ± 8.78	*	114.36 ±10.46	111.28 ±8.45	*
Aortic diastolic pressure (mmHg)	81.58 ± 6.29	82.36 ± 3.17	NS	80.96 ±4.43	82.40 ±1.83	*
Mean arterial pressure (mmHg)	95.89 ± 8.29	94.89 ± 5.33	NS	94.32 ±6.07	95.76 ±4.65	NS
Ejection Duration (ms)	33.25 ± 3.61	33.56 ± 3.42	NS	32.48 ±3.54	35.16 ±3.72	*
Subendocardial viability ratio	174.14 ± 30.59	177.17 ± 27.72	NS	179.48 ±28.61	165.64 ±28.20	*
Systolic pressure (mmHg)	125.44 ± 11.42	122.83 ± 9.62	*	123.60 ±10.42	121.80 ±7.32	NS
Diastolic pressure (mmHg)	80.78 ± 6.23	81.44 ± 3.14	NS	80.44 ±4.41	81.04 ±1.51	NS
Heart rate	64.25 ± 10.26	66.78 ± 9.01	NS	63.52 ±10.26	71.16 ±10.79	*

*Statistically significant at p< 0.05 level, NS – Not significant

7.5 Correlations between erectitile dysfunction scores and arterial stiffness variables

Variables	IIEF-5 Score	ED-QOL Score	EH Score
Pulse wave velocity	-.443*	-.026	-.212*
Augmentation pressure	-.101	.235	-.074
Augmentation index	-.051	.140	.013
Augmentation index @75%HR	-.010	.009	.086
Aortic pulse pressure	-.282*	.398	-.231
Aortic systolic pressure	-.077	.276	-.151
Aortic diastolic pressure	.175	-.256	.122
Aortic Mean Pressure	.094	.088	.015
Ejection Duration pre	.017	-.053	.039
Subendocardial Viability Ratio	.030	.143	-.014
Systolic pressure	-.087	.040	-.151
Diastolic pressure	.137	-.258	.075
Heart rate	-.038	-.188	-.045

n=105 *Statistically significant at p< 0.05 level, NS – Not significant

IIEF- International index of Erectile Function, ED-QOL- Erectile Dysfunction related Quality of Life, EH- Erection Hardness

7.3.4. Duration of CR

There was no significant difference in erectile function scores and pulse wave reflections between the CR programmes which ran for six weeks or 12 weeks (p>0.05).

7.4. Discussion

Among the 16 CR programmes, which agreed to participate in the study, three hospitals were regularly visited by the investigator to measure arterial stiffness and conduct the questionnaires. Four programmes only actively participated in the use of questionnaires. Other programmes had not delivered any questionnaires due to lack of staff. This is one of the major factors, which

affected the number of participants in the study. All the patients who were attending CR were invited for the study, yet 65% of the patients refused to participate in the study. Various reasons were acknowledged for this refusal or withdrawal of consent to participate in the study. They were shyness, age, associated diseases, inactive sexual life, no partners and partners' disagreement to involvement in the study. These factors also influenced the 60% withdrawal of consent to participate in the study. In addition, many of them reported to their cardiac rehabilitation nurse that the questionnaires were too invasive.

The prevalence of ED in cardiac patients who were attending CR was >50% (64%) in the current study which agrees with the previous studies on cardiac patients [54% in Maroto-motero *et al* (2008), 66% in Hodges *et al*, (2007)]. The participants were from different CR programmes, and the total number of exercise sessions varied in those programmes from six to 12 and the duration of CR varied from six to 12 weeks. Some of the programmes run the exercise sessions twice a week and others once a week. However, findings of this study showed that there was no difference between these alternative programme lengths.

Smoking has been shown to be a strong risk in causing ED. There was no significant correlation between severity of ED and smoking history in the current study. This may be due to the large number of missing values in the recorded smoking history. Drinking alcohol also had no correlation with the ED. It may be because of the alcohol consumption of more than 90% of participants who were consuming alcohol were within the limit recommended for an adult during the

CR. However, the recommendations for alcohol limit vary with the severity and the combination of the diseases. The previous history of the participants' alcohol intake was not completely known. The high use of drugs such as beta-blockers and ACE inhibitors must also have a positive influence in the prevalence ED in cardiac patients (Maroto-Montero *et al*. 2008).

7.4.1. Pulse wave reflections

The major original finding of this study is that cardiac rehabilitation improves arterial stiffness.

7.4.1.1. Pulse wave velocity (PWV)

The brachial artery PWV was significantly improved following cardiac rehabilitation in this study. PWV has been identified for its extensive prognostic significance (Baulmann *et al*. 2006). This improvement may be due to the decreased left ventricular afterload and hypertrophy, an increased subendocardial perfusion and an improvement in the mechanical stress of the larger arteries (Mustata *et al*. 2004). The strong positive correlation between PWV and augmentation pressures assures the reduction of arterial stiffness in patients undergoing CR. Three of the participants' PWV were increased post CR and one of them had coronary artery bypass graft and continued with CR. The increase in PWV may be due to the other risk factors such as life style and associated cardiac risk factors, which were not studied.

7.4.1.2. Augmentation Index (AIx)

The AIx was markedly reduced at the end of the CR. Mahmed *et al* (2001) suggest that the reduction may be due to the delaying of the wave reflections by decreasing pulse wave velocity, shorter left ventricular ejection duration or reducing the intensity of pulse wave reflection. The results from the current study are similar to their findings. However, their study did not measure the pulse wave velocity. The pulse wave intensity was reduced which is visible in the pulse waveforms and the reduction in the ejection duration was not significant. AIx also depends on other variables such as heart rate and the vasomotor tone of the arterial system, which can result in considerable variability and thus may limit its use as a surrogate measure of arterial stiffness (Wang *et al*. 2008). However, the strong correlation of the AIx with the pulse wave velocity in this study suggests that AIx can be an individual marker for arterial stiffness.

The improvement in the arterial stiffness and blood pressures correlates with the findings of Mustata *et al* (2004) who speculated that the improvement might be due to the effects of exercise training on the improvement of endothelial and smooth muscle function. The exercise training in CR is likely to have improved the exercise tolerance and VO_2 of the patients. Aortic stiffness is inversly related to VO_2 and exercise tolerance in cardiac patients suggesting that it is an independent predictor for them. The less compliant aorta influences the function of the left ventricular systolic energetics and mechanics. It also affects the left ventricular relaxation and filling pattern. These result in the impairment of the normal increase in cardiac output in response to exercise (Bonapace *et al*.

2003; Enko *et al*. 2008). Peripheral vascular abnormality may also be responsible for low VO_2 as flow-dependant, endothelial mediated vasodilatation is important for the skeletal blood flow, which defines exercise capacity (Enko *et al*. 2008). Therefore, the reduction in the arterial stiffness suggests that CR improves vascular endothelial function and aortic compliance and thus the exercise capacity.

7.4.1.3. Pulse Pressure (PP)

The faster the blood pressure changes within the artery, the lower the wall distensibility. Increased pulse pressure is one of the principal arterial alterations that results from arterial stiffness in coronary artery diseases. PP has been identified as an independent marker for cardiac events and mortality. Pulse pressure is modified predominantly by two mechanisms: (i) ventricular ejection intersecting with viscoelastic properties of the arterial bed and (ii) pressure wave deflections. The increase of both stroke volume and arterial stiffness led to an increase in PP (Papaioannou *et al*. 2004). The distensibility of arteries changes with age. In people <50 years of age, diastolic pressure is a strong predictor of coronary heart disease. In the transition period of 50-59 years, systolic, diastolic and pulse pressure are similar predictors of cardiovascular risk. Above 60 years, diastolic pressure is negatively related to the risk of coronary artery events and therefore, the pulse pressure is a better predictor than systolic pressure (Willum-Hansen *et al*. 2006). In the current study, diastolic pressure did not change significantly and there was a significant reduction in PP in all age groups. This means that the CR programmes are

effective in improving the arterial function. It is notable that it was reduction in systolic pressure after CR which helped in the reduction the pulse pressure.

7.4.1.4. Aortic blood pressure

Aortic blood pressures are most physiologically relevant to ventricular-vascular coupling. Systolic pressure at the ascending aorta is the pressure that the left ventricle has to confront and thus it is related to cardiac energy consumption and load. Central diastolic pressure determines the coronary blood flow. Increased systolic pressure, low diastolic pressure and wider pulse pressure are the common clinical findings in cardiovascular risk patients. There was a higher baseline systolic pressure than normal in the participants. The reduction in the aortic systolic pressure has a significant effect on reducing the pulse pressure. Generally, the current study participants had no abnormal mean diastolic pressure at baseline and this was maintained at the end of CR.

7.4.2. Erectile function

Fifty two percent of the participants with ED in the current study experienced ED after the cardiac event. Forty-eight percent participants experienced ED before the cardiac events, which ranged from a month to 10 years. Eighteen percent of the participants had not identified their erectile dysfunction, yet they were falling in the mild ED category. These results clearly show that ED is a strong comorbid condition and a marker of coronary artery disease.

7.4.2.1. International index of erectile dysfunction- 5

IIEF is a specific, treatment oriented and a well-documented diagnostic as well as prognostic tool. The five domains of IIEF are erectile function, orgasmic function, intercourse satisfaction and overall satisfaction. In this study, the subjects who had no erectile dysfunction before the cardiac rehabilitation had no significant change in their erectile function after CR. The CR might have helped them to maintain their erectile function for a longer period, but this was not studied and requires further research. In general, the participants with moderate to complete ED had no improvement in their erectile function following CR. No domains in IIEF-5 had changed following a six week or 12 week CR programme.

Interestingly, the subjects who had mild erectile dysfunction had an appreciable benefit from cardiac rehabilitation. The participants who had their IIEF-5 scores between 17-21 had a significant improvement in their erectile function. Their confidence on gaining an erection, i.e. one of the domains of IIEF, was improved significantly. This shows that CR improves the psychological wellbeing of the participants. However, the improvement was not clinically significant as they were not able to complete full sexual activity.

7.4.2.2. Effects on erectile dysfunction related quality of Life (ED-QOL)

The Ed-QOL shows a large number of participants who had ED were affected moderately (Score 30-50) or severely (Score >50) in their erectile dysfunction related quality of life (>50) irrespective of their IIEF scores and age. It is clear that the influence of erectile dysfunction on the quality of life varies between

individuals irrespective of the severity of their erectile dysfunction. It suggests that every individual with ED should be considered equally and carefully for the treatment options. ED should not be considered as just an epiphenomenon of age or underlying cardiovascular disease. It requires more attention and evaluation (Schwarz and Rodriguez 2005).

7.4.2.3. Erection hardness score (EHS)

Though there was a mild improvement in mean value of EHS score it was not statistically significant. The study findings show a direct relationship between IIEF and EHS scores. The positive correlation between the IIEF scores and EHS scores at the baseline (pre CR) as well as at the end of CR shows that EHS can be an effective assessment tool to measure erectile dysfunction quickly. As a single item scale, it is easy to complete, specific to understand and has a highly relevant outcome. It can be used as a proxy assessment for other detailed assessment tools (Goldstein *et al*. 2008).

There are the possibilities of a few major limitations in these questionnaires: (i) in spite of using the shortened versions, respondents are burdened with multiple detailed queries on sensitive topic, (ii) the items omitted in the questionnaires resulted in a difficult calculation of the total score and (iii) participants' misinterpretations of the lengthy questions (McKinlay 2000).

7.4.3. Erectile function and arterial stiffness

In this study, erectile function was not improved significantly in association with the improvement in arterial stiffness. Penile arteries are relatively small, with the

average cavernosal artery being 0.5 mm in diameter. The helican arteries, which run between the cavernosal artery and the sinusoids, are much smaller. These smaller arteries need to dilate up to 80% to provide the blood flow necessary to produce enough venous compression to sustain an erection (Carson *et al*. 2008). The findings of the study suggest that the improvement in the major arterial stiffness is not sufficient to produce a significant influence in the smaller arteries. It is also important to consider the negative effects of drugs such as beta-blockers and ACE inhibitors. It is possible that the improvement in the physical function following CR is not sufficient to overcome the effects of these drugs on erectile function. It is also not clear what is the required amount of improvement in carotid-radial pulse wave velocity to produce a relatively satisfactory level of improvement in penile arteries and erectile function.

7.4.4. Effects of specific treatment for ED

There were two participants already consuming PDE-5 inhibitors before joining the phase III CR. During the CR, among the participants who showed interest to know about the treatment options for ED, only six participants followed up with their consultants. Two of them agreed to take oral PDE-5 inhibitors and they were prescribed flexible doses of sildenafil citrate. However, none of the other participants was interested to take any further specific treatment of ED. This may be due to several reasons such as advanced age, organic and psychological diseases, problems in the relationships, lack of information and the fear of complications (Maroto-Montero *et al*. 2008).

Sildenafil accounted for a successful erection and hardness every time after consumption for the four participants. These stimulated erections lasted long enough for successful sexual intercourse. Their improvement in arterial stiffness was not significantly different from the improvement of the other participants who did not use a PDE-5 inhibitor. Though the number of consumers is small, the results could be supported by previous studies. Sildenafil increases cGMP levels in coronary vascular smooth muscles, enhancing the effects of NO and increasing coronary blood flow at rest and exercise. This may be due to the dilatation of coronary resistance vessels which results in increased blood flow in the ischemic blood supply. The current findings confirm that PDE-5 inhibitors do not worsen the ischaemia. The PDE-5 inhibitors are likely to improve anginal threshold and the exercise threshold after use. After consuming sildenafil, the workload achieved could be up to 8-METs, which is considerably greater than the energy expended during even vigorous sexual activity, i.e. five to six METs (Fox *et al*. 2003). However, the participants reported that there was no significant change in erectile function in those participants when the medicine was not consumed.

It was very clear that most of the participants in the current study were very apprehensive about re-engaging in sexual activity and seeking treatment of ED after experiencing a cardiac event. This may be due to the development of lack of concern about sexual life with age (Lowy *et al*. 2007). It may also be due to the fear of the risk of cardiac event during sexual activity. The incidence rate of death or infarction in cardiac patients during sexual intercourse is negligible i.e. one in million (Muller *et al*. 1996). The second Princeton Consensus (Jackson 2006) divides patients with ED as high risk, low risk and intermediate risk

according to their level of risks. The low risk category are asymptomatic, with less than three cardiovascular risk factors, controlled hypertension, mild, stable angina pectoris, post revascularization, post myocardial infarction (MI) (≥6 to 8 weeks), mild vascular disease, left ventricular dysfunction class I (NYHA). These patients can be safely encouraged to resume sexual activity. If required, the safe treatment options should be discussed and encouraged.

7.4.5. Limitations

Larger studies with a greater number of patients would be statistically more powerful. The long-term effects of the cardiac rehabilitation on arterial stiffness also need to be studied. The exercise tolerance level was not measured in the participants either at baseline or at post CR. A treadmill exercise test has been established as a reliable tool for determining the tolerance of sexual activity in MI.

The relationship between the changes in exercise tolerance levels, erectile function and arterial stiffness would have been a valuable finding, but it was not possible to arrange an exercise test with these participants.

The duration of CR was not similar for all the participants. Though there was no significant difference on the effects, previous studies suggest a longer duration of exercise programmes is necessary to cause substantial effects (Mustata *et al*. 2004).

The study was not designed to identify specifically how many participants really would have specifically wished to improve their sexual function and whether personal and social factors had influenced their sexual activity.

To secure the maximum validity of the data, the same equipment were used by a single operator for all the participants throughout the study. Although the transfer function has been validated, the accuracy of central aortic PP obtained with the SphygmoCor has been widely debated. The debate focused mainly on the validity of the transfer function but ignored a second possible source of error in the prescribed SphygmoCor procedure: calibration of the RA wave with brachial instead of radial blood pressure values (Verbeke *et al*. 2005).

7.5. Conclusions

The incidence of erectile dysfunction is very high and is also an early sign in patients with cardiac diseases. Both the patients and clinical care providers should give more attention to this serious problem. In general the CR programmes do not improve the erectile function to a clinically satisfactory level unless the condition is treated with specific treatment options. The CR programmes are effective in improving cardiovascular risk by reducing arterial stiffness. The improvement in arterial stiffness is not enough to produce a satisfactory erectile function. It is understood that the complex treatment of cardiac rehabilitation improves larger artery mechanism but not the smaller cavernosal arteries. Specific attention and motivation is needed for patients with ED in CR to utilize the available treatment options when not contraindicated. Larger, more controlled and stratified groups should be studied further to authenticate these findings.

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CHAPTER 8. METABOLIC SYNDROME – A LITERATURE REVIEW

Abstract

Incidence: Metabolic syndrome is a cluster of various cardiovascular risk factors such as obesity, dyslipidaemia, hyperinsulinemia and high blood pressure. Various definitions have been developed specific to ethnicity and countries. The prevalence of metabolic syndrome has been increasing all over the world. Women and the elderly are more prone to developing metabolic syndrome. The primary cause of metabolic syndrome varies due to different epidemiological factors such as nutrient levels, ethnicity, genetic and socioeconomic status etc. Physiologically, excessive fat is the primary cause of metabolic syndrome that contributes to other components such as dyslipidaemia, hyperinsulinemia and high blood pressure. Sedentary lifestyle and low cardiorespiratory fitness are largely associated with the prevalence of metabolic syndrome. **Management**: There is no specific treatment protocol available. Treating individual components of metabolic syndrome has been established as an effective strategy. A change in lifestyle with regular physical activities and a healthy diet is recommended. **Conclusion**: The prevalence of metabolic syndrome is continuously escalating worldwide. Early identification of metabolic syndrome could help to reduce the risks of cardiovascular disease. Lifestyle change is the key factor for the prevention and management of metabolic syndrome. Specific modes of treatment with more emphasis on healthy lifestyle and health education need to be established to improve the outcome.

8.1. Introduction

8.1.1. Development of definitions

Cardiovascular disease (CVD) is the main cause of mortality and morbidity throughout the world. Several risk factors for CVD have been identified. In recent decades, it is developing into a trend of studying the clustering of cardiovascular risks. Camus (1966) was the first one to introduce 'trisyndrome metabolique' which is a combination of gout, diabetes and dyslipidaemia. Later, the Framingham study (Kannel and McGee 1979) discussed the possibilities of the associations among diabetes, dyslipidaemia, hypertension and obesity. Orchard *et al* (1983) discussed the associations of hyperinsulinemia and blood lipids as an atherogenic risk. Modan *et al* (1985) found the link between hypertension, obesity and hyperinsulinemia. Stern and Haffner (1986) discussed the associations between the pattern of body fat distribution and hyperinsulinemia as the causes of diabetes. Later, Reaven (1988) noted that hypertension, glucose intolerance and altered lipid levels were commonly clustering together. He introduced this cluster of risk factors as 'Syndrome X' at the annual meeting of the American Diabetes Association (1988). Ten years later he restructured the definition including more factors such as altered haemodynamics, haemostatics and uric acid metabolism (Reaven 1999). In the mid-1990s it was termed as insulin resistance syndrome (DeFronzo and Ferrannini 1991). In that time, insulin resistance was considered as a major cause of metabolic syndrome until many epidemiological studies established that insulin resistance was not the sole cause of the condition (Saylor 2005).

The World Health Organisation (WHO) introduced the term 'metabolic syndrome' (1999) which is widely used internationally and a definition was derived by a WHO consultation (WHO 1999). The criteria are the presence of diabetes mellitus or glucose intolerance with any two of the other factors: obesity, high blood pressure, dyslipidaemia and microalbuminuria. The reference values for the various definitions are listed in table 8.1.

Later, the National Cholesterol Education Programme (NCEP) (2002) expert panel on detection, evaluation and treatment of high blood cholesterol in adults (Adult treatment panel III) (ATP III) introduced another definition. It gives equal weight to all the criterion factors. The National Heart, Lung and Blood Institute (NHLBI) and the American Heart Association (AHA) have released a report on criteria for diagnosing metabolic syndrome using the same ATP III's definition (Grundy 2005; Grundy *et al*. 2005b). The panels describe metabolic syndrome as the presence of any three of the following: abdominal obesity, dyslipidaemia (high levels of triglycerides, low HDL), increased blood pressure and increased fasting glucose. The ATP III criterion does not include microalbuminuria despite the strong associations with metabolic syndrome (Palaniappan *et al*. 2003).

In 2003, the American College of Clinical Endocrinologists (AACE) developed a new definition for insulin resistance syndrome which is a combination of the previous WHO and ATP III definitions (Einhorn *et al*. 2003). There was no specific number of risk factors for the diagnosis of the syndrome and it was left to clinical judgement.

The International Diabetes Federation (IDF 2006) has developed a new definition. The IDF takes central obesity as a pre-requisite for the diagnosis of metabolic syndrome in addition to any two of the following: raised triglycerides, reduced HDL cholesterol, raised blood pressure, raised fasting plasma glucose. An advantage in IDF is that it has derived ethnic specific abdominal obesity values for the criteria.

The Chinese Diabetes Society (CDS) has developed a definition for metabolic syndrome within the Chinese population as the presence of three or more of the following components: (1) BMI ≥25 kg/m^2; (2) blood pressure ≥140/90 mmHg or under antihypertensive medication; (3) serum triglyceride level ≥1.7 $mmol.L^{-1}$ or HDL-C <0.91 $mmol.L^{-1}$ in males and <1.0 $mmol.L^{-1}$ in females; (4) FBG level ≥6.1 $mmol.L^{-1}$ or under antidiabetic medication (Li *et al*. 2006).

Table 8.1 Comparison of the criteria of metabolic syndrome

Risk Factor	WHO Metabolic syndrome	NCEP ATP III Metabolic syndrome	IDF Metabolic syndrome	AACE Insulin resistance syndrome
Obesity	BMI ≥ 30 kg/m^2 and/or WHR > 0.90 in men and <0.85 in women	Waist >102 cm (>40") in men and >88 cm (>35") in women	Abdominal obesity with ethnic specific reference values	BMI ≥ 25 kg/m^2
Fasting Glucose	≥ 6.1 mmol.L^{-1} (110 mg.dL^{-1})	≥100 mg.dL^{-1}	≥100 mg.dL^{-1} or previously diagnosed type 2 diabetes	110 - 126 mg.dL^{-1}
Type II Diabetes	Included	Included but not compulsory	Included but not compulsory	Included but not compulsory
Insulin resistance	Impaired glucose tolerance (two-hour glucose levels of 140 to 199 mg.dL^{-1} [7.8 to 11.0 mmol.L^{-1}] on the 75g oral glucose tolerance test)	Not included	Not included	Type II diabetes or Postprandial glucose 140 to 200 mg.dL^{-1}
Triglycerides	≥1.7 mmol.L^{-1} (≥150 mg.dL^{-1})	≥150 mg.dL^{-1}	≥150 mg.dL^{-1}	≥150 mg.dL^{-1}
HDL Cholesterol	<35 mg.dL^{-1} (<0.9 mmol.L^{-1}) in men and <39 mg.dL^{-1} (>1.0 mmol.L^{-1}) in women	<40 mg.dL^{-1} (1.04 mmol.L^{-1}) in men and <50 (1.29 mmol.L^{-1}) mg.dL^{-1} in women	<40 mg.dL^{-1} in males and <50 mg.dL^{-1} in females	<40 mg.dL^{-1} in males and <50 mg.dL^{-1} in females
Microalbuminuria	Urine albumin excretion rate >20 µg/min or albumin-to-creatinine ratio ≥ 30 mg.g^{-1}	Not used	Not used	Not used
High blood pressure	≥140/90 mmHg or antihypertensive medicine	≥130/≥85 mmHg	≥130/≥85 mmHg	≥130/≥85 mmHg,
Others	None	None	None	Family history of type II diabetes, hypertension or CVD, polycystic ovarian syndrome, sedentary lifestyle, advancing age, ethnic groups of having high risk for type II diabetes or CVD

WHO- World Health Organization; NCEP ATP III- National Cholesterols Education Programme Adult treatment Panel III; IDF- International Diabetes Federation; AACE- American Association of Clinical Endocrinologists.

8.1.2. Controversies among definitions

The prevalence of metabolic syndrome varies with the definitions used for diagnosis. Reinehr *et al* (2007) compared eight different criteria for metabolic syndrome and found a huge variation of prevalence from 2% to 39%. There are many controversies and questions developed from these ambiguous definitions (Benedict 2006; Kahn *et al*. 2005; Saylor 2005). The WHO definition is not clear about the inclusion of raised blood pressure when it is controlled by interventions. Moreover, there are extra laboratory tests for glucose tolerance and urine albumin-creatinine. It is also not clear that both systolic and diastolic pressures must be high or either one of them. WHO also considers body mass index as a tool for obesity, yet body mass index cannot provide a valid information on visceral obesity (Després 2006).

There has been no justification why every new definition should include or exclude specific factors from the previous criteria. The current definitions have only outlined the values of individual risk factors just to identify their presence. However, highly altered values can lead to severe cardiac risk. As diabetes is already well known for its cardiovascular risk, it is questionable to include it in metabolic syndrome. The other lipids, low-density lipoproteins and total cholesterol are not included in the criteria though they are also important cardiovascular risks. Many other risk factors such as age, family history and lifestyle factors are not included in these definitions. The presence of more than the minimal number of criterion factors could be a higher CVD risk. This is not clear in any of the definitions. Solymoss *et al* (2004) divided 1108 patients with symptoms of coronary artery disease into six groups and scored them

according to the number of metabolic syndrome risk factors present, based on ATP III criteria. The metabolic syndrome score was significantly related to the severity of atherogenic changes in the angiogram. There is a need for a clear modified definition to clarify these disputes. Nevertheless, identification of metabolic syndrome using any definitions helps to warn of the risk of CVD. Huang *et al* (2008) found a weak association between metabolic syndrome and mortality using the IDF definition. However, Ko *et al* (2006) state that the WHO criterion has more predictive power for death than the other criteria.

The ATP III criterion is considered inappropriate for Asian population, because Asians have higher body fat percentage and abdominal obesity and lower body mass index than Caucasians. A lowered abdominal obesity criterion will be more appropriate (Tan *et al*. 2004). So far, only IDF's definition has ethnic specific abdominal obesity references to identify metabolic syndrome. Differences have been observed when using different definitions on Asian populations and higher prevalence observed when using the IDF criterion (He *et al*. 2006)

8.2. Pathogenesis of the component factors

Metabolic syndrome has a complex pathogenesis with various interlinked risk factors. Obesity and insulin resistance are described as the main components.

8.2.1. Obesity

The ATP III and IDF consider obesity as the main responsible pathogenic factor of metabolic syndrome. Overweight and obesity are common risk factors of many cardiovascular diseases. The findings from the third National Health and

Nutrition Survey, shows that 73.9% of the adolescents with metabolic syndrome were overweight (Ford *et al*. 2002).The association of android obesity with atherosclerosis and diabetes is long established (Vague 1956). Visceral obesity is considered a major component of metabolic syndrome (Fan 2007). Després (2006) states that abdominal obesity has a strong genetic link, yet it will only develop with the presence of a positive energy balance. The increasing proportions of low physical activity with an energy-dense refined diet contribute to the development of abdominal obesity. The fat cells from visceral adipose tissue have a higher lipolytic activity compared with other regions (Fan 2007). Visceral adipose tissue releases pro-inflammatory adipokines such as tumour necrosis factor alpha (TNFα) and interleukin-6 (IL-6) (Després 2006). Excessive adipose tissue also releases non-essential fatty acids (NEFA), cytokines, leptin, resistin, plasminogen activator inhibitor (PAI)-1 and adiponectin (Fan 2007; Grundy *et al*. 2004). These products exacerbate the cardiac risk factors. When NEFA levels are high in the plasma, it overloads lipids in muscles and liver and that enhances insulin resistance. High C-reactive protein levels with obesity is a known proinflammatory state and is signified by the excessive release of cytokines. The increase in PAI-1 signifies the increase in fibrinogen and is known as a prothrombotic state (Grundy *et al*. 2004). In addition, adipose tissue releases various receptors such as insulin, glucagon, glucocorticosteroids, thyroid hormone and catecholamine in response to signals from hormones and the central nervous system (Fan 2007). All these factors, associated with abnormal body fat distribution, are also indirectly linked to metabolic syndrome.

8.2.2. Insulin resistance

Insulin resistance is a marker of diabetes and cardiovascular disease. Many studies consider insulin resistance as a primary cause of metabolic syndrome due to its genetic origin and associations with other cardiac risk factors (Borgman and McErlean 2006; Ferrannini *et al*. 1991; Reaven 1988). Presence of insulin resistance will lead to the development of type 2 diabetes within 10 years (Borgman and McErlean 2006). Insulin resistance subsequently leads to hyperinsulinemia with hypertension. These may be due to increased sympathetic tone, endothelial proliferation and increased sodium retention (DeFronzo and Ferrannini 1991). The influence between insulin resistance and obesity is not clear. Insulin resistance increases with body fat levels and most obese people (BMI≥30 kg/m2) have a low insulin sensitivity and postprandial hyperinsulinemia (Abbasi *et al*. 2002). However, a spectrum of insulin resistance has been identified in overweight individuals (BMI=25-30 kg/m^2) and also in normal weighed people (BMI <25 kg/m^2) (Grundy *et al*. 2004).

8.2.3. Dyslipidaemia

Insulin resistance or hyperinsulinemia plays a major role in resulting dyslipidaemia. There is an increased release of free fatty acids from fat lipolysis and decreased uptake in the periphery. It causes an increased level of free fatty acids in the liver that results in the release of very low-density lipoprotein (VLDL), triglycerides and apolipoprotein-B. Cholesterol ester transfer protein (CETP) is a plasma protein that facilitates the transport of cholesteryl esters and triglycerides between lipoproteins. It collects triglycerides from VLDL or low-density lipoproteins (LDL) and exchanges them for cholesteryl esters from high-

density lipoproteins (HDL), and vice versa. The removal of cholesteryl esters from LDL and HDL results in an increased small dense LDL and a decreased HDL. Thus, there is a decreased availability of HDL for reversed cholesterol transport (Bhatheja and Bhatt 2006). The association of dyslipidaemia with obesity and insulin resistance varies considerably due to a high modulation of lipid metabolism by genetic variation (Grundy *et al*. 2004). However, obesity and insulin resistance themselves have been established to be highly influenced by a latent genetic factor and other factors to a lesser degree (Hong *et al*. 1997).

8.2.4. High blood pressure

Every 20/10 mmHg increase in blood pressure doubles the risk of complications such as diabetes, renal insufficiency and heart failure. Hyperinsulinemia may lead to hypertension due to several mechanisms such as increased renal Na+/water reabsorption, sympathetic nervous system activation and decreased Na+-K+-ATPase activity, increased Na+-H+ pump activity, increased cellular Ca2+ accumulation and stimulation of growth factors (DeFronzo and Ferrannini 1991).

8.2.5. Age

The prevalence of metabolic syndrome increases with age. Ford *et al* (2002) found an increase in the prevalence of metabolic syndrome, increasing from 6.7% among those aged 20 years to 43.5% among those aged 29 years and then to 42.0% among those aged ≥60 years in America. Recently, Lloyd-Jones *et al* (2010) reported the age-specific prevalence ranged from 20.3 % in age group 20 to 39 years, 40.8% in age group 40 to 59 and 51.5 % in age group

over 60 years in American men. Among women, the age-specific prevalence ranged from 15.6% in age group 20 to 39, 37.2% in age group 40 to 59 years and 54.4% in age group over 60 years. Sharifi *et al* (2009) also found a huge increase from 7.5% in <30 years to 45.6% in >50 years. This may be due to the influence of advancing age on all the levels of pathogenesis (Grundy *et al*. 2004). Childhood overweight is also a cause for metabolic syndrome later (Carnethon *et al*. 2004). From the Princeton prevalence study and a 25 years follow up study, it is clear that childhood metabolic syndrome is a predictor of metabolic syndrome in adulthood and further cardiovascular risk (Morrison *et al*. 2007).

8.2.6. Gender

Gender differences in the prevalence of metabolic syndrome have been observed in many studies. Ford *et al* (2002) found 57% higher prevalence in African-American women and 26% higher in Mexican-American women compared with men in the same population. Asian and African women also had higher prevalence compared with men (Table 8.2). this may be due to the relative high obesity prevalence in women (Agyemang *et al*. 2012). One possible explanation is that women frequently develop peripheral obesity at premenopausal stage and develop central obesity at (Regitz-Zagrosek *et al*. 2006) postmenopausal stage. However, the mechanism of this physiological change is not clear. Lai (Lai *et al*. 2010) found increased CRP (C-reactive protein) levels with a stronger association with metabolic syndrome compared with men. It suggests that chronic inflammation could be the reason for higher prevalence of metabolic syndrome in women.

8.2.7. Lifestyle

8.2.7.1. Diet

Dietary habits play a major role in the prevalence of metabolic syndrome. Barnard *et al* (1998) claim that diet is the primary cause of metabolic syndrome. They found a development of insulin resistance and hyperinsulinemia within two weeks of commencing a high fat diet on rats. The other manifestations of metabolic syndrome occurred later and the obesity was the last to develop in their study. Total fat intake in the diet is associated with the prevalence of metabolic syndrome (Freire *et al*. 2005). Damiao *et al* (2006) found eating red meat increases the chances of metabolic syndrome. Lack of fibre in dietary intake is associated with obesity, elevated plasma lipid levels and fasting glucose (Ludwig *et al*. 1999). High fat intake such as fried food is associated with the risk of metabolic syndrome (Freire *et al*. 2005). The intake of calorically sweetened soft drinks especially high fructose corn syrup have strong association with excessive energy intake, weight gain and development of type 2 diabetes and metabolic syndrome (Allman-Farinelli 2009; Dhingra *et al*. 2007; Malik *et al*. 2010).

8.2.7.2. Physical activity

Low cardiorespiratory fitness levels are strongly associated with metabolic syndrome. Many studies have found an inverse relationship between cardiorespiratory fitness and the incidence of metabolic syndrome in various age groups and both sexes (Arat *et al*. 2008; Hassinen *et al*. 2008; LaMonte *et al*. 2005; Spies *et al*. 2005). Regular physical activity can maintain or improve

cardiorespiratory fitness and young adults with regular physical activity had a low risk of metabolic syndrome (Carnethon *et al*. 2004). Holme *et al* (2007) studied the leisure time physical activity of men in their middle age (~50 years) and followed them up after 28 years. They found a strong inverse relationship between physical activity and prevalence of metabolic syndrome. Laaksonen *et al* (2002) measured leisure time physical activity and the physical fitness of high risk 612 middle aged men without metabolic syndrome and followed them up. After four years, metabolic syndrome was observed in 107 (17%) participants. They found strong negative correlations between intensity of leisure time activity, physical fitness and the risk of metabolic syndrome.

8.2.7.3. Socioeconomic factors

Dallongeville *et al* (2005) found that household income was inversely proportional to the prevalence of metabolic syndrome in women after controlling the data for lifestyle factors. They also found an association between metabolic syndrome and occupational category, working status and accommodation type in both men and women. Household wealth was also found to influence the prevalence of metabolic syndrome (Perel *et al*. 2006). In contrast, Ramsay *et al* (2008) found a weak influence of socioeconomic status on metabolic syndrome. However, they found strong association between socioeconomic status and social behaviours that cause metabolic syndrome. Mental status is also associated with metabolic syndrome. Mentally depressed women were twice as likely to have metabolic syndrome compared with non-depressed women (Kinder *et al*. 2004)

8.2.7.4. Education

Education levels are associated with the prevalence of metabolic syndrome (Dallongeville *et al*. 2005). Obese people seem to consider that the cause of obesity is due to genetic factors rather than over eating or inadequate physical activities (Lichtman *et al*. 1992). Carnethon *et al* (2004) found higher prevalence of metabolic syndrome in people with lower education. This may be due to the limited health care and higher physical and personal stress. Findings from the SHIELD study (Lewis *et al*. 2008) reported a huge lack of knowledge about metabolic syndrome among people with metabolic syndrome (0.6% were aware of metabolic syndrome among 25.9% prevalence of the condition).

8.2.8. Relationship between metabolic syndrome and cardiovascular disease

Metabolic syndrome has a strong link to the risk of developing cardiovascular disease. The presence of metabolic syndrome showed an elevated odds ratio for coronary heart disease (1.66, 95% CI 1.31 to 2.10) in an elderly population (He *et al*. 2006). Lakka *et al* (2002) found 1-11% mortality due to CHD (coronary heart disease) and 1-6% due to CVD (cardiovascular disease) in patients with metabolic syndrome (data adjusted for age and all the risk factors). Grundy *et al* (2004) analysed the Framingham data to establish the risk for CHD due to metabolic syndrome. They found that men had a 10-20% increased risk on 10 years follow up and women had relatively less risk on eight years follow up. After adjusting for Framingham's usual risk factors and age, there was not a significantly increased risk of CHD due to metabolic syndrome. However, the risk of CHD in metabolic syndrome cannot be underestimated.

8.3. Prevalence of metabolic syndrome

The prevalence of metabolic syndrome varies according to the populations studied and the definition used. The prevalence found in various studies all over the world is listed in Appendix III. The prevalence also varies with the age group and gender. Elderly and particularly women are mostly affected. It is also important to note that there were only 38% of people with none of the factors of metabolic syndrome in some prevalence studies (Ferrannini *et al*. 1991; Rupp 1992).

8.3.1. United States of America

The prevalence of metabolic syndrome has been continuously escalating. The prevalence was 24% in men and 23.4% in women among adults in the USA (United States of America) from the Third National Health and Nutrition Examination Survey (NHANES) (1988-1994) (Ford *et al*. 2002). Later, the prevalence had increased to 29.3% in women and 25.2% in men from NHANES 1999–2000 (Ford *et al*. 2004). The recent statistics by the American Heart Association (Lloyd-Jones *et al*. 2010) established a further increase. In total ~34% of adults had metabolic syndrome and it was 35.1% in men and 32.6% in women. The ethnic specific prevalence of metabolic syndrome in men vs. women were 37.2% vs. 31.5% in non-Hispanic white, 25.3% vs. 38.8% in non-Hispanic black and 33.2% vs. 40.6% in Mexican American. The Mexican American had a high prevalence of metabolic syndrome in other studies too (Ford *et al*. 2002). Overweight and obesity in young age is the major cause of metabolic syndrome in America. Cook *et al* (2003) carried out an analysis from the Third National Health and Nutrition Examination Survey 1988-1994

(NHANES III) found that 4% of USA adolescents (12-19 years) had metabolic syndrome and 28.7% of the adolescents with metabolic syndrome were overweight. In 2006, 30% of American adults were overweight (BMI 25-29.9 kg/m^2), 32% were obese (BMI ≥ 30 kg/m^2) and 5% of them were extremely obese (BMI ≥ 40 kg/m^2) (Ogden *et al*. 2006).

