CENTRAL ARTERIAL IMPEDANCE AND PHYSICAL ACTIVITY-INDUCED CHANGES IN STROKE VOLUME IN HYPERTENSION

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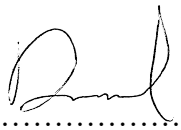
A Dissertation submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of Master of Science in Medicine

Johannesburg, 2020

Declaration

I, Daniel Marcus Da Silva Fernandes declare that this dissertation is my own, unaided work unless otherwise stated. It is being submitted for the Degree of Masters in Science in Medicine at the University of the Witwatersrand, Johannesburg. The work in this dissertation has not been submitted for any Degree or examination in this University or any other University.



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……30.th……day of….March……..20.20……in…Johannesburg

I certify that the studies contained in this thesis have been approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, Johannesburg. The ethics approval number is M17-02-71.

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Angela J. Woodiwiss (Supervisor 1)

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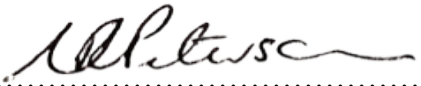

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Vernice R. Peterson (Supervisor 2)

Date: ……30/03/2020…….

Dedication

I dedicate this work to my parents, Victor and Linda who have supported me unconditionally through all my studies. I would also like to extend my gratitude to my brother Victor and my two sisters Carla and Elvira for all the advice and continued support.

Conference presentation

"Physical Activity Without Resistance Exercise Decreases Wave Reflection in Treated Refractory Hypertensives" Renin-Angiotensin-Aldosterone System Satellite Meeting held in Cape Town, South Africa from the 28-30th November 2018. (First Prize- Clinical Science Investigator Award).

Abstract

Regular physical activity is recommended as part of the management of hypertension. However, physical activity in hypertension is often symptom limited, an effect that may in-part be attributed to an inability to increase stroke volume (SV) and hence cardiac output (CO). The extent to which this effect is determined by impedance to flow in the proximal aorta generated by increases in aortic stiffness is uncertain. In 56 hypertensives recruited from a hypertension referral clinic (age=56.9±12.8 years) with resting BP values <160/100 mm Hg, I assessed the extent to which proximal aortic characteristic impedance (Zc) determines the impact of modest physical activity (stationary supine bicycle or handgrip) on activity-induced increases in SV. Haemodynamic effects were determined from aortic velocity and diameter assessments in the left ventricular outflow tract (echocardiography) and central arterial pressure measurements (applanation tonometry and SphygmoCor software). Average resting blood pressures (BP) on medication were 140±18 mm Hg systolic and 79±9 mm Hg diastolic BP, with 60.7% controlled to target. Physical activity resulted in an increase in SV (128±43 to 161±68 mls/beat, p=0.0001) and CO (p<0.0001) and a decrease in systemic vascular resistance (SVR) (p<0.005). The increase in SV was strongly and inversely associated with Zc (p<0.0001) and SVR (p<0.0001) at baseline and directly correlated with decreases in SVR with activity (p<0.0001). However, in the same regression model, activity-induced decreases in SVR contributed far more to increases in SV (partial r=-0.755, CI=-0.880 to -0.604) than did variations in Zc either at baseline (partial r=-0.344, CI=-0.556 to -0.083) or immediately after physical activity (partial r=-0.165, CI=-0.411 to 0.107)(p<0.05 for comparison of partial r values). In conclusion, although the function of the proximal aorta (stiffness) does contribute to the extent to which flow increases with physical activity in hypertension, the contribution is modest in comparison to the impact of activity on arteriolar function (vasodilator effects).

Acknowledgements

I would firstly like to thank my supervisors, Professor Angela J. Woodiwiss and Dr. Vernice R. Peterson for their amazing support and patience. They have truly been inspirational through this enthralling journey, and as such I have always strived to achieve my best in everything I have done. I would furthermore like to extend my gratitude to Professor Gavin R. Norton, for always giving me great advice and guidance on writing skill and critical thinking. Lastly, I would like to thank the National Research Foundation for the financial aid which made the completion of my study possible.

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Nomenclature

A: Late diastolic filling

a': late diastolic flow velocity

AIx: Augmentation Index

BMI: Body Mass Index

BP: Blood Pressure

CO: Cardiac Output

CRF: Cardio-Respiratory Fitness

cm: centimeter

DBP: Diastolic Blood Pressure

E: Early diastolic filling

e': early diastolic flow velocity

E/A: Ratio of early-to-late diastolic filling

e'/a': ratio of early-to-late mitral annulus flow velocity

ECG: Electrocardiogram

ED: Ejection Duration

EDD: End Diastolic Diameter

EDV: End Diastolic Volume

E/e': diastolic filling pressure

EF: Ejection Fraction.

FS: Fractional Shortening

g/dl: gram(s) per deciliter

HbA1c: Glycosylated haemoglobin

HFpEF: Heart Failure with a preserved Ejection Fraction

HR: Heart Rate

IMT: Intima Media Thickness

IVSd: Inter Ventricular Septum in diastole

IVS: Inter Ventricular Septum

IVSs: Inter Ventricular Septum in systole

kg/m^2 : kilogram(s) per meters squared

kg.m/min: kilogram(s) per meter per minute

LDL: Low-Density Lipoprotein

LV: Left Ventricle

LV EDD: Left Ventricular End Diastolic Diameter

LV EDV: Left Ventricular End Diastolic Volume

LV ESV: Left Ventricular End Systolic Volume

LVIDd: Left Ventricular Inner Diameter in diastole

LVIDs: Left Ventricular Inner Diameter in systole

LVM: Left Ventricular Mass

LVMI: Left Ventricular Mass Index

LVOT: Left Ventricular Outflow Tract

LVPWd: Left Ventricular Posterior Wall Thickness in diastole

LVPWs: Left Ventricular Posterior Wall Thickness in systole

MAP: Mean Arterial Pressure

mls: millilitres

mmHg: Millilitres of Mercury

mmol/l: millimole(s) per litre

M-Mode: Motion Mode

Pa: Augmented Pressure

Pb: Backward Wave Pressure

Pf: Forward Wave Pressure

PP: Pulse Pressure

PPc: Central Pulse Pressure

PWV: Pulse wave Velocity

Q: Aortic Flow

RM: Reflection Magnitude

SBP: Systolic Blood Pressure

SD: Standard Deviation

SV: Stroke Volume

SVR: Systemic Vascular Resistance

TPR: Total Peripheral Resistance

VTI: Velocity Time Integral

Zc: Characteristic Impedance

Zi: Input Impedance

μmol/l: micromole(s) per litre

CHAPTER 1: INTRODUCTION

1.1 Introduction

Globally hypertension, which is characterised by an increase in brachial blood pressure (BP) defined as a BP ≥140/90mmHg, is responsible for approximately 9.4 million deaths per annum from cardiovascular events including stroke, myocardial infarction, heart failure and renal failure (Roman et al., 2007; Campbell et al., 2016). According to the Global burden of disease study, an increased BP has been rated as the second leading global risk factor for cardiovascular disease (Lim et al., 2010). Data from the INTERHEART study (29972 participants from a total of 52 countries worldwide), show that hypertension contributes to 18% of the population attributable risk for the development of a myocardial infarction (Guimara˜es et al., 2010; Okamoto et al., 2007). Furthermore, data from the Framingham Heart Study show that 8.2% of men develop coronary artery disease and 5.2% of woman develop stroke as a first event due to hypertension (Kawano et al., 2006). Hence, it is clearly evident that controlling BP in hypertensives is imperative to achieve global health.

South Africa has the highest prevalence of hypertension in Sub-Saharan Africa as it has been shown that 90.7% of those aged 60 years and above are on anti-hypertensive therapy (Statssa.gov.za, 2016). Currently, the clinical management of hypertension is through the reduction of brachial BP to values below 140/90 mm Hg by means of lifestyle therapy, which includes regular physical activity and a balanced diet, as well as through anti-hypertensive therapy (Whelton et al., 2017; Persell, 2011). Physical activity is recommended as first-line therapy for at least the first 6 months in pre- and mild hypertensives and as an adjuvant to anti-hypertensive therapy in all hypertensives. The effects of regular physical activity on BP are due to the benefits produced on peripheral as well as central arterial BP (Whelton et al., 2017).

Bearing in mind the high burden of hypertension in developing countries such as South Africa and that these countries are resource limited, it is particularly important in such countries to identify cost effective approaches to the management of hypertension. In this regard, primordial prevention is of particular importance in developing countries. A key component of primordial prevention is lifestyle modification, including increased physical activity. However, exercise capacity may be limited in hypertensives (Molmen-Hansen et al., 2012), hence impacting on their ability to exercise sufficiently to obtain BP benefits.

In order to improve exercise prescription in those with co-morbid conditions such as hypertension, it is important to understand the mechanisms that limit physical activity in hypertensives. However, there is currently little understanding as to why exercise capacity is limited in hypertensives. In this regard, in addition to the ability of muscles to extract and utilise oxygen, cardiac output (CO) is a crucial variable that determines oxygen consumption and hence the capacity to perform physical activity (Paolillo et al., 2018). Hence, exercise capacity may be limited by cardiac mechanisms or vascular mechanisms that impose increased loading conditions (systolic wall stress) on the heart and thereby reduce CO. Although, hypertensives often have underlying hypertensive heart disease (Vieira et al., 2016; Paolillo et al., 2018), it is currently not clear whether changes in resistance to aortic flow impact on stroke volume and hence CO during incremental exercise. Systemic vascular resistance (SVR) is the dominant factor determining systolic wall stress (Wigfull and Cohen, 2005); however SVR decreases during aerobic exercise (Reddy et al., 2017). Nevertheless, the impact of impedance to flow (resistance to flow in a pulsatile system) generated by the aorta (Zc) a change which often characterizes elderly hypertensives, needs to be considered. Indeed, increases in Zc are often reported to be associated with decreases in aortic flow at rest (Nichols et al., 2011). However, there are limited data to show an effect of Zc on aortic flow during exercise.