8.3.2. Europe

The prevalence of metabolic syndrome in Europe is similarly varying with different studies. Most of the studies show that the prevalence of metabolic syndrome is higher in men than in women (Appendix III). However, the immigrant Asians had a higher prevalence overall compared with Europeans and Asian women had a larger prevalence than men (Tillin *et al*. 2005).

8.3.3. Asia

Asians also have high prevelence of metabolic syndrome including immigrant Asians. Lloyd-Jones *et al* (2010) found a high prevalence ranging from 26.8% to 38.2% in immigrant Asian Indians depending on the definitions used. The prevalence of metabolic syndrome varied with the criterion used and increased with age in both central (China) and South Asia (India) (Appendix III). Enas *et al* (2007) claim that South Asians have a high level of metabolic syndrome prevalence due to the following reasons: (1) epidemiological transition, (2) genetic predispositions or ethnic susceptibility, (3) nutritional transition and (4) low physical activity. South Asians have a high prevalence of metabolic syndrome compared with other populations due to the higher prevalence of obesity and insulin resistance. Moreover, diabetes and premature coronary

heart diseases occur more often and 10 years earlier than in the other populations in the world (Enas *et al*. 2007). Another report (Gupta 2007) claims that low birth weight could account for the increase in the prevalence of metabolic syndrome in India. The lack of islet cells due to low weight at birth results in low insulin levels which could develop to diabetes later. Secondly, the children with low birth weight are getting more attention with overfeeding and high caloric food that could result in obesity (Gupta 2007). The patterns of infant BMI levels were also associated with the development of metabolic syndrome in a follow-up study from birth to 21 years on an Indian population (Fall *et al*. 2008).

8.4. Management of metabolic syndrome

There is no special treatment for managing metabolic syndrome other than treating the involved individual factors (Benedict 2006). Controlling individual risk factors in metabolic syndrome can prevent CVD. Wong *et al* (2003) treated individual factors of metabolic syndrome using ATP III criteria. Treating all the risk factors prevented CVD events in 51.3% men and 42.6% in women and controlling these risk factors to optimal level prevented CVD events up to 85.5% in men and 82.1% in women.

The International Diabetic Federation (2006) recommends uncompromising and aggressive management for metabolic syndrome. It considers lifestyle changes that includes moderate calorie restriction, moderate increase in physical activity and change in dietary composition as primary management. For those having a high risk of CVD and when lifestyle management is not enough, drug therapy is considered as secondary intervention to reduce the impact of all the risk factors: lowering triglycerides, raising HDL, reducing high blood pressure (antihypertensive therapy) and controlling insulin resistance/hyperglycaemia. The secondary interventions need to prioritize the care programme according to the primary risk (Benedict 2006). The interventions need to focus primarily on either stabilizing blood sugar or hypertension before controlling other factors.

8.4.1. Management of hypertension

The JNC 7 report suggests treating hypertension with antihypertensive drugs for those having blood pressure 140/90 or greater and 130/80 or greater with diabetes or kidney disease (Chobanian *et al*. 2003). However, no specific class

of antihypertensive drugs has been identified for patients with metabolic syndrome. Dumas (2003) suggests that use of drugs such as beta-blockers can reduce further endothelial damage. Low salt diet should be encouraged and weight loss of 4.5 kg could be effective in reducing 10 mmHg of blood pressure (Dumas 2003)

8.4.2. Management of insulin resistance

In case of hyperglycaemia, hypoglycaemic agents and lifestyle therapies should be used to maintain haemoglobin A1c levels (Grundy *et al*. 2004). Increased physical activity and weight reduction can reduce insulin resistance. Currently there are two classes of drugs available for insulin resistance: metformin and insulin sensitizers such as thiazolidinediones. Both of these drugs are currently used for type II diabetes or impaired glucose tolerance. However, these drugs are not recommended for the reduction of CVD risk as there are no CVD end-point studies available on people with metabolic syndrome (Grundy *et al*. 2004). Metformin is recommended for normalizing blood glucose level (Dumas 2003). Dietary supplements such as chromium are also effective to increase glucose utilization and decrease insulin resistance (Dumas 2003).

8.4.3. Management of dyslipidaemia

A healthy diet is an effective way to reduce lipid levels. Pharmacological management is also available. Statins and fibrates are cholesterol-lowering drugs commonly known for their effectiveness in the reduction of LDL cholesterol levels. Their effectiveness in the reduction of CVD risk has been established in patients with metabolic syndrome (Grundy *et al*. 2004). Evening

doses of statin are recommended to maximize the effect as the peak cholesterol synthesis occurs during the night (Dumas 2003). Ezetimibe is another lipid lowering drug which reduces the absorption of dietary cholesterol at small intestine level and thus lowers the amount of cholesterol delivered to the liver (Dumas 2003).

8.4.4. Weight loss

ATP III recommends obesity to be a primary target in the management of metabolic syndrome. Physical activity should be a first line therapy. Weight loss could help in achieving the following: reduction in serum levels of cholesterol, triglycerides, C-reactive protein, and PAI-1, reduction in blood pressure, glucose and insulin resistance, and increases in HDL cholesterol.

A vigorous weight loss plan should be administered to reduce 7-10% of total body weight in the first year and then progressed slowly until reaching a BMI of about 20-25. Diet should be reduced by 500-1000 caloric intake per day rather than reducing it drastically (Grundy *et al*. 2005a). The use of exercise or di*et al*one is not enough to achieve a substantial weight loss but it is effective when they are combined (Wood 1993). The National Institute of Health (NIH) suggests that a pharmacologic therapy could be used if only a patient is not able to maintain a weight reduction for six months with controlled diet and exercise.

8.4.5. Lifestyle

Lifestyle change is the most important stratagy to manage metabolic syndrome. Rush *et al* (2007) achieved a significant reduction in abdominal obesity and lipid levels with changes in lifestyle within five months in Asian Indian population who were older than 50 years. Enas *et al* (Enas *et al*. 2007) states that a healthy lifestyle should be adopted as early as from childhood or adolescence due to the genetic predisposition and epidemiological transition of components of metabolic syndrome.

8.4.5.1. Exercise

A combination of cardiorespiratory fitness, endurance and resisted muscle strength exercise is proposed as an optimal exercise programme for metabolic syndrome (Eriksson *et al*. 1997). A prior exercise testing and physical examination would help to prescribe optimal intensities of exercise. Petrella *et al* (2005) conducted a controlled cohort study on a 59-75 year old Canadian population. The subjects were administered supervised exercises regularly and followed up for 10 years. The exercised group had developed less metabolic abnormalities and higher physical fitness than the control group. This finding shows that regular exercise can help in preventing or delaying metabolic syndrome. Despite the success of regular exercise in the management of metabolic syndrome, there are no exercise programmes such as cardiac rehabilitation established in health care systems specifically for it.

8.4.5.2. Diet

A lack of awareness of caloric intake exists among people with obesity. Lichtman *et al* (1992) found a significant discrepancy in calorie intake of obese participants. The actual calorie intake was substantially higher than the self-reported values and their physical activity was overestimated in their reports. According to ATP III's recommendations, everyday diet should be restricted as listed in table 8.3 (Grundy *et al*. 2005a). However, a balance on energy intake and expenditure on physical activities should be maintained (Anderson *et al*. 2006). Therefore, health education on dietary intake and balancing it with physical activities needed to be improved.

Table 8.2 Diet recommendations by ATP III

Nutrient	ATP III Recommendations
Total cholesterol	<200 mg
Total fat	25% -35% of total daily calories per day
Saturated fat	< 7% of total daily calories per day
Polyunsaturated fat	≤ 10% of total daily calories per day
Monosaturated fat	≤ 20% of total daily calories per day
Soluble fibres	20-30 grams per day
Carbohydrate	45%-50% of total daily calories
Protein	15% of total daily calories per day
Total energy intake	Balanced (can be gradually reduced 500-1000 calories per day)

(Grundy *et al*. 2005a)

8.4.6. Prevention

Vigorous preventive measures should be taken for those having a family history of diabetes and CHD. Therapeutic lifestyle changes should be encouraged from

childhood. Healthy eating habits should be emphasized. Detection of one component of metabolic syndrome should lead to investigations for other components and further management. Adequate nutrition should be maintained during the intra uterine period in South Asian countries where malnutrition is one of the causes of metabolic syndrome (Misra *et al*. 2007). Adequate intake of dietary supplements should be encouraged such as folic acid and vitamin B6 (decreases homocysteine which is related to heart disease), vitamin E (helps in breakdown of LDL while increasing HDL and also reduces the risk of thrombus formation), garlic (reduces the total cholesterol level) and omega-3 fatty acids (lowers total cholesterol and triglycerides levels) (Dumas 2003). Physical abuses such as smoking, heavy alcohol consumption and overeating need to be corrected. Regular exercise with optimum intensity and time should be encouraged as lifestyle behaviour.

8.4.7. Future research

A uniform definition for metabolic syndrome needs to be established. Theoretically, changing lifestyle is the most effective treatment for metabolic syndrome but it is practically difficult to achieve. Further studies using valid measures to minimize errors should be undertaken. Programmes will involve enhancing health education and developing more flexible exercise opportunities. New specific methods for encouraging lifestyle changes need to be developed and studied. Home-based exercise programmes could be an effective alternative for centre-based exercise programmes. Studies are needed on the effectiveness of home-based programmes on metabolic syndrome. Further, investigations are needed to validate home-based exercise

programmes, using recently developed communication technologies such as mobile phones and the internet.

8.5. Conclusions

The prevalence of metabolic syndrome is continuously escalating worldwide. A uniform, globally acceptable definition is necessary to establish the prevalence of metabolic syndrome and for the development of effective and unique treatment strategies. Early identification of metabolic syndrome could help to reduce the risks of cardiovascular disease. Monitoring the development of the risk factors from childhood or adolescence can help the early identification. A sedentary lifestyle is the major cause of metabolic syndrome. Lifestyle change is the key factor for the prevention and management of metabolic syndrome. More emphasis on changing to a healthy lifestyle with health education is necessary. More investigations are needed on alternative methods such as home-based exercise programmes and the use of information technologies on health education.

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CHAPTER 9. PREVALENCE OF HYPERTENSION, OBESITY, DIABETES AND METABOLIC SYNDROME IN NEPAL

Abstract

Background: Early detection of cardiovascular risk in underdeveloped countries in Asia, such as Nepal, is one method to control disease prevalence. This study was carried out to establish the prevalence of cardiovascular risks such as hypertension, obesity and diabetes in Eastern Nepal. This study also establishes the prevalence of metabolic syndrome (MS) and its relationships to those cardiovascular risk factors and lifestyle. **Methods**: 14,425 subjects aged 20-100 (mean 41.4±15.1) were screened. Physical examination included blood pressure, weight, height, waist and hip circumferences. Blood test included fasting plasma glucose and lipids. Both the International Diabetic Federation (IDF) and National Cholesterol Education Programme's (NCEP) definitions for MS were used and compared. **Results**: According to the revised values for South Asians, 34% of the participants had hypertension and 6.3% were diabetic. 28% were overweight (BMI =22-24.9) and 32% were obese (BMI> 25). 22.5% of the participants had metabolic syndrome based on IDF criteria and 20.7% according to the NCEP definition. Prevalence was higher in the less educated, people working at home and females. There was no significant correlation between the participants' lifestyle factors and the prevalence of MS. **Conclusion**: The prevalence of MS increased with age and females had higher prevalence of MS compared with men. The incidence of low levels of high-density lipoprotein cholesterol and high levels if triglycerides, and abdominal obesity could be the major contributors to MS in Nepal. Education also appears to be related to the prevalence of MS.

9.1. Introduction

According to the World Health Organization's recent update (WHO 2009), diabetes, hypertension and obesity are one of the top five continuing risk factors for cardiovascular deaths in the world. Obesity is increasing substantially and is one of the major contributors of disease prevalence due to its pathophysiological link to other cardiovascular risks such as hypertension and diabetes. It is estimated that in 2010, 6.4% of adults would have diabetes mellitus affecting 285 million in the world and it will increase to 7.7% by 2030, affecting 439 million adults [2]. Of special note is that, there will be a 67% increase in the prevalence of diabetes in developing countries from 2010 to 2030 (Shaw *et al*. 2010).

Metabolic syndrome (MS) is a constellation of overweight/obesity, hypertension, and disturbances of lipid and carbohydrate metabolism. The definition of MS was debated for a long time to produce a standardized clinical criterion. The World Health Organisation describes MS as the presence of type II diabetes or impaired glucose tolerance with any two of the following characteristics; obesity, high levels of triglycerides, low levels of high-density lipoprotein and hypertension. The International Diabetes Federation (IDF) takes central obesity as a pre-requisite for the diagnosis of MS with the association of any two of the other factors i.e. high blood pressure, abnormal blood glucose, high levels of triglycerides and low levels of high-density lipoprotein. In addition, the IDF has derived specific reference values for central obesity for different ethnicities. The National Cholesterol Education Programme (NCEP 2002) expert panel on detection, evaluation and treatment of high blood cholesterol in adults (Adult treatment panel, or ATP, III), the National Heart, Lung and Blood Institute and

the American Heart Association (Grundy *et al*. 2004) have released a report on the criteria for diagnosing and managing MS. The panel describes MS as the presence of any three of the following: abdominal obesity, dislipidaemia (high levels of triglycerides, low HDL), increased blood pressure and elevated fasting glucose. This definition has been extensively reviewed and accepted by the greatest number of researchers. For the purpose of this paper, the ATP III and IDF's definitions are used and compared.

Each component of MS is a known risk factor for the development of type 2 diabetes, atherosclerosis and coronary artery disease (CAD). People with MS are 3-10 times more likely to develop cardiovascular disease commensurate with a high risk of morbidity and mortality (Eberly *et al*. 2006; Nestel *et al*. 2007). Central obesity, one of the components of MS, predicts the occurrence of diabetes and overall cardiovascular risk (Poirier and Despres 2003). The NCEP ATP III (NCEP 2002) states that MS is equal to cigarette smoking as a contributing factor for premature cardiovascular disease.

The prevalence of metabolic syndrome is increasing all over the world with different regions having individual clusters of epidemic risk factors (Cheung and Thomas 2007; Eberly *et al*. 2006) and in particular there is evidence of a high prevalence of MS and diabetes in South Asians (Misra *et al*. 2009). Substantial increase in the prevalence of type 2 diabetes in Asia in recent years has raised serious concerns about cardiovascular consequences for these populations (Nestel *et al*. 2007; Scott *et al*. 2008). However, in developing countries, many of these subclinical conditions are not diagnosed until the onset of complications such as myocardial infarction or stroke (Ringborg *et al*. 2009). It

is essential to initiate early detection of these chronic diseases in underdeveloped countries in Asia, such as Nepal, so that preventative action can minimize the consequences.

This study aims to establish the prevalence of hypertension, diabetes, obesity and metabolic syndrome in the participants of a major health screening programme in Nepal. This study also aims to establish the relationship between the components of MS and lifestyle of the participants.

9.2. Methods

9.2.1. Subjects

Nepal is one of the poorest countries of the world at the 136th position of human development index. The total population of Nepal is 27 million. The subjects were the participants of the 'Programme for Detection and Management of Chronic Kidney Disease, Hypertension, Diabetes & Cardiovascular Disease,' a community based screening programme in Eastern Nepal (Sharma *et al*. 2010) . A raw dataset was obtained with permission to use in the current study and published (Sharma *et al.* 2011).

9.2.2. Research team and demographic data collection

In this community-based programme a series of community awareness programmes were conducted in a specific locality with the help of local leaders, medical students and community volunteers. Various screening centres such as permanent centres (in health clinics, community centres, etc.) and temporary screening centres (in schools, clubs, houses of worship and private homes)

were used to screen the population. Each centre used a group of five to seven people as community volunteers and consisted of local leaders (priest, administrator, school teachers, and local political leaders), a laboratory technician, and nurse. Medical students (approximately 100 in number) and nursing students (around 25) assisted the community volunteers.

Prior to screening, the community volunteers went from door-to-door to record the number of family members residing permanently and to inform the members of the family, about the need of the project. All people of ≥20 years were invited to come to a predefined place in very close vicinity to their house. They were requested to avoid food for the previous 12 hours. Pregnant or menstruating women at the time of analysis, people with a fever or acute illness, and those who had recently engaged in heavy exercise were excluded.

The research team also collected general information on the participants' demographic data, diet, smoking, alcohol consumption and physical activity. The data recorded included family and medical history for kidney disease, high blood pressure, diabetes, cardiovascular disease and any current medication or treatment.

9.2.3. Physiological measurements

Blood pressure was measured by the auscultatory method with a random zero mercury sphygmomanometer and standard cuff (12 x 34 cm). The blood pressure measurement was taken in the seated position, quietly in a chair with feet on the floor and an arm support at the heart level.

Hypertension was defined according to the guidelines of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (Chobanian *et al*. 2003), i.e. systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg and/or concomitant use of antihypertensive medications. Body weight and height were assessed with all subjects standing without shoes and heavy outer garments to the nearest 0.1 kg and 1 cm, respectively. Body mass index was estimated according to standard nomograms. Waist circumference was measured over light clothing at a level midway between the lower rib margin and the iliac crest in centimetres rounded up to nearest 0.5 cm. Abdominal obesity is defined as an abdominal circumference > 102 cm (40 in) in males and > 88 cm (35 in) in females for NCEP criteria and > 90 cm in males and >80 cm in females for IDF criteria for South Asians.

Plasma glucose concentration was determined by the glucose oxidase-peroxidase method (Vitalab Selectra-2, Merck, Germany). The diagnosis of diabetes was defined by either casual plasma glucose >200 mg.dL-1 associated with symptoms of diabetes and on fasting samples, plasma glucose >126 mg.dL-1. Individuals with self-reported, prior physician-diagnosis of diabetes were classified as having previously diagnosed diabetes.

Serum lipids that include total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and triglycerides (TG) were also measured (Vitalab Selectra-2, Merck, Germany).

9.2.4. Quality control

The result from any person having a history of hypertension or found to have hypertension were verified by qualified doctors. All biochemical abnormalities were reconfirmed. The biochemical tests were completed in semiautomatic analysers (Microlab 300, Vital Scientific, The Netherelands). The tests were undertaken in the same machine using standard biochemical reagents. Regular internal quality controls were undertaken and routinely crosschecked with other laboratories.

9.2.5. Data Handling

Data were stored in a central electronic database using 'Epidata' software. Epidata refers to a group of applications used in combination for creating documented data structures and analysis of quantitative data. In this study, Epidata was used for simple and programmed data entry and data documentation.

9.2.6. Data analysis

Data were extracted from 'Epidata' and imported to SPSS 18.0 software. The data were re-coded as necessary and frequencies were analysed. The IDF and NCEP ATP III's criteria for metabolic syndrome were used to calculate and compare the frequency of metabolic syndrome. The NCEP criterion was used to find the correlations with other findings. The relationship between the prevalence of cardiovascular risk factors, demographic details, lifestyle and physiological test results were analysed using the Spearman correlation test. Further, the differences in the categorical variables were examined using chi-

squared test. Odds Ratios (ORs) and their 95% confidence interval was calculated using logistic regression.

9.3. Results

In total, 14,425 people, aged 20-100 (Mean age 41.4±15.1) were included in the study. Among them, 99.9% were South Asians who were living in Nepal.

The participants' demographic and lifestyle details are listed in Table 9.1. The participants were a mixture of various levels of education. The percentage of education level is illustrated in accordance to the number of years in education (1-5 years – Primary, 6-10 years- Secondary, >10 years- Higher Secondary level). The participants were divided into four categories according to their work: labourer/farm, office, house and none/unknown. The age was divided into four categories. Participants' physical activities were defined according to the time spent every day on physical activity as >60 min, 30-60 min and <30 min/day and none. This information was recorded verbally.

Table 9.1 Demographic and lifestyle details of the participants

Demographic detail		% in total participants
Age (n= 14425)		20-40 Years- 53.6% (n= 7729)
		41-60 Years- 33.8% (n=4880)
		61-80 Years- 11.9% (n= 1716)
		80-100 Years- 0.7% (n= 100)
Gender (n= 14009)		Male - 38% (n=5327)
		Female - 62% (n=8682)
Level of education (n= 14009)		Higher Secondary - 33.1% (n= 4635)
		Secondary - 22% (n= 3079)
		Primary - 14.9% (n=2092)
		None- 30% (n= 4197)
Work category (n= 13982)		Labour - 12.9% (n= 1797)
		House - 57.1% (n=7977)
		Office - 14.9% (n=2090)
		None - 15.1% (n=2118)
Physical activity (n= 14001)		>60 min/day - 37.1% (n= 5190)
		30-60 min/day - 25.3% (n= 3543)
		<30 min/day or None - 37.6% (n= 5628)
Fruits & vegetables in diet (n= 14009)		Everyday - 31.4% (n= 4403)
		1-5 days - 56% (n=7842)
		Once/week or None - 12.6% (n= 1764)
Smoking (n= 14004)	Current – 11.9% (n=1673)	>10 years – 8.5%
		1-10 years – 32.3%
		< 1 year – 59.2%
	Previous – 8.8% ((n= 1232)	
Alcohol consumption (n= 13998)	Total - 24.8%	Every day – 6% (n= 838)
		Once/week- 9.5% (n= 1189)
		Once/month- 9.3% (n= 1306)

9.3.1. Obesity, diabetes and hypertension

Abdominal obesity was observed in 11.5% (n= 1607/14002) of the participants as per NCEP criteria (mean waist circumference: male-107.38 ± 6.19 cm, female - 94.84 ± 5.84 cm) and in 34.7% (n= 5006/14418) of the participants as per IDF criteria. According to the revised BMI values specifically for south Asians as outlined by Razak *et al* (2007), 10.6% (n= 1534/14423) were underweight (BMI< 18.5 kg/m^2), 28.2% (n= 4065/14423) were overweight (BMI =22-24.9 kg/m^2) and 32.5% (n= 4689/14423) were obese (BMI> 25 kg/m^2).

Diabetic prevalence was 6.3% (889/14008) of which 4.8% (n= 673/14008) were under treatment. A figure of 12.3% (n= 1718/14009) had a family history of diabetes. Hypertension was observed in 33.9 % (n= 4894/14422) of the participants (mean systolic 138.72 ± 18.03 mmHg and mean diastolic 93.09 ± 8.45 mmHg). Only 12.9% (1812/14009) were previously diagnosed and 8.5% were receiving treatment for hypertension. A history of coronary artery disease was present in 1.6% (n = 218/14007) and 1% (n=142) were under treatment for ischemic heart disease or stroke.

Table 9.2 shows the goodness of fit for the prevalence of obesity, hypertension and diabetes. The comparison was against the latest available prevalence data (IDF 2009; Vaidya *et al*. 2010; World-Hypertension-League 2008). Prevalence of hypertension showed no difference from these data and obesity showed only a small difference. Diabetes showed a large statistically significant difference from the previous available data.

Table 9.2 Chi-squared 'goodness of fit' for the prevalence of cardiac risk factors in participants

Category		Observed n	Expected n	Chi-Squared Significance (p)
Obesity (n= 14423)	No	9734	9605.7	0.024*
	Yes	4689	4817.3	
Hypertension (n=14422)	No	9528	9547.4	0.733
	Yes	4894	4874.6	
Diabetes (n =14008)	No	13119	13461.7	0.001**
	Yes	889	546.3	

**Significant at the 0.01 level (2-tailed) Significant at the 0.05 level (2-tailed).

The percentage of the participants who had abnormal lipid profile that includes total serum cholesterol, serum LDL cholesterol, serum HDL cholesterol, serum triglycerides are listed in Table 9.3.

Table 9.3 Percentage of participants' abnormal lipid profile

Prevalence	Percentage among participants	Mean (mg.dL-1)	Reference Value (mg.dL-1) (American Heart Association)
High Cholesterol	17.2% (n= 1663/9696)	227.9±34.06	>200
High LDL	36.2% (n= 791/2188)	129.91 ± 27.09	>100
Low HDL	56.7% (n= 1242/2192)	Male - 33.63 ± 3.83 Female - 39.08 ± 5.71	Male <40 Female <50
High Triglycerides	48.3% (n= 4681/9689)	231.52 ± 101.91	> 150

9.3.2. Prevalence of metabolic syndrome

There were 2191 set of data eligible to meet the criteria for metabolic syndrome. MS was observed in 22.5% (n=494/2191) of the participants according to the IDF criteria and 20.7% (454/2191) according to the NCEP criteria. The

percentages of individual MS risk factors among the total participants and the participants with MS are illustrated in Figure 9.1 and Figure 9.2. Generally, among the total participants and the specific participants with MS, the presence of abnormal lipids was higher than the other factors defining MS. However, the presence of abdominal obesity was higher among MS participants using IDF criteria (Figure 9.2).

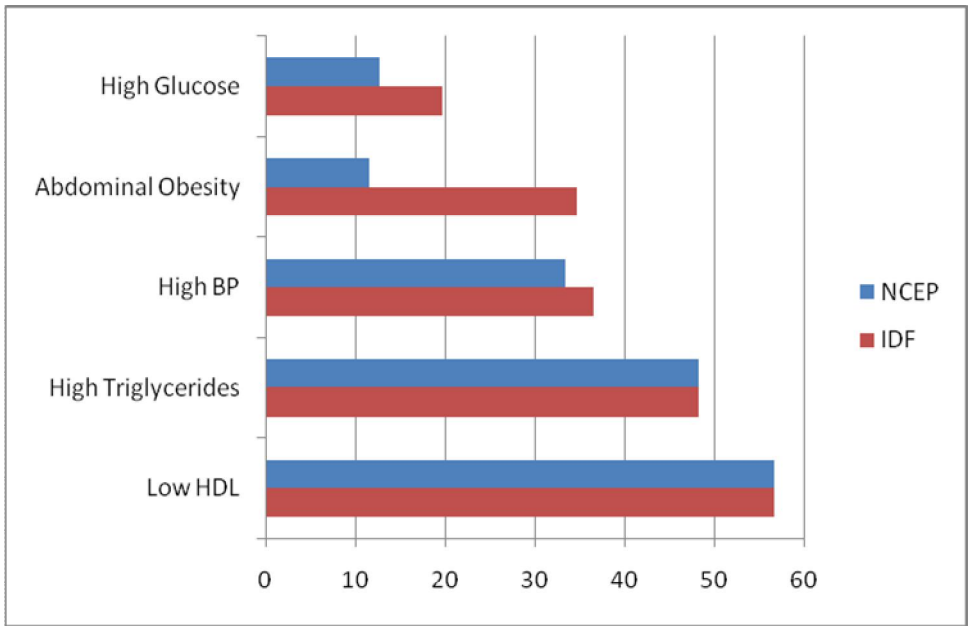

Figure 9.1 Percentage of traits of metabolic syndrome in the total participants

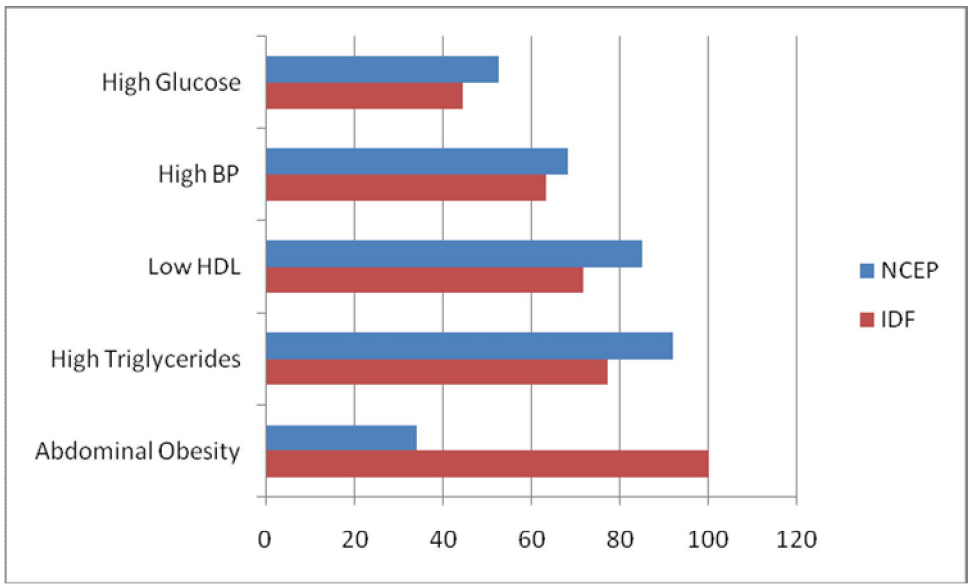

Figure 9.2 Percentage of individual risk factors among participants with MS

Table 9.4 provides the MS prevalence in relation to demographic and lifestyle factors. The females had a higher prevalence of MS than males. According to the NCEP criteria, the age groups 41-60 and 61-80 had a higher prevalence of MS then the lower age group. According to IDF criteria, the age groups 41-60 and 20-40 had a higher prevalence of MS. The prevalence of MS was higher in participants with less education. The participants who worked at home had a high incidence of MS according to both the criteria used. The sedentary group had a higher incidence of MS than the participants who were physically active.

Table 9.4 Demographic details and prevalence of metabolic syndrome and other risks

		Disease prevalence in participant category				
		Obesity/ Overweight	Diabetes	Hypertension	MS – NCEP Criteria	MS – IDF Criteria
Gender	Male	59.1% n=3146/53	8.1% n=429/532	40.7% n=2164/5327	18.6% n=150/805	17.1% n=138/805
	Female	61.8% n=5360/86	5.3% n=460/868	30.0% n=2603/8679	21.9% n=304/1386	25.7% n=356/138
Age Group	20-40 Years	55.5% n=4293/77	1.9% n=140/751	19.6% n=1514/726	9.8% n=110/1124	13.1% n=147/112
	41-60 Years	70.5% n=3440/48	10.2% n=480/472	46.1% n=2252/4880	31.4% n=256/815	34.7% n=283/815
	61-80 Years	56.7% n=973/171	15.4% n=257/166	62% n=1064/1726	34.8% n=86/247	25.1% n=62/247
	80-100 Years	48% n=48/100	12.2% n=12/98	64% n=64/100	40% n=2/5	40% n=2/5
Level of education	Higher Secondar	59.9% n=2775/46	5.1% 238/4634	27.2% n=1262/4633	13.3% n=117/880	15.8% 139/880
	Secondar y	64.1% n=1972/30	5.3% n=163/307	27.8% n=857/3078	19.2% n=69/360	22.2% 80/360
	Primary	63.9% n=1337/20	8.3% n=174/209	38.3% n=802/2092	22.7% 90/396	25.5% 101/396
	None	57.6% n=2419/41	7.5% n=314/419	44.0% n=1847/4197	32.1% n=178/555	31.4% 174/555
Work category	Labour	56.5% n=1015/17	5.3% n= 96/1997	35.4% n=636/1797	17.9% n=40/224	17% n=38/224
	Office	69.3% n=1448/20	7.8% n=162/209	34.7% n=724/2089	16% n=58/362	21.5% n=78/362
	House	69.3% n=1448/20	6.3% n=506/797	34% n=2712/7975	23.9% n=303/1269	25.1% n=318/126
	None	50.2% n=1064/21	5.8% n=122/211	32.6% n=690/2118	15.8% n=53/336	17.5% n=60/336
Physical activity	>60 min/day	62% n=3215/51	5.2% n=270/519	29.6% n=1535/5187	22.3% n=79/355	24.2% n=86/355
	30-60 min/day	62.8% n=2226/35	8.2% n=291/354	37.6% n=1333/3543	23.6% n=154/653	25.0% n=163/653
	<30 min/day	59.1% n=1805/30	6.9% n=212/305	36.9% n=1128/3053	25.4% n=171/674	26.3% n=177/674
	None	56.7% n=1805/30	5.1% n=114/221	34.8% n=770/2215	9.8% n=50/509	13.4% n=68/509
Fruits & vegetable in diet	Every day	61.0% n=2686/44	7.4% n=325/440	32.2% n=1416/4400	23.2% n=68/293	23.5% n=69/293
	3-5 days/wee	61.3% n=4804/78	5.8% n=451/784	34.0% n=2664/7842	20.3% n=326/1604	23.6% n=378/160
	Once/wee k	58.1% n=947/163	6.0% n=97/1630	38.3% n=637/1630	21.0% n=57/272	16.9% n=46/272
	None	51.5% n=69/134	11.9% n=16/134	41.0% n=55/134	13.6% n=3/22	4.5% n=1/22

The univariate correlations between cardiac risk factors are shown in Table 9.5 and the chi-squared independence of them in the metabolic syndrome prevalence is listed in Table 9.6.

Table 9.5 Relationship between the prevalence of MS and other cardiovascular risks

		Hypertension	Diabetes	Metabolic syndrome
Spearman's Correlation Coefficient	Obesity	0.150**	0.070**	0.153**
	Hypertension		0.101**	0.234**
	Diabetes			0.384**

** Correlation is significant at the 0.01 level (2-tailed)

Table 9.6 Chi-squared independence of cardiac risk factors in the prevalence metabolic syndrome

	Hypertension	Obesity	Diabetes
Metabolic Syndrome	31.9%** n=292/914	34.8%** n=241/693	58.6%** n=78/133

(n=2191) ** Correlation is significant at the 0.01 level (2-tailed)

The NCEP scores had a significant positive relationship with education levels and physical activity. There were significant positive correlations between physical activity and the three individual MS components: high glucose ($r=0.03$, $p<0.01$), high BP ($r=0.04$, $p<0.01$) and low HDL ($r= 0.23$, $p<0.01$). There was no correlation between physical activity and the other two MS components: high triglyceride ($r=0.003$, $p>0.05$) and abdominal obesity ($r=-0.003$, $p>0.05$). There was no relationship with diet and work. The NCEP scores had a positive correlation between the family history of diabetes ($r=0.83$, $p<0.01$) and hypertension ($r=0.115$, $p<0.01$). Although a number of these correlations show high levels of significance, the common variance is extremely low, suggesting that the sample size is having a major impact on the significance. As a result of this, it is not proposed to develop this outcome in any great detail.

Table 9.7 lists the chi-squared independence, odds ratios and confidence intervals in the association between age, gender and specific lifestyle factors in metabolic syndrome prevalence. The sensitivity (B) shows the direction of the relationship. Odds ratio (OR) values show the predicitvity of the categorical variables on the prevelance of metabolic syndrome. Aging, lower physical activity, lower education, house work and smoking showed associations with the higher prevelnce of metabolic syndrome.

Table 9.7 Chi-squared significance for the independence, Odds Ratios and 95% confidence interval of age, gender and life style factors in the prevalence of metabolic syndrome

		Chi-squared independence Sig (p)	B	SE	Odds Ratio (ORs)	95% Confidence Interval
Gender		NS	-0.204	0.111	0.815	0.655-1.014
Age		#	0.049	0.004	1.050**	1.043- 1.059
Education Level	Higher Secondary	**	-0.473	0.15	0.623**	0.464-0.837
	Secondary		-0.689	0.162	0.502**	0.366-0.690
	Primary		-1.125	0.135	0.325**	0.249-0.423
Work	Labour	**	0.15	.230	1.161	0.740-1.821
	Office		0.02	.207	1.019	0.679-1.529
	House		0.52	.164	1.675*	1.216-2.308
Fruit/Veg in diet	Everyday	NS	.649	.636	1.914	0.550-6.664
	3-5 days/week		.480	.624	1.616	0.475-5.492
	Once a week		.518	.639	1.679	0.480-5.873
Smoking	Current	**	.286	.189	1.332	0.919-1.929
	Former		.562	.187	1.754*	1.215-2.532
Physical Activity	>60 min/day	**	.966	.196	2.628**	1.789-3.859
	30-60 min/day		1.041	.175	2.833**	2.010-3.993
	<30 min/day		1.138	.173	3.121**	2.222-4.383

** Correlation is significant at the 0.01 level (2-tailed). *Correlation is significant at the 0.05 level (2-tailed)

NS- Not significant B- Sensitivity SE- Standard error #Not available as they are continuous variables

9.4. Discussion

It is important to observe the prevalence of diabetes, hypertension, and obesity individually and also the cluster of risk factors as metabolic syndrome to predict the risk of cardiovascular disease. Any association between lifestyle factors and these risk factors would provide the opportunity to encourage a change in lifestyle to promote lower levels of subsequent CVD.

9.4.1. Education, work and physical activity

The large number of poorly educated people and the large number of school dropouts could be linked to the disease prevalence. The prevalence of hypertension and metabolic syndrome in poorly educated people was large when compared with the educated participants. Though the results are not generalized, the relationship between education levels and the prevalence of hypertension agrees with earlier studies (de Gaudemaris *et al*. 2002; Samal *et al*. 2007). These found that education levels significantly influence the knowledge of hypertension and the awareness of cardiovascular risk. This suggests that there is a need to improve the awareness of health and use education to prevent or reduce the risk of MS and cardiovascular risks in these groups. The office workers had a lower prevalence of MS (NCEP scores) than the other groups. A considerable number of office workers (64%) undertook regular physical activity of more than 30 min/day. This may be due to health awareness gained from higher education. Most of the poorly educated or less educated people were labourers or home workers. The labourers had a lower MS prevalence than the home workers did. This may be due to the physical activities involved in their work. The home workers education levels and

physical activities were comparatively lower than the other work groups. These findings clearly show that education and physical activity have an influence on the prevalence of MS. Most of the females were home workers (75.5%) and their education was comparatively lower than the males. This may be the reason for the higher prevalence of MS in females. The amount of physical activity involved in home workers is unknown, but the results suggest it is less than that undertaken by other workers.

Asian populations continue to modernize and levels of physical activity are declining as (i) home and work place jobs become more automated and sedentary and (ii) transportation is more readily available [7]. The prevalence of MS among the participants who had no physical activity was surprisingly no different from others. This may be due to a higher than average number of missing values in these data (2191/14425 complete data to meet the criteria for MS) or to other unknown socioeconomic factors.

9.4.2. Diet and age

Controversially, there was a high prevalence of MS among people, who regularly ate fruit and vegetables. Lee *et al* (Lee *et al*. 2008) found that a higher intake of macronutrients such as fruits and vegetables is associated with general obesity. However, it is not clear how the vegetables and fruits were eaten e.g. overcooked, processed etc. The exact quantity of the dietary intake was not recorded, as it was not the primary area of focus of the study. In these populations, several dietary imbalances have been reported in previous studies. These tend to report a low intake of mono-unsaturated fats (MUFA), n-3

polyunsaturated fats (PUFA) and trans-fatty acids (mostly related to widespread use of vanaspati, a hydrogenated oil) (Misra *et al*. 2009). The healthy traditional plant-based diets are being replaced by cheaper calorie dense high fat foods. These changes are resulting in a rapid increase in the prevalence of obesity throughout Asia and the subsequent development of MS (Cheung and Thomas 2007). Ness and Powles also found in their review (Ness and Powles 1997) that many studies were reporting the null or negative effects of fruit and vegetable intake on the prevalence of cardiovascular diseases. However, the correlations found in those studies were generally low, as seen in the current study. Further, they suggest that a food-based analysis would complement the nutrient based analysis to clarify these issues (Ness and Powles 1997). In Nepal, the regular diet in addition to fruits and vegetables, i.e. such as rice, which is high in carbohydrates and the methods of cooking, may be dietary causes of metabolic syndrome. Generally in Nepal, a small quantity of single, locally grown seasonal vegetable is a common constituent of meals. This may not be sufficient to achieve a healthy lifestyle.

The age groups 40-60 had a large prevalence of MS in this study. In addition, it is important to note that this middle-aged group had a high incidence of overweight or general obesity and abdominal obesity. The other age groups had a lower prevalence of MS than the 40-60 years old, yet it was still relatively high. This included the younger population (20-40 years) at nearly 10%. Inadequate maternal nutrition in pregnancy, low birth weight and childhood obesity may be important factors for the development of metabolic syndrome and diabetes (Misra *et al*. 2009). Specifically in children and young individuals, a high intake of n-6 PUFA is correlated with hyper-insulinaemia. In adults, high

carbohydrate meal consumption is related to hyper-insulinaemia, post-prandial hyperglycaemia and hypertricylglycerolaemia (Misra *et al*. 2009).

9.4.3. Obesity and lipids

Unger described metabolic syndrome as “a failure of the system of intracellular lipid homeostasis which prevents lipotoxicity in organs of over nourished individuals” (Unger 2003). In this study, a large number of participants had increased triglycerides levels and low HDL levels. In addition to low levels of HDL, the HDL particles are small, dense and dysfunctional in South Asians (Enas *et al*. 2007). These are strong predictors of cardiovascular disease. Hypertriglyceridaemia is a direct reflection of an insulin resistance condition and it is interrelated to the low HDL concentrations in developing endothelial dysfunction (Eckel *et al*. 2005).

In Nepal, a high number of the participants had abdominal obesity and were over-weight/obese, according to their BMI. The BMI is a simple useful measure for overall abnormal weight, yet not a standard measure for obesity. BMI cannot differentiate between whether the condition was due to unusual muscular development or the accumulation or distribution of fat in the body (Lakka *et al*. 2002; Marks 2003). Despite the low prevalence of general body obesity *compared with* western countries, metabolic syndrome is growing into a significant public health problem in Asia (Pan *et al*. 2008). This may be mainly due to the large number of people with central obesity, a feature that was also observed in this study. The higher prevalence of MS in females is also more likely to be due to a higher incidence of abdominal obesity. Abdominal obesity is

an important factor because metabolic syndrome and increased abdominal fat is related to a reduction of adiponectin, an adipocyte-derived hormone with anti-atherogenic and anti-inflammatory properties (Salmenniemi *et al*. 2004). The abdominal adipose tissue results in release of free fatty acids directly in the portal veins and altered lipid levels in the blood (Larsson *et al*. 1984). Further abdominal adiposity increases insulin secretion and it would be exaggerated by decreased hepatic clearance leading to hyperinsulinemia (Bjorntorp 1990). The free fatty acid release also results in endothelial dysfunction that develops hypertension. Thus abdominal obesity is an important indicator of cardiovascular disease due to its link to dyslipidaemia, hyperinsulinemia, hypertension and impaired fibrinolytic capacity (Folsom *et al*. 2000).

9.4.4. IDF vs. NCEP definitions

Tan *et al* (2004) states that if the NCEP's criteria were applied to the Asian population it might underestimate the prevalence of metabolic syndrome and the risk of cardiovascular disease. So a reduced cut off point for abdominal obesity for Asians was suggested. IDF's specific reference values for abdominal obesity make a substantial difference to the prevalence of MS between the two criteria. The IDF's cut off points for South Asians' waist circumference is lower than the NCEP's general cut off points (≥90 cm vs ≥102 cm in men and ≥80 cm vs ≥88 in women). Another study on Chinese population also found a large increase in the prevalence of metabolic syndrome using IDF criteria compare with NCEP criteria (He *et al*. 2006). However, in the current study both the definitions demonstrated a higher prevalence of metabolic syndrome (20.7 – 22.5%) in Nepal when compared with the studies done in other Southeast Asian

countries such as Thailand (12%-18% using NCEP definition) and India (18.3% using IDF definition) (Grundy 2008). These findings suggest the need for specific attention to control the disease prevalence in Nepal.

9.4.5. Limitations

The current study has several limitations that should be considered. Although data were prospectively collected, they may not be generalizable outside of Eastern Nepal. The results did not show substantiate relationship between smoking histories, diet, family history of cardiovascular and metabolic syndrome. Matched groups may be more appropriate to explore these relationships.

9.5. Conclusions

There was high prevalence of hypertension and obesity in Nepal. High triglycerides and low HDL levels substantially contribute the prevalence of MS in Nepal. Abdominal obesity, with the revised reference values, is an important risk due to its physiological relationship to the other MS risk factors. There was also a high level of blood glucose. The MS prevalence may be due to lack of awareness and unhealthy lifestyles, so health education and more preventive measures should decrease the prevalence of MS and cardiac risks in Nepal.

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CHAPTER 10. ACUTE CHANGES IN ARTERIAL STIFFNESS FOLLOWING EXERCISE IN PEOPLE WITH METABOLIC SYNDROME IN INDIA

Abstract

Background: Metabolic syndrome is a cluster of specific cardiovascular risk factors. Exercise capacity is recognised as an important diagnostic and prognostic tool for cardiovascular disease. Non-invasive measurement of arterial stiffness using pulse wave analysis is a recently developed tool to identify cardiovascular risk. This study aims to examine the changes in arterial stiffness, immediately following sub-maximal exercise in people with metabolic syndrome. **Methods**: Ninety-four adult participants (19-80 years) with metabolic syndrome were measured for arterial stiffness using a SphygmoCor (SCOR-PVx, Version 8.0, Atcor Medical Private Ltd, USA) immediately before and within 5-10 min after an incremental shuttle walk test. The arterial stiffness measures used were pulse wave velocity (PWV), aortic pulse pressure (PP), augmentation pressure, augmentation index (AI), subendocardial viability ratio (SEVR) and ejection duration (ED) **Results**: There was a significant increase in most of the arterial stiffness variables following exercise ($p<0.05$). Exercise capacity had a strong inverse correlation with arterial stiffness and age ($p<0.01$) **Conclusion**: Age influences arterial stiffness. Exercise capacity is inversely related to arterial stiffness and age in people with metabolic syndrome. Exercise induced changes in arterial stiffness measured using pulse wave analysis is an important tool that provides further evidence in studying cardiovascular risk in metabolic syndrome.

10.1. Introduction

Metabolic syndrome (MS) is a cluster of cardiovascular risk factors. It includes a combination of increased blood glucose, alterations in the lipid levels, increased abdominal obesity and increased blood pressure. The prevalence of metabolic syndrome is increasing all over the world. Different countries show different clusters of epidemic risk factors. There is an increased risk of coronary artery disease as well as cerebrovascular disease in Asians with MS (Cheung and Thomas 2007). There is evidence for a large prevalence of MS and diabetes in South Asians and it is continuously escalating (Misra *et al*. 2007). Poor exercise capacity is one of the clinical characteristics of cardiovascular disease with low cardio respiratory fitness commonly observed in metabolic syndrome (LaMonte *et al*. 2005).

Arterial stiffness is also identified as a marker of cardiovascular diseases. Generally, an increase of arterial stiffness occurs with age. The increase in arterial stiffness is exacerbated by common cardiac risk factors (Mitchell 2006). Metabolic syndrome is independently associated with arterial stiffness, with the presence of carotid artery plaque and increased arterial wall thickness (Rundek *et al*. 2007). Components of metabolic syndrome alter the structure and function of the large arteries. There is an increase in circumferential wall stress and flow mediated shear stress of the arterial wall. Further, metabolic syndrome can accelerate vascular aging (Scuteri *et al*. 2004).

Exercise capacity is related to arterial stiffness as cardiac output is determined by aortic compliance. The reason is that proximal aortic compliance is the primary factor that determines pulse pressure and thus myocardial consumption

(Kingwell 2002). Acute exercise results in immediate changes in arterial compliance. Generally, there is an increase in vasodilatation of the vasovasorum of the aortic wall (independent of the increase in mean arterial pressure) due to various factors such as increase of temperature and nitric oxide in exercising muscles. The possible mechanism is the decrease in smooth muscle tone which transfers the stress forces from the stiff collagen fibres to the extensible elastin fibres (Kingwell *et al*. 1997).

Pulse wave analysis is one of the recently developed methods to measure arterial stiffness non-invasively. Alterations in both structure and function of the microcirculation occur during aging and this may play an important role in the pathophysiology of cardiovascular and metabolic diseases associated with aging (Gates *et al*. 2009). To the investigators' knowledge, the immediate changes in arterial stiffness following acute sub-maximal intensity exercise have not been studied on people with metabolic syndrome in India.

This study was carried out to establish the immediate changes in arterial stiffness using pulse wave analysis following acute sub-maximal exercise in people with metabolic syndrome.

10.1.1. Objectives

For people with metabolic syndrome:

- To establish the immediate changes in pulse wave velocity, pulse pressure, augmentation pressure, augmentation index, ejection duration

and sub-endocardial viability ratio following sub-maximal exercise using pulse wave analysis with applanation tonometry

- To establish the relationship between sub-maximal exercise capacity and arterial stiffness

- To establish the relationship between age, arterial stiffness and exercise capacity

10.1.2. Hypotheses

For people with metabolic syndrome

H1- There will be a significant change in arterial stiffness following acute sub-maximal exercise.

H2- There will be a significant relationship between exercise capacity and arterial stiffness.

H3- There will be a significant relationship between age, arterial stiffness and exercise capacity in people with metabolic syndrome

10.2. Methods

10.2.1. Subjects

After achieving institutional ethical approval, a free health screening for metabolic syndrome was carried out at Father Muller Medical College & Hospitals, Mangalore, India. The International Diabetic Federation's (IDF) definition was used to diagnose metabolic syndrome. The people diagnosed

with metabolic syndrome were invited to participate in the study. The participants were excluded if they had a resting heart rate >120 beats/ min after a 15 min rest, a systolic blood pressure >200 mmHg and/or a diastolic blood pressure > 100 mmHg, a history of any cardiovascular disorders such as unstable angina and myocardial infarction and a physical disability that prevented the safe performance of the test. In total, 94 eligible people with metabolic syndrome volunteered to participate in the study.

10.2.2. Sub-maximal exercise and exercise testing

The incremental shuttle walk test (ISWT) was the sub-maximal intensity exercise used to determine the participants' sub-maximal exercise capacity (Singh *et al*. 1992).

A medical history was obtained before the test to establish any contraindications to exercise testing. Participants rested for 15 min before starting the shuttle test. All the participants completed a Physical Activity Readiness Questionnaire (PAR-Q) and an International Physical Activity Questionnaire (IPAQ) to assure the safety before the test.

Two cones were placed nine metres apart and the distance to walk around the cones was 10 metres. The participant was required to walk between two cones in time to a set of auditory beeps played from a CD. Initially the walking speed was very slow and increased progressively to running. The ISWT had 12 levels and 1020 metres of maximum distance to be covered. The participants walked as long as they could until either they were too breathless to continue or not

able to pace themselves with the speed of the audio beeps. The completed number of shuttles were counted and recorded in metres.

The ISWT was measured twice with 30 min rest between the tests. This is to avoid the learning effects, as many individuals tend to perform better in repeated administration of the test (The Australian Lung Foundation 2009). The best result of the two tests was recorded. Only the standardized instructions from the developers' guidelines were used. The walking track was the same for all the participants. Exercise termination criteria was used as per the American Thoracic Society guidelines (2002), however none of the participants had to terminate the test due to any abnormal signs or symptoms. Rate of perceived exertion was measured using BORG's scale (6-20 scale) before, during (every min) and at the end of the test. The exercise was also terminated when the participants reached 17 (very hard) on BORG's scale.

10.2.3. Measurement of Arterial stiffness

The procedures for measuring arterial stiffness are given in detail in Chapter 3.2.2. The measurements were repeated within 5-10 min after the completion of an incremental shuttle walk test.

10.2.4. Statistical analysis

Data analysis was carried out using statistical software SPSS for windows (18.0). A paired t test was used to compare the changes in arterial stiffness variables following exercise. Pearson's correlation test was used to find the relationship between the variables used. A Levene's test was used to confirm

the homogeneity of the variances. The baseline differences among age groups were analysed using ANOVA and Tukey's test. ANCOVA was used to test the influence of age and sex in the arterial stiffness changes after exercise.

10.3. Results

10.3.1. Physical characteristics and exercise capacity

In total, 57 females and 37 males participated in the study aged from 19 to 80 (49.5 ± 13.8). According to age they were divided into three groups, young (19-40 years, n= 24, 31.1 ± 7.1), middle (41-60 years, n= 45, 50.5 ± 5.9) and old (61-80 years, n= 25, 65.4 ± 4.9). Their physical characteristic details are given in table 11.1. There was no significant difference in body mass index among the age groups (p= 0.103). The exercise capacity, measured by the distance achieved in the ISWT is listed in table 11.1 with age and gender differences. Young age groups and males had higher exercise capacity.

Table 10.1 Physical characteristics and exercise capacity of the participants

	HEIGHT (Mean± SD) cm	WEIGHT (Mean± SD) kg	BODY MASS INDEX (Mean± SD)	ISWT distance (m)	
Total	161.5 ± 9.6	72 ± 17.5	26.8 ± 4.0	Male	Female
Age 19-40 years (n=24)	165.5 ± 9.2	77.1 ± 13.5	28.1 ± 3.9	950.0 ± 111.8	786.4 ± 129.6
Age 41-60 years (n=45)	160.9 ± 9.2	72.2 ± 19.0	26.6± 4.5	722.9 ± 221.4	557.9 ± 171.6
Age 61-80 years(n=24)	158.8 ± 9.9	68.6±17.7	25.7± 2.7	497.1 ± 239.0	427.7 ± 183.6

10.3.2. Total group changes

The changes in arterial stiffness variables following exercise for the total group are illustrated in table 11.2. There was a significant increase in augmentation pressure and decrease in augmentation index following exercise. The ejection of blood from the ventricle into the aorta generates an aortic pressure pulse. In many cases, the timing of the peak pressure does not coincide with the timing of peak flow, such that peak pressure may occur later. In this event, there is usually a systolic shoulder on the ascending limb pressure curve, which coincides with peak flow, then a rise in pressure to the systolic peak. This increase in pressure is described as the augmentation pressure. The amount of augmentation pressure is quantified in terms of the relative change over the whole pulse. That is, once the early systolic shoulder and the peak or the late systolic shoulder is identified, the absolute augmentation is calculated. Then the augmentation index is defined.

There was a significant increase in ejection duration. Ejection duration is usually measured by detecting the beginning of the pulse and the closure of the aortic valve, using the incisura as a marker of the second heart sound. In the current study, the ejection duration was increased significantly after exercise in all the age groups. The heart rate significantly increased following exercise (table 11.2).

There was a significant decrease in SEVR following exercise. Subendocardial viability ratio (SEVR) is the ratio of energy supply and the demand of the heart. By transferring the ejection duration, the area under the systolic (atrial systole)

and diastolic (atrial diastole) part of the pulse curve can be calculated. The systolic part has been shown to be associated with the work of the heart and oxygen consumption. The diastolic part is associated with the pressure and time for coronary perfusion. Thus, they are related to energy supply of the heart.

When the heart contracts it generates a pulse or energy wave that travels through the circulation. The speed of travel of this pulse wave is termed the pulse wave velocity. The carotid-radial pulse wave velocity significantly increased immediately after exercise. There was a significant increase also in systolic pressure, mean pressure, heart rate, aortic systolic pressure and aortic diastolic pressure following exercise.

Table 10.2 Changes in pulse wave analysis variables following exercise

Variable	Measured time	Mean	±SD	Sig
Pulse Wave Velocity (m/s)	Before Exercise	8.15	±1.48	**
	After Exercise	8.50	±1.40	
Augmentation Pressure (mmHg)	Before Exercise	9.46	±4.74	*
	After Exercise	10.63	±6.08	
Aug Index	Before Exercise	25.83	±10.27	**
	After Exercise	22.50	±12.46	
Aug Index@75	Before Exercise	25.36	±9.31	NS
	After Exercise	25.86	±10.61	
Aortic Pulse Pressure (mmHg)	Before Exercise	36.17	±9.19	NS
	After Exercise	37.12	±11.98	
Aortic systolic Pressure (mmHg)	Before Exercise	121.33	±13.43	*
	After Exercise	124.65	±17.95	
Aortic Diastolic Pressure (mmHg)	Before Exercise	85.18	±9.44	*
	After Exercise	87.52	12.01	
Mean Pressure (mmHg)	Before Exercise	101.29	±10.42	**
	After Exercise	104.28	±13.80	
Ejection Duration (ms)	Before Exercise	37.89	±4.41	**
	After Exercise	42.37	±5.57	
Subendocardial Viability Ratio	Before Exercise	142.28	±26.44	**
	After Exercise	117.88	±25.22	
Systolic Pressure (mmHg)	Before Exercise	131.37	±13.80	**
	After Exercise	136.53	±18.65	
Diastolic Pressure (mmHg)	Before Exercise	83.94	±9.44	NS
	After Exercise	85.73	±11.76	
Heart Rate (bpm)	Before Exercise	73.85	±12.23	**
	After Exercise	83.83	±15.22	

n=94 *Significant at p<0.05 **Significant at p<0.01 NS- Non-significant

10.3.3. Age group changes

The differences in the changes in arterial stiffness variables in various age groups are listed in table 11.3. Changes in SEVR, heart rate and ejection duration were observed in all three age groups. A significant increase in pulse wave velocity was observed in those above 40 years. The change in augmentation index was significant only in young and middle age (41-60) groups. A significant increase in mean pressure, diastolic pressure and aortic diastolic pressure was observed only in the middle age group. A significant increase in systolic pressure and aortic systolic pressure was observed only in the old (61-80) age group. The increase in pulse pressure following exercise was statistically significant in the elderly group. The pulse pressure was markedly increasing with age following exercise (Table 11.3 and Table 11.4). Aortic pulse pressure is the systolic pressure minus the diastolic pressure. Theoretically, the systemic pulse pressure can be conceptualized as being proportional to stroke volume and inversely proportional to the compliance of the aorta. In myocardial disease progression, the ischemic threshold lowers with stiffer arteries.

10.3.4. Sex and age group differences

There were significant differences between sexes in the baseline measures of pulse wave velocity, augmentation pressure, SEVR, heart rate, ejection duration and augmentation indexes (Table 11.4). There was significant difference between the age groups in the baseline measures of augmentation pressure, heart rate, ejection duration, aortic pulse pressure and augmentation indexes (Table 11.4). The individual age group differences are listed in table 11.5.

However, there were no significant differences when the age groups and sex were combined. The changes following ISWT were not significantly different between the sexes. There was a significant difference between the age groups in SEVR, heart rate, ejection duration, aortic PP and augmentation index. However, there were no differences when the sex and age groups were combined.

Table 10.3 Comparison of changes in arterial stiffness with different age groups following exercise

		Age 19-40			Age 41-60			Age 61-80		
Variable	Time	Mean	±SD	Sig	Mean	SD	Sig	Mean	SD	Sig
Pulse Wave Velocity (m/s)	Before Exercise	8.20	±1.66	NS	8.33	±1.37	*	7.68	±1.49	*
	After Exercise	8.23	±1.34		8.62	±1.25		8.51	±1.77	
Aug. Pressure (mmHg)	Before Exercise	6.16	±3.60	NS	9.90	±3.99	NS	12.15	±5.45	NS
	After Exercise	6.87	±5.79		10.63	±4.35		14.77	±7.18	
Aug Index	Before Exercise	17.48	±10.66	**	27.97	±7.91	*	30.33	±9.61	NS
	After Exercise	9.54	±11.39		25.25	±9.24		30.75	±8.59	
Aug Index@ 75	Before Exercise	19.79	±10.04	NS	26.60	±8.55	NS	28.75	±7.73	NS
	After Exercise	18.44	±11.99		27.73	±8.11		29.93	±10.38	
Aortic PP (mmHg)	Before Exercise	29.90	±6.59	NS	36.73	±8.05	NS	41.84	±10.20	*
	After Exercise	29.89	±7.93		36.02	±8.98		47.54	±14.61	
Aortic SP (mmHg)	Before Exercise	114.71	±9.85	NS	122.96	±13.11	NS	125.05	±15.52	*
	After Exercise	115.73	±14.50		125.59	±16.22		132.46	±21.39	
Aortic DP (mmHg)	Before Exercise	84.81	±8.72	NS	86.26	±9.84	*	83.23	±9.45	NS
	After Exercise	85.78	±10.82		89.59	±12.74		84.88	±11.33	
Mean Pressure (mmHg)	Before Exercise	98.83	±8.97	NS	102.34	±10.60	*	101.69	±11.54	NS
	After Exercise	99.65	±12.40		105.95	±13.82		105.72	±14.72	
Ejection Duration (ms)	Before Exercise	40.11	±3.41	**	37.43	±4.02	**	36.47	±5.43	**
	After Exercise	47.37	±4.28		40.94	±5.22		40.00	±4.16	
SEVR	Before Exercise	132.40	±19.00	**	146.12	±24.23	**	144.75	±35.38	**
	After Exercise	97.70	±19.44		124.42	±24.52		125.74	±20.79	
Systolic Pressure (mmHg)	Before Exercise	127.33	±10.51	NS	132.18	±13.69	NS	134.05	±16.72	**
	After Exercise	130.89	±15.43		136.23	±17.43		143.44	±22.82	
Diastolic Pressure (mmHg)	Before Exercise	83.38	±8.95	NS	85.07	±9.72	*	82.05	±9.47	NS
	After Exercise	83.65	±10.61		87.95	±12.52		83.11	±10.77	
Heart Rate (bpm)	Before Exercise	79.75	±8.55	**	72.01	±11.25	**	71.41	±15.77	**
	After Exercise	98.84	±9.62		79.43	±12.51		76.96	±15.03	

n=94 *Significant at p<0.05 **Significant at p<0.01 NS- Non-significant PP- Pulse pressure, SEVR – Subendocardial viability ratio, Aug - Augmentation

Table 10.4 Comparison of arterial stiffness measures before and after ISWT in relation to sex and age groups

Variables	Comparison within pre ISWT measures- Significance			Comparison of pre ISWT and post ISWT measures- Significance		
	Sex	Age Group	Sex & Age Group	Sex	Age Group	Sex & Age Group
PWV (m/s)	**	NS	NS	NS	NS	NS
Aug Pressure (mmHg)	**	**	NS	NS	NS	NS
Aug Index	**	**	NS	NS	**	NS
Aug Index@75	**	**	NS	NS	NS	NS
Aortic Pulse Pressure (mmHg)	NS	**	NS	NS	*	NS
Aortic Systolic Pressure (mmHg)	NS	*	NS	NS	NS	NS
Aortic Diastolic Pressure (mmHg)	NS	NS	NS	NS	NS	NS
Mean Pressure (mmHg)	NS	NS	NS	NS	NS	NS
Ejection Duration (ms)	**	*	NS	NS	**	NS
SEVR	**	NS	NS	NS	**	NS
Systolic Pressure (mmHg)	NS	NS	NS	NS	NS	NS
Diastolic Pressure (mmHg)	NS	NS	NS	NS	NS	NS
Heart Rate (bpm)	**	*	NS	NS	**	NS

n=94 *Significant at p<0.05 **Significant at p<0.01 NS- Non-significant (Aug-Augmentation, SEVR- Subendocardial Viability Ratio)

Table 10.5 Comparison of pre ISWT arterial stiffness variables in relation to detailed age groups (significance)

Age Group (years)		PWV (m/s)	AUG P (mmHg)	AUG INDEX	AUG INDEX @75	AORTIC PP (mmHg)	AORTIC SP (mmHg)	AORTIC DP (mmHg)	MEAN P (mmHg)	EJECTION DURATION (ms)	SEVR	SP (mmHg)	DP (mmHg)	HR (bpm)
19-40	41-60	NS	**	**	**	**	*	NS	NS	NS	NS	NS	NS	NS
	61-80	NS	**	**	**	**	**	NS	NS	NS	NS	NS	NS	NS
41-60	61-80	NS	*	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
61-80	41-60	NS	*	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS

n=94 *Significant at p<0.05 **Significant at p<0.01 NS- Non-significant

PWV – Pulse Wave Velocity, SP- Systolic Pressure, DP- Diastolic Pressure, SEVR– Subendocardial Viability Ratio, HR- Heart Rate, Aug – Augmentation, PP- Pulse pressure

10.3.5. Relationships

In general, there was a negative correlation between shuttle walk exercise capacity (distance covered in metres) and certain arterial stiffness variables including systolic pressure, augmentation pressure, augmentation index, augmentation index @75 and aortic pulse pressure (Table 11.6). The significance was observed in augmentation pressure and aortic pressure in both sexes. The relationship between age and arterial stiffness variables are also listed in table 11.6. Augmentation pressure, aortic pulse pressure, augmentation index and augmentation index@75 had positive correlations with age in general as well as in different sexes.

The correlations among the arterial stiffness variables are also illustrated in Table 11.6. SEVR had a negative correlation with most of the other arterial stiffness variables and it was significant with heart rate, ejection duration, augmentation pressures and augmentation index @75. Augmentation pressure variables had a positive relationship with aortic pulse pressure.

The correlations between arterial stiffness and physical characteristics are given in Table 11.7. Height and weight had a negative correlation with augmentation pressure and the augmentation indexes. Height also had negative correlation with ejection duration and positive correlation with SEVR.

The exercise capacity was measured by distance covered in metres. Age had a strong negative correlation with exercise capacity ($r = -0.678$, $p=0.001$). The exercise capacity was higher in young age groups and lower in older age groups.

Table 10.6 Correlations between exercise capacity, age and arterial stiffness variables (correlation coefficients)

		PWV	Aug P	Aug Index	Aug Index @75	Aortic PP	Aortic SP	Aortic DP	Mean P	Ejection Duration	SEVR	SP	DP	HR
Exercise Capacity	All	.020	-.501**	-.403**	-.443**	-.425**	-.325	-.049	-.176	-.003	.077	-.235*	-.042	-.020
Age	Males	-.004	-.423**	-.343*	-.318	-.476**	-.204	.122	-.017	.086	-.011	-.086	.114	.074
	Females	-.275*	-.349**	-.240	-.253	-.346**	-.386**	-.206	-.300*	.153	-.144	-.356	-.210	.090
	All	.011	.552**	.547**	.478**	.497**	.381**	.071	.216*	-.178	.106	.243*	.069	-.185
Arterial Stiffness Variables	Males	.036	.495**	.561**	.426**	.522**	.308	-.021	.123	-.249	.206	.137	-.011	-.347*
	Females	.129	.570**	.494**	.497**	.457**	.408**	.137	.271*	-.257	.184	.307*	.136	-.198
	Aug P	0.14		0.73**	0.87**	0.70**	0.63**	0.22*	0.46**	0.27*	-0.34**	0.52**	0.20	0.19
	Aug Index	0.00			0.86**	0.45**	0.43**	0.18	0.29**	-0.20	0.17	0.18	0.19	-0.35**
	Aug Index @75	0.07				0.35**	0.43**	0.28*	0.39**	0.26*	-0.27*	0.24	0.26*	0.18
	Aortic PP	0.10					0.69**	0.03	0.35**	-0.14	-0.05	0.68**	0.02	-0.23*
	Aortic SP	0.20**						0.74**	0.91**	-0.04	-0.05	0.95**	0.73**	-0.04
	Aortic DP	0.18							0.94**	0.07	-0.02	0.68**	1.00**	0.15
	Mean P	0.23*								0.09	-0.10	0.86**	0.93**	0.14
	Ejection Duration	0.13									-0.84**	0.07	0.02	0.85**
	SEVR	-0.08										-0.15	0.03	-0.80**
	SP	0.20											0.66**	0.10
	DP	0.18												0.10
	Heart Rate	0.13												

n=94 *Significant at p<0.05 **Significant at p<0.01

PWV – Pulse Wave Velocity (m/s), SP- Systolic Pressure (mmHg), DP- Diastolic Pressure (mmHg), SEVR– Subendocardial Viability Ratio, HR- Heart Rate, Aug – Augmentation, PP- Pulse pressure (mmHg), Ejection duration (ms), HR (bpm)

Table 10.7 Correlations between physical characteristics and arterial stiffness

Variables	HEIGHT	WEIGHT	BODY MASS INDEX
PWV (m/s)	.172	-.095	-.136
Aug Pressure (mmHg)	-.396**	-.205*	-.070
Aug Index	-.366**	-.287**	-.155
Aug Index@75	-.488**	-.235*	-.080
Aortic PP (mmHg)	-.113	-.137	-.077
Aortic SP (mmHg)	-.130	-.129	.042
Aortic DP (mmHg)	-.084	-.051	.125
Mean P (mmHg)	-.119	-.088	.109
Ejection Duration (ms)	-.214*	.013	.176
SEVR	.212*	.027	-.109
SP (mmHg)	-.040	-.045	.101
DP (mmHg)	-.068	-.053	.114
HR (bpm)	-.181	.126	.154

n=94 *Significant at p<0.05 **Significant at p<0.01

PWV – Pulse Wave Velocity, SP- Systolic Pressure, DP- Diastolic Pressure, SEVR– Subendocardial Viability Ratio, HR- Heart Rate, Aug – Augmentation, Pulse pressure

10.4. Discussion

The results show that there are noticeable changes in arterial stiffness variables immediately after exercise.

10.4.1. Changes in arterial stiffness following acute exercise

10.4.1.1. Pulse wave velocity

Similar to the currentresults, many studies found an increase in pulse wave velocity within 10 min after acute exercise (McClean *et al*. 2007; Naka *et al*. 2003). Pulse wave velocity is inversely related to plasma viscosity and arterial distensibility (Peterson 1954). Acute exercise results in an expansion in plasma volume and decreased blood viscosity (Thompson *et al*. 2001). Following exercise, endothelial and neurohumoral influences results in vasodilatation and

the distensibility of the artery is decreased (Naka *et al*. 2003). Aizawa and Petrella (2008) studied the changes in arterial stiffness (arterial distensibility and β stiffness index using ultrasound following exercise in hypertensive patients. They found no changes in arterial stiffness immediately (10 min) and after 24 hrs of exercise. They suggest that there is an increase in oxidative stress in older age and cardiovascular risks such as hypertension. It leads to an impaired endothelium dependant vasodilatation. Therefore, it could be assumed that the increase in pulse wave velocity after acute exercise depends on the severity of endothelial dysfunction due to either age or any other subclinical cardiovascular risks.

10.4.1.2. Augmentation index

In the current study, augmentation index reduced after acute exercise. Previous studies had contradictory results. Some of them had an increase (DeVan *et al*. 2005; Yoon *et al*. 2010) and some had a decrease (Munir *et al*. 2008; Sharman *et al*. 2005) in augmentation index following acute exercise. Studies claim that the effects of vasodilatation following exercise results in this reduction (Munir *et al*. 2008). However, Munir *et al* (2008) found a reduction in all arterial stiffness variables including pulse wave velocity following acute exercise. The contradictions may be due to the differences in the severity of the endothelial dysfunction and the combined effect of the vasodilatation. Exercise increases the arterial distensibility by stretching and increases the intravascular diameter. At the same time, it decreases arterial distensibility by reducing the involvement of arterial muscle tone to arterial stiffness (Naka *et al*. 2003). Another study (Aizawa and Petrella 2008) found a statistically non-significant increase in augmentation index immediately after exercise and then a non-significant

decrease after 20 weeks aerobic training with hypertensives. They state that the changes depend on the age, the aerobic capacity, and their effects in vasodilatation. The augmentation index corrected for 75% (AIx@75%) heart rate is another important variable in arterial stiffness because of the influence of the heart rate on augmentation index. Wilkinson *et al*.(2000) found a linear reduction in augmentation index when pacing the heart rate from 60 to 110 on pacemakers. In the current study, AIx@75%HR did not change significantly after exercise. Therefore, it can be assumed that the reduction in augmentation index in the current study was due to the influence of the increased heart rate during exercise.

10.4.1.3. Aortic pulse pressure (PP) and subendocardial viability ratio (SEVR)

Aortic pulse pressure also showed a considerable increase with age. Similar to the currentresults, Sharman *et al*.(2005) also found an increase in central and peripheral systolic/diastolic pressures, pulse pressure and mean arterial pressure. Aortic stiffness is stimulated during exercise, resulting in the increase in pulse pressure and decrease in myocardial perfusion (Kingwell 2002). The reduction in myocardial perfusion is confirmed as SEVR also significantly reduced following exercise. Similar reduction were found in healthy non-smokers and light-smokers (Doonan *et al*. 2011; Edwards *et al*. 2008) This becomes important because of its relationship with ischemic risk when combined with increased ejection duration, heart rate and shortening of the diastolic period (O'Rourke 2005).

10.4.2. Age and arterial stiffness

The results show that the arterial stiffness increases with the age. The increased arterial pressure in higher age groups compared with lower age groups confirms the changes in vascular structure due to aging. Aging elicits several changes in the endothelium by gradually altering its phenotype from an anti-atherosclerotic to a pro-atherosclerotic one (Brandes *et al*. 2005). These changes are associated with the endothelial dysfunction mediated with nitric oxide deficiencies and increased production of reactive oxygen species (Versari *et al*. 2009). These lead to thick and stiff arterial walls and an increased number and size of smooth muscle cells. Further, it results in increased peripheral resistance and increased afterload (Heckman and McKelvie 2008). This stiffening effect is progressive with age and reduces the cushioning function of the arteries and leads to devastating effect on the myocardial micro circulation (O'Rourke and Hashimoto 2007). Nagai *et al*., (1998) also found that carotid intima-media thickness was increasing with age.

In the current study, the augmentation pressure increased significantly following exercise. Augmentation pressure and augmentation index are strong predictors of cardiovascular disease (Nurnberger *et al*. 2002; Weber *et al*. 2004). In the current study, there was statistical significance in the changes in the augmentation pressure. It is important to note the increase in augmentation pressure with age (Table 11.3) and the positive correlations with age and exercise capacity (table 11.6). Augmentation pressure and augmentation index showed nearly two-fold increase in the older ages (Table 11.3). Vaitkevicius *et al* (1993) also found relatively similar results, up to 2.5-fold increase in augmentation pressure in healthy people, with advancing age. Another study on

a Chinese population also had a similar result. There was 2.4-fold increase in arterial stiffness in 80 year olds compared with 20 year old groups (Avolio *et al*. 1983).

10.4.3. Exercise capacity and arterial stiffness

Another important finding in the current study is that most of the arterial stiffness variables including augmentation pressure, augmentation index, and aortic pulse pressure had an inverse correlation with exercise capacity. That means that the higher the exercise capacity, the lower the arterial stiffness. Vaitkevicius *et al* (1993) also found an inverse relationship between $VO_{2\ max}$ and arterial stiffness in sedentary adults. It confirms that arterial stiffness could be a determinant of exercise capacity in metabolic syndrome. A previous study on healthy volunteers also finds an association between arterial stiffness and exercise capacity (Hagg *et al*. 2005). The changes in arterial stiffness were correlated with echocardiograph changes in coronary flow velocity reserve, intima–media thickness, stiffness index of coronary artery and flow mediated vasodilatation of the forearm.

Each of the components of metabolic syndrome may account for the observed reduction in exercise capacity. Fang *et al*. (2005) studied the exercise capacity, echocardiography and heart rate recovery of type 2 diabetic patients. They found that the reduced exercise capacity in patients with type 2 diabetes was associated with diabetes control, subclinical LV dysfunction and impaired heart rate recovery. Fagard *et al*. (1991) studied blood pressure in exercise testing on hypertensive men and followed them up for >7 years. They found that intra-arterial pressure at rest, sub maximal exercise and peak exercise could

significantly predict mortality and the incidence of cardiovascular disease, independent of age. However many studies emphasize that poor exercise capacity can individually account for cardiovascular risk. Myers *et al* (2002) studied >6000 consecutive men, with or without a history of cardiovascular disease, referred for treadmill exercise test and followed them more than six years. They found that exercise capacity was a more powerful predictor of mortality than other established risk factors for cardio vascular disease. Jae *et al* (2010) found an inverse correlation between cardio respiratory fitness and arterial stiffness in people with and without metabolic syndrome. However, there was higher arterial stiffness in people with metabolic syndrome. Spies *et al*. (2005) found that metabolic syndrome with coronary artery disease is associated with poor exercise capacity and heart rate recovery independent of its components (increased glucose, blood pressure and adiposity). Another study found a significantly poor exercise capacity in metabolic syndrome in the absence of coronary artery syndrome, even though there was no systolic dysfunction and vascular pathology (Arat *et al*. 2008). Wong *et al*. (2005) studied the myocardial function with tissue Doppler imaging, arterial stiffness using radial applanation tonometry and exercise capacity using expired gas analysis in people with metabolic syndrome. They found that subclinical myocardial dysfunction was associated with metabolic burden and reduced cardio respiratory fitness. They suggest that metabolic syndrome with subclinical myocardial abnormalities and reduced exercise fitness may have higher risk of cardiovascular disease events and heart failure. Further, the low exercise capacity may contribute to adverse outcomes associated with metabolic syndrome.

10.4.4. Limitations

A larger number of participants would have improved the significance of the arterial stiffness changes. The measurements were taken at different times both morning and afternoon due to participants' schedules and availability. A same time measurement would have avoided any diurnal variation on the measurement. The study could not control for the medications used by the participants, who were under treatment for different conditions such as diabetes, hypertension and obesity. Due to lack of researchers and participants' availability, no control group was studied. An age matched control group would be more informative in the arterial stiffness changes in people with metabolic syndrome.

10.5. Conclusions

Age influences arterial stiffness. Age is one of the major contributing factors for structural vascular changes. Exercise capacity is inversely related to arterial stiffness and age. Acute exercise increase arterial stiffness in metabolic syndrome. Non-invasive measurement of arterial stiffness after exercise is an important and easy to use tool that increases knowledge of cardiovascular risk in metabolic syndrome.