In order to provide a background to understanding the rationale for performing the study described in the present dissertation, in the present chapter I will first discuss the effects of different modes of physical activity on peripheral blood pressure, as described by the most recently prescribed guidelines for the management of hypertension. As an understanding of central aortic blood pressure, is crucial to appreciating the possible role of aortic characteristic impedance (Zc) in limiting physical activity, I will introduce central aortic blood pressure. I will then compare the mechanisms that explain the differences between peripheral and central blood pressure, and then explain why central aortic pressure is poorly indexed by peripheral blood pressure. The effects of physical activity on central aortic blood pressure will then be discussed. I will then describe the possible cardiac and vascular mechanisms that may limit exercise capacity, particularly in persons with hypertension at an older age. In so doing I will highlight the lack of evidence to support a role for aortic stiffness and hence aortic characteristic impedance (Zc) as one such vascular factor that may limit exercise capacity. This chapter will therefore provide the argument for performing the study described in the present dissertation.

1.2 Benefits of Physical Activity on Blood Pressure

Guidelines for the diagnosis and management of hypertension, recommend physical activity as an adjuvant to pharmacological therapy to reduce BP (Whelton et al., 2017; Persell, 2011). Although the extent of the impact of physical activity on BP may vary, physical activity in some circumstances can achieve similar BP reductions as compared to pharmacological therapy (Molmen-Hansen et al., 2012). Although there are documented cases where exercise training in hypertensives may have been responsible for a cardiovascular event (Molmen-Hansen et al., 2012) generally, as long as BP is within mild to-moderate ranges, recent

guidelines consider not only aerobic exercise, but also dynamic (full body) resistance and isometric resistance exercises as safe to perform in hypertensives (Whelton et al., 2017). The benefits of physical activity on BP have been well-described over several decades. What is the extent and type of exercise required to achieve BP reduction and what is the extent of the BP change that may occur with physical activity?

1.2.1 Effects of Aerobic Physical Activity on Peripheral Blood Pressure

Based on extensive evidence obtained over many years, guideline committees currently recommend 90-150 minutes/week of aerobic physical activity at 65-75% of heart rate reserve (Whelton et al., 2017). Based on a large meta-analysis consisting of 54 randomised controlled trials, aerobic physical activity has been shown to decrease mean resting systolic BP (SBP) by 5 mm Hg and diastolic BP (DBP) by 8 mmHg in hypertensives and SBP by 4 mm Hg and DBP by 3 mmHg in normotensives (Whelton et al., 2002). Moreover, studies conducted with 24-hour ambulatory BP monitoring (which limit white-coat effects and detect masked hypertensive effects) show that regular aerobic lower limb exercise for greater than 4 weeks results in an average decrease in resting SBP and DBP of 3 and 2.4mmHg respectively, and an average decrease in daytime ambulatory SBP and DBP of 3.3/3.5 mmHg respectively (Cornelissen and Fagard, 2005). Importantly, these exercise-induced reductions in BP were more pronounced in hypertensives compared to normotensives (Cornelissen and Fagard, 2005; Molmen-Hansen et al., 2012).

1.2.2 Effects of Resistance Physical Activity on Peripheral Blood Pressure

1.2.2.1 Effects of Dynamic Resistance Physical Activity on Peripheral Blood Pressure

Dynamic resistance physical activity refers to activity which is performed on more than one muscle group on different parts of the body (Collier et al., 2010; Whelton et al., 2017). Typical examples of this type of exercise would be 3 sets of 10 repetitions of bench press, leg curl, leg extension, bent-over row, military (shoulder) press, close-grip bench press (triceps), biceps curls and abdominal curls in accordance to standard guideline protocols. In this regard, BP reduction is observed with 90-150 min/week of dynamic resistance physical activity at 50-80% repetition maximum which should include 6 exercises, 3 sets/exercise, and 10 repetitions/set (Whelton et al., 2017). According to a meta-analysis consisting of 16 studies reviewed in guidelines (Whelton et al., 2017), this form of physical activity causes an average decline in SBP and DBP of 4 mmHg in hypertensives and 2 mmHg in normotensives (Cornelissen et al., 2013).

1.2.2.2 Effects of Isometric Resistance Physical Activity on Peripheral Blood Pressure

In contrast to dynamic resistance physical activity, where muscle lengthening and shortening occurs, isometric resistance physical activity is characterised by forms of activity in which the joint angle and muscle length remain constant during contraction (Cornelissen et al., 2013). These include examples such as isometric wall squats and isometric hand grip exercises (Whelton et al., 2017; Wiles et al., 2017). Guideline committees recommend that 4 sets of 2-minute-long sessions of isometric handgrip exercises (joint angle and muscle length do not change during contraction) with 1-minute resting periods between exercises (Whelton et al., 2017). A minimum of 3 sessions per week are recommended at an intensity of 30-40%

of maximum voluntary contraction. Based on a meta-analysis which includes 93 randomized controlled trials, an average decrease in BP (both SBP and DBP) of 5 mmHg in hypertensives and 4 mmHg in normotensives has been reported (Cornelissen and Smart, 2013; Whelton et.al 2017). Other studies have however suggested that higher intensity hand grip exercise training produce further improvements in BP. In a study by Carlson et al, high intensity handgrip exercise training at 30% of maximum voluntary capacity for 8 weeks caused an overall drop in SBP of 7 mmHg ($p=0.03$), DBP of 4 mmHg ($p=0.02$) and mean arterial pressure (MAP) of 4 mmHg ($p<0.01$) (Carlson et al., 2016). Nevertheless, in that study a group of very well controlled hypertensives were randomly recruited. Whether, a similar effect is observed in controlled hypertensives with higher BP values requires further study.

1.2.2.3 Mechanisms of Effects of Resistance Physical Activity on Peripheral Blood Pressure

Importantly, high intensity upper limb resistance exercise training has been suggested to decrease BP as a result of changes in peripheral vascular tone (total peripheral resistance or systemic vascular resistance, TPR or SVR) which may improve systemic blood flow to skeletal muscle during exercise and reduce left ventricular (LV) afterload in well controlled hypertensives (Okamoto et al., 2007; Ashor et al., 2014; Zhang et al., 2018). Whether, similar effects are observed in hypertensives with higher BP values is unknown. The aforementioned studies give us an indication that modest dynamic resistance exercise is indeed beneficial in those with controlled BP. It is however unknown whether the same applies to those of advancing age with uncontrolled BP.

1.3 Central Arterial Blood Pressure and Physical Activity

As described in the aforementioned section, there is extensive evidence to show a benefit of exercise training on peripheral arterial BP. In this regard, the arterial pulse is generated in the central aorta and is transmitted peripherally. Therefore, peripheral BP acts as an important surrogate of the adverse effects of BP and the benefits of exercise on BP reduction detected at the peripheral pulse are likely to show similar effects centrally. However, the peripheral pulse also shows several features which are quite distinct from the pulse generated centrally. Thus, although sharing many similar determinants, which will be discussed in the subsequent sections, there are several determinants of the central arterial pulse that may not be adequately indexed by the peripheral pulse. An important question is therefore whether all of the factors that cause damage through increases in BP centrally are modified by exercise programs known to reduce peripheral BP. Before discussing the impact of exercise on the determinants of BP load, it is first important to identify the differences between central and peripheral BP and the determinants of central BP.

1.3.1 Differences Between Central and Peripheral Blood Pressure

Unlike DBP which remains relatively constant across the arterial tree, central arterial SBP, including SBP in the aorta, is lower than SBP measured in peripheral arteries including the brachial artery. These differences may be as much as 20-30 mm Hg. This effect which is attributed to amplification of pulse pressure (PP) from central to peripheral arteries is explained by two factors (Nichols et al., 2011). In this regard, peripheral arteries are narrower in diameter and more muscular than central arteries such as the aorta, which are elastic in nature. Consequently, peripheral arteries generate a higher stiffness and hence impedance

(resistance in a pulsatile system) to flow than the central arteries. The consequent impedance mismatch between the central and peripheral arteries therefore amplifies PP as it is transmitted outward to peripheral arteries (Nichols et al., 2011).

The second factor that may explain PP amplification is that the forward travelling pressure wave generated by ventricular ejection is transmitted to points of vascular tapering where wave reflection occurs and on their return to the proximal aorta, reflected waves summate with the forward travelling pressure wave (Nichols et al., 2011). In the periphery the reflected wave returns at points of forward wave antinodes (pressure waves are oscillating waves around the arterial wall with both positive [antinodes] and negative [nodes] pressure wave components in the lumen) thus producing considerable overlap with positive waves and maximal summation. In contrast, the reflected wave returns sufficiently late in the aorta. Hence, the overlap between the forward and reflected wave is more at forward wave pressure nodes and hence the extent of overlap of positive components of pressure waves and hence summation is considerably less (Nichols et al., 2011).

As will be discussed in a later section, the factors that explain SBP differences between peripheral and central arteries have varying effects at different ages and with different combinations of risk factors. Consequently, differences in SBP between central and peripheral arteries (PP amplification) vary considerably from person to person. Therefore, the question that arises is whether central or peripheral arterial SBP differ in their ability to detect cardiovascular damage?