10.6. References

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CHAPTER 11. EFFECTS OF AN IT-SUPPORTED HOME-BASED EXERCISE PROGRAMME ON METABOLIC SYNDROME IN INDIA

Abstract

Background: Lifestyle modification with more physical activity and diet control is an important strategy in the management of metabolic syndrome. This study aimed to establish the effectiveness of a home-based exercise programme with information technology (IT) support in people with metabolic syndrome in India. **Methods**: 94 participants with metabolic syndrome (mean age 49.5±13.8) were randomized into two groups. Both the groups received a 12-week customized home exercise programme and group-2 received additional IT support for health education. Before and after the exercise programme, both the groups were measured for arterial stiffness using pulse wave analysis, exercise capacity using an incremental shuttle walk test (ISWT) and quality of life (QoL) using SF-36 questionnaire. **Results**: There was a significant reduction ($p<0.05$) in systolic pressure, mean pressure and aortic systolic pressure within both the groups following the exercise programme. Pulse wave velocity, aortic pulse pressure and aortic diastolic pressure showed significant reductions ($p<0.05$) only in the IT-supported group-2. There were no changes in characteristics of quality of life except on vitality ($p<0.05$) in group-2. There were a significant improvement in fasting blood glucose ($p<0.05$) in group-2, cholesterol ($p<0.05$) in group-1 and triglycerides ($p<0.05$) in both the groups. **Conclusion**: Metabolic syndrome is reversible in 16% of the participants with regular home-based exercises. Home-based exercise programmes can improve arterial stiffness, hyperglycaemia and dyslipidaemia in metabolic syndrome. IT support through mobile texts has an additional impact by increasing exercise duration and frequencies, on the home-based exercises for people with metabolic syndrome.

11.1. Introduction

11.1.1. Metabolic syndrome

Metabolic syndrome is a cluster of cardiovascular risk factors. They are increased blood glucose, increased blood pressure, high triglycerides, low level of high-density lipoproteins and abdominal obesity (Grundy *et al*. 2004). In recent decades, this condition has been given importance in numerous clinical studies due to its increasing prevalence all over the world. The risk of developing cardiovascular disease is 3-10 times higher in people with metabolic syndrome (Nestel *et al*. 2007). Various criteria have been developed and the definitions of the National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III) (Grundy *et al*. 2004) and International Diabetic Federation (IDF 2006) are extensively reviewed and widely used.

Poor exercise capacity has been observed in people with metabolic syndrome and it was found that every individual component of metabolic syndrome is related to poor exercise capacity (Arat *et al*. 2008). An increased arterial stiffness was also found in people with metabolic syndrome that is independent of its relationship with the known cardiovascular risk factors (Sipila *et al*. 2007) People with metabolic syndrome have shown impaired health related quality of life compared with people without metabolic syndrome (Han *et al*. 2009).

11.1.2. Exercise programmes

A lack of physical activity is closely related to metabolic syndrome and it increases its risk (DuBose *et al*. 2004). In the management of metabolic syndrome, lifestyle modification with more physical activities, control of weight

and diet are the major recommendations by the American Heart Association (AHA) and the National Heart, Lung, and Blood Institute (NHLBI) (Grundy *et al*. 2005). Exercise training programmes were shown to be effective in improving the individual criterion risk factors of metabolic syndrome. Aerobic exercise programmes especially, were proven as an effective treatment strategy in the management of metabolic syndrome (Katzmarzyk *et al*. 2003). Griel *et al* (2003) found that a 12-week exercise programme for people with metabolic syndrome was effective when using two different intensities. They observed that the higher the intensity, the higher the effectiveness in reducing the cardiac risk factors. Roberts *et al* (2006b) found a significant improvement in insulin sensitivity and vascular inflammatory markers with a short-term (21 days), intensive supervised exercise and diet programme. Regular exercise programmes were also effective in the elderly with metabolic syndrome (Kemmler *et al*. 2009).

11.1.3. Home-based exercise programme

Structured, hospital-based, 6-12 weeks exercise-based cardiac rehabilitation programmes have been running successfully for patients with cardiac disease. Hospital-based cardiac rehabilitation programmes have been effective in improving exercise capacity and characteristics of metabolic syndrome (Gayda *et al*. 2008; Onishi *et al*. 2009). However, poor attendance has been observed in hospital-based programmes due to various barriers. Lack of awareness, travelling, scheduling interference with activities of daily living, dislike of programme format and financial issues are the major patient oriented barriers for hospital-based programmes (Thomas 2007; Witt *et al*. 2005). Home-based studies are providing a viable alternative to the hospital-based programmes at a low cost. Many studies proved that home-based exercise programmes were as

equally effective as supervised hospital or centre-based group exercise programmes (King *et al*. 1991; Jolly *et al*. 2007; Jolly *et al*. 2009; Dalal *et al*. 2010). A Cochrane systemic review and meta-analysis states that home-based cardiac rehabilitation programmes are as equally effective as hospital-based programmes in improving cardiac health and health related quality of life (Dalal *et al*. 2010).

Regular structured physical activities such as exercise, sports and dancing could reduce the incidence of metabolic syndrome. They are more beneficial than lifestyle physical activities such as house work and occupation (DuBose *et al*. 2003). Simple home-based walking exercise programmes also have been effective in improving functional status, symptoms and disease perception in cardiac disease (Corvera-Tindel *et al*. 2004).

Early identification of cardiovascular threats and appropriate management can prevent cardiac incidents and the associated costs. However, to the investigators' knowledge, in India, there are no early programmes introduced for people with cardiac risk factors prior to an incidence of cardiovascular disease. This study has been designed to establish the effectiveness of a home-based exercise programme for people with metabolic syndrome.

11.1.4. Information technology (IT) support

Telehealth counselling can increase motivational lifestyle behaviour changes and extend the reach and efficacy of cardiovascular risk prevention programmes (Nolan *et al*. 2011). Mobile phones are one of the important developments in communication and have become an unavoidable part of many

people's lives. Use of text messages and phone calls through mobile phones have increased the uptake of home-based cardiac rehabilitation in pilot studies (Marlien Varnfield 2011). Reminder text messages can improve exercise frequencies and so the implementation of a home-based exercise programme (Prestwich *et al*. 2009). The current study has been designed to establish the effects of IT support through texts and calls through mobile phones in a home-based exercise programme for metabolic syndrome.

11.1.5. Objectives

For people with metabolic syndrome in India:

- To establish the effectiveness of a home-based exercise programme on arterial stiffness using pulse wave analysis
- To establish the effectiveness of a home-based exercise programme on exercise capacity using a shuttle walk test
- To establish the effectiveness of a home-based exercise programme on health related quality of life
- To establish the effectiveness of IT support in addition to a home-based exercise programme

11.1.6. Hypotheses

For people with metabolic syndrome in India:

H1 - There will be significant improvement in arterial stiffness, quality of life and exercise capacity following a home-based exercise programme

H2 - There will be significant effect of IT support on arterial stiffness in addition to a home-based exercise programme

11.2. Methods

The same participants as in chapter 10, volunteered in this study. In total, there were 94 people (male = 43, female = 51) aged 19-80 years (mean age 49.5±13.8) with metabolic syndrome according to the International Diabetic Federation's (IDF) criterian. All the participants completed a health related quality of life questionnaire (SF-36 Version 2) (Ware *et al*, 1993 and 2000). The participants were randomized into two groups. Both groups underwent an exercise programme. In addition to that, group-2 received IT support.

Blood tests were carried out at the time of screening for metabolic syndrome and then after a 12 weeks follow-up. The participants were asked to fast for a minimum of nine hours before sampling their blood and were measured for blood glucose, total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides.

11.2.1. Sub-maximal exercise and exercise testing

The incremental shuttle walk test (ISWT) was the sub-maximal intensity exercise used to determine the participants' sub-maximal exercise capacity (Singh *et al*. 1992). A medical history was obtained before the test to establish any contraindications to exercise testing. All the participants completed a Physical Activity Readiness Questionnaire (PAR-Q) (Adams 1999) and an International Physical Activity Questionnaire (IPAQ) (Booth 2000) before the

test. Participants were asked not to smoke for three hours before the study. Participants took a rest for 15 min before starting the shuttle test.

Two cones were placed nine metres apart and the distance to walk around the cones was 10 metres. The participant was required to walk between two cones in time to a set of auditory beeps played from a CD. Initially the walking speed was very slow and increased progressively to running. The ISWT had 12 levels and 1020 metres was the maximum distance to be covered. The participants walked as long as they could until either they were too breathless to continue or not able to pace themselves with the speed of the audio beeps. The completed number of shuttles were counted and recorded in metres.

The ISWT was measured twice with 30 min rest between the tests. This is to avoid the learning effects as many individuals tend to perform better in repeated administration of the test. The best result from the two tests was recorded. Only the standardized instructions from the developers' guidelines were used. The walking track was the same for all the participants. Exercise termination criteria was used as per the American Thoracic Society guidelines (2002), however none of the participants had to terminate the test due to any abnormal signs or symptoms. Rate of perceived exertion was measured using Borg's scale (6-20 scale) (Borg 1998) before, after each minute during the test and at the end.

11.2.2. Arterial stiffness

The procedures for measuring arterial stiffness are given in detail in Chapter 3.2.2. The measurements were taken immediately before and within 5-10 min after incremental shuttle walk test.

11.2.3. Exercise programme

All the participants were instructed in how to participate in the customized home exercise programme. The exercise programme was structured with aerobic exercises that included a sufficient warm up and cool down phases. The exercises included stretching of major muscle groups, walking, marching on the spot, sit-ups in a chair, step up and down on a stair, circuit training with small weights. The participants were trained to monitor their breathlessness using Borg's scale and advised to maintain a target level of somewhat hard (11-13). A printed booklet with instructions and pictures of exercises was given to them. All the participants were encouraged to exercise at least for 30 min or more and five days per week. They were encouraged to carry out brisk walking for at least 30 min a day as often as possible. They were issued with and asked to maintain an exercise record sheet. They were also advised on the importance of weight control, diet and implementation of a balanced diet in relation to their lifestyle.

11.2.4. IT support

All the participants were given an explanation and encouraged to adopt a healthy lifestyle with modification in diet, smoking cessation and regular exercise as needed. For the next 12 weeks the participants of group- 2 were regularly provided IT support on health education and group- 1 acted as control group. They were sent two personalized mobile texts per week that carried information on their health and management of metabolic syndrome. This included reminders for exercises, importance of exercises, details of diet and diet control, smoking cessation, information on blood glucose and lipid levels etc. All the text messages were sent to the participants' mobile phones through

the internet using multi-messaging software. In India, too many uncontrolled advertising and anonymous mobile texts were limiting the participants' ability to read all the texts delivered to their mobile. In view of this limitation, the mobile texts were sent to the participants' mobile phones with a specific acronym and the participants were familiarized to it for an easier identification. They also received regular phone calls at least once a week to discuss their health and were encouraged to exercise regularly.

All the participants were tested again for arterial stiffness, exercise capacity and health related quality of life at the end of exercise programme i.e. after 12 weeks.

11.2.5. Statistical analysis

The International Diabetic Federation's (IDF) criterion for metabolic syndrome was used as it had specific abdominal obesity cut off points for South Asians (IDF 2006). It is >90 cm for men and >85 cm for women.

Data analysis was carried out using statistical software SPSS for windows (18.0). Data were checked for univariate and multivariate outliers using standard Z-distribution cut-offs and Mahalanobis distance tests respectively. Normality of distribution was tested using Kolmogorov-Smirnov test. A paired t-test was used to analyse the changes within groups following the exercise programme. A mixed-within subject analysis of variance was used to compare the changes in the measured variables between groups following the exercise programme. A two-way ANCOVA test was used to find the differences in the

variables in relation to sex and age. Statistical significance was indicated if $p<0.05$.

11.3. Results

11.3.1. Changes in arterial stiffness

Among 94 initial participants, 61 participants (Group–1 = 28: Group–2 = 33) completed the post intervention tests. The changes in arterial stiffness variables following exercise within groups and between groups are listed in table 12.1. There was a significant reduction in the following arterial stiffness variables in the particiapnts following the exercise programme: pulse wave velocity, aortic pulse pressure and aortic diastolic pressure in group- 2 and systolic pressure, mean pressure, and aortic systolic pressure in both groups. However, there was no significant difference between the groups for these changes.

Table 11.1 Changes in arterial stiffness variable following exercise programme between the groups

		Group- 1 Home-based exercise (n=28)		Group- 2 Home-based exercise + IT support (n=33)		Between Groups Sig
		Mean ± SD	Within Group Sig	Mean ± SD	Within Group Sig	
Pulse Wave Velocity (m/s)	Pre	8.1 ±1.6	NS	7.9 ±1.5	*	NS
	Post	8.0 ±1.6		7.4 ±1.5		
Aug Pressure (mmHg)	Pre	9.0 ±5.1	NS	7.6 ±4.6	NS	NS
	Post	8.6 ±3.6		6.6 ±4.5		
Aug index	Pre	25.4 ±11.3	NS	23.6 ±11.2	NS	NS
	Post	27.5 ±12.1		22.17 ±13.0		
Aug index @ 75HR	Pre	24.0 ±10.9	NS	21.9 ±10.4	NS	NS
	Post	26.0 ±10.0		20.2 ±11.8		
Aortic Pulse Pressure (mmHg)	Pre	36.4 ±7.7	NS	33.9 ±9.3	*	NS
	Post	33.8 ±7.4		30.9 ±7.8		
Aortic Systolic Pressure (mmHg)	Pre	121.8 ±13.5	**	118.9 ±12.1	**	NS
	Post	117.0 ±13.4		112.7 ±12.2		
Aortic Diastolic Pressure (mmHg)	Pre	85.3 ±12.3	NS	85.1 ±8.2	*	NS
	Post	83.2 ±9.7		81.8 ±9.9		
Mean Pressure (mmHg)	Pre	101.4 ±12.8	*	100.1 ±8.6	*	NS
	Post	98.4 ±11.0		95.5 ±10.2		
Ejection Duration (ms)	Pre	38.3 ±3.9	NS	37.0 ±5.0	NS	NS
	Post	37.1 ±4.9		37.5 ±3.7		
SEVR	Pre	144.1 ±29.6	NS	146.8 ±22.5	NS	NS
	Post	141.9 ±23.8		148.2 ±31.4		
Systolic Pressure (mmHg)	Pre	131.8 ±13.2	*	129.2 ±11.5	**	NS
	Post	126.4 ±15.3		122.2 ±12.4		
Diastolic Pressure (mmHg)	Pre	84.4 ±12.4	NS	84.0 ±8.1	NS	NS
	Post	81.9 ±9.8		80.6 ±9.6		
Heart Rate (bpm)	Pre	72.0 ±12.0	NS	71.4 ±9.0	NS	NS
	Post	72.0 ±11.6		70.1 ±11.0		

*Significant at p<0.05 **Significant at p<0.01 NS- Non Significant

Abbreviations: SEVR – Subendocardial Viability Ratio; Aug – Augmentation

11.3.2. Changes in health related quality of life

The changes in quality of life are listed in table 12.2. There were no significant changes in any of the health related quality of life measures following the exercise programme within the groups. There were no significant differences in quality of life changes between the groups, except vitality scores. Group-2 had a higher statistical improvement in vitality compared with group-1.

Table 11.2 Changes in health related quality of life following exercise programme between the groups

		Group-1 Home-based exercise (n=28)			Group-2 Home-based exercise + IT support (n=33)			Between Group sig
		Mean	±SD	Within Group Sig	Mean	±SD	Within Group sig	
Physical Functioning	Pre	69.8	±26.0	NS	72.6	±23.0	NS	NS
	Post	74.5	±24.3		76.7	±23.9		
Role Physical	Pre	78.6	±37.7	NS	80.2	±32.3	NS	NS
	Post	79.5	±31.2		74.1	±34.4		
Bodily Pain	Pre	76.4	±24.1	NS	72.6	±25.4	NS	NS
	Post	72.9	±24.5		71.5	±27.2		
General Health	Pre	65.1	±17.8	NS	68.4	±20.4	NS	NS
	Post	65.3	±16.9		70.0	±19.4		
Vitality	Pre	58.2	±15.7	NS	64.0	±12.8	NS	*
	Post	60.0	±15.3		67.1	±12.9		
Social Functioning	Pre	75.5	±21.4	NS	76.7	±24.3	NS	NS
	Post	77.7	±20.5		78.9	±20.9		
Role-Emotional	Pre	78.6	±38.7	NS	72.4	±39.9	NS	NS
	Post	78.6	±35.4		78.2	±35.9		
Mental Health	Pre	72.4	±19.9	NS	73.1	±15.7	NS	NS
	Post	74.6	±17.7		75.3	±15.4		
Physical Functioning NB	Pre	45.3	±9.3	NS	45.7	±9.6	NS	NS
	Post	46.4	±10.2		47.4	±10.0		
Role Physical NB	Pre	50.2	±10.6	NS	50.6	±9.1	NS	NS
	Post	50.4	±8.8		48.9	±9.7		
Bodily Pain NB	Pre	52.6	±10.3	NS	51.0	±10.9	NS	NS
	Post	51.1	±10.5		50.5	±11.6		
General Health NB	Pre	47.7	±8.3	NS	49.2	±9.6	NS	NS
	Post	47.7	±7.9		50.0	±9.1		
Vitality NB	Pre	50.6	±7.4	NS	53.3	±6.1	NS	*
	Post	51.4	±7.2		54.8	±6.1		
Social Functioning NB	Pre	46.5	±9.3	NS	47.0	±10.5	NS	NS
	Post	47.4	±8.8		48.0	±9.1		
Role-Emotional NB	Pre	48.5	±12.2	NS	46.6	±12.6	NS	NS
	Post	48.5	±11.2		48.4	±11.4		
Mental Health NB	Pre	48.4	±11.3	NS	48.8	±8.9	NS	NS
	Post	49.6	±10.1		50.0	±±8.7		
Physical Component Summary	Pre	47.1	±7.8	NS	47.6	±8.6	NS	NS
	Post	47.0	±8.7		47.2	±8.1		
Mental Component Summary	Pre	49.1	±10.2	NS	49.3	±8.4	NS	NS
	Post	50.0	±8.5		51.1	±7.4		

*Statistically significant at p<0.05, **Statistically significant at p<0.01, NS- Not Significant

11.3.3. Changes in metabolic syndrome

There was a significant reduction in fasting blood glucose in group-2 and cholesterol in group-1 (table 12.3). The level of triglycerides was significantly reduced in both the groups following the exercise programme. However, there was no difference in these changes between groups. There was a mild reduction in waist circumference following exercise programme in both the groups, although it was not statistically significant (table 12.3). Among the participants who returned for post programme examination, 43 complete datasets were available to analyse for the metabolic syndrome criteria. Among them, 16.3% participants (15.8% in group-1 and 16.7% in group- 2) were no longer categorized as having metabolic syndrome after the exercise programme.

Table 11.3 Changes in blood glucose, lipids and abdominal obesity following exercise programme between groups

Variables		Group- 1 Home-based exercise (n=28)			Group- 2 Home-based exercise + IT support (n=33)			Between Groups Sig
		Mean ± SD		Sig	Mean ± SD		Sig	
Fasting Blood glucose (mg.dL-1)	Pre	127.6	±51.0	NS	127.7	±40.0	**	NS
	Post	122.6	±51.1		122.5	±36.7		
High density lipoprotein (HDL) (mg.dL-1)	Pre	37.1	±6.0	NS	38.5	±5.4	NS	NS
	Post	38.6	±8.1		40.4	±6.0		
Triglycerides (mg.dL-1)	Pre	198.8	±79.1	*	222.5	±142.5	**	NS
	Post	168.7	±62.3		199.1	±142.7		
Cholesterol (mg.dL-1)	Pre	225.2	±55.5	**	238.5	±60.3	NS	NS
	Post	207.0	±47.6		227.6	±64.2		
Low density lipoprotein (LDL) (mg.dL-1)	Pre	111.4	±37.5	NS	115.9	±26.7	NS	NS
	Post	107.0	±31.8		113.6	±28.4		
Waist Circumference (cm)	Pre	103.0	±10.7	NS	101.0	±7.0	NS	NS
	Post	102.7	±10.8		100.9	±7.8		
Body Mass Index (kg/m^2)	Pre	26.0	±4.5	NS	26.9	±4.2	NS	NS
	Post	26.2	±4.1		26.8	±4.1		

*-Statistically significant at p<0.05 **-Statistically significant at p<0.01 NS- Non Significant

11.3.4. Effects of age and gender

There was no significant difference in most of the arterial stiffness variables due to the effects of age and sex (table 12.4). A significant difference was observed in the following variables with a low effect size: aortic pulse pressure (sex vs. group effect size 0.075) and SEVR (age effect size 0.127 and age vs. group effect size 0.148)

Table 11.4 Changes in arterial stiffness due to the effects of age and sex between the groups

Variable	Sex	Sex vs. Group	Age	Age vs. Group
Pulse Wave Velocity (m/s)	NS	NS	NS	NS
Augmentation Pressure (mmHg)	NS	NS	NS	NS
Augmentation index	NS	NS	NS	NS
Augmentation index @ 75HR	NS	NS	NS	NS
Aortic Pulse Pressure (mmHg)	NS	*	NS	NS
Aortic Systolic Pressure (mmHg)	NS	NS	NS	NS
Aortic Diastolic Pressure (mmHg)	NS	NS	NS	NS
Mean Pressure (mmHg)	NS	NS	NS	NS
SEVR	NS	NS	*	*
Ejection Duration (ms)	NS	NS	NS	NS
Systolic Pressure (mmHg)	NS	NS	NS	NS
Diastolic Pressure (mmHg)	NS	NS	NS	NS

*-Statistically significant at p<0.05 **-Statistically significant at p<0.01 NS-Non Significant

11.3.5. Changes in exercise capacity

The participants' exercise capacity was not changed significantly, though there was a small improvement in the ISWT distance. The participants in group-1 improved from 685 ± 266.4m to 690 ± 259.3m (p=0.718) and the participants in

group-2 improved from 732 ±230.6m to 748 ± 233.6m (p= 0.162). There was no significant age or sex related difference in the changes in ISWT distance following the exercise programme (p values: sex=0.554, sex vs. group = 0.367, age= 0.09, age vs. group= 0.152). From the exercise record of the participants, 84.7% of group- 1 and 90% of group- 2 exercised for >30 min a day. There was a significant difference in the exercise duration between the groups. Out of 12-weeks exercise programme, the mean duration of regular exercise was 7.2 ± 4.7 weeks for group-1 and 10.0 ± 4.0 for group- 2 (p=0.019).

11.4. Discussion

11.4.1. Changes in blood glucose, lipids and metabolic syndrome

Previous studies have demonstrated that exercise training has been beneficial in the reduction of hyperglycaemia in metabolic syndrome (Dumortier *et al*. 2003; Katzmarzyk *et al*. 2003). Exercise training increases phosphorylation of glucose and stimulates muscle glycogen synthesis and insulin sensitivity (Perseghin *et al*. 1996). In the current study, low to moderate intensity exercises (11-13 on Borg's scale) were used for a minimum of 30 minutes. In general, at least 30 min of exercise is recommended as an effective physical activity by the American College of Sports Medicine (Pate *et al*. 1995). Johnson *et al* (2007) found that moderate intensity exercise is more effective than the high intensity exercise in improving exercise capacity. They also found that moderate intensity exercises improve insulin sensitivity and triglyceride response. Dumortier *et al* (2003) claim that lipid oxidation increases with exercise training. Similar reductions were found in the current study participants for triglycerides, glucose, total cholesterol and LDL cholesterol (Table 12.3). However, the waist

circumference and BMI were not changed significantly in the current study. In the current study, the IT support must have aided regular moderate physical activity to reduce the fasting blood glucose significantly (table 12.3).

Roberts *et al* (2006a) found nine of 15 participants in their study were no longer categorized with metabolic syndrome following a supervised exercise and diet control programme for three weeks. Similar results were achieved in long-term studies. Kemmler *et al* (2009) trained elderly women with metabolic syndrome for 12-months using an exercise programme and found significant reduction in central obesity and blood lipids. Gayda *et al* (2008) studied the effectiveness of 12-months cardiac rehabilitation in people with metabolic syndrome with and without coronary heart disease. At the end of one year 20% of their participants without coronary heart disease and 31% with coronary heart disease no longer had metabolic syndrome. In the heritage study, after a 20 weeks supervised exercise programme, 30.5% of the participants no longer had metabolic syndrome (Katzmarzyk *et al*. 2003). Similar results were found in the current study with a home-based exercise programme regardless of IT support after 12 weeks. This may be due to the range of age groups in the current study. The current results confirm that for some people, metabolic syndrome is reversible with home-based regular exercises.

11.4.2. Exercise capacity

The participants showed mild improvement in exercise capacity yet it was not statistically significant. Laaksonen *et al* (2002) observed leisure time physical activity of 612 men and followed them up for four years. They found 107 men

developed metabolic syndrome and lesser physical activity was highly related to low cardiac fitness and the prevalence of metabolic syndrome. LaMonte *et al* (2005) found similar results on their 5.7 years follow up on 9007 men and 1491 women. They stated that low cardiorespiratory fitness was an important predictor of metabolic syndrome. The current study participants showed mild improvement in exercise capacity yet it was not statistically significant. However, a longer follow-up would be appropriate to confirm the changes in exercise capacity.

11.4.3. Changes in arterial stiffness

In the current study, significant reductions were observed in many key arterial stiffness variables following home-based exercise programme (Table 12.1). Aizawa *et al* (2009) also found similar reduction in mean arterial pressure following exercise training for people with metabolic syndrome. Exercise training enhances endothelial function. Advanced-Glycation-End products (AGE) on the arterial wall induce cross-linking of collagen molecules that leads to loss of collagen elasticity and the compliance of the arteries. This collagen cross-linking is associated with aging, diabetes, hyper-cholesterol and hyperlipaemia (Aronson 2003). Inhibition of this collagen cross-linking might have occurred during exercise (Aizawa *et al*. 2009). Secondly, the increase in blood pressure and heart rate during exercise might stretch collagen fibres and repeated stretch with regular exercise might result in the reduction of the arterial stiffness (Aizawa *et al*. 2009). Thirdly, increased vascular nitrous oxide bioavailability following exercise training results in an increase in microvascular density and reduction in inflammation (Frisbee *et al*. 2006).

No measurements were taken on inflammatory markers such as C-reactive protein in the current study. However, a reduction in high-sensitivity C-reactive protein, resistin and other inflammatory biomarkers has been established by exercise training in patients with diabetes and metabolic syndrome (Balducci *et al*. 2010; Kadoglou *et al*. 2007) and coronary heart disease (Milani *et al*. 2004). These studies claim that the anti-inflammatory effect of exercise training is independent of weight reduction and drugs. This statement is acceptable as the participants of the current study showed improvement in arterial stiffness variables without changes in their body mass index.

Changing to a healthier diet such as (i) reduction of salt intake (Avolio *et al*. 1986; Gates *et al*. 2004), (ii) use of dietary soy protein (Clarkson 2002), (iii) taking supplements of red clover isoflavones (Teede *et al*. 2003) or fish oil (McVeigh *et al*. 1994) may help to improve arterial compliance and reduce arterial stiffness. In the current study, all the participants were educated and advised to follow a healthy diet. Despite the limitation that it was not possible to monitor their diet, the improvement in arterial stiffness in both the groups could have been achieved through changes to a healthier diet.

11.4.4. Quality of life

The changes in quality of life with short term exercise programmes are debatable. Chien *et al* (2008) state in their systemic review that home-based exercise programmes can only improve exercise capacity, but not quality of life of patients with heart failure. Later, Chien *et al* (2011) found a significant improvement in quality of life and exercise capacity following an eight weeks

home-based exercise programme in patients with heart failure. Izawa *et al* (2004) found a significant improvement in all subscales (physical functioning, role physical, general health, and vitality) of quality of life after a home-based exercise programme. The current study showed improvement only in vitality. However, regardless of supervision by a researcher or a clinician, long-term exercise programmes are showing the potential for improving quality of life (King *et al*. 2000; Spirduso and Cronin 2001). The current results suggest that a 12-week exercise programme is not long enough to produce marked changes in any of the subscales of quality of life.

11.4.5. IT support and home exercise programme

Mobile phone usage has surpassed 5 billion globally (Wireless-Intelligence 2011) and in developing countries like India, the mobile usage is as high as 865 million (72% of the population) and increasing rapidly (TRAI 2011). Text messaging in the form of SMS is available in all the handsets currently used globally. Many clinical studies have used this mode of communication in disease prevention and management. Marlien Varnfield (2011) states that patients can be mentored and motivated through mobile phone interactions and the goals of cardiac rehabilitation can be achieved through a tailored home-based approach. Text messaging has been demonstrated as a powerful tool for behavioural change towards disease prevention and management (Cole-Lewis and Kershaw 2010). The use of mobile phones in health promotion is cost effective, generally available and lower levels of skills are needed to access them (Blake 2008).

Nevertheless, this study showed no additional increase in exercise capacity in the participants who received IT support. The reminders with IT support were demonstrated to help in achieving improvements in regular exercise and total exercise duration. The IT support might have improved the awareness of cardiac diseases and importance of lifestyle modifications.

There was no significant change in the participants BMI following the home-based exercise programme. A 12-week programme was used in the study and a longer and more intensive follow-up would be more effective for a significant weight reduction. Patrick *et al*. (2009) used an everyday customized SMS and multimedia messages for four months in a weight reduction programme and found a significant reduction in weight of up to 5kg. Studies that compared the use of phone and mail in addition to conventional treatment showed weight reduction of up to 2.2 kg at the end of one year and up to 1kg at the end of two years (Jeffery *et al*. 2003; Sherwood *et al*. 2006). Another study followed up obese participants for two years with supervised and remote interventions using telephone, study-specific website and email. There was a significant weight reduction of up to 4.6kg in the remote intervention. The group who received supervised as well as remote programme also had a significant weight reduction of up to 5.1 kg. Nevertheless, weight reduction difference between the groups was not significant (Appel *et al*. 2011). These studies confirm the effectiveness of long-term, remote, weight reduction programmes.

The key findings of the current study on IT support are the improvement in arterial stiffness variables and hyperglycaemia following home-based exercises. The effect of IT support is clear as more arterial stiffness variables had

significant improvement compared with the control group. The current study promotes home-based exercise programmes in developing countries like India where there is a lack of availability of clinically established rehabilitation programmes.

11.4.6. Limitations

There are several limitations in the current study. The exercises were supervised only at the learning phase on the first day. In addition, the diet modifications were not measured due to huge variation in the dietary pattern of the participants. All the testing and measurements were carried out at various times on testing days, due to the availability of the participants. The medications and other treatment for the participants' individual conditions were not controlled. These limitations may have influenced the blood lipids test results and variations. The effectiveness of text messaging would have been understood better if the participants were able to reply to the texts. This was not possible due to the cost limitations. A longer duration IT support and follow up could be more effective, but this was not possible due to the limited availability of the researcher in India.

11.5. Conclusions

Regular exercise and diet control are emphasised as primary preventive measures and in the management of metabolic syndrome. A home-based exercise programme can improve arterial stiffness, hyperglycaemia and dyslipidaemia for people with metabolic syndrome. Metabolic syndrome in many cases is reversible with regular home-based exercises. IT support, through

mobile texts and calls, improves the efficacy of the home-based exercises for those with metabolic syndrome. More structured lifestyle modification programmes will be beneficial in improving health care in developing countries like India. More cost effective methods need to be identified to improve awareness of healthy lifestyle and to reduce the cardiovascular risk.

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CHAPTER 12. SUMMARY AND CONCLUSIONS

The final chapter of this thesis presents an opportunity to review the whole thesis and to emphasise the main conclusions. Instead of summarising in the conventional prose style, this summary follows the model used in the British Medical Journal and others. It is presented in the form of brief bullet points relating to what is known on the topic and what the current research adds to the topic. This will provide a clear and concise summary of the work undertaken.

12.1. Summary of the individual chapters

CHAPTER 2: ARTERIAL STIFFNESS – A LITERATURE REVIEW

What is already known

- There are several molecular, cellular and genetic mechanisms causing arterial stiffness
- Arterial stiffness is a marker for cardiovascular disease and is associated with the initial stages of CVD risk factors
- Measurement of arterial stiffness has a long history and applanation tonometry is a standard non-invasive method for measuring arterial stiffness

What this chapter adds

- The reference values for non-invasive arterial stiffness measurement have not been established for various ethnic populations
- Carotid-radial pulse wave analysis is a less intrusive technique, yet less used. More studies are needed to establish the validity of this technique
- Applanation tonometry is recognised for its prognostic validity more than diagnostic validity. Simpler methods of the technique such as carotid-radial analysis, have only been reported infrequently

CHAPTER 3: REPRODUCIBILITY OF ARTERIAL STIFFNESS MEASUREMENTS FROM NON-INVASIVE PULSE WAVE ANALYSIS

What is already known

- Validity of non-invasive pulse wave analysis has been established using advanced invasive techniques
- Pulse wave analysis using applanation tonometry has a high hour-to-hour reproducibility and a lesser week-to-week reproducibility

What this chapter adds

- This is the first study to produce values of carotid-radial pulse wave analysis using applanation tonometry on young, healthy, Indian adults
- Carotid-radial pulse wave analysis is significantly reproducible on continuous measurements. However, the repeatability slightly reduces over a 24-hour period
- Among the variables of carotid-radial pulse wave analysis, pulse wave velocity has the best reproducibility over a 24-hour period

CHAPTER 4: ACUTE CHANGES IN ARTERIAL STIFFNESS FOLLOWING EXERCISE IN HEALTHY CAUCASIANS vs. SOUTH ASIANS

What is already known

- Exercise capacity is inversely related to arterial stiffness
- Differences due to ethnicity are established for arterial stiffness and exercise capacity
- Exercises increase arterial stiffness acutely due to increase in central pressures.

What this chapter adds

- There is an acute increase in carotid-radial arterial stiffness following exercise, which is similar to other techniques of pulse wave analysis
- There is no difference between Caucasians and South Asians in the acute changes in the arterial stiffness following sub-maximal exercise
- There was no significant difference in sub-maximal exercise capacity between Caucasians and South Asians

CHAPTER 5: RELATIONSHIP BETWEEN BODY ADIPOSITY AND ARTERIAL STIFFNESS IN YOUNG INDIAN ADULTS

What is already known

- There is a strong positive relationship between adiposity and arterial stiffness
- Larger arterial compliance has significant negative correlations with skinfold thickness; also smaller arteries have a significant negative correlation with waist-hip-ratio
- Obesity in young adults has a higher risk of developing arterial stiffness and cardiovascular disease

What this chapter adds

- Arterial stiffness measured by carotid radial pulse wave analysis is strongly related to adiposity measured from skinfold thickness in young Indian adults
- Skinfold thickness may be a more valid method to measure body fat and associated arterial stiffness than waist-hip-ratio
- Young Indian females had higher percentage of body fat and stronger associations with carotid-radial arterial stiffness than men

CHAPTER 6: REVIEW OF LITERATURE - ERECTILE DYSFUNCTION AND CARDIAC REHABILITATION

What is already known

- Erectile dysfunction and cardiovascular disease have similar risk factors and erectile dysfunction is also a marker for cardiovascular disease
- Arterial stiffness is the major cause of erectile dysfunction in people with cardiovascular risk
- Cardiac rehabilitation programmes are effective in improving cardiac risks

What this chapter adds

- There are few studies on the benefits of sexual function from cardiac rehabilitation in the UK
- Studies on the associations of arterial stiffness with erectile function in cardiac rehabilitation are limited
- There are no extensive studies on the prognosis of arterial stiffness following cardiac rehabilitation using non-invasive techniques

CHAPTER 7: CHANGES IN ERECTILE DYSFUNCTION AND ARTERIAL STIFFNESS FOLLOWING CARDIAC REHABILITATION

What is already known

- Erectile dysfunction is highly prevalent and increasing worldwide
- Various management methods are available to treat erectile dysfunction
- Resumption of full sexual function is one of the goals of cardiac rehabilitation programmes, but is often omitted

What this chapter adds

- Cardiac rehabilitation programmes improve major arterial stiffness indices measured by applanation tonometry
- In general cardiac rehabilitation programmes do not improve moderate to severe erectile dysfunction unless treated specifically
- Arterial stiffness that is measured using applanation tonometry is associated with erectile dysfunction and can be used as a prognostic tool in cardiac rehabilitation programmes in the UK

CHAPTER 8: METABOLIC SYNDROME – A LITERATURE REVIEW

What is already known

- Metabolic syndrome is a cluster of various cardiovascular risk factors and the prevalence of metabolic syndrome has been increasing all over the world
- A number of criteria have been developed in diagnosing metabolic syndrome. Only a few of them have specific reference values for different ethnic populations
- Age, gender and lifestyle have a strong influence on the prevalence of metabolic syndrome

What this chapter adds

- There are no specific programmes structured and established for the management of metabolic syndrome
- The prevalence of metabolic syndrome is not known in many developing and poor countries
- Early identification of risks may help in the prevention, yet has not been studied

CHAPTER 9: PREVALENCE OF HYPERTENSION, OBESITY, DIABETES AND METABOLIC SYNDROME IN NEPAL

What is already known

- Cardiovascular disease and risks are highly prevalent worldwide. Populations from South Asian countries have a higher risk than many other countries.
- Cardiovascular risks are often not diagnosed until the onset of cardiovascular disease in developing countries.