1.3.1.1 Differences Between Central and Peripheral Blood Pressure in Their Ability to Detect Cardiovascular Damage

Several studies suggest that aortic SBP or PP is associated with cardiovascular end-organ measures, including left ventricular mass index (LVMI), left ventricular function, carotid intima-media thickness, and glomerular function better than or independent of brachial BP (Boutouyrie et al., 1999; Covic et al., 2000; Wang et al., 2009; Roman et al., 2010; Neisius et al., 2012; Norton et al., 2012; Wohlfahrt et al., 2017) and this topic has been extensively reviewed by Roman and Devereux, 2014. More recently a meta-analysis of studies evaluating relationships between either central or peripheral SBP or PP and end-organ changes suggests that aortic SBP or PP are associated with end-organ measures beyond peripheral SBP or PP (Kollias et al., 2016). Furthermore, several studies show that aortic SBP or PP predicts cardiovascular outcomes better than or independent of brachial SBP or PP (Safar et al., 2002; Williams et al., 2006; Wang et al., 2009; Benetos et al., 2010; Benetos et al., 2012; Regnault et al., 2012; Jankowski et al., 2008; Pini et al., 2008; Roman et al., 2007; Roman et al., 2009).

In this regard, earlier studies suggested that beyond brachial BP, central aortic PP or SBP were predictors of cardiovascular events in those with end-stage renal disease (Safar et al., 2002), in patients undergoing coronary angiography (Jankowski et al., 2008), in the elderly (Pini et al., 2008), and in the general population (Roman et al., 2007 & 2009). However, in some studies brachial but not central aortic SBP was reported to predict cardiovascular events (Dart et al., 2006). Importantly, in a meta-analysis of these studies published at that time, the ability of aortic versus brachial BP to predict risk did not show a significantly greater effect for aortic SBP or PP, although a trend for a better effect was noted ($p=0.057$) (Vlachopoulos et al., 2010). This meta-analysis was nevertheless criticised

for several reasons including the inclusion of studies where the calibration of central pressure waveforms may have been inappropriate (Dart et al., 2006). This meta-analysis also excluded data from the Conduit Artery Function Evaluation (CAFE) study (and obviously other later studies) which also reported on relations between aortic versus brachial BP and cardiovascular outcomes (Williams et al., 2006) as well as a study conducted in Taiwan which had only just been published at the time of the meta-analysis (Wang et al., 2009) which similarly demonstrated an enhanced ability of aortic as compared to brachial BP to predict risk.

Nevertheless, data from the Framingham Heart Study, which was similarly not published at the time of the meta-analysis, was also not included. In this regard, the Framingham Heart Study demonstrated that aortic SBP failed to offer an ability to risk predict beyond brachial SBP (Mitchell et al., 2010). However, in the Framingham Heart Study, little difference between aortic and brachial BP (PP amplification) was noted across the adult lifespan, a finding which because of the generally excellent BP control in this community, may be attributed to the remarkably low mean brachial BP values observed at the time of the study (Mitchell et al., 2010). Hence, it is perhaps unsurprising that aortic SBP failed to provide prognostic information beyond brachial BP in the Framingham Heart Study (Mitchell et al., 2010).

The inconsistent findings in studies exploring the relative role of central arterial as compared to peripheral BP in risk prediction has prompted several groups, including our own, to consider the possibility that the individual determinants of central versus peripheral SBP and PP may better associate with cardiovascular end organ measures or damage than SBP or PP *per se*. What are the determinants of central arterial PP and hence SBP?

1.3.2 Determinants of Aortic Pulse Pressure

Pulsatile loads on the cardiovascular system are determined by several components that extend well beyond that provided in undergraduate textbooks on cardiovascular physiology. The pressure waves that contribute to aortic PP are the incident or forward (Pf) and the reflected or backward (Pb) pressure waves (Murgo et al., 1981; Nichols and O'Rourke, 2005). What are the determinants of Pf and Pb?

The forward travelling pressure wave, the peak of which is designated Pf (Figure 1.1) is generated by left ventricular ejection into an elastic conduit, the aorta. Consequently, the factors that determine aortic flow (stroke volume), such as cardiac contractility, afterload to the left ventricle and ventricular filling (Frank-Starling effect) are major determinants of the magnitude of Pf and hence PP and SBP (Nichols et al., 2011). As the aorta has a large diameter and at a young age is elastic and hence compliant, it creates a cushioning effect during ventricular ejection and generates little resistance to flow in a pulsatile system in the absence of reflected waves (characteristic impedance or Zc) (Mitchell et al., 2010; Wang et al., 2010; Nichols et al., 2011). The high degree of elasticity of the aorta is such that it may store 60 to 70% of the ejected stroke volume (SV). The subsequent elastic recoil during diastole drives blood flow in distal vessels. In a young person without risk factors, Zc contributes little to Pf and hence Pf is determined largely by flow and hence ventricular ejection. However, with aging and the impact of several risk factors including hypertension, diabetes mellitus, smoking and dyslipidaemia, fragmentation of elastic fibres in the aorta occurs, collagen and its cross-linked properties increase, the aorta calcifies and aortic stiffness increases (Nichols et al., 2011). The increased aortic stiffness enhances Zc, an effect which drives increases in Pf and hence PP (Nichols et al., 2011). Under these circumstances, the magnitude of Pf depends less on flow itself, and more on the aortic characteristic

impedance to flow. With increases in Zc produced by changes in stiffness, the aorta is unable to expand as much as normal during systole and this reduces the extent of the elastic recoil, with a consequent drop in flow during diastole, a change that may explain reductions in DBP at an older age. Increases in aortic stiffness, Zc and Pf are thought to be major determinants of increases in PP, particularly with an older age and are the central factors that govern increments in PP and hence SBP in isolated systolic hypertension (Lee et al., 1999; Phan et al., 2016).

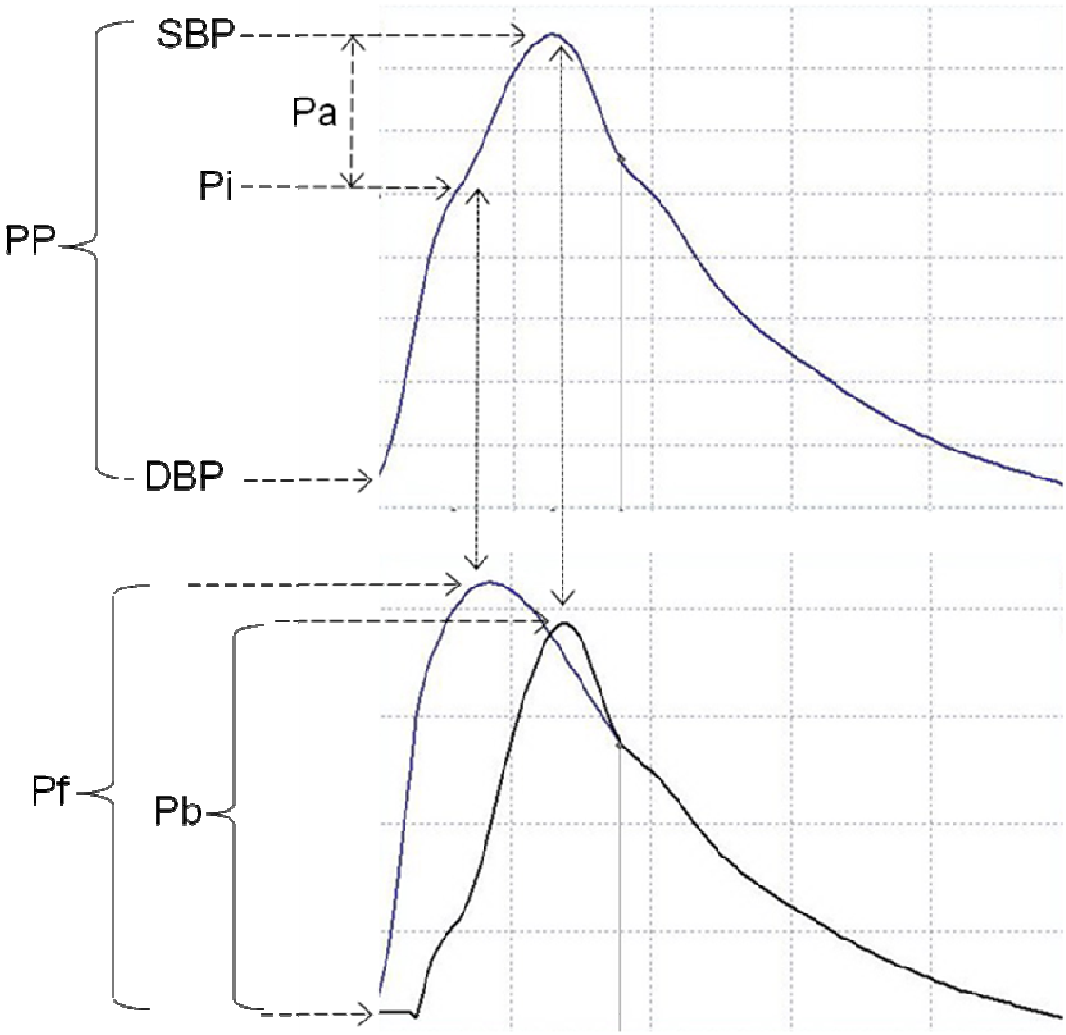

Figure 1.1. Central aortic pressure waveform (upper panel) and its component waves (lower panel). The upper panel shows the summation of the forward and backward waves to produce the aortic pressure wave. The lower panel shows the component forward and backward pressure waves derived from wave separation analysis. DBP, diastolic blood pressure; Pa, augmented pressure; Pb, reflected wave pressure; Pf, forward wave pressure; Pi, point of inflection on the upstroke of the aortic pressure wave; PP, pulse pressure; SBP, systolic blood pressure. Augmentation index (AIx) = Pa/PP.

Whilst aortic stiffness effects on Pf are relatively straightforward, the impact of aortic diameter is complex. The aortic root increases in diameter with age (Mao et al., 2008; Devereux et al., 2012), an effect that reduces resistance and hence impedance to flow. This would normally be considered to decrease Pf and hence PP. However, the large diameter of the aorta may contribute little to resistance to flow in a pulsatile system at any age. Rather, an increased aortic diameter may transfer the load from less stiff elements in the aortic wall such as elastin to stiffer elements such as collagen. Thus, diameter changes with aging may increase Pf by enhancing stiffness and thus Zc. Nevertheless, the debate as to whether aortic diameter increases or decreases aortic PP is presently unsettled and several studies suggest that a relative reduction in aortic diameter (less of an increase with aging) is associated with increases in aortic PP (Vasan, et al., 1995; Farasat et al., 2008).

Although the peripheral pulse is largely driven by variations in aortic flow and Zc, which is systematically amplified through reductions in impedance mismatches and through reflection phenomena centrally, several additional pressure waves summate and contribute to central aortic PP and hence SBP. As indicated in the above discussion, as forward travelling pressure waves encounter sites of high impedance such as artery-arteriolar junctions and arterial branch points, including the interface between muscular arteries and arterioles, it is reflected and returns to the ascending aorta (Mitchell et al.,2010). While peripherally, the impact of wave reflection is driven by reflected waves within local beds. In this regard, it is likely that numerous small reflections from various reflecting sites summate on return to the proximal aorta to form a relatively discrete composite reflected wave (Mitchell, 2008). These reflected pressure waves therefore generate what appears to be a single backward travelling pressure wave, the peak of which is designated Pb (Figure 1.1). These reflected pressure waves are of benefit if these waves return slowly and augment pressure during diastole. In this regard, it is thought that an impact of wave reflection on DBP will enhance coronary

blood flow, which mainly occurs in diastole (Mitchell, 2008). However, by early adulthood the speed of the pressure wave is sufficiently fast, that the reflected wave arrives early enough to coincide with the late systolic period of the same cardiac cycle. When this occurs, it overlaps with the forward pressure wave to augment aortic PP (Murgo et al., 1980).

This increase in aortic PP generated by aortic Pb returning early in the cardiac cycle is called aortic augmentation pressure (Pa) and is often expressed as augmentation index (AIx=AP/aortic PP or Pa/aortic PP) to account for the impact of Pf on Pb (Figure 1.1 and as discussed below) and to avoid calibration errors of central pressures. With respect to the impact of Pf on Pb, through inertial effects (Newton's 1st Law of Motion) and Newton's 3rd Law of Motion (for every action there is an equal and opposite reaction), the magnitude of Pf has a major effect on the amplitude of Pb (Nichols et al., 2011). Therefore, Pb is in-part determined by Pf through the impact of Newton's Laws of Motion. Importantly however, reflected waves are also determined by both arteriolar tone (systemic vascular resistance) and by alterations in more proximal arteries (Safar et al., 2003). Thus, a component of backward wave effects can be modified by vascular tone (Safar et al., 2003).

The approach to assessing wave reflection using Pa or augmentation index (AIx) has been employed for several years and is incorporated in all major commercial software. In this regard, augmented pressures generally make a much smaller contribution to PP than those factors that influence pressure up until the inflection point (generally the maximal pressure generated by the product of aortic flow [Q] and Zc). What this approach has not however considered is the contribution of wave re-reflection to both Pf and PP (Phan et al., 2016). As previously mentioned, the forward pressure wave is thought to be driven primarily by the product of Q and Zc. However, the maximum pressure generated by Q x Zc is normally at a point close to the first systolic shoulder of the pressure wave (just before the inflection point) and hence occurs well before peak Pf. Thus, as recently highlighted (Phan et al., 2016) there

is clearly an excess pressure in Pf that cannot be ascribed to either Q or Zc. In this regard, the excess pressure in the forward wave is attributed to wave re-reflection (Phan et al., 2016). Wave re-reflection occurs when the backward travelling waves reflect forward on return to the proximal aorta and add to forward wave pressures (Nichols et al., 2011; Phan et al., 2016). Once again, through Newton's 1st and 3rd Laws of Motion, the magnitude of the re-reflected wave is likely to be determined by the magnitude of wave reflection (Phan et al., 2016; Nichols et al., 2011). Importantly, when accounting for wave re-reflection, at the time point where maximal PP occurs, the sum of the contribution of the pressure generated by the backward travelling pressure wave and re-reflected waves by far exceeds the contribution of the pressure generated by the product of Q and Zc. Thus, in fact the contribution of reflected waves to peak PP exceeds that of the pressure generated by the product of Q and Zc. In short, Pf overestimates the impact of Q and Zc on aortic PP and Pa underestimates the total contribution of wave reflection to aortic PP.

1.3.3 Relative Role of Factors That Determine Central Arterial Pulse Pressure

What is the evidence for or against a relatively more important role of one pulsatile pressure wave as opposed to another in contributing to cardiovascular disease? Although a meta-analysis of several studies assessing the ability of central aortic AIx to predict events demonstrated robust effects (Vlachopoulos et al., 2010), subsequent studies published at a similar time failed to demonstrate similar effects beyond steady-state pressures (Mitchell et al., 2010). However, as indicated in the previous section, in the context of wave re-reflection, AIx is likely to markedly underestimate the impact of wave re-reflection (Phan et al., 2016) and hence reflected waves (Booysen et al., 2015) on aortic PP and end organs. Thus, we turn to data on the role of Pf and Pb. In this regard, it is only in more recent years that several

studies (Wang et al., 2010; Weber et al., 2012; Chirinos et al., 2012; Zamani et al., 2014; Booysen et al., 2015; Sibiya at al., 2015; Cooper et al., 2015; Zamani et al., 2015; Kaess et al., 2016) have provided the data to show the impact of Pb relative to Pf on end organ measures and cardiovascular events beyond steady-state pressures.

Two studies (Zamani et al., 2014; Booysen et al., 2015; Sibiya et al., 2015) conducted in large community-based samples, one from the Multiethnic Study in Atherosclerosis (MESA) (Zamani et al., 2014) provide strong evidence with all appropriate adjustments included in the analysis that Pb rather than Pf is the major determinant of left ventricular mass (LVM). In contrast, the Framingham Heart Study showed that Pf rather than Pb is the main determinant of LVM (Kaess et al., 2016). How then do we explain these contrasting data (Zamani et al., 2014; Booysen et al., 2015; Sibiya et al., 2015; Kaess et al., 2016)? In this regard, in none of these studies was the extent to which Pf effects on LVMI attributed to wave re-reflection evaluated. Hence, the extent to which the dominant Pf effects on LVM in the Framingham Heart Study are attributed to wave re-reflection and hence wave reflection is unknown. In addition, assuming that neither wave reflection nor re-reflection contribute to LVM in the Framingham Heart Study, then one must consider whether the lack of effect of wave reflection and re-reflection is not simply through marked antihypertensive effects. In this regard, it is conceivable that in community samples such as the Framingham Heart Study where BP control is excellent that reflected waves play little role in contributing to central aortic PP (Mitchell et al., 2010). In contrast, in other studies where BP control is generally considered to be poor, reflected waves may make a major contribution (Zamani et al., 2014; Booysen et al., 2015; Sibiya et al., 2015). Consequently, when decreasing BP to very low levels, Pb may no longer be a determinant of cardiovascular damage. These contrasting results (Zamani et al., 2014; Booysen et al., 2015; Sibiya et al., 2015; Kaess et al., 2016) therefore do not negate the importance of reflected waves, but rather emphasize the

importance of accounting for wave re-reflection as a determinant of Pf, or the relatively greater role of reflected waves in the hypertensive as opposed to the normotensive BP range.

What is the relative impact of Pf and Pb on alternative end organs? Only one large community-based study, has reported on the impact of Pb as compared to Pf with appropriate adjustments included in the analysis, on several additional end organ measures including carotid intima-media thickness (IMT) and aortic pulse wave velocity (PWV) (Sibiya et al., 2015). As with LVM (Booysen et al., 2015), beyond steady-state pressures, Pb was noted to play a more important role than Pf (Sibiya et al., 2015). However, subsequent analyses demonstrated organ-specific effects, with Pf influencing IMT, whilst Pb affected LVM and PWV (Kolkenbeck-Ruh et al., 2019). Whether similar effects are noted in vascular beds of smaller arteries, for example in the lower limb (ankle-brachial index or femoral plaque), or in intracranial arteries, requires further study. What of the relative role of Pf and Pb as predictors of events beyond steady-state pressures?

As with end-organ measures, few large community-based or clinical studies have reported on the relative impact of Pf and Pb as predictors of events beyond steady-state pressures and all confounders. In this regard, whilst the Framingham Heart Study reported that Pf, but not Pb predicted events (Cooper et al., 2015), the MESA reported Pb and not Pf as a predictor of events (Chirinos et al., 2012; Zamani et al., 2015). This is consistent with the differences noted between Framingham and MESA with respect to the relative impact of Pf and Pb on LVM (Zamani et al., 2014; Booysen et al., 2015; Sibiya et al., 2015; Kaess et al., 2016) and may be explained in the same way. That is, the lack of impact of wave reflection on events in the Framingham Heart Study may have simply been because the authors failed to account for the role of wave re-reflection in determining Pf and hence PP. As discussed above, the possibility also exists that in the Framingham Heart Study a better BP control overall than alternative studies may have been noted. As a result, fewer participants may have

had increases in PP that are determined by Pb. Once again therefore, these contrasting results (Chirinos et al., 2012; Zamani et al., 2015; Cooper et al., 2015) do not negate the importance of reflected waves, but rather emphasize the importance of accounting for wave re-reflection as a determinant of Pf, or the relatively greater role of reflected waves in the hypertensive as opposed to the normotensive BP range.