What this chapter adds

- Metabolic syndrome and risk factors such as hypertension, obesity and dyslipidaemia are highly prevalent in Nepal
- Abdominal obesity is an important risk as the International Diabetic Federation's ethnic specific reference values make a substantial difference in identifying the prevalence of metabolic syndrome in Nepal
- Lack of awareness and unhealthy lifestyle may be the major cause of metabolic syndrome in Nepal

CHAPTER 10: ACUTE CHANGES IN ARTERIAL STIFFNESS FOLLOWING EXERCISE IN PEOPLE WITH METABOLIC SYNDROME IN INDIA

What is already known

- Poor exercise capacity is one of the clinical characteristics of metabolic syndrome
- Metabolic syndrome is associated with increased arterial stiffness
- Acute increase in arterial stiffness following exercise is observed in healthy people and those with CVD, using various techniques

What this chapter adds

- There is an acute increase in arterial stiffness variables measured by carotid-radial applanation tonometry following exercise
- The increase in arterial stiffness following exercise, in people with metabolic syndrome was no different from the increase observed in healthy people
- Acute increase in arterial stiffness following sub-maximal exercise depends on the severity of endothelial dysfunction due to age or any associated cardiovascular risks

CHAPTER 11: EFFECTS OF AN IT SUPPORTED, HOME-BASED EXERCISE PROGRAMME IN PEOPLE WITH METABOLIC SYNDROME IN INDIA

What is already known

- Metabolic syndrome is highly prevalent in South Asian populations
- Life style factors, such a lack of physical activity and an unhealthy diet, contribute to the prevalence of metabolic syndrome
- Home-based exercises are effective and can be an alternative for centre-based exercise programmes

What this chapter adds

- Home-based exercise programme improves arterial stiffness, hyperglycemias and dyslipidaemia and reverse metabolic syndrome in developing countries such as India
- Cost effective methods, such as IT support through mobile texts, could improve the efficacy of home-based exercise
- Applanation tonometry can be a simple and efficient prognostic tool for home-based programmes

12.2. Recommendations for future research

- Larger cohort studies are needed to establish generalised reference values for applanation tonometry. Larger longitudinal observations are needed to establish the carotid-radial pulse wave analysis as a diagnostic tool for various cardiovascular risks
- Future research is needed to optimize the IT support in addition to home-based exercise programmes. The research would emphasise the improvement of arterial stiffness, with a focus on individual components of metabolic syndrome
- Future research is needed to identify the risk of cardiovascular disease as early as possible, so that appropriate preventive measures can be undertaken. One of the important approaches may be the evaluation of arterial stiffness using the simple, portable non-invasive techniques. This could become routine in patients' first-contact clinical centres such as general practices
- A uniform definition for metabolic syndrome needs to be established that can be applicable for every ethnic group in the world
- Investigations are needed on the associations of arterial stiffness in erectile dysfunction in patients with metabolic syndrome and subsequently be of use in prognostic investigations

12.3. Practical limitations of the thesis

For the erectile dysfunction and cardiac rehabilitation study (Chapter 7), it took more than a year to achieve approval from National Ethics Committee and research and development departments from the individual National Health Service Trusts. More than 400 patients were approached and only 157 patients agreed to participate. Among them only 114 participants completed erectile function questionnaires. Various reasons were observed as shyness, partner's unwillingness, not important due to age, single or sexually not active etc. it was planned to investigate the changes in erectile dysfunction and arterial stiffness following an exercise programme in India. As a pilot, 12 cardiac patients were invited to participate in a customized exercise programme and all of them refused to fill the erectile dysfunction questionnaire. It shows that sexual dysfunction is still considered as a socially forbidden topic in developing countries in South Asia. Due to the lack of participants' interest, the study was withdrawn.

Following the IT-supported home exercise programme in India for metabolic syndrome (Chapter 12), a study was designed to implement similar IT-supported home exercise programme for diabetes and metabolic syndrome in the UK. Following National Ethics Committee's approval, nearly 100 GPs were contacted through mails, emails and telephone for participation. Surprisingly, only one GP agreed to participate. There were 70 eligible patients from the GP who were invited to participate and 12 of them consented to participate. They underwent initial measurements and the IT-supported home exercise programme. Finally, only five of them returned for the follow-up measurements. Due to the failure in achieving required number of participants, the study was

withdrawn and excluded from the thesis. The failure of the study was mainly due to lack of participation of GPs. It may have increased the participation of GPs and patients If there were a substantial amount of funds available.

12.4. Integrated summary of the thesis

Work on this thesis started as a development of previous research in the Bucks New University and it was focused on establishing the effects of cardiac rehabilitation on erectile dysfunction and arterial stiffness (Chapter 7). Erectile dysfunction is a marker of cardiovascular disease (CVD). Strong associations were established between arterial stiffness and erectile dysfunction. Cardiac rehabilitation is an established exercise-based programme in the UK. These are specially designed for treating CVD and reducing cardiovascular risks, and are effective in improving arterial stiffness. However, they are not successful in resuming complete sexual function for the cardiac patients, so special attentions and more specific approaches are needed in those patients with erectile dysfunction. These implications are very different for the developing countries such as India. The failure to initiate similar approaches in India shows that more emphasis is needed in health education on sexual dysfunction and its associations with cardiovascular diseases. Further, socially convenient measures are needed to initiate early diagnosis and the specific management of erectile dysfunction within populations with high cardiovascular health risk.

Further, this thesis focused on other cardiovascular risks and their management. Metabolic syndrome is a cluster of cardiovascular risk factors and it is highly prevalent in developed as well as developing countries with differences in the severity of individual risk factors. The prevalence of metabolic

syndrome is not known in many developing countries. In this thesis, a high prevalence of metabolic syndrome and risk factors such as hypertension, obesity and dyslipidaemia was found in Nepal. In contrast, prevalence of metabolic syndrome in people having private health care in the UK is comparatively very low. This may be due to a more extensive and supportive health care system in the UK's private sector or the patients take good care of their health by following a healthy lifestyle.

Early management can reduce cardiovascular risk factors. There are no specific programmes structured and established for the management of metabolic syndrome. Home-based exercise programme can be an alternative to centre-based programmes to reduce cardiovascular risk in those with metabolic syndrome. Cost effective methods, such as IT support through mobile texts, could improve the efficacy of home-based exercise. The support of IT in home-based exercise programmes helps promote the regularity of exercises. In this thesis, the home-based exercise programme was found to be a potential and convenient intervention in developing countries such as India. More support and studies are needed to establish these programmes in other developed and developing countries.

Arterial stiffness is the consistent thread throughout this thesis and arterial stiffness measurement using carotid-radial applanation tonometry was investigated. Compared with other non-invasive techniques, it is a simpler, less intrusive and an equally reliable prognostic tool for interventional studies. The associations of arterial stiffness with cardiovascular risks and its prognostic values are confirmed in this thesis. Obesity is a cardiovascular risk factor and

the prevalence is increasing globally. Carotid-radial arterial stiffness is strongly associated with body adiposity in young South Asian females and there are gender differences in the stiffness indices. These findings emphasize the need to establish gender and ethnic based reference values. Similarly, age also had a strong influence on arterial stiffness measures. Age based reference values also need to be established.

All the previous studies, discussed in the chapters, have measured only few of the arterial stiffness variables. Mostly, pulse wave velocity, augmentation pressure and augmentation index were studied and emphasized on their clinical importance on arterial stiffness. In addition to these variables, for the first time, this thesis has measured many additional variables from the carotid-radial applanation tonometry such as ejection duration and subendocardial viability ratio. The findings on these variables showed a non-significant improvement on interventional studies on arterial stiffness. However, these findings may be useful for the further studies on these variables. This thesis demonstrated significant improvement in arterial stiffness variables following centre-based as well as home-based exercise programmes. It has also been shown that exercise can improve arterial stiffness without or before showing significant improvement in exercise capacity. The possible mechanisms for the improvement in arterial stiffness may be (i) acute increase blood pressure and heart rate during each bout of exercise results in repeated pulsatile stretching of collagen fibres and break down of collagen cross links in the arteries (ii) increase in elastin content replacing collagen cross links (iii) reduced basal sympathetic activity and enhanced vagal sympathetic activity that results in reduced vascular tone (iv) inhibited smooth muscle proliferation and improved

endothelial function due to increased production and availability of nitric oxide availability (v) decreased left ventricular afterload and increased endocardial perfusion.

Overall, this thesis has established the associations of arterial stiffness with the most prevalent and specific cardiovascular risk factors. Further, the thesis has explored the possibilities of using convenient exercise programmes in improving arterial stiffness in economically and culturally different countries. These findings could help in improving health care and promoting further research in such countries.

APPENDIX I. Bland- Altman plots showing reliability of arterial stiffness variables with gender difference for Chapter 3

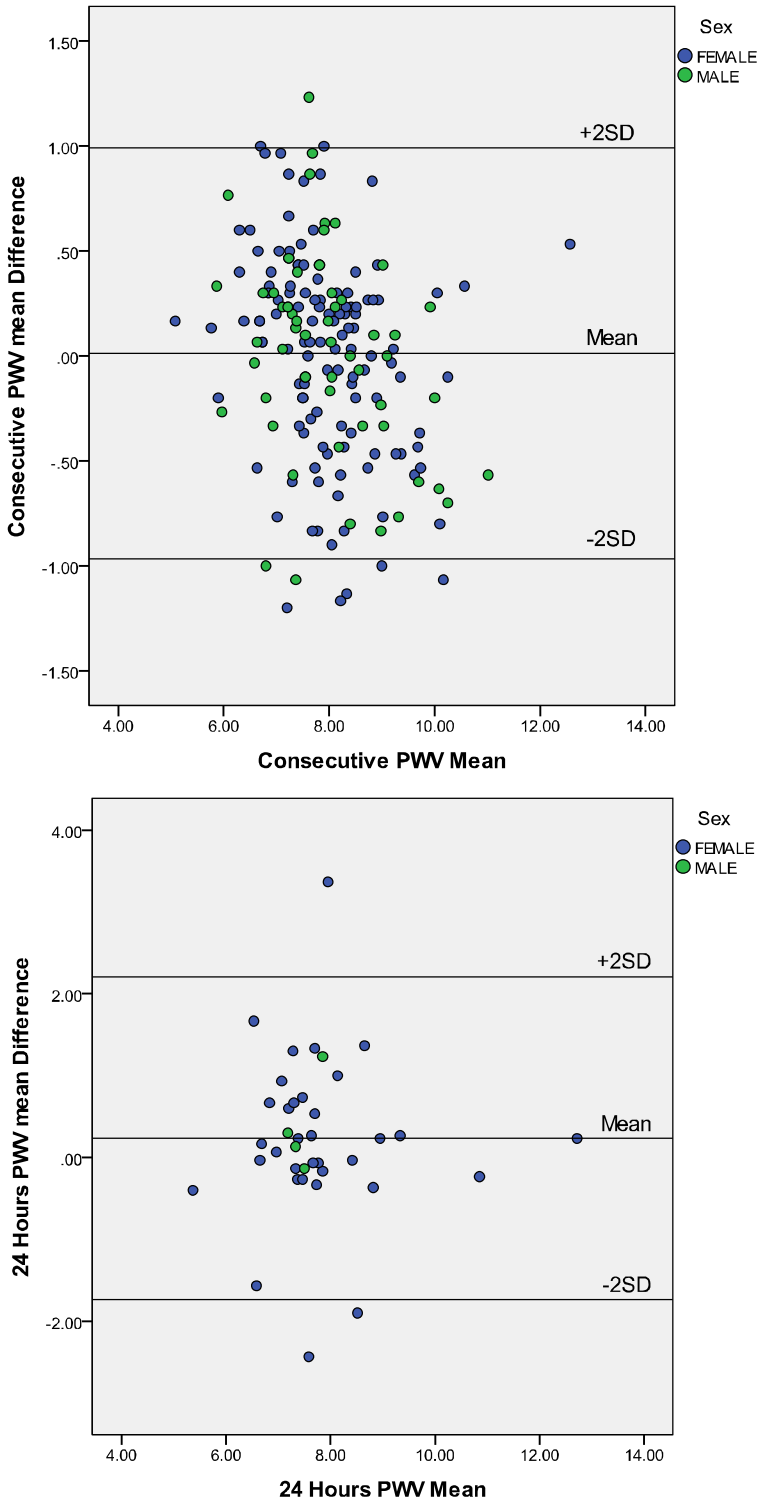


Figure A.1.1. Bland - Altman limits of agreement in pulse wave velocity (consecutive and 24 hours difference)

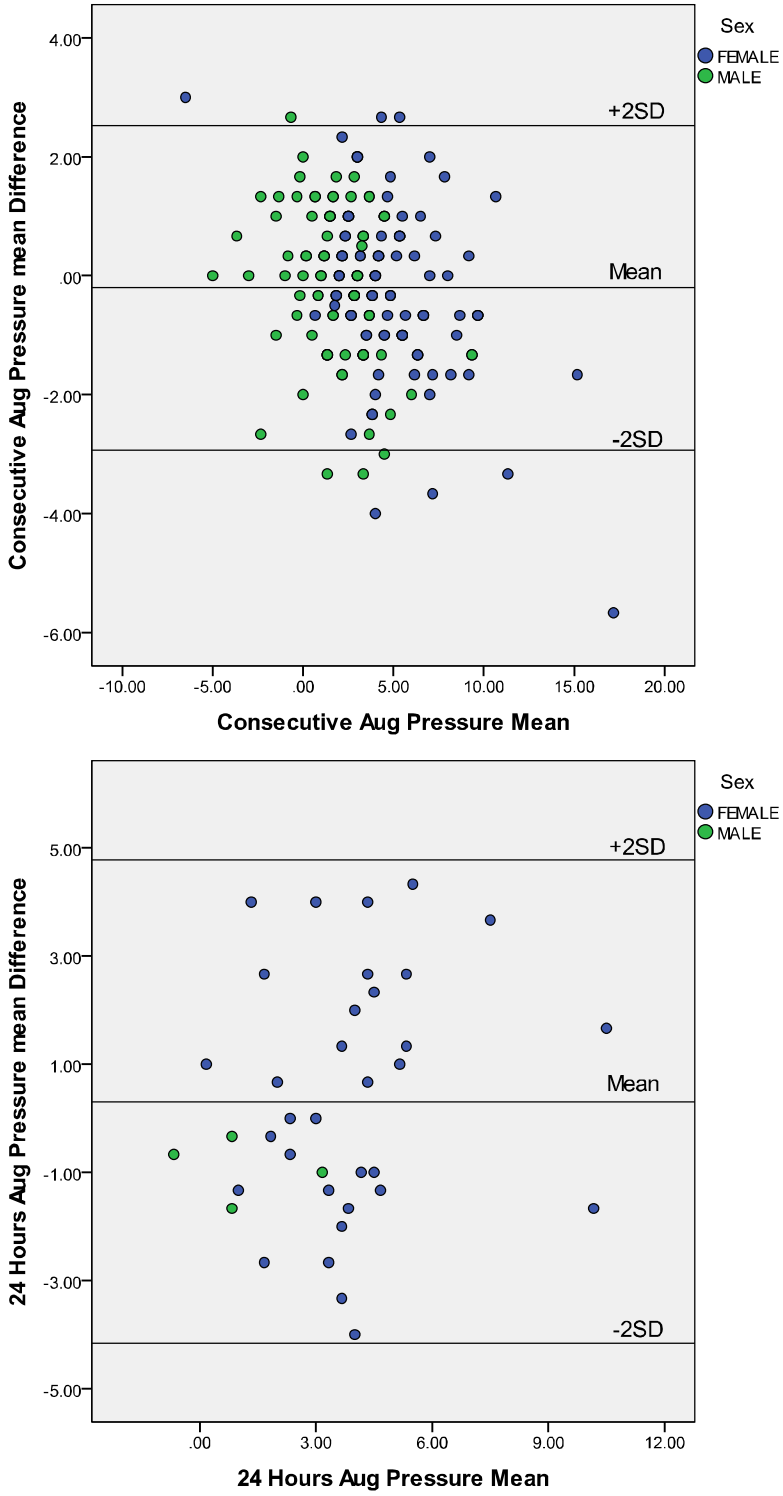


Figure A.1.2. Bland - Altman limits of agreement in augmentation pressure (consecutive and 24 hours difference)

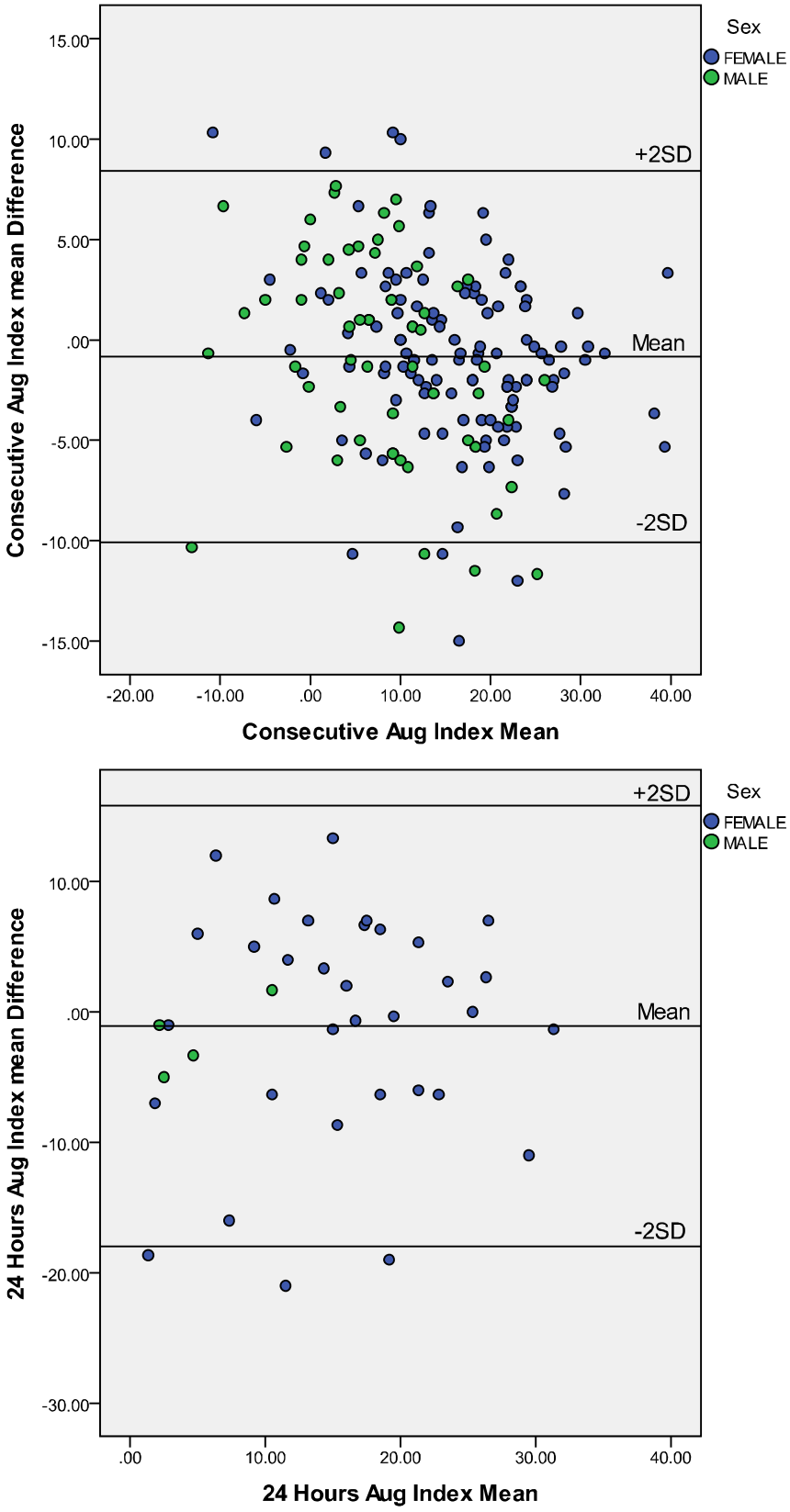
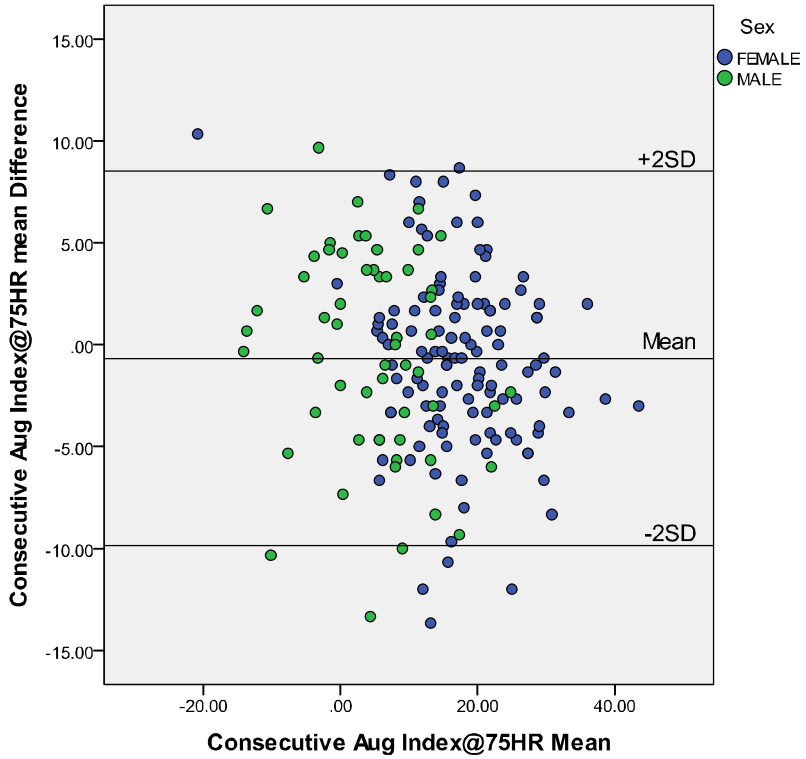


Figure A.1.3 Bland - Altman limits of agreement in augmentation index (consecutive and 24 hours difference)



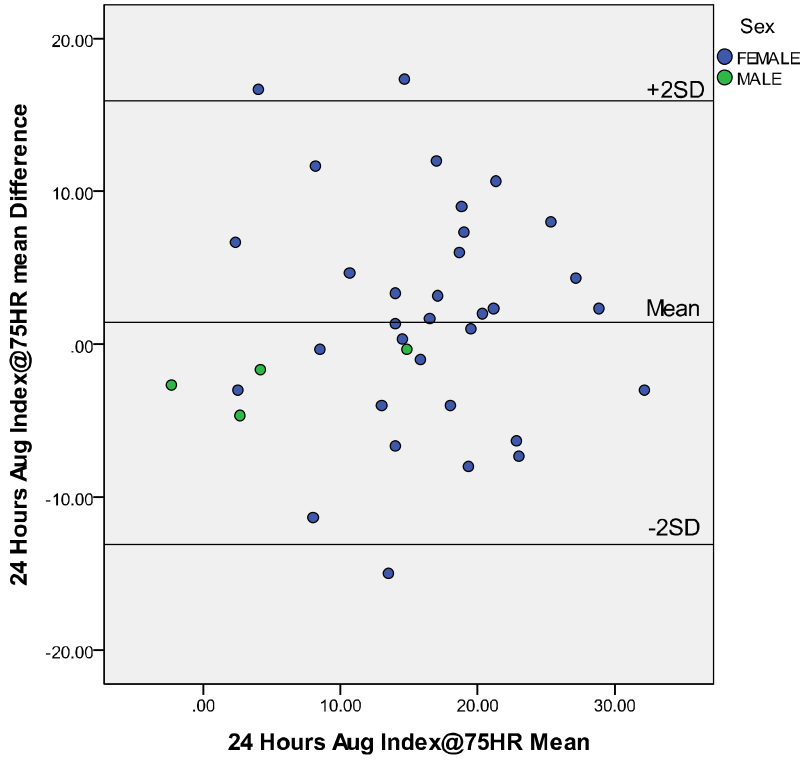


Figure A.1.4 Bland - Altman limits of agreement in augmentation index at 75% heart rate (consecutive and 24 hours difference)

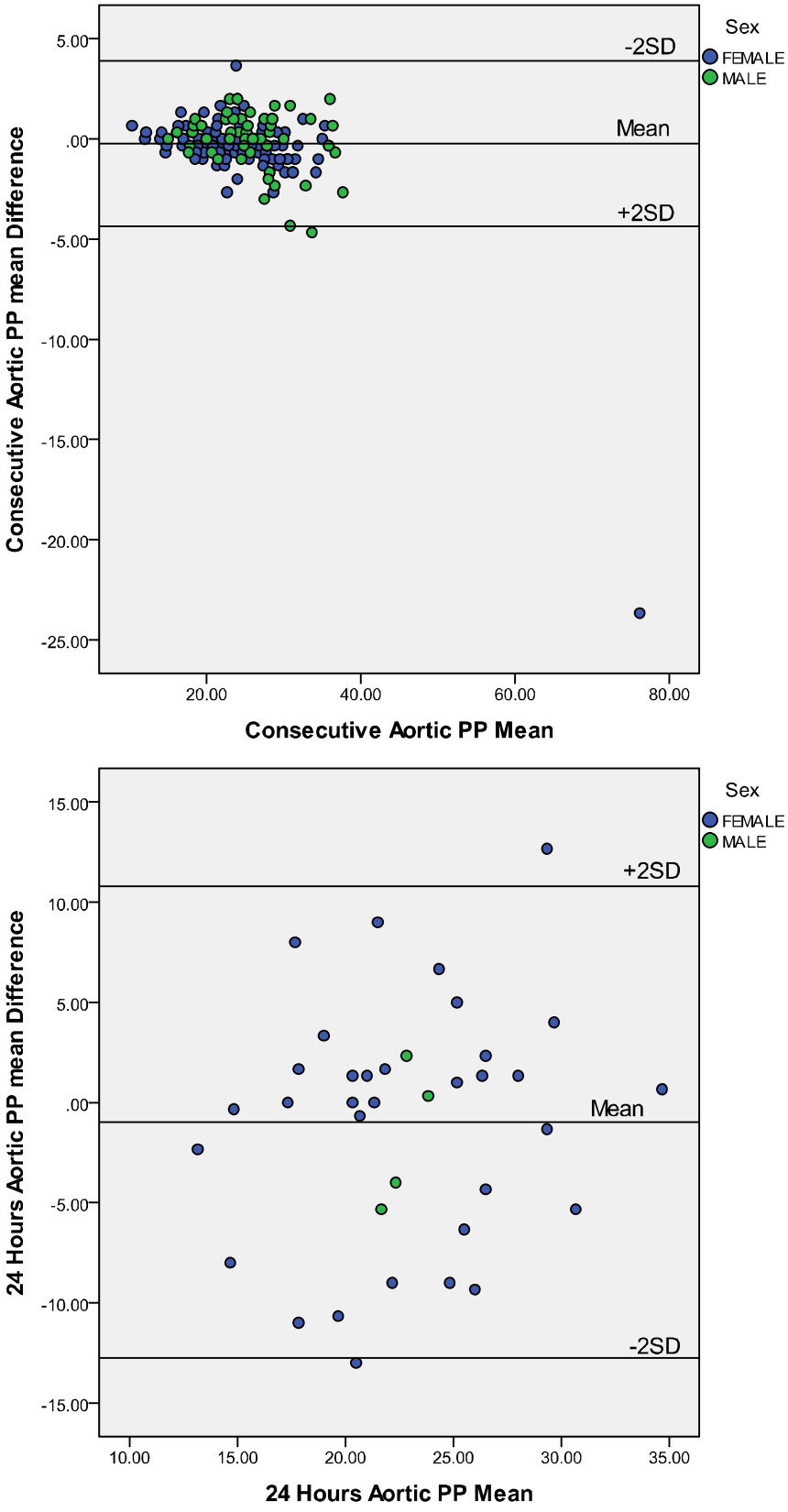


Figure A.1.5. Bland - Altman limits of agreement in aortic pulse pressure (consecutive and 24 hours difference)

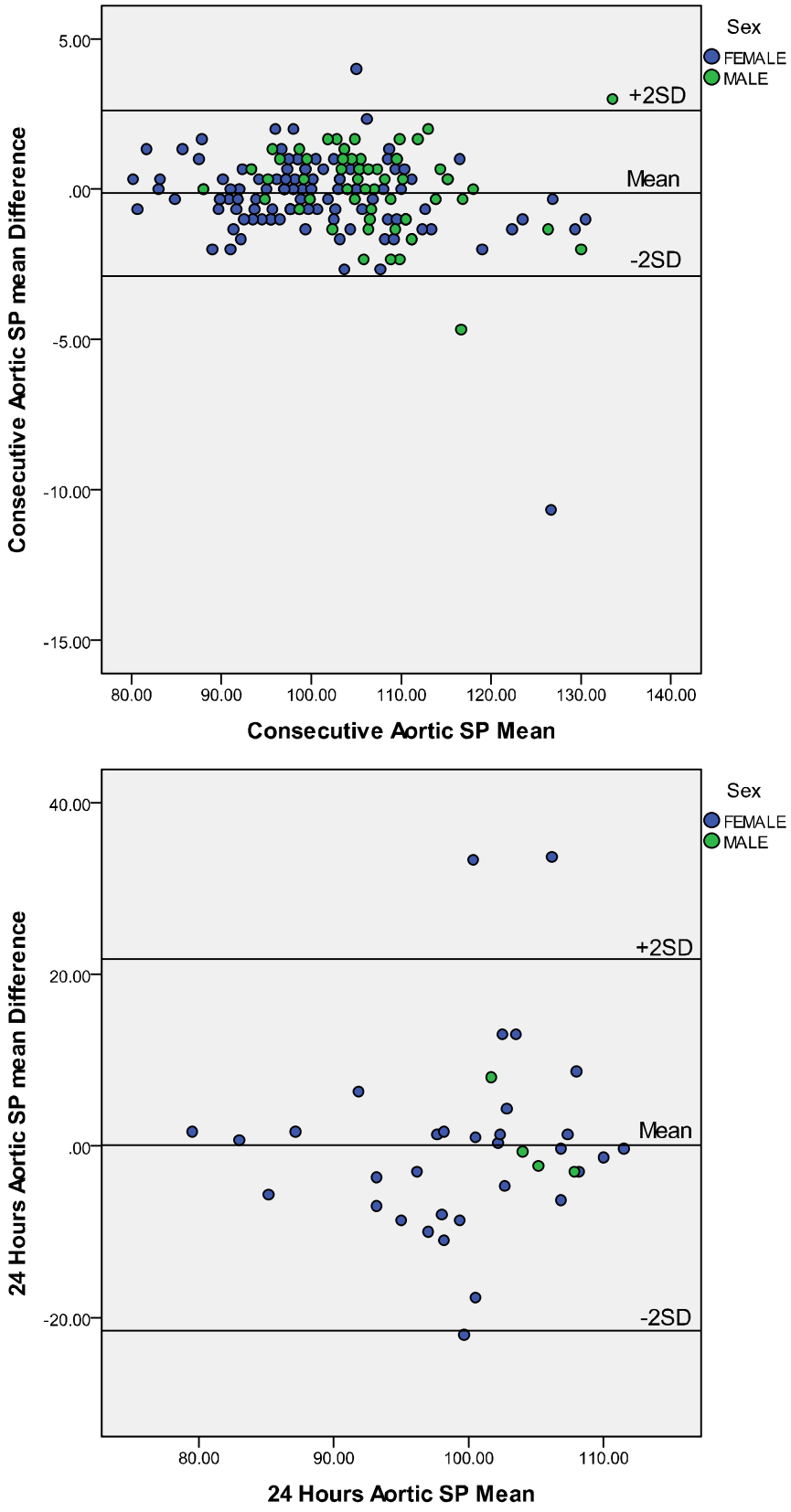
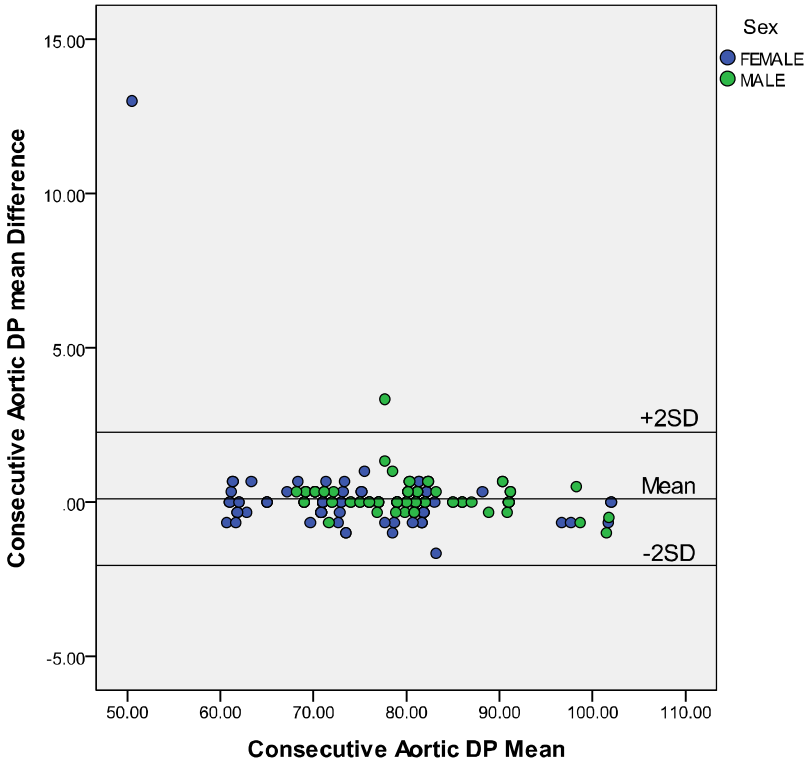


Figure A.1.6. Bland - Altman limits of agreement in aortic systolic pressure (consecutive and 24 hours difference)



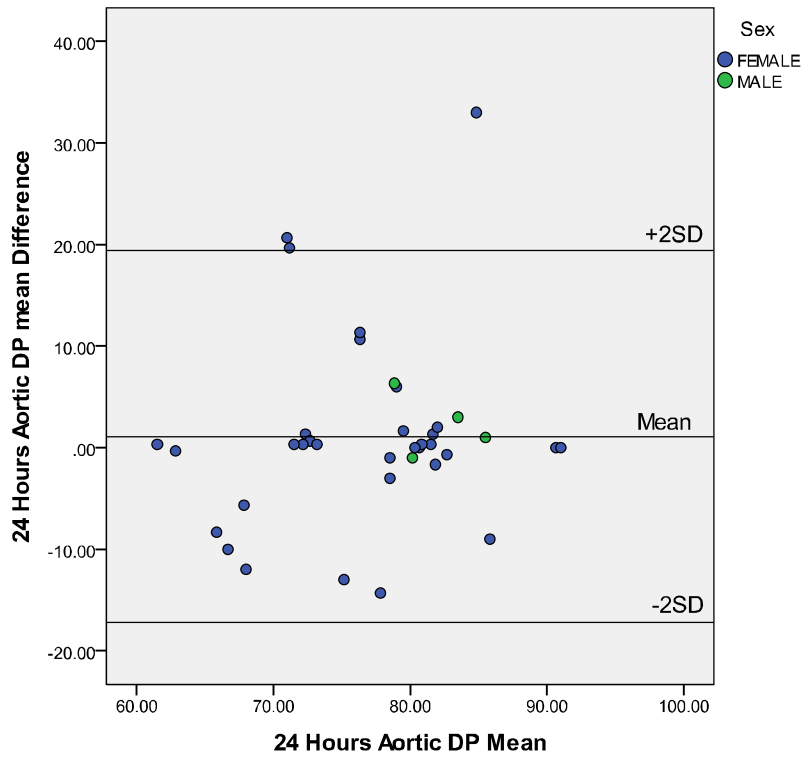
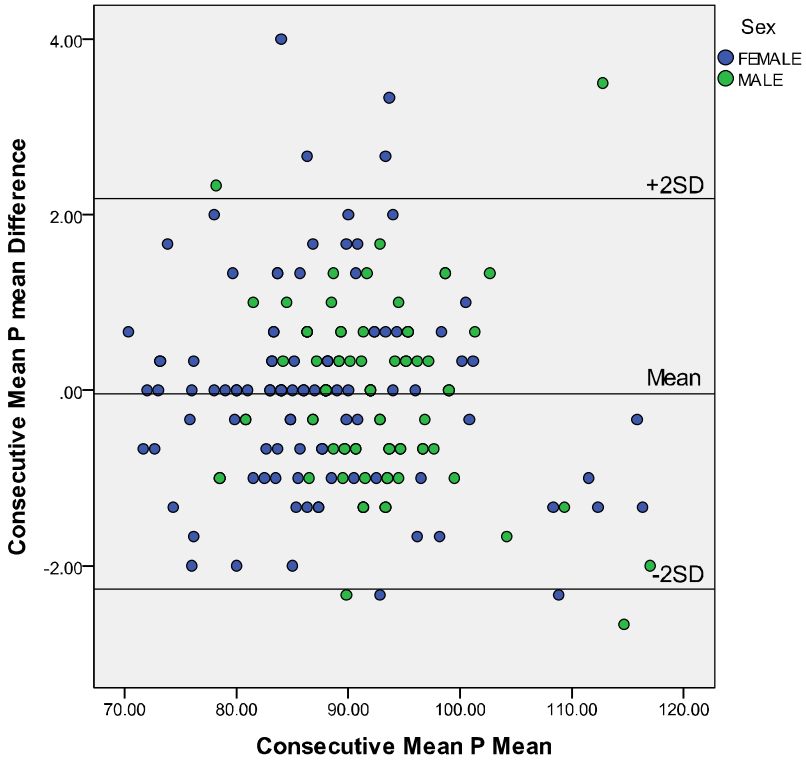


Figure A.1.7 Bland - Altman limits of agreement in aortic diastolic pressure (consecutive and 24 hours difference)



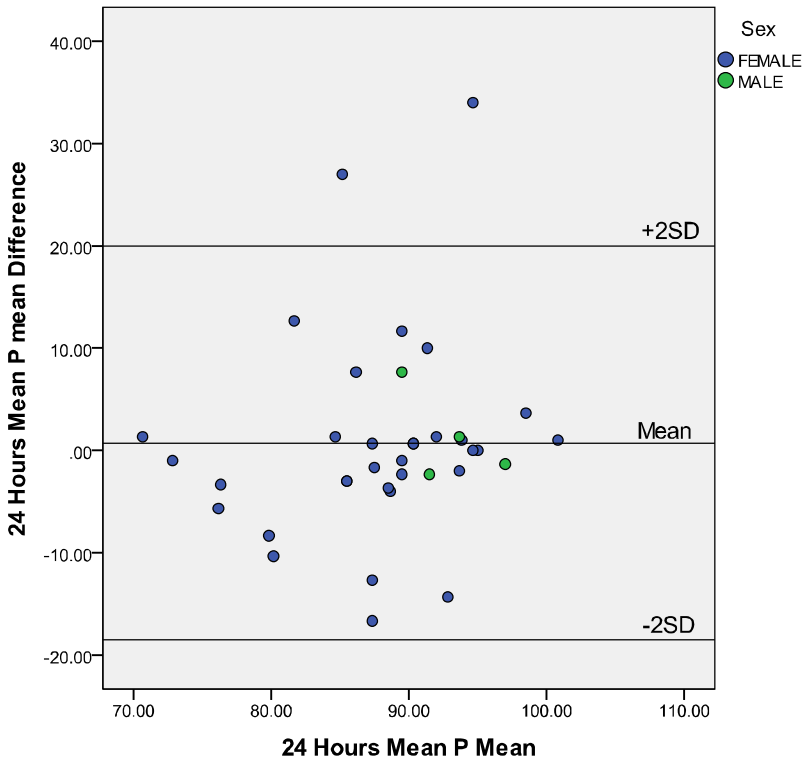
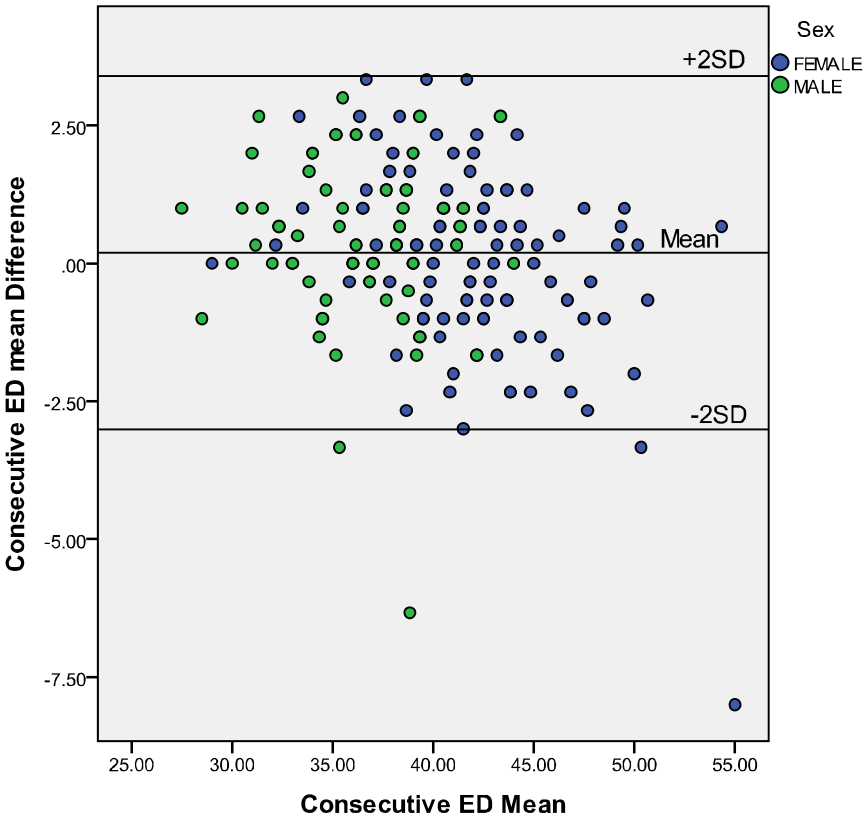