1.3.4 Age Related Factors Which Determine Central Arterial Pressures That Are Poorly Indexed at the Brachial Pulse

Two changes influence the differences between central and peripheral arterial PP. First, through aging and risk factors, the aorta loses its elasticity (increases its stiffness), an effect attributed to arteriosclerotic changes. However, stiffness in more distal arteries changes little with age (Mitchell et al., 2004). Consequently, with aging and risk factors, whilst the impedance in the aorta increases, distal arterial impedance changes little, thus decreasing the impedance mismatch between the aorta and more distal vessels (Smulyan et al., 2016). Thus with aging and risk factors, aortic to brachial PP amplification decreases and brachial PP more closely resembles central arterial PP.

The second factor which influences differences between central and peripheral arterial PP has been highlighted above, and that is the degree of wave reflection. With aging, three changes occur which enhance the extent to which reflected waves augment central arterial PP. First, Pb increases linearly across the adult lifespan (Hodson et al., 2017) and this correlates well with the decrease in PP amplification that occurs with age (Sibiya et al., 2015). Second, with age-induced increases in ventricular ejection duration, the time to the peak of the Pf increases and this enhances the chance that the reflected wave returns in synchrony with the Pf antinode (Tade et al., 2017). Age-induced increases in the time to the

peak of the Pf therefore markedly influence aortic, but not peripheral PP, and decrease PP amplification. Thirdly, age-induced increases in the speed of wave reflection, presumably due to increases in aortic stiffness or a movement of reflection points closer to the heart, also enhances the chance that the reflected wave returns in synchrony with the Pf antinode (Nichols et al., 2011). In short, several age-induced changes in factors that influence wave reflection or the impact thereof are responsible for PP amplification and age-related decreases in PP amplification.

1.3.5 Long Term Effects of Regular Physical Activity on Central Blood Pressure

As there are several key determinants of pulsatile load that are poorly indexed by BP determined at the brachial pulse, it is important to understand whether the impact of regular exercise on BP as determined at the peripheral pulse, is an appropriate surrogate of what occurs in central arteries. Importantly, the benefits of exercise training on BP in those with cardiovascular disease is thought to occur mainly through reductions in MAP (steady-state pressures) as a result of peripheral vascular changes (a decreased systemic vascular resistance, SVR) (Ashor et al., 2014; Parker et al. 2012). In this regard, MAP is well recognised as being a strong determinant of aortic distention, which shifts the normal aortic pressure-volume relationship up the curve (Figure 1.2). Thus, through passive effects on aortic stiffness, MAP increases aortic stiffness and hence Zc, the consequence being an increased Pf and hence PP and SBP. Thus, a critical mechanism responsible for the beneficial effects of regular physical activity on both DBP (which is determined by cardiac output X SVR) and SBP (through distending pressure effects on aortic stiffness, Zc, Pf and hence PP and SBP) is a decrease in arteriolar tone. However, several alternative effects of exercise training may influence pulsatile load as well.

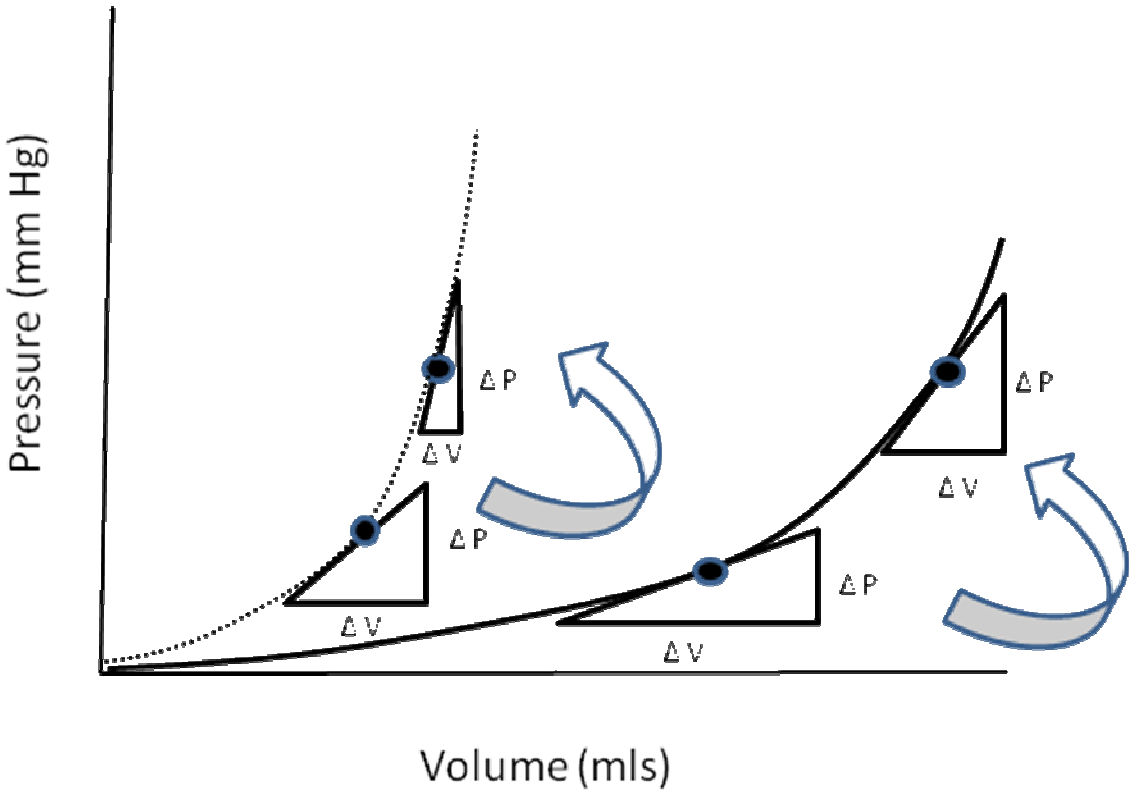

Figure 1.2. The pressure-volume relationship showing the impact of increases in pressure (MAP, which is represented by the block arrows) on stiffness in a complaint (solid line) and a less compliant (dotted line) vessel. Stiffness = Δ pressure (P)/Δ volume (V). Δ=change in.

In a recent meta-analysis (Zhang et al., 2018), the effects of 3 exercise training modalities (resistance, aerobic and combined) on central arterial function were assessed in a total of 38 randomised controlled trials with 2089 patients with hypertension, heart disease and stroke conducted over the past 27 years. This study suggested that improvements in aortic systolic pressure occur in patients with cardiovascular disease performing aerobic exercise training. In hypertensives (but not in those with heart disease and stroke), aortic systolic pressure improved ($p=0.001$) in those ≤ 50 years of age ($p=0.01$) and in those > 50 years of age ($p=0.004$) who trained for a minimum of 8 weeks ($p=0.0004$) regardless of sex (Zhang et al., 2018). No improvements were noted in DBP with aerobic exercise training (Zhang et al., 2018), suggesting that in disease states the main effect of regular exercise is on pulsatile load rather than through steady-state pressures. When pooling the results for the effects of aerobic exercise in those with hypertension, stroke and heart disease, AIx ($p<0.0001$) (which as indicated in previous discussion is a surrogate of reflected wave pressures, Pb) improved in patients aged 50-60 years as a result of 24 weeks of aerobic exercise ($p=0.003$) regardless of sex, disease and baseline heart rate (Zhang et al., 2018). In an alternative meta-analysis assessing exercise effects in a total of 1627 participants with cardiovascular disease from a total of 42 studies, aerobic exercise training was noted to improve peripheral vascular tone and AIx ($p=0.05$) (Ashor et al., 2014). Furthermore, the benefits of aerobic exercise in relation to intensity were shown to be correlated to the degree of baseline peripheral vascular tone as well as age in those with cardiovascular disease (Ashor et al., 2014; Parker et al., 2012). Thus, an important mechanism that may explain a large proportion of the benefits of regular physical activity on central arterial BP, effects which may not be adequately detected at the peripheral pulse, is through an impact on wave reflection, as mediated by alterations in peripheral vascular tone. However, as indicated in prior discussion, because of an inability to account for re-reflected wave effects, there is now

significant evidence that AIx is a poor index of wave reflection (Hughes et al., 2013; Wilenius et al., 2016; Booysen et al., 2015, Phan et al., 2016) and there are no data to show what the impact of regular physical activity is on Pb or the Pf-independent index of wave reflection, reflection magnitude (Pb/Pf x 100). Therefore, considerably more data is required to identify whether regular aerobic physical activity contributes to decreases in central arterial BP through an impact on wave reflection beyond arteriolar effects.