Figure A.1.8 Bland - Altman limits of agreement in aortic mean pressure (consecutive and 24 hours difference)



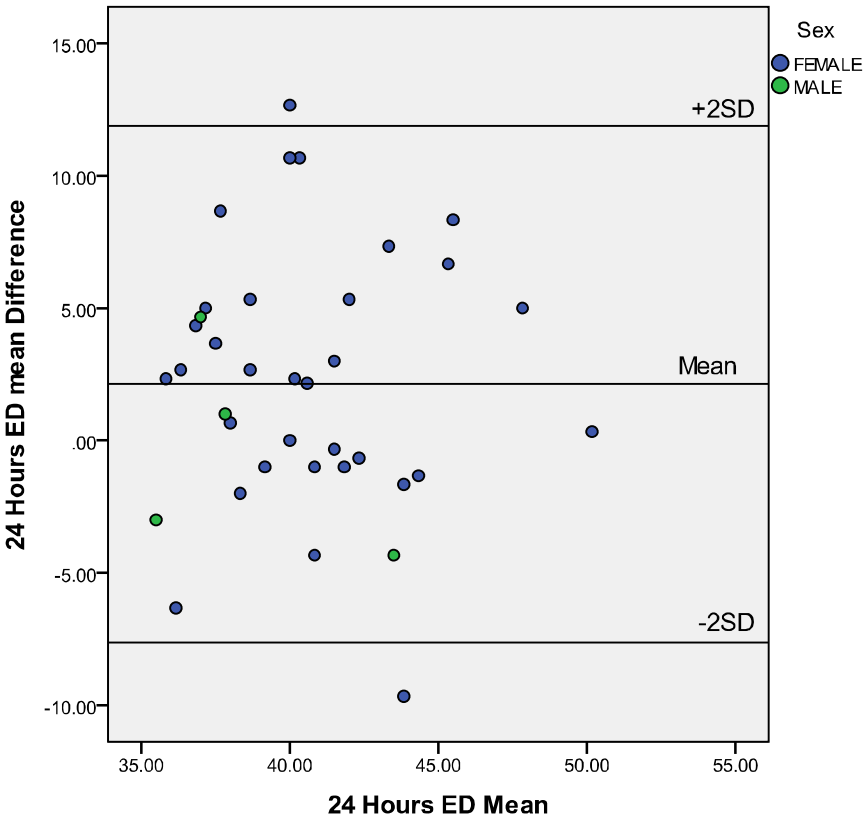


Figure A.1.9 Bland - Altman limits of agreement in ejection duration (consecutive and 24 hours difference)

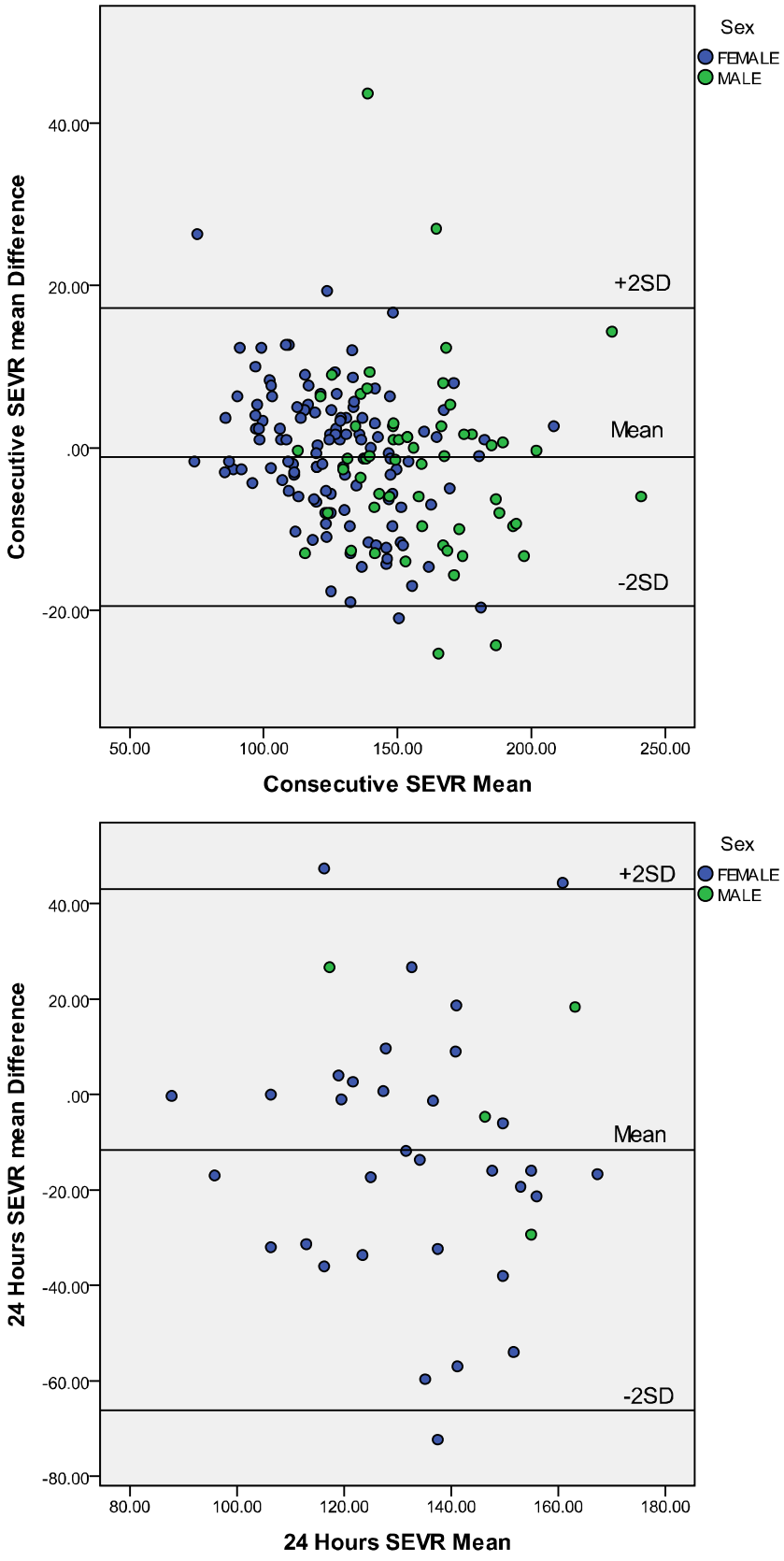
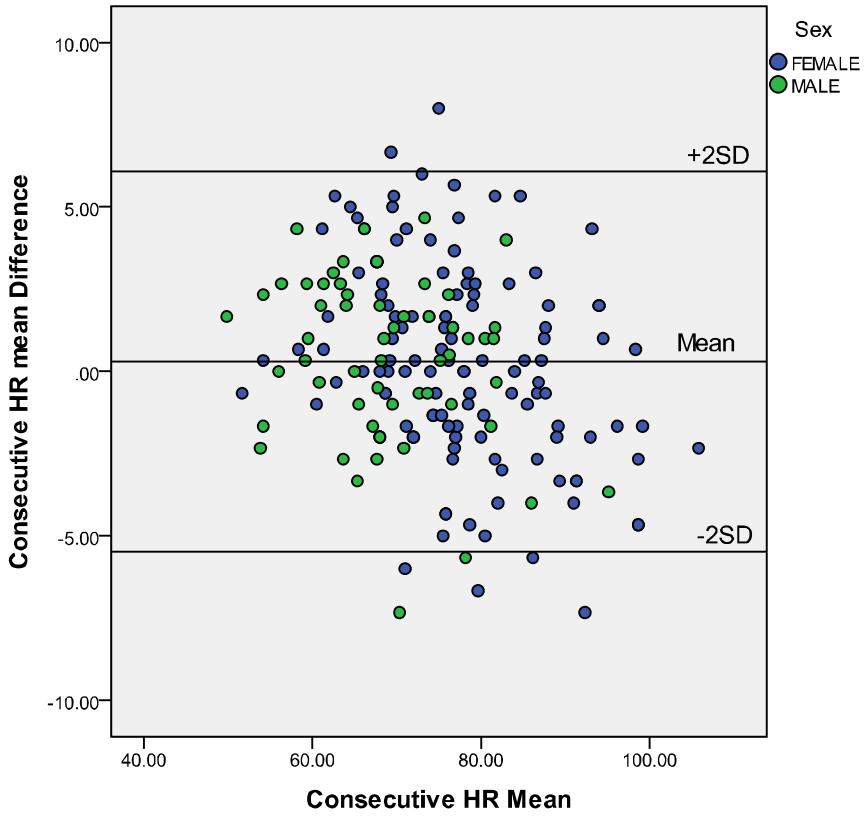


Figure A.1.10 Bland - Altman limits of agreement in subendocardial viability ratio (consecutive and 24 hours difference)



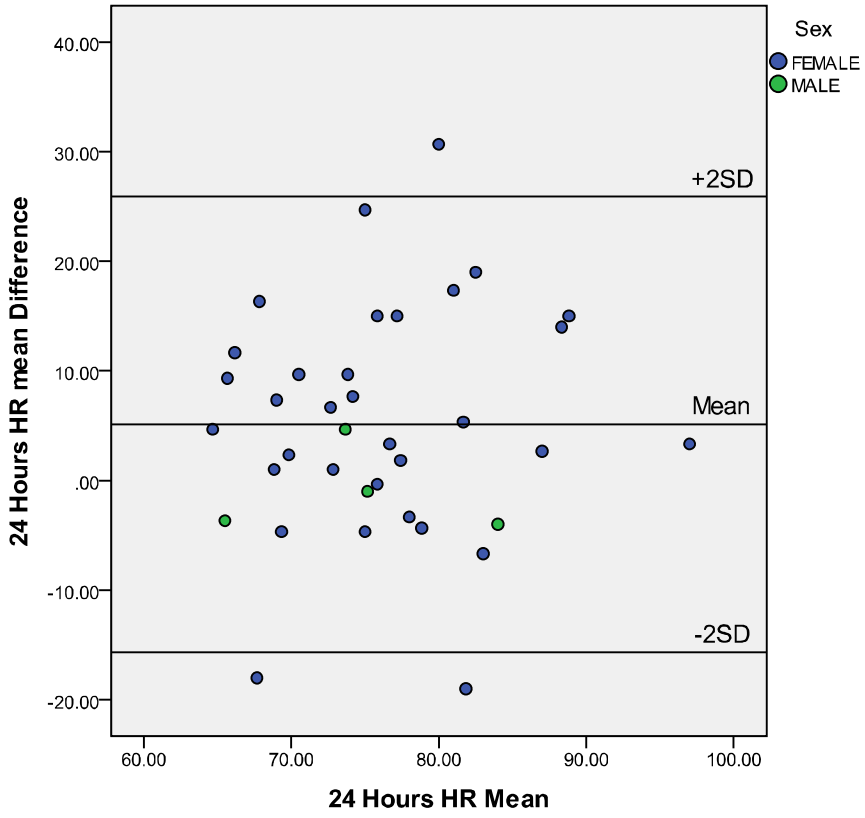


Figure A.1.11 Bland - Altman limits of agreement in heart rate (consecutive and 24 hours difference)

APPENDIX II. Scatter graphs showing relationship between $VO_{2\ Peak}$ and arterial stiffness variables with gender differences for Chapter 4

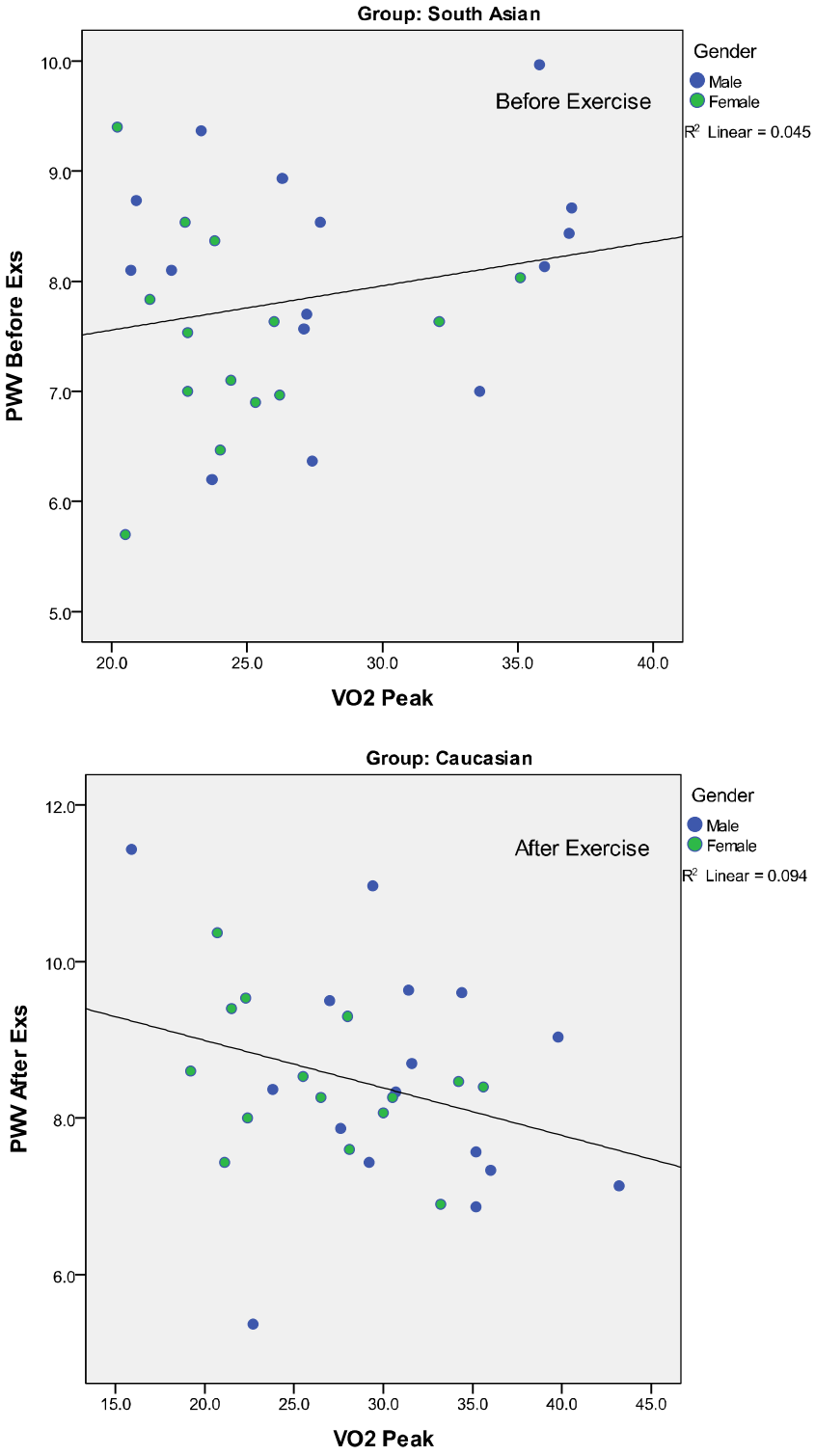


Fig A.2.1 $VO_{2\ Peak}$ vs. pulse wave velocity (PWV) before and after exercise in Caucasians

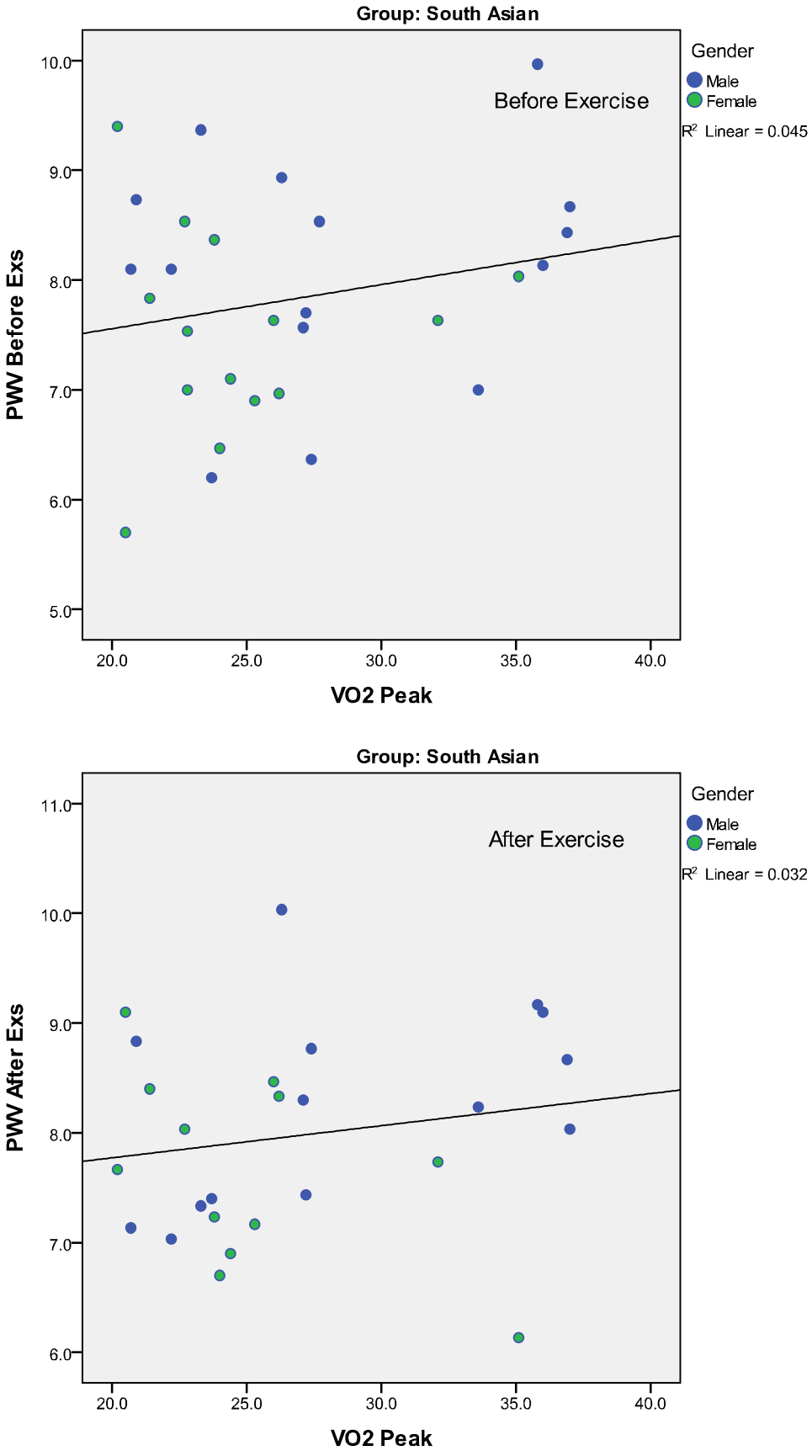


Fig. A.2.2 $VO_{2\ Peak}$ vs. pulse wave velocity (PWV) before and after exercise in South Asians

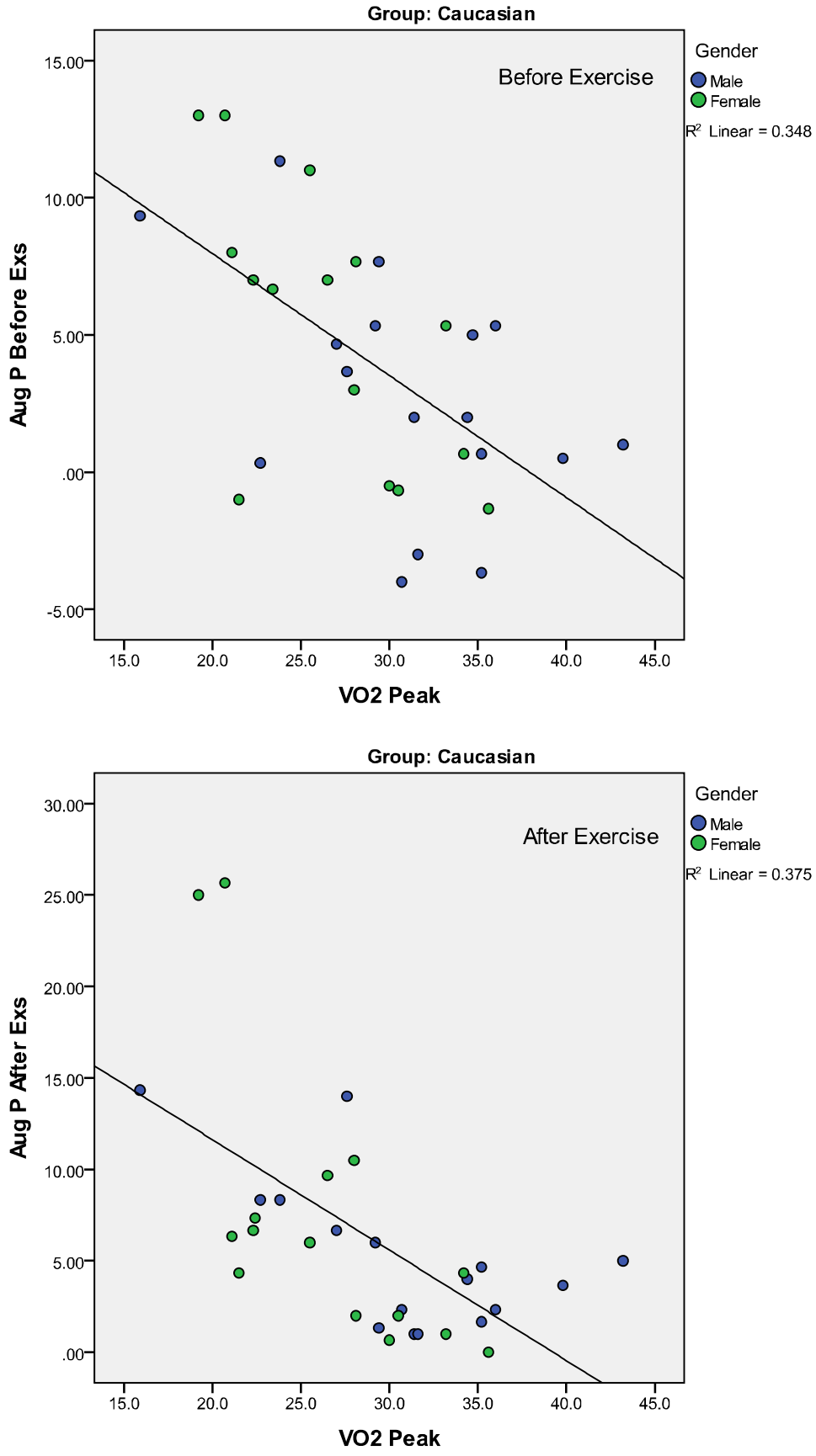


Fig. A.2.3 $VO_{2\ Peak}$ vs. augmentation pressure (Aug P) before and after exercise in Caucasians

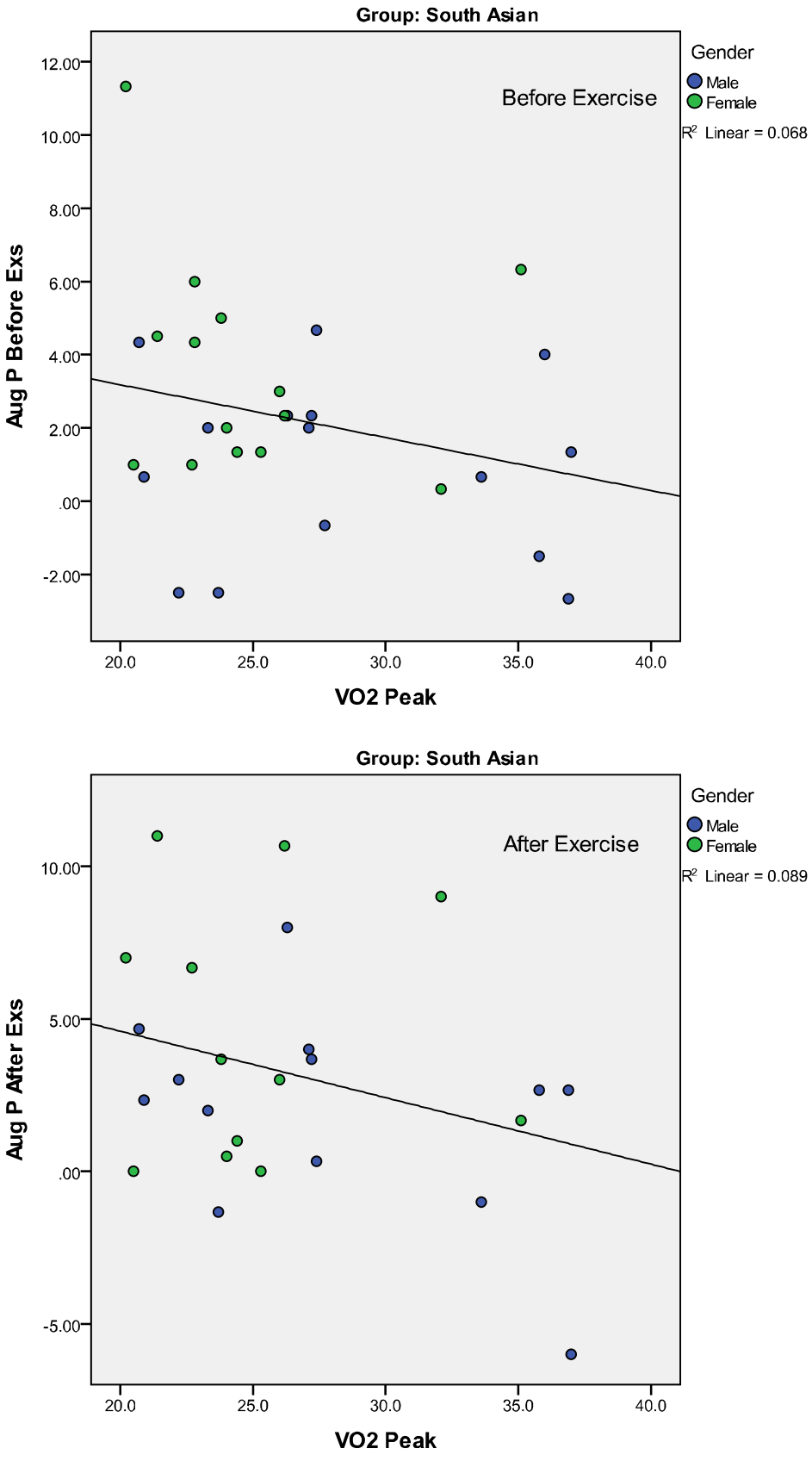


Fig. A.2.4 $VO_{2\ Peak}$ vs. augmentation pressure (Aug P) befor and after exercise in South Asians

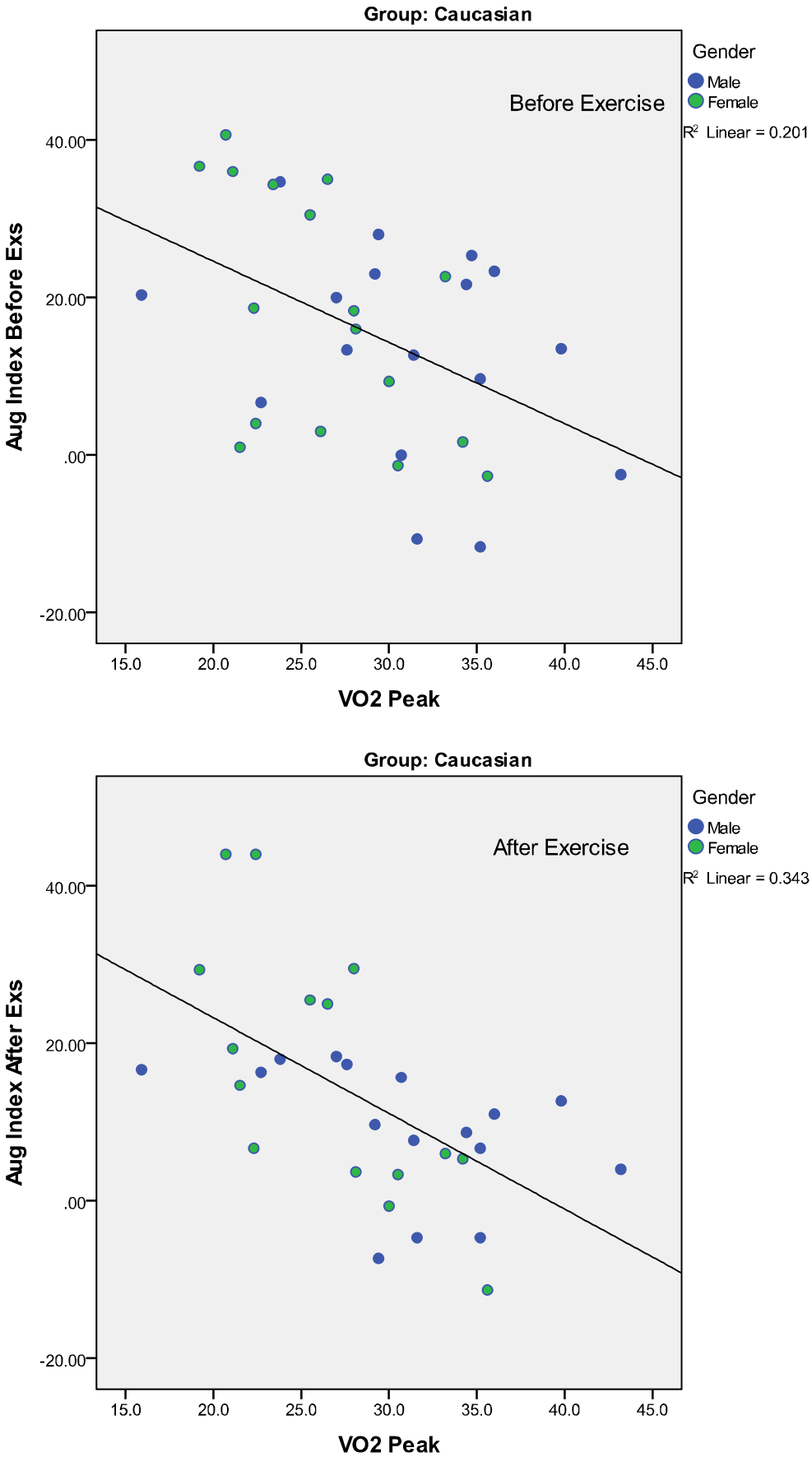


Fig. A.2.5 $VO_{2\ Peak}$ vs.augmentation index before and after exercise in Caucasians

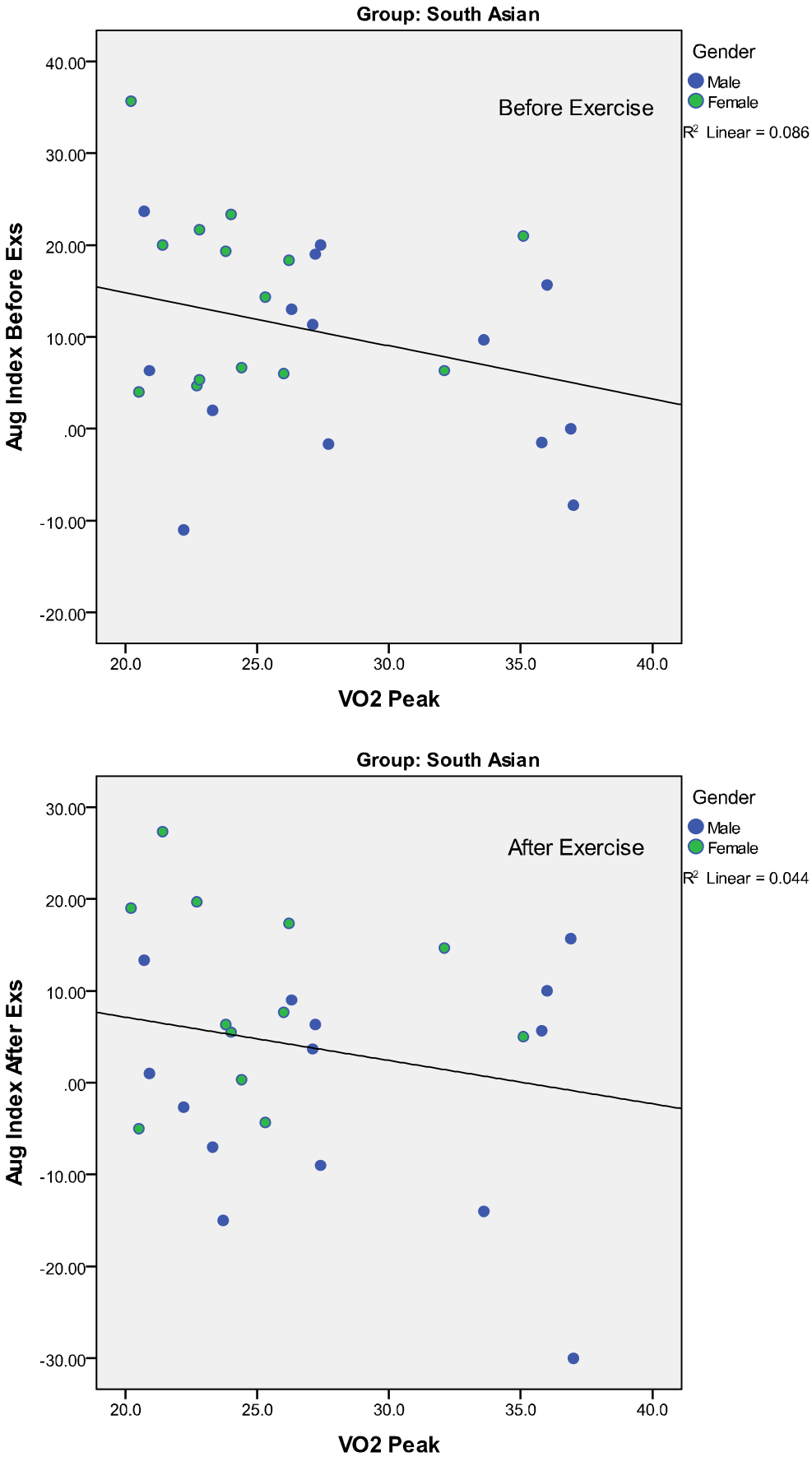
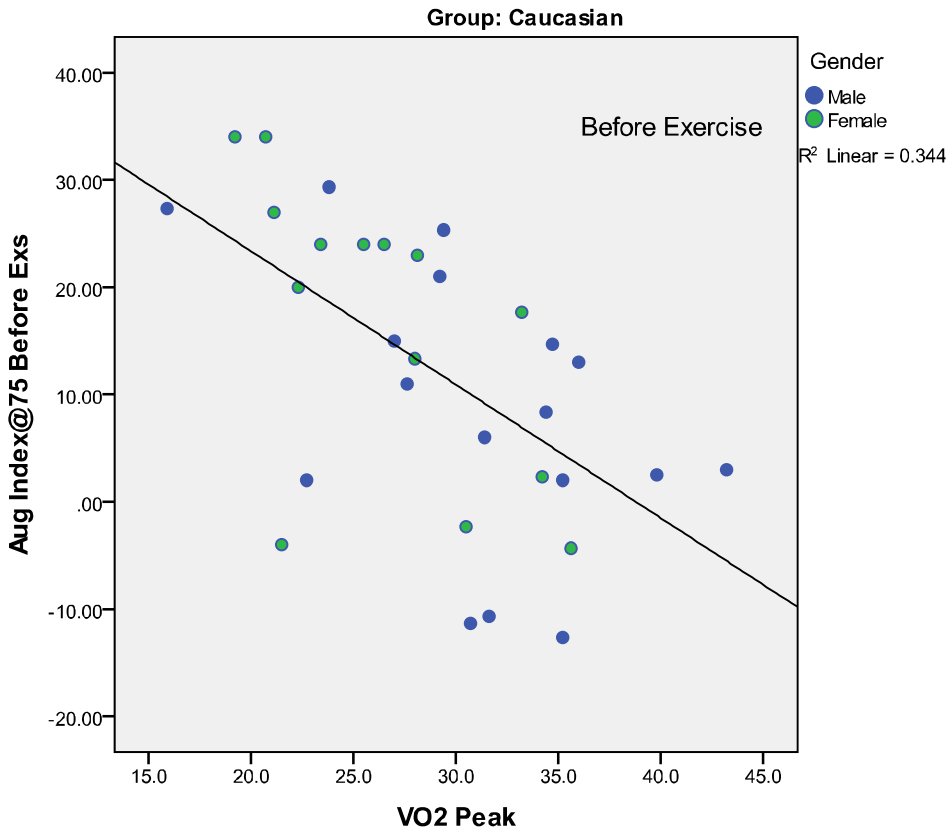


Fig. A.2.6 $VO_{2\ Peak}$ vs. augmentation index before and after exercise in South Asians



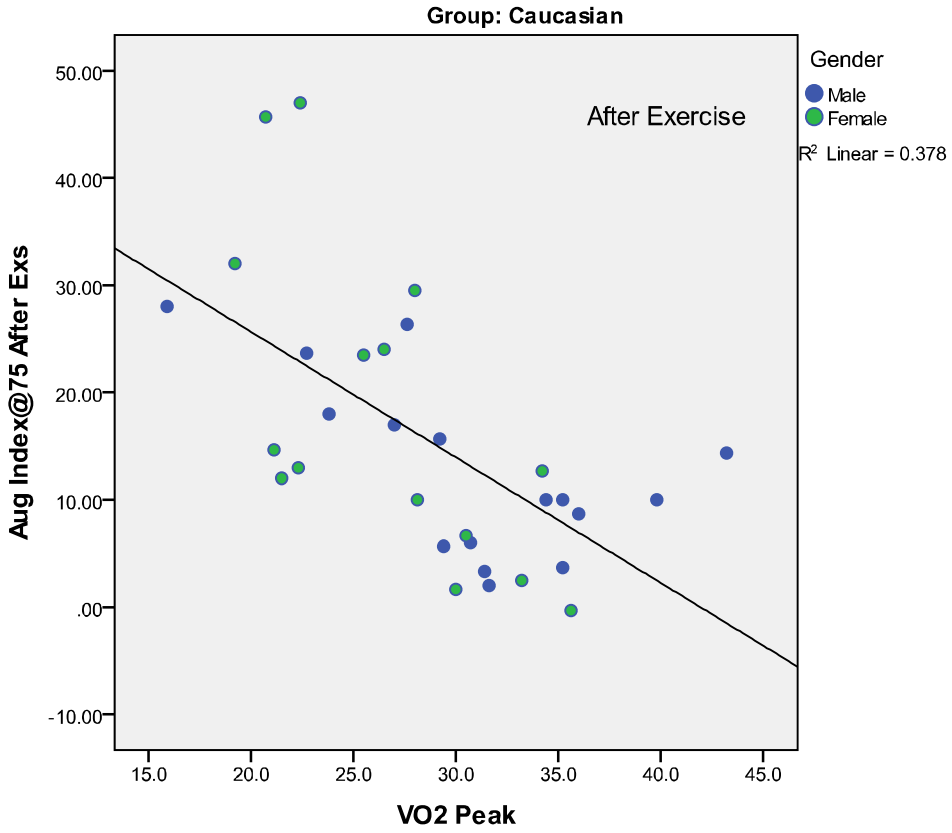
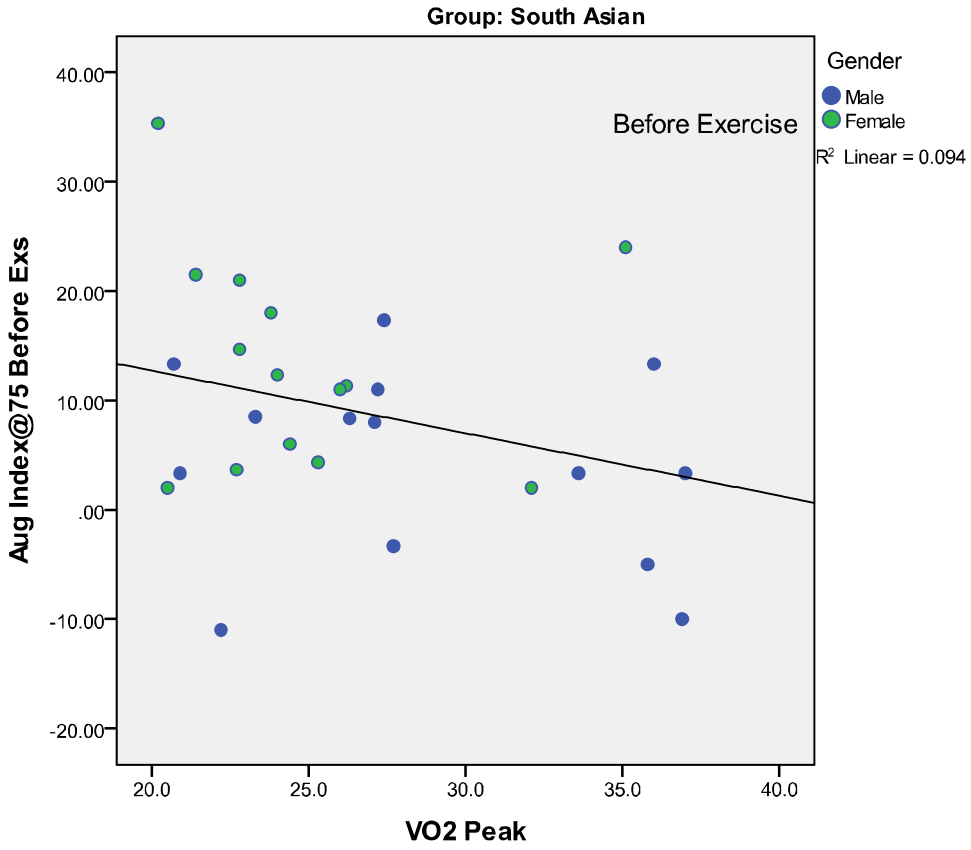


Fig. A.2.7 $VO_{2\ Peak}$ vs. aortic augmentation index at 75% heart rate before and after exercise in Caucasians



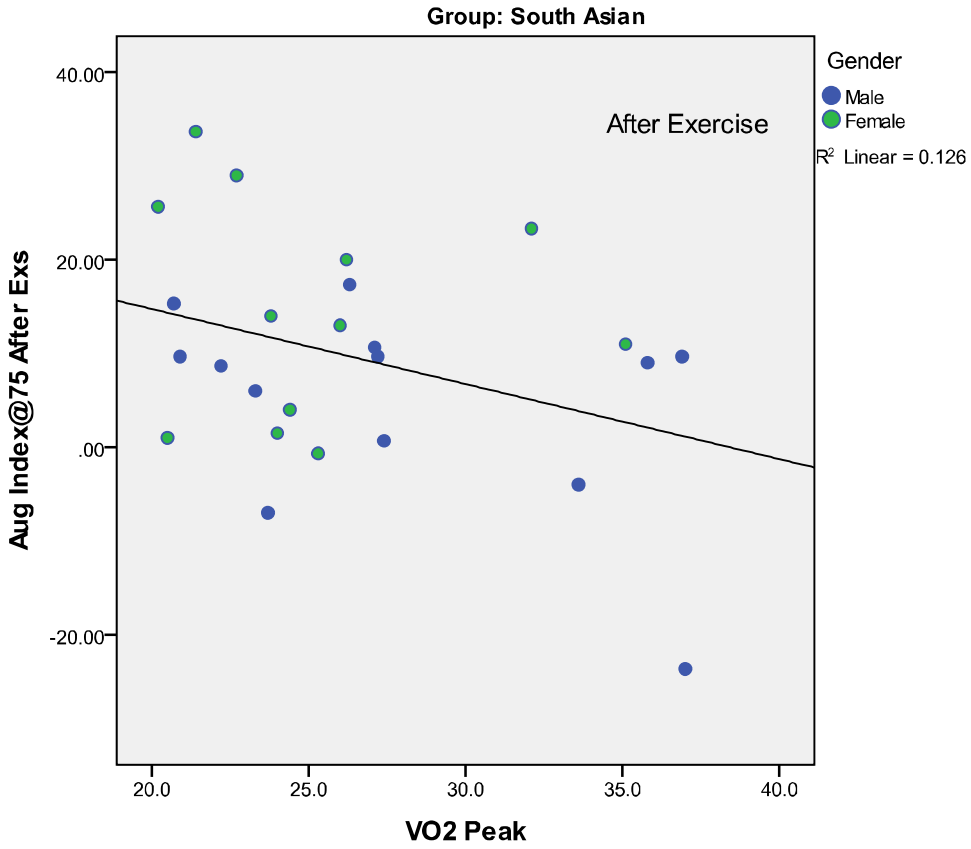


Fig. A.2.8 $VO_{2\ Peak}$ vs. aortic augmentation index at 75% heart rate before and after exercise in South Asians

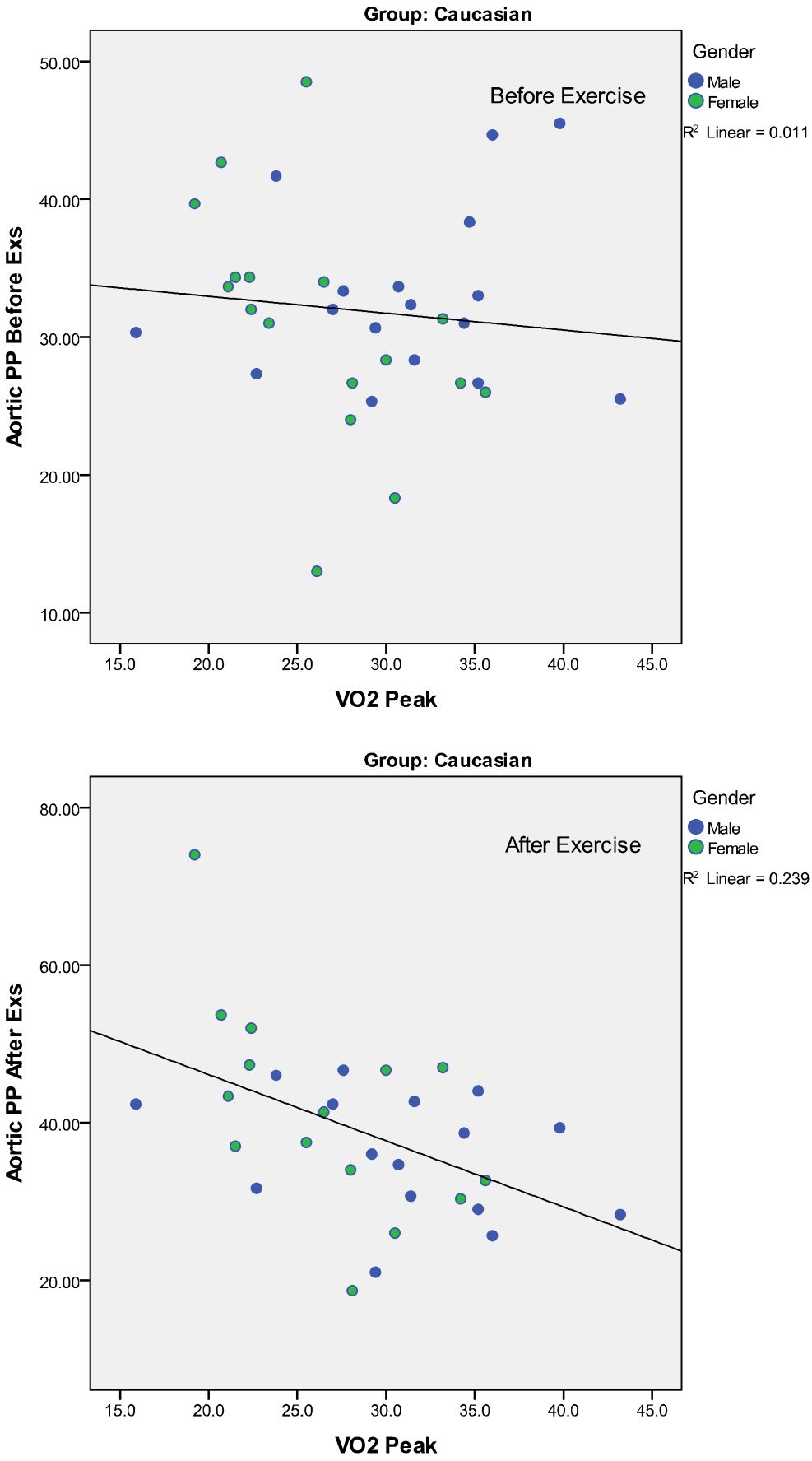


Fig. A.2.9 $VO_{2\ Peak}$ vs. aortic pulse pressure (PP) before and after exercise in Caucasians

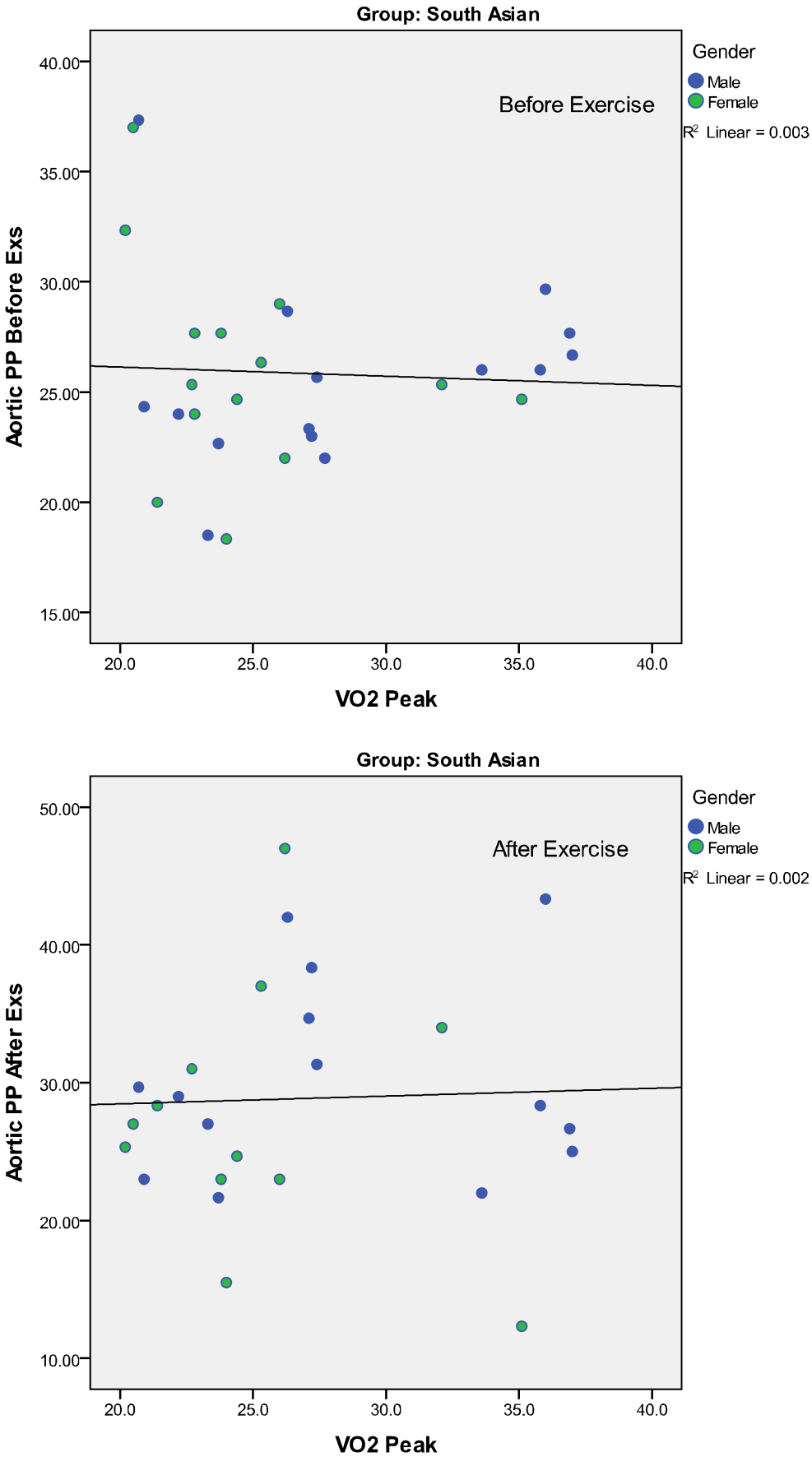


Fig. A.2.10 $VO_{2\ Peak}$ vs. aortic pulse pressure (PP) before and after exercise in South Asians

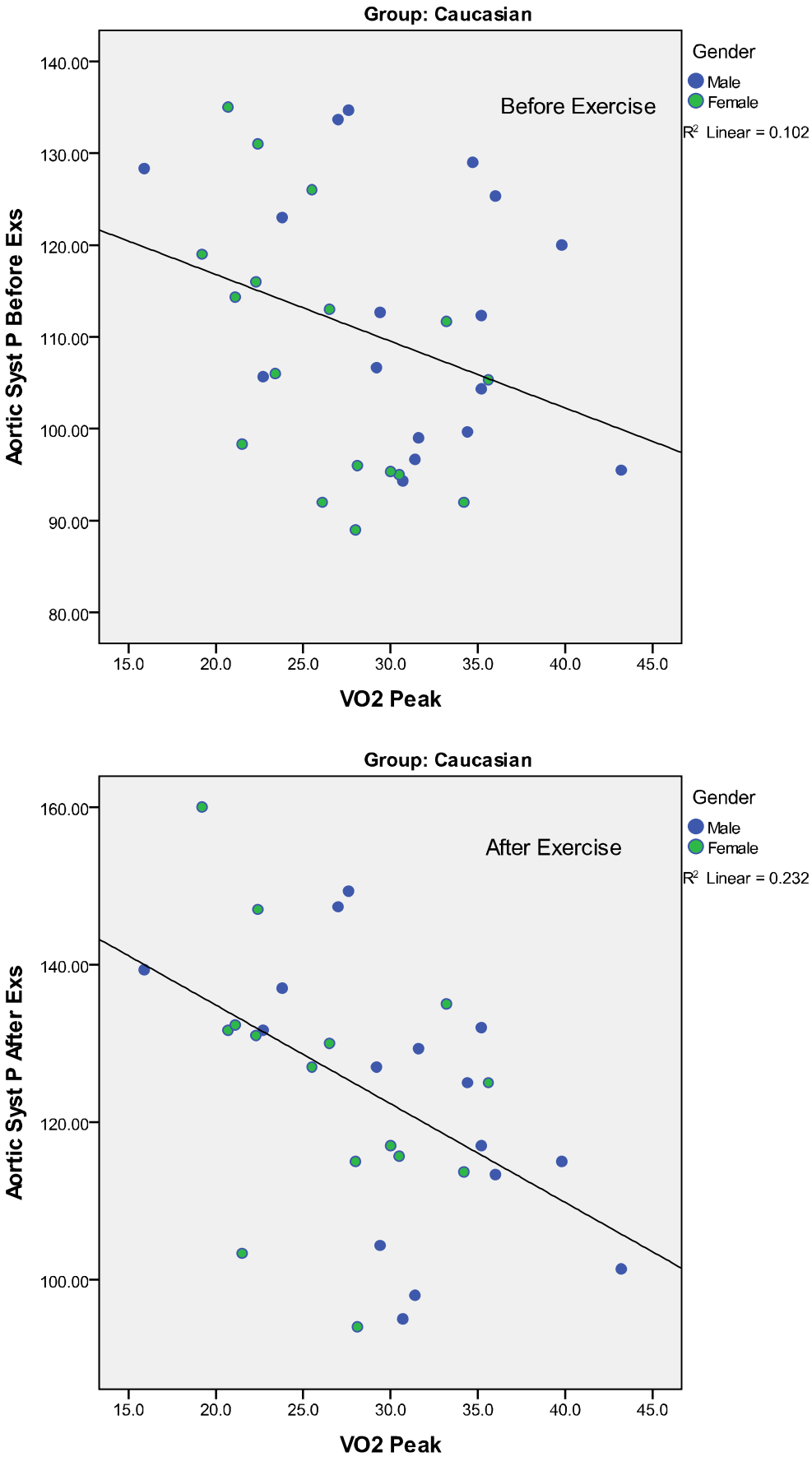


Fig. A.2.11 $VO_{2\ Peak}$ vs. aortic systolic pressure before and after exercise in Caucasians

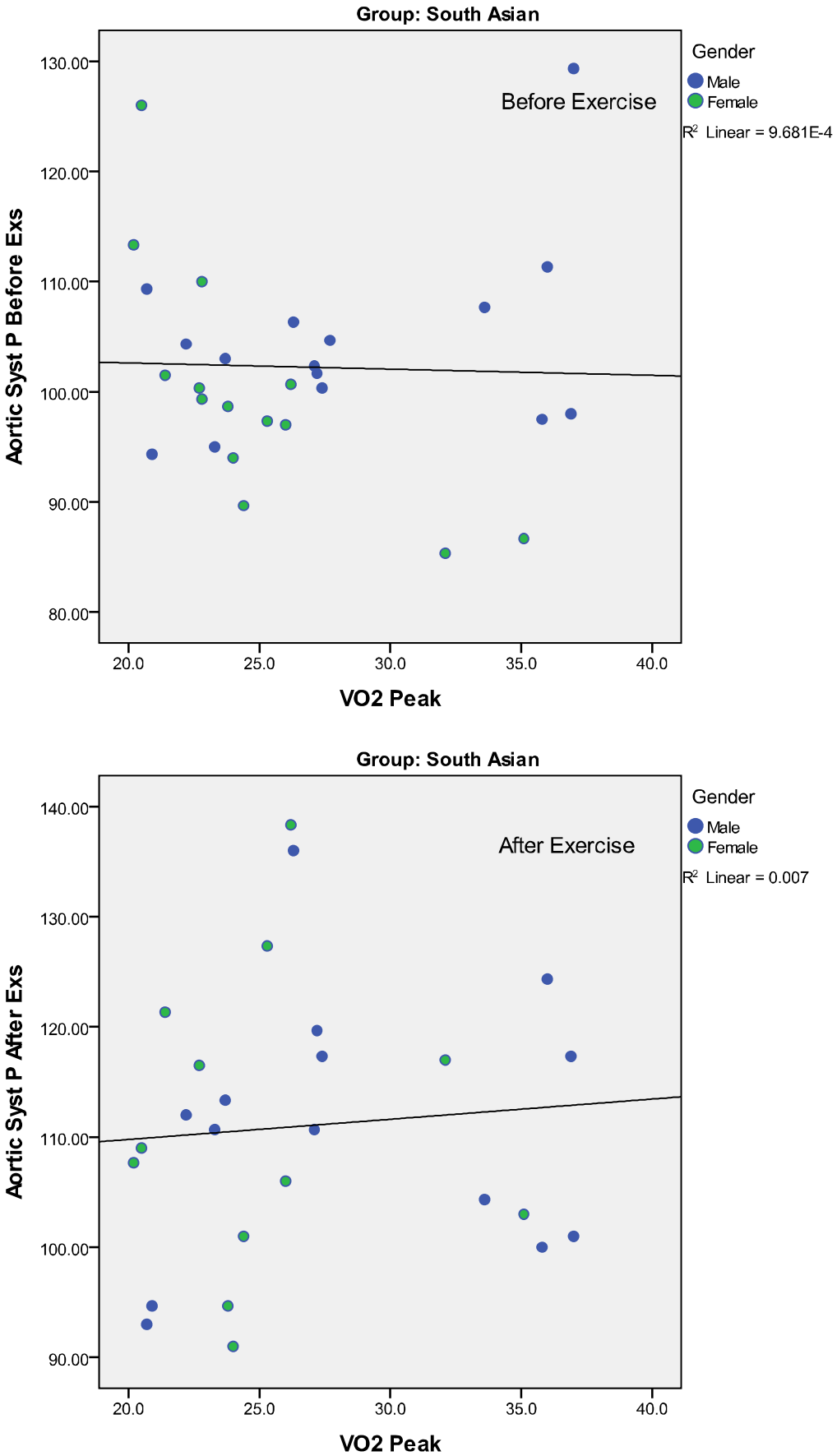


Fig. A.2.12 $VO_{2\ Peak}$ vs. aortic systolic pressure before and after exercise in South Asians

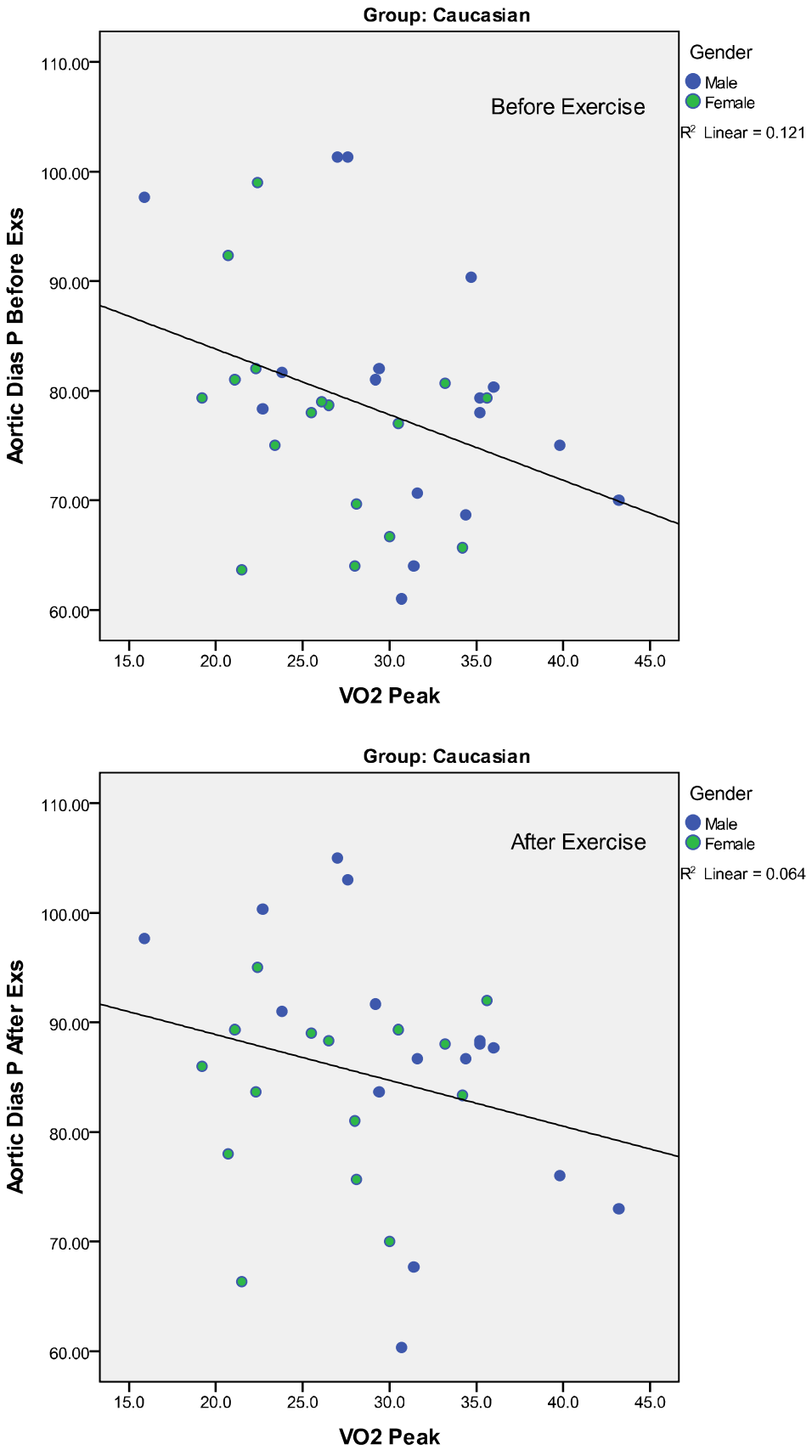


Fig. A.2.13 VO2 $_{Peak}$ vs. aortic Daistolic pressure before and after exercise in Caucasians

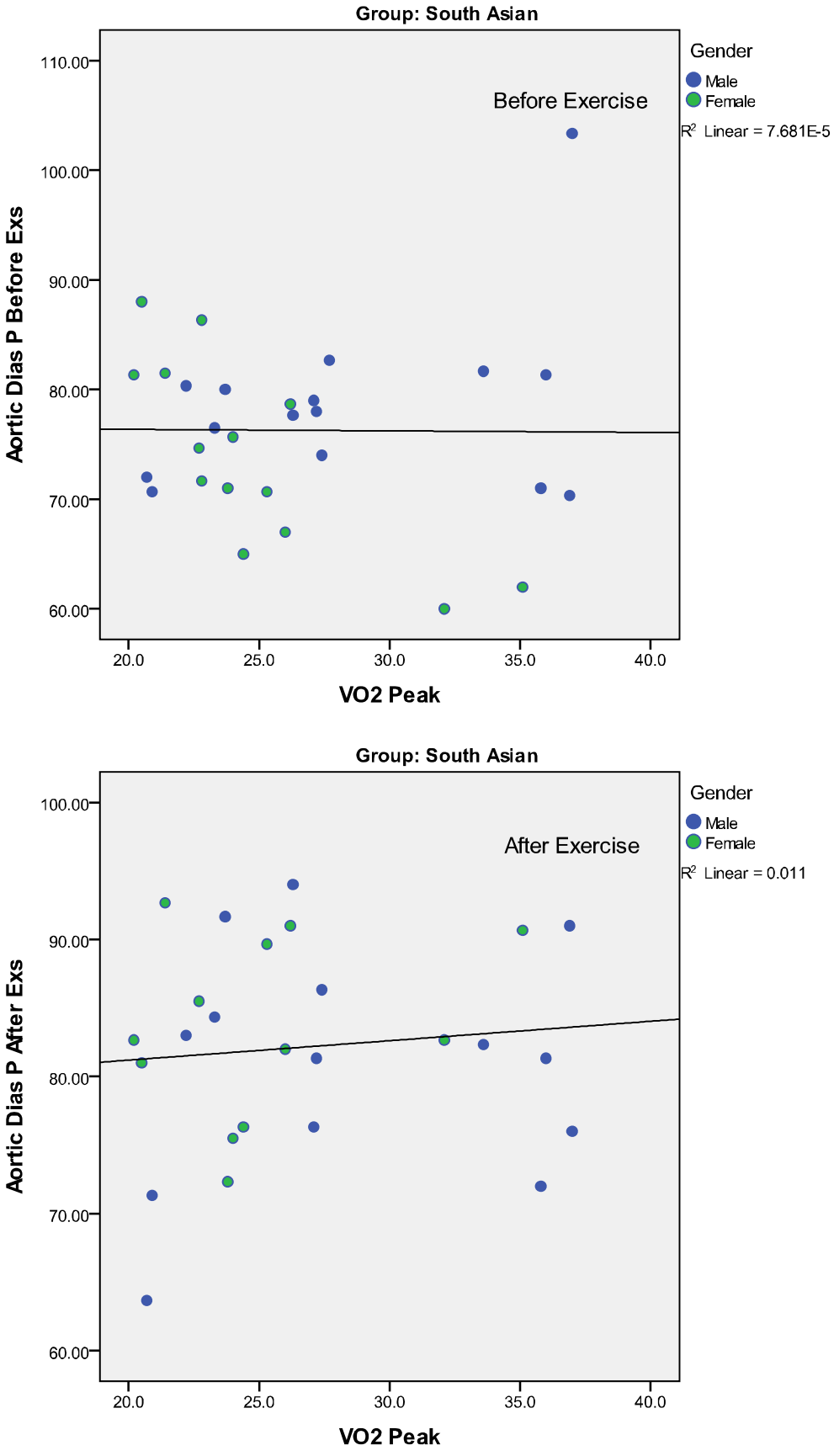
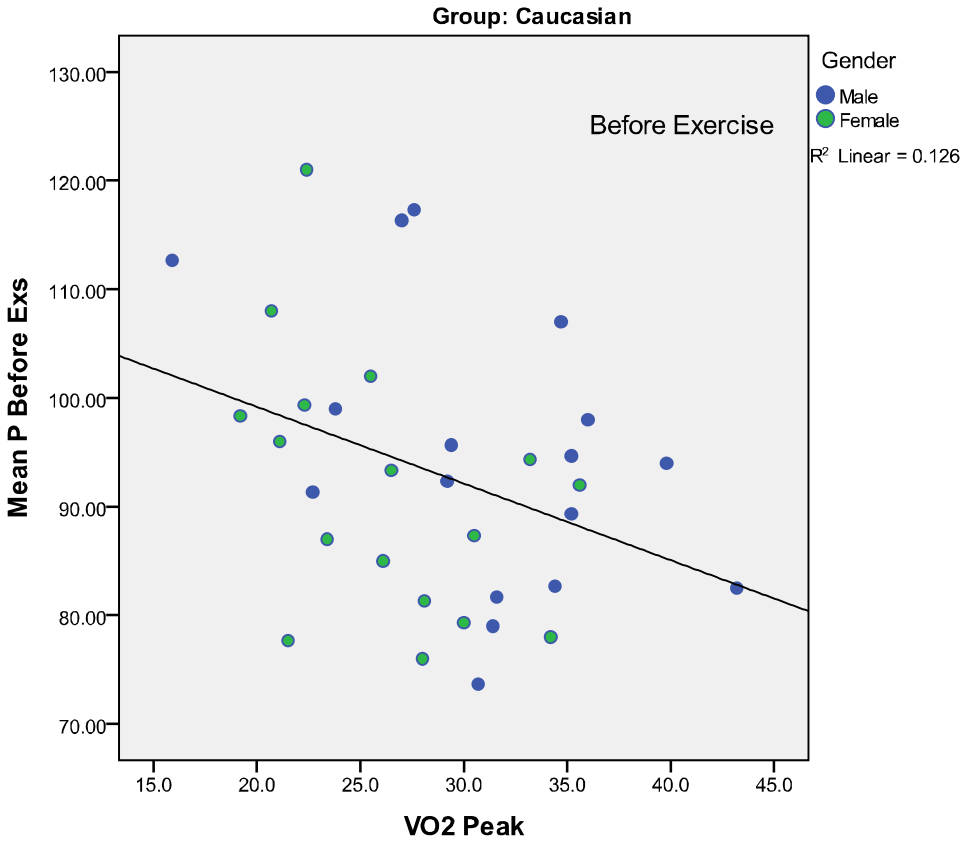


Fig. A.2.14 VO2 $_{Peak}$ vs. aortic Daistolic pressure before and after exercise in South Asians



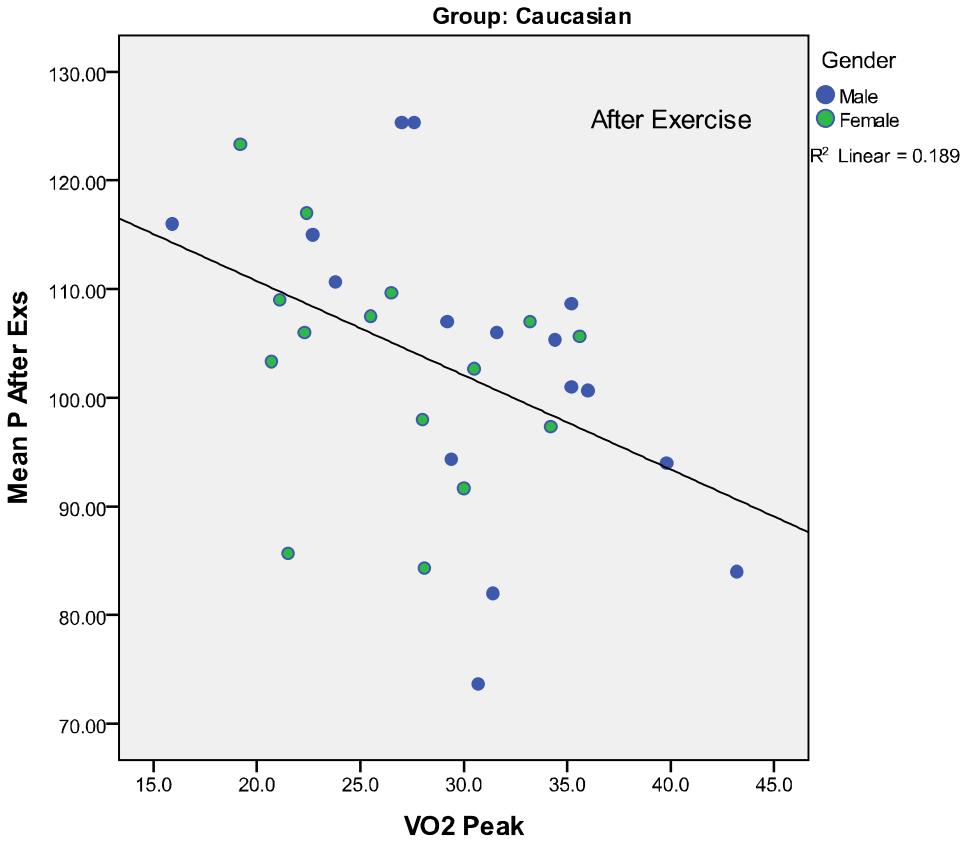


Fig. A.2.15 VO2 Peak vs. mean pressure before and after exercise in Caucasians

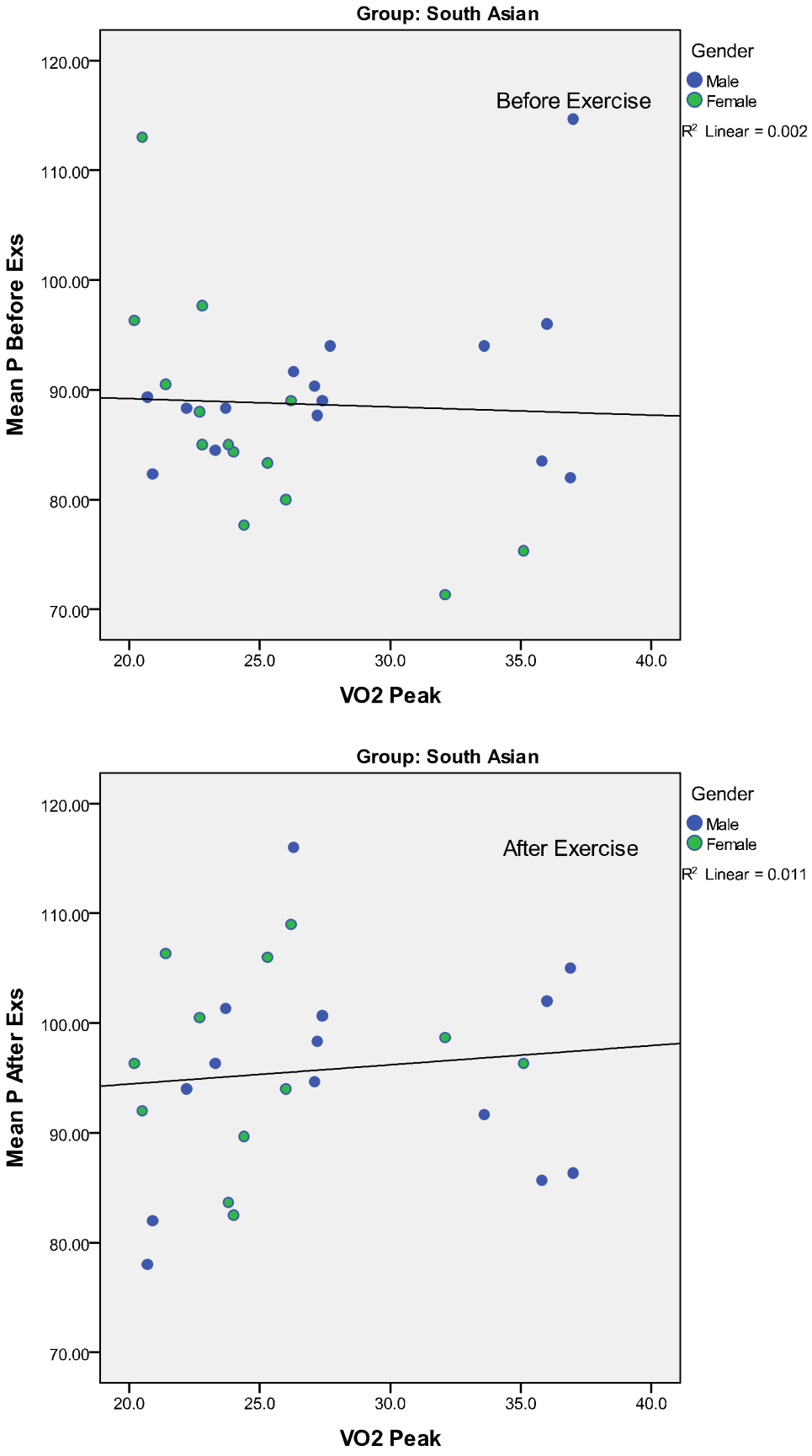
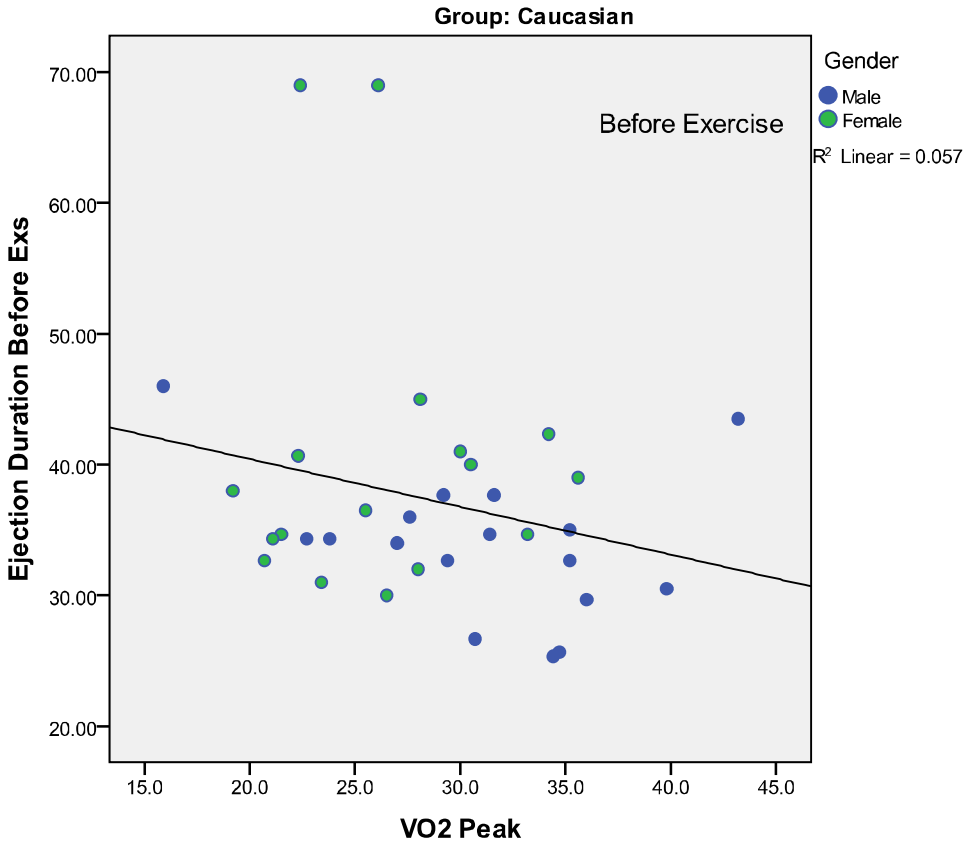