In contrast to the impact of aerobic physical training, which may produce improvements in central arterial pressures through an impact on vascular tone and hence wave reflection (AIx), resistance exercise training may mediate central arterial effects through different mechanisms (Heffernan et al., 2013; Zhang et al., 2018). In both hypertensives as well as pre-hypertensives resistance exercise training has been shown to be beneficial to central BP through improvements in impedance to flow in more peripheral vessels than the aorta (Heffernan et al., 2012). This is proposed to enhance blood flow during diastole (improved reservoir function) thus reducing loading pressures within the LV at rest (Parker et al., 2012) and decreasing Pf without affecting wave reflection (Heffernan et al., 2013; Zhang et al., 2018). Indeed, resistance exercise training does not produce improvements in AIx (Ashor et al., 2014). The changes in central pressures with isometric resistance activity are similar to the changes in dynamic resistance activity (Ashor et al., 2014). Although high intensity resistance exercise has been shown to improve brachial SBP and DBP, the effect on central BP still remains unclear (Collier et al., 2008). As regular physical activity is clearly beneficial to BP, there is no question as to the importance of implementing exercise programs in hypertensives. However, hypertensives often have co-morbid conditions which limit the capacity to exercise. In this regard, a question that has not been adequately addressed is whether alterations in central arterial haemodynamics limit the capacity to exercise in hypertension?

1.4 The Effects of Physical Activity on Stroke Volume and Cardiac Output

With any form of physical activity, regardless of modality, cardiac output (CO) increases in order to meet the oxygen demand of skeletal muscles (Vieira et al., 2016). These changes in CO rely on rapid increases in heart rate and stroke volume (SV) driven by sympathetic induced increases in sino-atrial nodal firing and myocardial contractility (Vieira et al., 2016). Furthermore, physical activity increases oxygen demand by the skeletal muscles which in turn vasodilate and increase venous return (Casey and Hart, 2008). Together with the capacity of muscles to extract and utilise oxygen, CO is a critical variable that determines oxygen consumption and hence the capacity to perform physical activity (Paolillo et al., 2018). Consequently, an ability to perform regular physical activity in hypertension will depend on generating sufficient increases in CO during exercise.

The degree of SV change depends on the intensity of physical activity, and similarly, the intensity of physical activity which can be performed depends on how much SV can be generated by the heart (Vieira et al., 2016). Increases in SV are equally as important to increases in heart rate to generate an enhanced CO and in healthy participants both SV and heart rate increase linearly relative to each other as oxygen consumption increases during physical activity (Paolillo et al., 2018). Indeed, with any form of physical activity, the increase in CO is achieved through enhancements in both heart rate (HR) and SV (Higginbotham et al., 1986).

In those with hypertensive heart disease however, SV increases are inadequate with CO changes mostly depending on changes in HR (Vieira et al., 2016; Paolillo et al., 2018). Moreover, in those with cardiovascular disease, because SV does not increase as much as in normal individuals, HR increases have been shown to display a steeper rise compared to SV in response to the progressive increase in oxygen consumption accompanying physical

activity (Paolillo et al., 2018). Hence, cardiovascular pathology hinders the magnitude of change in SV and hence CO in response to physical activity. The limited ability of the heart to generate an increased SV in certain circumstances may in-part be attributed to a reduced myocardial function, effects produced by cardiac pathology. Nevertheless, in certain circumstances including in hypertension it may not be only cardiac function which limits the ability of the heart to generate an increased SV during exercise. In this regard, it is important to understand the haemodynamic determinants that limit SV and hence CO in general and how these may be modified in hypertension.

With physical activity, the classical thought is that SV reaches a plateau, and there have been a considerable number of studies which suggest that in healthy participants, SV peaks at approximately 50 % of maximal exertion capacity (Stohr et al., 2011; Mortensen et al., 2005; Mortensen et al., 2008; Notomi et al., 2006). However, in response to progressive aerobic activity in trained as well as untrained athletes as compared to normal untrained participants, SV continues to rise and only plateaus at maximal physical activity in athletes (Rowland, 2009). Alternative studies suggest that in both trained as well as untrained athletes, SV can plateau before maximal physical activity (Rowland, 2009). However, in elite athletes SV may continue to rise progressively and only reach a plateau at maximal aerobic activity levels (Stohr et al., 2011; Rowland, 2009). Nevertheless, exercise-induced increases in cardiac ejection fraction (EF), a marker of systolic function, are no different between athletes as compared to non-athletes (Rowland, 2009; Rowland et al., 2002; Gingzton et al., 1989; Ahmad et al., 1990). Thus, differences in the capacity to generate an increased CO with exercise in athletes versus non-athletes may be driven by differences in filling volumes (Frank-Starling effects).

1.4.1 Determinants of Stroke Volume and Cardiac Output During Physical Activity

The functional capacity of the heart can be described in terms of the effects of a compression pump where during diastole the muscle actively relaxes, encouraging filling and immediately following this event, the ventricles contract and blood is ejected (Kerkhof et al., 2018). The degree of cardiac filling (which generates a Frank-Starling effect), the extent of ventricular muscle contraction (contractility) and afterload to the heart are the essential determinants of ventricular function (Stohr et al., 2011; Kerkhof et al., 2018). The inability to increase filling volume at a very high HR (reduced time for filling) is thought to be the main factor that determines a plateau in SV during submaximal aerobic physical activity in both athletes and normal participants (Stohr et al., 2011; Mortensen et al., 2005). Obviously in individuals with underlying cardiac pathology, a limited capacity to increase cardiac muscle pump function with exercise or to adequately relax and fill decreases the ability to increase SV and CO. This is worsened by the presence of higher HR generated by increased baseline sympathetic tone, which limits filling during exercise. In this regard, as indicated in the above discussion hypertensives often have underlying hypertensive heart disease, where either filling and/or ejection may be reduced, thus limiting exercise capacity. However, what is not clear is the impact of resistance to flow on SV and hence CO during incremental exercise levels in hypertensives.

Importantly, afterload to the left ventricle is determined by several factors all of which increase wall stress. In this regard, although systemic vascular resistance (SVR) is the dominant factor determining systolic wall stress (Wigfull and Cohen, 2005) and SVR decreases during aerobic exercise (Reddy et al., 2017), what is seldom given due consideration is the impact of the impedance to flow (resistance to flow in a pulsatile system) generated by the aorta (Zc) a change which often characterizes elderly hypertensives or more

severe forms of hypertension. As with a steady-state system where MAP=CO x SVR and hence when MAP is held constant, CO is determined by SVR, pulsatile systems follow the same principle where PP=peak aortic flow (Q) x Zc (resistance to flow in a pulsatile system) and hence when PP is held constant, Q is determined by Zc. Thus, Zc may influence systemic blood flow by increasing afterload to the LV or by creating resistance to flow. In this regard, increases in Zc are often reported to be associated with decreases in aortic flow at rest (Nichols et al., 2011), but there are limited data to show an effect of Zc on aortic flow during exercise. What is the impact of age and hence hypertension-induced changes in Zc on the capacity to generate an increased SV and CO during exercise? Moreover, how does this compare with the impact of SVR on SV or CO? In this regard, an important consideration is first the factors thought to account for the impact of age and hypertension *per se* on exercise capacity.

1.5 The Effect of Age on Cardiac Responses to Aerobic Physical Activity

Age has a marked effect on the cardiac response to physical activity. Advancing age in healthy men causes a decline in EF and CO in those performing supine physical activity (Stratton et al., 1994). Despite SV responses to physical activity being similar, the elderly tend to augment SV through increases in cardiac filling (increases in LV end diastolic volume) but without any significant changes in EF, while the young rely on increases in EF without the need for LV volume expansion (Stratton et al., 1994; Yin et al., 1981). Since the elderly adapt to incremental aerobic activity through Frank-Starling effects (SV increases in response to a greater degree of filling) rather than through the enhanced EF, SV will reach an early plateau before maximal activity. This will occur because the ability to generate an increased SV and hence tolerate exercise will be sensitive to HR (as indicated in

aforementioned sections, LV filling decreases at higher heart rates) (Vieira et al., 2016; Stratton et al., 1994). An important question is therefore what determines the limited capacity to generate an exercise-induced increase in EF and hence SV with age?

As indicated in aforementioned discussion, with aging and with risk factors such as hypertension, central arterial (mainly aortic) stiffness increases (Tomoto et al., 2017; Pierce, 2017). Age (and risk factor)-induced decreases in aortic compliance (increased stiffness) may make a marked contribution to cardiac energetic cost at a given SV (Bonapace et al., 2003; Theoleyre et al., 2016). In this regard, as previously discussed, the main role of the aorta is to buffer pressure and flow generated by the LV and hence to maintain a low LV load, which in turn modulates LV dynamics as well as coronary perfusion (Bonapace et al., 2003; Pierce, 2017). With respect to effects on LV load, as indicated in aforementioned sections, an increased aortic stiffness creates a resistance to flow in a pulsatile system (Zc) and this enhances Pf and central aortic pressures in early systole while ejection occurs. A reduction in proximal aortic distensibility as accompanied by advancing age therefore causes increases in PP and SBP (afterload). As afterload increases, wall stress in the heart is enhanced and myocardial oxygen demand increases. This limits the ability to generate sufficient oxygen required for increases in EF and hence SV with exercise. With respect to effects on coronary flow, a stiff aorta reduces flow during diastole (elastic recoil is reduced) and hence DBP, which in turn limits coronary perfusion (which occurs during diastole) (Bonapace et al., 2003). Thus, a mismatch between oxygen demand and supply is the consequence and increases in EF and hence SV with exercise are reduced. Thus, a possible reason why the elderly develop an intolerance to physical activity is because of the presence of a stiffer aorta impeding increases in EF and hence SV. The consequence is that exercise-induced increases in SV are dependent on increases in filling volume producing Frank-Starling effects, effects which are diminished at higher heart rates (reduced filling time) (Bonapace et al., 2003;

Stratton et al., 1994; Pierce et al., 2017). What must also be considered is that increases in Zc simply generate a resistance to aortic flow (Q) during ventricular ejection which limits the ability to increase SV when EF fails to increase with exercise. Indeed, as previously discussed, Zc is often inversely associated with Q. What is important to note however is that there are limited data to show how aging-induced increases in Zc influence aortic flow during exercise.

1.6 The Effect of Hypertension on Cardiac Responses to Aerobic Physical Activity

It is well-recognised that repeated bouts of physical activity have beneficial vascular effects. Indeed, physical activity promotes laminar blood flow as well as shear stress and consequently improves endothelial function (Pierce, 2017). However, regular aerobic physical activity does not modify large elastic artery compliance in hypertension (Ferrier et al., 2001). Possibly as a consequence of irreversible increases in proximal aortic stiffness, as with aging, hypertension may similarly limit aerobic physical activity. Indeed, as with the elderly, hypertensives have a limited capability to increase EF during exercise thus possibly causing intolerance to physical activity (Stratton et al., 1994; Bonapace et al., 2003; Li et al., 2014). Indeed, hypertensives also show a reduced exercise-induced increase in EF and CO as compared to healthy individuals (Stratton et al., 1994; Paolillo et al., 2018; Austin et al., 2010; Bonapace et al., 2003). Through the associated cardiac hypertrophy that often accompanies hypertension (which increases myocardial oxygen demand), the abnormality in oxygen demand-to-supply ratio produced by increases in aortic stiffness may even be greater in hypertensives than in those with aging-induced increases in aortic stiffness (Alves et al., 2018). What is important to note however is that there are limited data to show how hypertensive-induced increases in Zc influence aortic flow during exercise.

1.7 Evidence for Vascular Impedance Effects Limiting Exercise Capacity

As described in the above sections, striking decreases in exercise capacity with increased ageing are well documented and these effects are thought to be largely through a limited capacity of the heart to increase function with exercise. Indeed, as reviewed above, decreases in maximal exercise capacity, CO and HR with ageing have been well described (Robinson et al., 1978; Strandell, 1964; Port et al., 1980). Although, age associated decreases in inotropic and chronotropic responses of the heart may play a role in the age-related decline in exercise capacity (Conway et al., 1971; Lakatta et al., 1975; Yin et al., 1981); the heart is coupled to the vasculature and hence cardiac function depends upon the state of the vasculature (ie. impedance to flow in the proximal aorta and peripheral vasodilation). What is the evidence that increases in resistance to flow generated by aging-induced changes in the vasculature, limit exercise capacity?

A number of studies have reported relationships between oxygen consumption and measures of arterial stiffness. In normotensive adults, age-related increases in carotid-femoral (aortic) PWV (a measure of arterial stiffness) were associated with lower maximum oxygen consumption (Vaitkevicius et al., 1993), and in younger and older adults inverse relationships between PWV and maximum or peak oxygen consumption were observed (Boreham et al., 2004; Fernberg et al., 2017; Gando et al., 2010). Furthermore, in middle-aged and elderly men (61% hypertensive), arterial stiffness was negatively correlated with peak oxygen consumption independent of age and body fat (Tanisawa et al., 2015), and in patients with coronary artery disease and history of prior myocardial infarction, peak oxygen consumption was inversely correlated with PWV, independent of age (Alves et al., 2018). Moreover, recently a large study which assessed the relationship between cardio-respiratory fitness (CRF) and PWV in 9232 participants of which 34% were hypertensives, PWV was shown to

be inversely related to peak oxygen consumption independent of age, gender, body mass index (BMI), low-density lipoprotein (LDL) cholesterol, diabetes mellitus, HbA1c, smoking, MAP and hypertension (Sung et al., 2018).

Although, none of these prior studies related either measures of arterial stiffness or oxygen consumption to SV or CO, one small (n=19) study in healthy elderly men reported that acute vasodilation induced by the calcium channel blocker verapamil, acutely decreased PWV and was associated with an increased SV and oxygen consumption during submaximal exercise (Chen et al., 1999). Furthermore, in patients with dilated cardiomyopathy (average EF at rest of 34%), peak oxygen consumption was inversely correlated with PWV and positively correlated with SV (Bonapace et al., 2003). Moreover, in the latter study PWV and SV together accounted for 34% of the variance of peak oxygen consumption; hence suggesting that aortic stiffness and its impact on SV could partially explain exercise intolerance in patients with dilated cardiomyopathy. Similarly, in patients with non-ischaemic dilated cardiomyopathy (average EF at rest of 30%), increased PWV was associated with decreased peak oxygen consumption, decreased LV systolic function (as assessed by the amplitude of tissue Doppler index systolic wave, [SV was not assessed]) and decreased diastolic function (increased LV diastolic filling [E/e']) (Patrianakos et al., 2009). However, in patients with hypertrophic cardiomyopathy (average EF at rest of 64%), on multivariate analysis only age and PWV, but neither EF nor LV end diastolic volume (SV was not assessed) were independent predictors of maximum oxygen consumption (Austin et al., 2010). These contrasting data may suggest that impaired exercise capacity related to increases in PWV and associated reductions in SV only occurs in patients with reduced systolic function. Nevertheless, further, in support of afterload-induced reductions in cardiac function and hence exercise intolerance; in patients with heart failure with preserved ejection fraction (HFpEF), total arterial compliance and cardiac output reserve were reduced during

submaximal exercise compared to hypertensive controls, despite similar mean arterial pressures (Reddy et al., 2017). Moreover, in patients with HFpEF, inorganic nitrite-induced increases in total arterial compliance during submaximal exercise were accompanied by improvements in CO during submaximal exercise (Reddy et al., 2017).

The measurements of PWV and total arterial compliance (SV/central PP) in the aforementioned studies, assess total aortic rather than proximal aortic stiffness and hence may provide very little evidence regarding the impact of proximal aortic distensibility on the heart and hence exercise capacity. Indeed, maximum oxygen consumption was shown to be more strongly determined by proximal than distal aortic stiffness (Tomoto et al., 2017; Tanaka et al., 1998). In comparison to PWV which is measured along the length of the aorta and aortic stiffness differs along the length of the aorta (Mitchell et al., 2004), proximal aortic Zc is defined as the pressure change generated by the aortic flow wave in the proximal aorta (Nichols et al., 2011). Proximal aortic Zc is therefore a good index of the aortic compliance and geometry which contributes to the arterial pulsatile load faced by the LV during ejection independent of LVMI (Bollache et al., 2015; Chirinos et al., 2010). Zc can be obtained through the frequency domain which takes into account the entire cardiac cycle or the time domain which only considers systolic upslopes based on 95% of peak aortic flow (Bollache et al., 2015; Mitchell et al., 2010; Segers et al., 2017). There is currently consensus that either the time or the frequency domain may be used (Segers et al., 2017) and indeed, Zc obtained in both the frequency and the time domain, has been confirmed to be higher in hypertensives as compared to healthy controls (Bollache et al., 2015). However, there are few studies which assess the impact of Zc on changes in SV or CO with exercise.

There are currently no human studies assessing the impact of Zc on SV or CO and hence exercise capacity. However, in a study in 8 healthy dogs, experimentally induced decreases in aortic compliance (created by diverting blood flow through a rigid aortic bypass

graft) caused an increase in peak systolic blood pressure, ejection duration and left ventricular end diastolic diameter (LVEDD) while SV remained unchanged thereby causing a drop in EF (Urschel et al., 1968). The findings of this study suggest that ventricular performance is dependent on the characteristics of the aorta such that decreases in aortic compliance increase the tension load on the myocardium and the impedance to aortic ejection velocity (Urschel et al., 1968). In another study in dogs, it was shown in old dogs that incremental physical exercise resulted in increases in Zc and decreases in TPR but with no increase in SV. In comparison in young dogs, the same levels of incremental aerobic physical exercise (treadmill running) resulted in no increases in Zc, decreases in TPR and increases in SV (Yin et al., 1981). These data suggest that in old dogs (who tended to have a higher resting Zc compared to young dogs), during aerobic physical exercise, resistance in a pulsatile system (aortic Zc) is a major factor in limiting SV response to exercise. Although oxygen consumption was not assessed in this study, all except for one of the young dogs, but none of the old dogs could complete the period of extreme exercise.

1.8 Problem Statement

Regular physical activity is recommended as an adjunct to pharmacological therapy in the management of hypertension. However, physical activity in hypertensives may be symptom limited due to a reduced capacity to increase SV and CO. The exact mechanisms responsible for the reduced capacity to perform physical activity are not only limited to reductions in cardiac performance, but may also be strongly determined by increases in the resistance to flow, even when BP is controlled to target. Although evidence from studies conducted in animals suggests that stiffness in the proximal aorta, which influences the resistance to flow in a pulsatile system (characteristic impedance, Zc) is a major limitation to increases in flow

during exercise, there are no studies conducted in human hypertension assessing the impact of Zc on physical activity associated increases in flow. In this regard, human studies suggest that aortic stiffness across the full length of the aorta (a poor index of proximal aortic stiffness) may limit the capacity to perform physical activity in hypertension. However, no study has assessed whether these relations are explained by the impact of proximal aortic Zc on flow.

1.9 Aims

In the present study I aimed to determine the relative impact of aortic Characteristic Impedance (Zc) versus alternative factors which influence resistance to flow (systemic vascular resistance) on increases in stroke volume (SV) induced by physical activity in hypertensives receiving antihypertensive therapy.

CHAPTER 2: METHODS

2.1 Ethical Approval

The present study was conducted according to the established principles which have been outlined in the Helsinki declaration. Ethical approval of the protocol was obtained from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (approval number: M17-02-71).