Fig. A.2.16 $VO2_{Peak}$ vs. mean pressure before and after exercise in South Asians



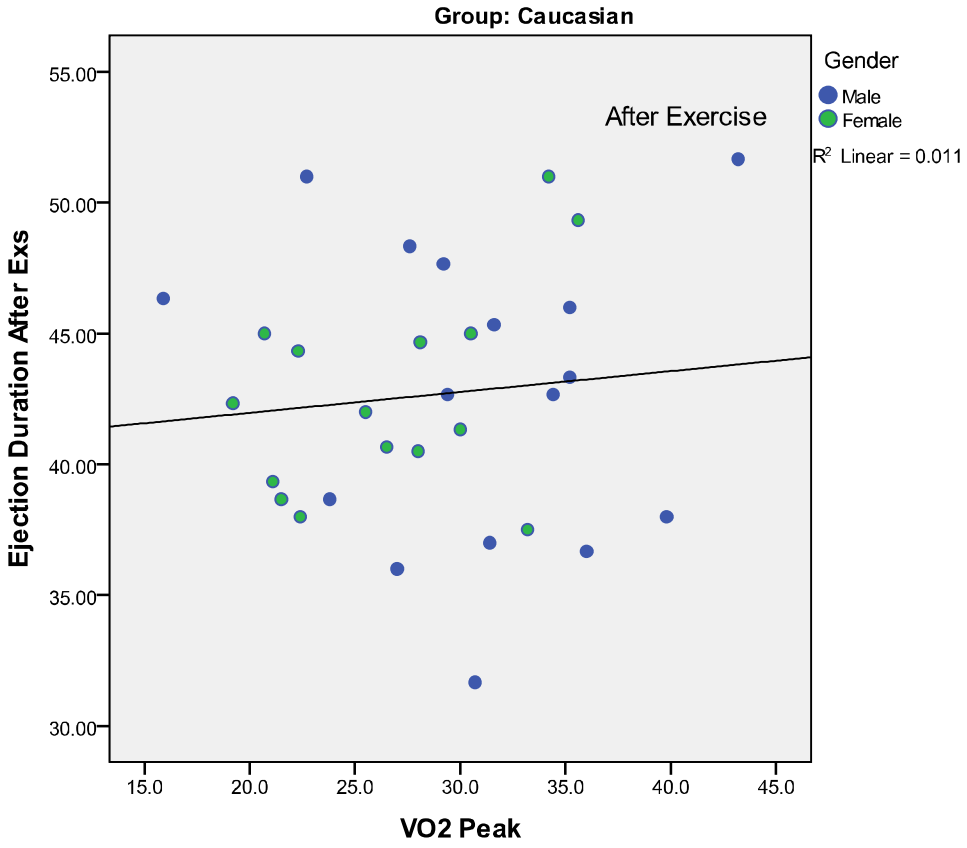


Fig. A.2.17 $VO2_{Peak}$ vs. aortic ejection duration before and after exercise in Caucasians

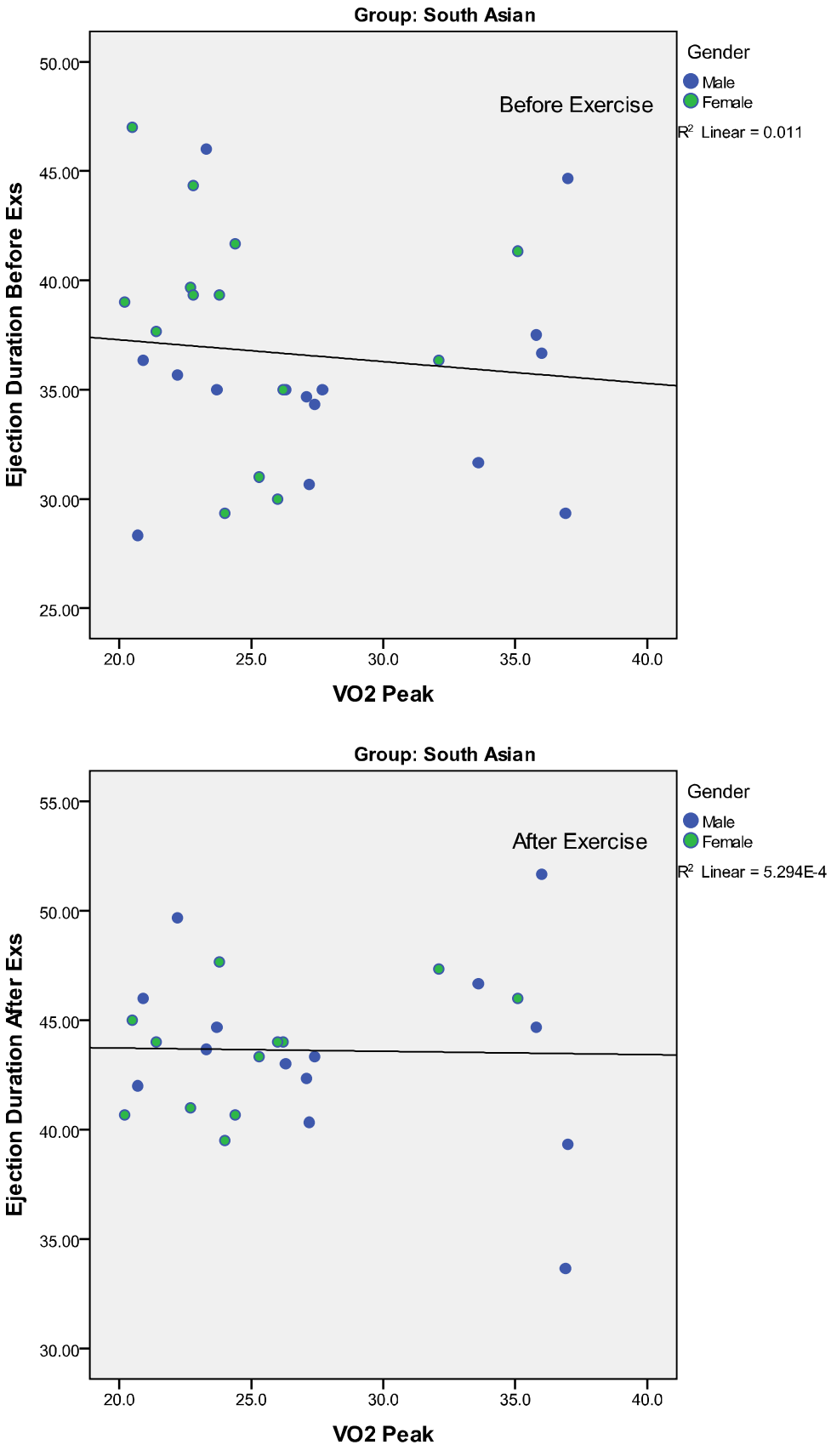


Fig. A.2.18 $VO2_{Peak}$ vs. ejection duration before and after exercise in South Asians

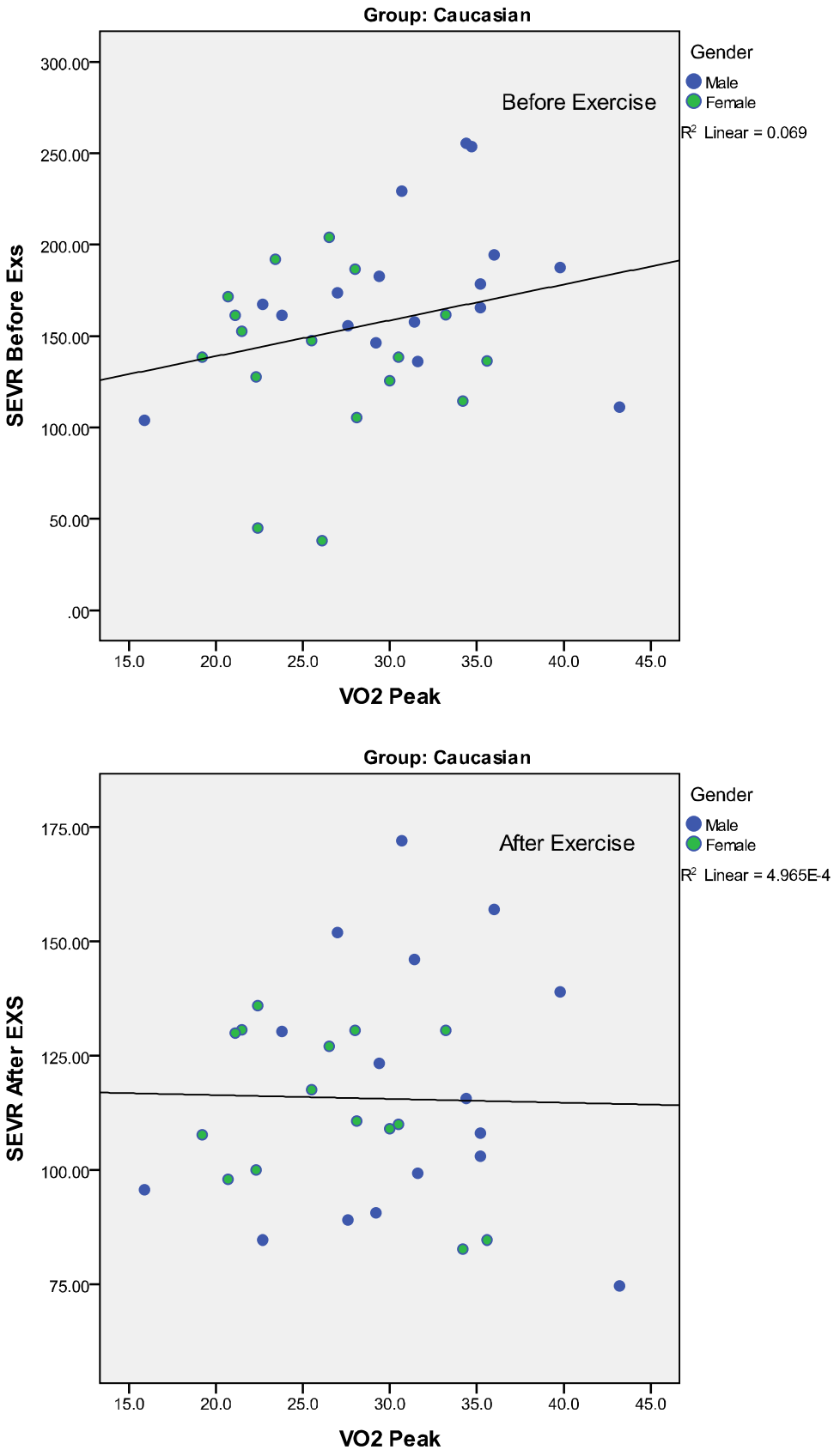


Fig. A.2.19 $VO2_{Peak}$ vs. subendocardial viability ratio (SEVR) before and after exercise in Caucasians

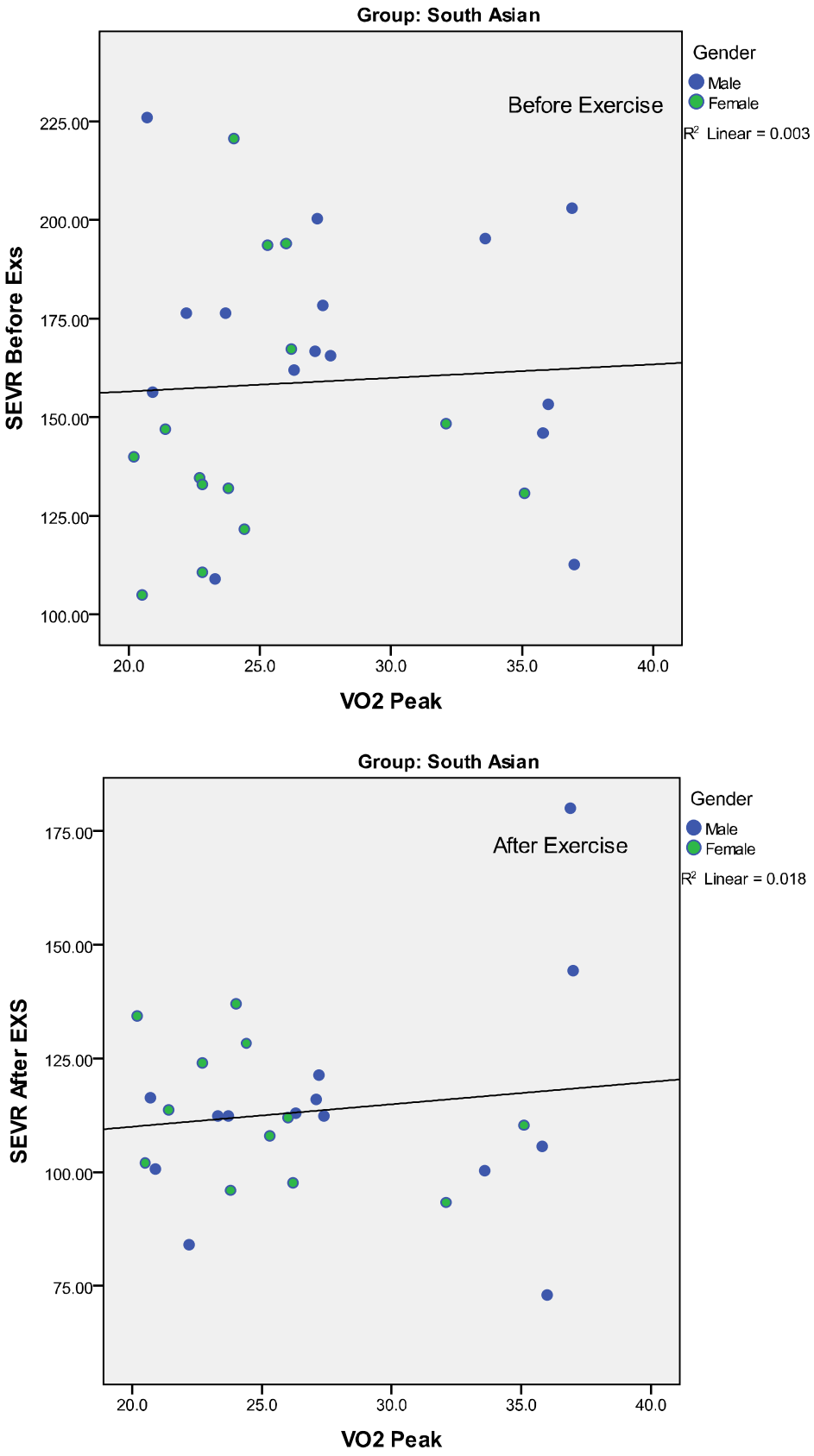
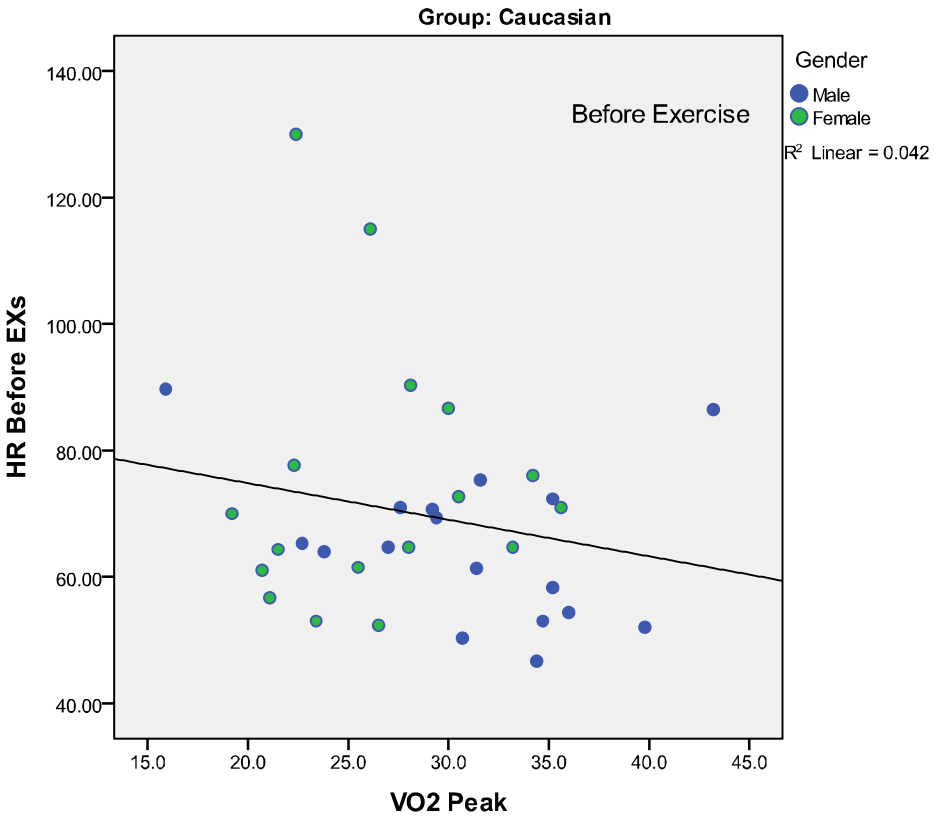


Fig. A.2.20 $VO2_{Peak}$ vs. subendocardial viability ratio (SEVR) before and after exercise in South Asians



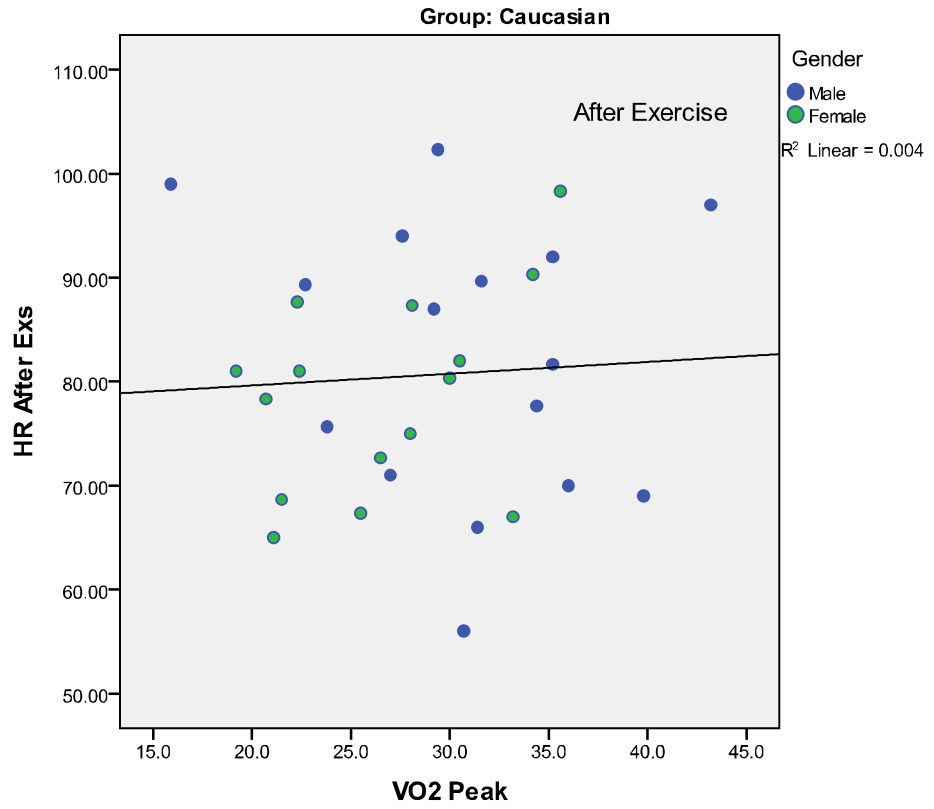


Fig. A.2.21 $VO2_{Peak}$ vs. heart rate before and after exercise in Caucasians

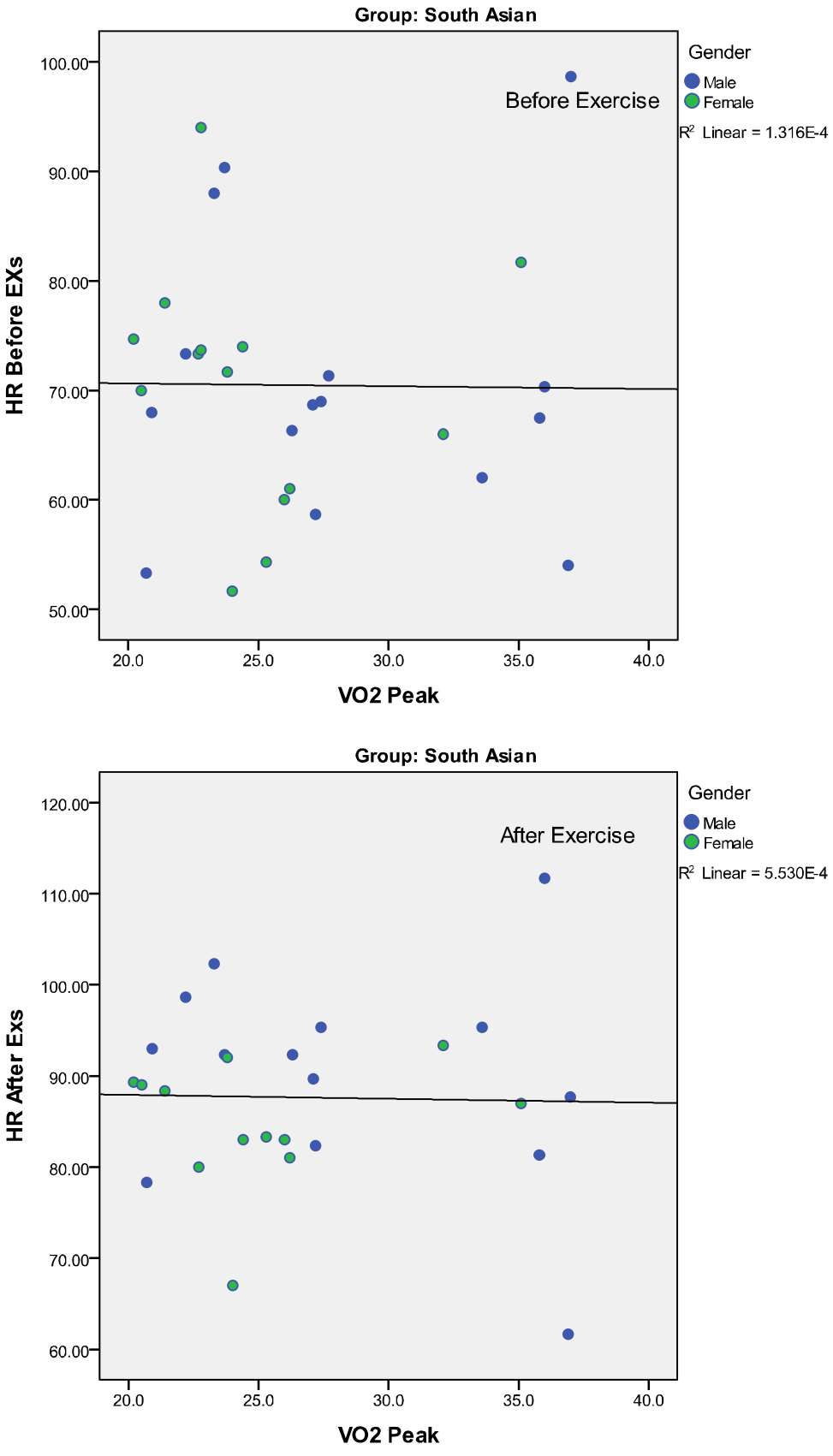


Fig. A.2.22 $VO2_{Peak}$ vs. heart rate before and after exercise in South Asians

APPENDIX III. Previous literatures showing the prevalence of metabolic syndrome worldwide

Author and year	Country/ Area	Age (yr)	Sample size		Criterion used for diagnosis	Prevalence (%)		
			Men	Women		Total	Men	Women
Central and South Asia								
Gu *et al* (2005)	China	35–74	15540		ATP III		9.8%	17.8%
Fan *et al*. (2005)	China (Shanghai)	Mean 52.4	1218	1957	ATP III	22.9%		
He *et al* (2006)	China	60-95	2334		ATP III IDF	30.5% 46.3%	17.6% 34.8%	39.2%5 4.1%
Yang *et al* (2007)	China	35–74	15838		IDF	16.52%		
					ATP III	23.3%		
Fan *et al* (2008)	China (Shanghai)	20–88	1524	2379	ATP III	15.3%		
Li *et al* (2006)	China (Beijing)	20–90	8807	7541	CDS	13.2%	15.7%	10.2%
Ko *et al* (2005)	China, Hong Kong	18-66	1513		ATPIII WHO	9.6% 13.4%		

					EGIR	8.9%		
Ko *et al* (2006)	China, Hong Kong	16-95	5202 diabetic		WHO	49.2-58.1%		
Feng *et al* (2006)	China	25–64	18630		ATP III ATP III-modified for Asians IDF	5.8% 9.5% 8.5%		
Lao *et al* (2006)	China	50–85	10362		ATP III IDF	15.7% 25.8%		
Lu *et al* (2006)	China	30+	1039		ATP III IDF WHO	55.7% 50.0% 70.0%		
Pei *et al* (2007)	China	20+	560		ATP III modified for Asians	FCHL - 36.7 FHTG - 33.3% FH - 17.6 Normolipidemic - 16.3%		
Misra *et al* (2001)	India (North)	>18	170	362	ATP III		13.3%	15.6%
Misra *et al* (2004)	India (South, urban)	≥20	1070		EGIR	11.22%		
Ramachandran *et al* (2003)	South India (urban)	20–75	4752		ATP III		36.4%	46.5%
Deepa *et al* (2007)	India (South, urban)	≥20	23505		WHO ATP III IDF	23.2% 18.3% 25.8%		

Gupta *et al* (2004)	India (North, urban)	>20	532	559	ATP III		22.9%	39.9%
Misra *et al* (2005)	North India (urban)	Mean; 38.9	6402		ATP III		11%	10.5%
Gupta *et al* (2007)	India (North, urban)	>20	532	559	ATP III		22.9%	31.6%
Chow *et al* (2008)	India (rural)	≥30	4535		ATPIII		32.5%	23.9%
Eastern Countries								
Boonyavarakul *et al* (2005)	Thailand	35+	404		ATP III	18%		
Lohsoonthorn *et al* (2006)	Thailand	20–70	1383		ATP III	12.8%	15.7%	11.7%
Pongchaiyakul *et al* (2007)	Thailand	20-90	602		ATP III	15%	15.3%	14.6%
Huang *et al* (2008)	Taiwan	20-94	124,513		IDF AHA	13.9% 22.4%		
Lin *et al* (2007)	Taiwan, Taichung	40-64 65+	2359		ATP III		35.32% 43.23%	24.19% 51.82%
Heng *et al* (2006)	Singapore	Adult	3954		ATP III		14.1%	12.3%
Tan *et al* (2004)	Singapore (Malays, Asian Indians, and	18–69	4723		ATP III		20.9%	15.5%

	Chinese ethnicity)						
Lee *et al* (2007)	Singapore cardiovascular	18-69	4334	IDF AHA	17.7% 26.2%		
Son le *et al* (2005)	Vietnam, Ho Chi Minh	18+	611	ATP III	12%		
Ishizaka *et al* (2005)	Japan	19–88	8144	ATP III		19%	7%
Tanaka *et al* (2005)	Japan	30–79	6985	ATP III		30.2%	10.3%
Yoshinaga *et al* (2005)	Japan, Kagoshima	06-11	471 overweight or obese	ATP III	8.7% in overweight, 17.7% in obese		
Arai *et al* (2006)	Japan	20-79	3264	ATP III Modified	7.8%	12.1%	1.7%
Aizawa *et al* (2006)	Japan	40+	11941	ATP III	14.9		
Oh *et al* (2004)	Korea (urban)	30–80	2692	ATP III		29%	16.8%
Park *et al* (2006)	Korea	20–80	6824	IDF		13.5 %	15.5%
Park *et al* (2004)	Korea	20–80	3937 4713	ATP III		14.2%	
Middle East							

Azizi *et al* (2003)	Iran (Tehran, urban)	>20	4397	5971	ATP III		24%	42%
Sharifi *et al* (2009)	Iran (urban)	>20	1396	1545	ATP III	23.7%	23.1%	24.4%
Esmaillzadeh *et al* (2006)	Iran	10-19	1413	1623	ATP III	10.10%	10.3%	9.9%
Al-Lawati *et al* (2003)	Oman	>20	695	724	ATP III		19.5%	23%
Ozsahin *et al* (2004)	Turkey	20–79	1637		ATP III		23.7%	39.1%
Agirbasli *et al* (2006)	Turkey	10-17	1385		ATP III	2.20%		
Demiral *et al* (2006)	Turkey, Izmir	24-60	450 men		ATP III	17.80%		
Onat *et al* (2002)	Turkey	>31	1130	1166	ATP III		27%	38.6%
Cameron *et al* (2007)	Mauritius	>24	3198		ATPIII		20.3%	
Australia and New Zealand								
Alberti *et al* (2006)	Australia	25–75	11,247		EGIR	15.8%		
					ATPIII	18.2%		

Gentles *et al* (2007)	New Zealand	35-74	4022		ATP III	32% (Maori), 39% (Pacific/Polynesian aborigines) 16% (European descendants)		
Europe								
Hu *et al* (2004)	DECODE Study Group, 11 European cohort studies	30–89	6156	5356	WHO	15%	15.7%	14.2%
Balkau *et al* (2003)	France, Central-Western (DESIR cohort study)	30-64	2109	2184	ATP III		10.0%	7.0%
Maumus *et al* (2005)	France, Nancy in northeast Stanislas	28-64	1366		ATP III		5.9 %to 7.2% in 5 years	2.1% to 5.4% in 5 years
Dallongeville *et al* (2005)	France	35–64	3359		ATP III		23%	16.9%

Bataille *et al*.(2006)	France	50–59	10 592		ATP III IDF WHO		29.7% 38.9% 35.5%	
Gustiene *et al*.(2005)	Lithuania (Kaunas)	Mean 38.8	192	241	IDF		28.1%	16.6%
Bonora *et al* (2003)	Italy, Bruneck	40-79	888 adults		ATPIII WHO	17.8% 34.1%		
Bo *et al* (2005)	Italy, Asti in northwest	45-64	1877		ATP III	22.2%	24%	22%
Invitti *et al* (2006)	Italy, North	6-16	588 obese		WHO	23.30%		
Alegria *et al*.(2005)	Spain, Valencia	45.4 ± 9.8	7256		ATP III	10.20%	8.7%	3%
Jerico *et al* (2005)	Spain	41.9±9.2 HIV	710		ATP III	17%		
Lopez-Capape *et al*.(2006)	Spain	4-18	429		ATP III	18% Hispanic (32%) Caucasian (16%)		
Lorenzo *et al* (2006)	Spain	35–64	2540		ATP III IDF		22.3 % 27.7%	30.7 % 33.6%
Assmann *et al* (2007)	Germany		4816	2315	ATP III IDF		23.5 % 31.6%	17.6 % 22.6%

Dekker *et al* (2005)	Netherlands	50–75	1364	ATP III WHO		19.0 % 26.0%	32.0 % 26.0%
Gorter *et al* (2004)	Netherlands	18–80 CHD	1117	ATP III	46%		
Santos and Barros (2003)	Portugal	18–90	1436	ATP III	23.9%	19.1%	27%
Athyros *et al* (2005)	Greece	Adults	9669	ATP III IDF	24.5 % 43.4%		
Kolcic *et al* (2006)	Croatia	18–88	996	ATP III	34%		
Lawlor *et al* (2006)	UK	60–79	3589	ATP III IDF WHO			29.8 % 47.5% 20.9%
Tillin *et al* (2005)	UK	40–69	2346 Europeans (76% male)	ATP III WHO		18% 19%	14% 9%
			1711 South Asians (83% male)	ATP III WHO		29% 46%	32% 31%

			803 African-Caribbeans (57% male)	ATP III WHO		16% 27%	23% 26%
Boronat *et al* (2005)	Canary Islands	30+	1193	ATP III WHO		20.3% 26.5%	21.1% 17.6%
Skoumas *et al* (2007)	Greece	Adults FCHL	706	ATP III	41.8%	63%	37%
Herva *et al*.(2006)	Finland	Adults with Depression and Anxiety	5698	ATP III	37%	47%	25%
North and South America							
Park *et al* (2003)	USA, 3rd NHANES survey	20	12,363	ATP III	23%	22.8%	22.6%
Ford *et al* (2008)	USA NHANES Survey	≥20	3601	IDF	34.5%	33.7%	38.1%
Ford *et al* (2002)	USA NHANES Survey	≥20	8814	ATP III	23.7%		

Goodpaster *et al* (2005)	USA, Pittsburgh & Membis	70-79	3075	ATP III	39%		
Florez *et al* (2005)	Venezuela	>20	3108	ATP III	31.22% Amerindian (17%) Black (27.2%) Caucasian (33.3%) Mixed (37.4%)		
Hidalgo *et al* (2006)	Ecuador	≥40 Post menopausal Women	325	ATP III			41.5%
Sherry *et al*.(2005)	Dominican Ancestry	2–20 Obese	428	Multiple risk factors	14%		
Tull *et al* (2005)	US Virgin Islands	Caribbean-Born Adults – No history of diabetes	893	ATP III	20.5%		
Hashimoto *et al* (2007)	Brazil	30–60 Japanese Brazilian	721	ATP III	53%		
Damiao *et al* (2006)	Brazil	40–79 Japanese Brazilian	151	ATP III		36.9%	38.8%

Lanz *et al* (2006)	Brazil	Adults Going Under 1st Time Angiography	385		WHO		39.7%	58.7%
Freire *et al* (2005)	Brazil	≥30 Japanese Brazilians	877		ATP III		49.8%	43%
Pousada *et al* (2006)	Brazil	Spanish Migrants	479		ATP III	26.3%	29.6%	22.6%
Alvarez *et al*.(2006)	Brazil	12–19 overweight and non- overweight		388	ATP III			
de Oliveira *et al* (2006)	Brazil (Cavunge)	25–87	102	138	I BGDT MS	24.8%	18.6%	
Barbieri *et al* (2006)	Brazil (Ribeirao Preto)	23–25	2063		ATP III		10.7%	
Aguilar-Salinas *et al* (2005; 2003)	Mexico	20–69	2158		WHO ATP III	13.62% 26.6%		

I BGDT MS First Brazilian Guideline for Diagnosis and Treatment of Metabolic syndrome, CDS - (Chinese Diabetes Society), EGIR- European Group for the Study of Insulin Resistance, FCHL- Familial Combined Hyperlipaemia; FHTG- Familial Hypertriglyceridaemia, FH- Familial Hypercholesterolaemia