2.2 Study Population

All participants gave informed, written consent. A total of 56 severe or refractory hypertensive participants (with no history of smoking or alcohol abuse) who had been receiving anti-hypertensive therapy with controlled brachial blood pressures (<160/100 mmHg) were randomly recruited from the Charlotte Maxeke-Johannesburg Academic Hospital Hypertension Clinic from February 2018 until March 2019. Participants with evidence or history of cardiovascular disease (congestive heart failure, angina pectoris, myocardial infarction, stroke, peripheral arterial disease, valvular disease), secondary hypertension, hypokalaemia or hyperkalaemia (serum potassium ≤ 3.2 mmol/L or ≥ 5.6 mmol/L respectively), insulin dependent diabetes mellitus (HbA1c >7.0%), serum creatinine ≥ 160 μmol/l , severe anaemia (haemoglobin < 10 g/dl), as well as any severe clinical condition which precluded inclusion in the study were excluded. Pregnant patients were not recruited for this study.

2.3 Clinical, Demographic and Anthropometric Measurements

A standardized questionnaire was administered to obtain demographic data. The questionnaire was made available in English, but trained study assistants (a nursing sister and

trained technician) familiar with the home (first) languages of the patients assisted with the completion of each questionnaire. Assistance was only provided when requested. Nonetheless, the majority of participants were reasonably proficient in the English language (primary and secondary education is largely conducted in the English language). The questionnaire sought specific answers to date of birth, gender (designated as either male of female). Most of these questions required a simple response of either "YES" or "NO" as answers. Clinical data were extracted from the patient's clinical file. These data included associated clinical conditions and classes of antihypertensive agents and the doses employed. Each participant's anthropometric measurements (height and weight) were determined with participants standing, wearing light clothing and no shoes. For anthropometry, height (in centimetres) and weight (in kilograms) were measured using a stadiometer (Seca 217) (Manufacturer: Seca Deutschland) and a bathroom scale (Healthometer 160LBS) (Manufacturer: Medline Industries, Inc. Chicago, United States of America) respectively. Body mass index (BMI) was then derived from weight and height as weight in kg, divided by height squared (kg/m^2).

2.4 Brachial Blood Pressure

Brachial blood pressure (BP) was obtained using both an accredited oscillometric BP monitor (HBP-1300, Tateishi Electric Manufacturing Company, Kyoto, Japan) and an accredited sphygmomanometer (Mercurial Alpk2, Manufacturer: Advanced Technocracy Inc. Grain Market, Ambala, India). Recordings obtained with the oscillometric device were used to calibrate SphygmoCor recordings with participants in the supine position. Auscultatory BP recordings were obtained in the seated position to record the actual BP on that day. Auscultatory BP was measured by a trained nurse-technician, according to guidelines of the

American Heart Association and European Society of Hypertension recommendation using a standard mercury sphygmomanometer (O'Brien et al., 2003; Pickering et al., 2005; Whelton et al., 2017). Blood pressure was recorded to the nearest 2 mm Hg. Korotkoff phases I and V were employed to identify systolic and diastolic BP respectively, and care was taken to avoid auscultatory gaps. Five consecutive BP readings were obtained, at least 30 seconds apart in a sitting position after 10 minutes of rest using an appropriately sized cuff for each of the participants, and the average of the five readings was subsequently employed for statistical analysis. For both auscultatory and oscillometric BP measurements, standard cuffs were used with an inflatable bladder with a length of 22 cm and a width of 12 cm, except when arm circumference exceeded 31 cm larger cuffs with a 31 x 15 cm bladder were employed.

2.5 Acute Activity

Participants performed 3 minutes of standardised cycling on a Quinton 845T supine bicycle, or if participants were physically unable to perform the cycling they underwent 3 minutes of standardised acute resistance activity through the use of a Camry handgrip dynamometer (model: EH101, China). In order for handgrip activity to be standardised, participants were required to squeeze the hand-held dynamometer at maximal voluntary capacity. Once maximal capacity was obtained, participants performed 3 minutes of hand-grip activity at a third of their maximum voluntary capacity. Alternatively, in order for supine cycle activity to be standardised, participants exercised at 200 kg.m/min (~30 Watts) for 1 minute and thereafter had the workload increased by 200kg.m/min (with each increment lasting 1 minute each) until heart rate (HR) started to increase. Participants then cycled at their respective workload for 3 minutes to achieve 60% of age predicted maximum HR.

2.6 Central Aortic Haemodynamics

Following the 15 minute resting period in the supine position, as well as immediately after the acute activity described above, participants had arterial waveforms recorded by applanation tonometry for 8-seconds from the radial artery pulse site of their non-dominant arm by means of a high-fidelity SPC-301 micromanometer (Millar Instrument, Inc., Houston, Texas) which was computationally interfaced with SphygmoCor version 9.0 software (AtCor Medical Pty. Ltd., West Ryde, New South Wales, Australia) (Figure 2.1). These recordings were repeated immediately after 3 minutes of cycling on a Quinton 845T supine bicycle, or immediately after 3 minutes of acute resistance activity through the use of a handgrip dynamometer. In order to record aortic BP, brachial BP using an Omron professional digital BP monitor (HBP-1300, Tateishi Electric Manufacturing Company, Kyoto, Japan) which was taken before and after recordings were obtained and used for the calibration of pulse wave acquisition. The peripheral pressure waveform was converted into a central aortic waveform using a validated generalized transfer function incorporated in SphygmoCor software (Figure 2.2). Recordings where the systolic or diastolic variability of consecutive waveforms exceeded 5% or the amplitude of the pulse wave signal less than 80 mV were discarded. In addition, the electronic average mean arterial aortic pressure (not the 1/3 method as commonly used) was obtained from the SphygmoCor system. Aortic backward wave (Pb) and forward wave (Pf) pressures were obtained through SphygmoCor-derived wave separation analysis using a 'triangular flow wave' based on the aortic waveforms. Reflection magnitude (RM) which was calculated as Pb/Pf, aortic pulse pressure (PPc) calculated as the difference between aortic systolic BP (SBP) and aortic diastolic BP (DBP), PP amplification calculated as the ratio of brachial to aortic PP and augmentation index (AIx) calculated as Pa/PP and expressed as a percentage. Augmented pressure (Pa) was determined as the

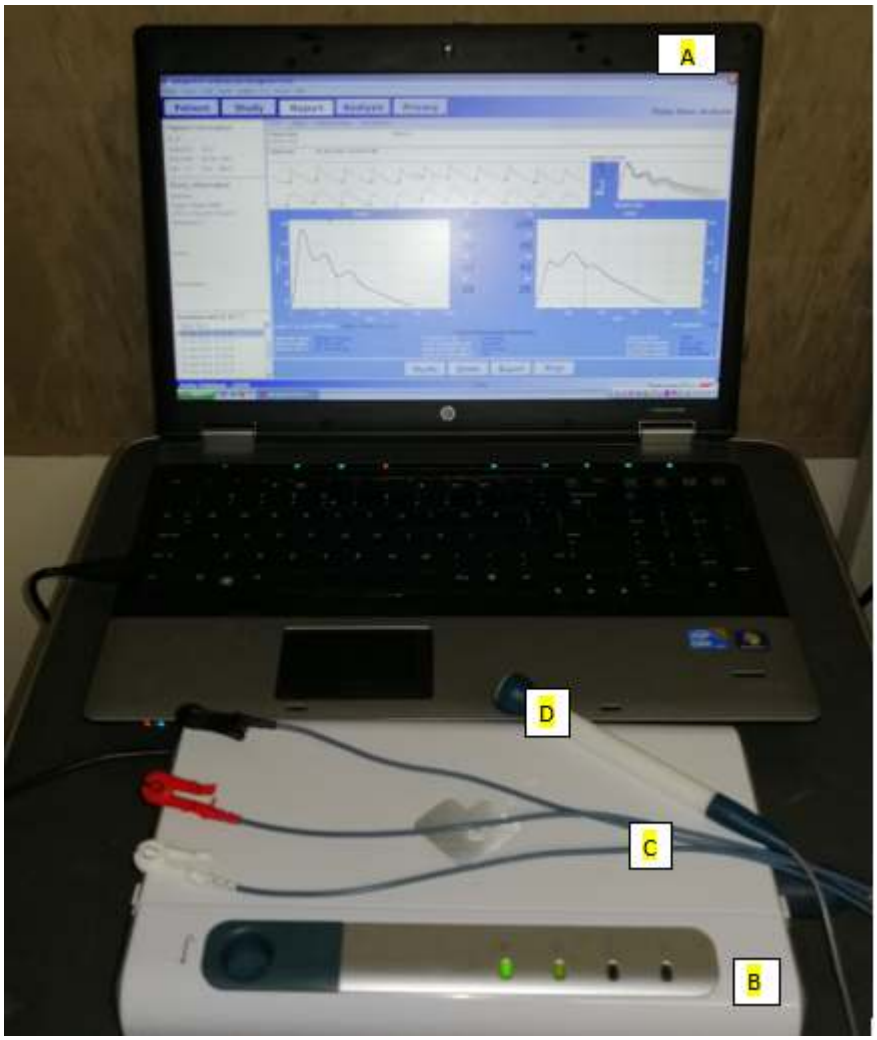

Figure 2.1: SphygmoCor system interfaced with a computer employing SphygmoCor, Version 9.0 software (AtCor Medical Pty. Ltd., West Ryde, New South Wales, Australia). A is the computer with which the SphygmoCor device is interfaced with, B is the SphygmoCor device, C are the electrocardiogram leads and D is the pressure transducer.

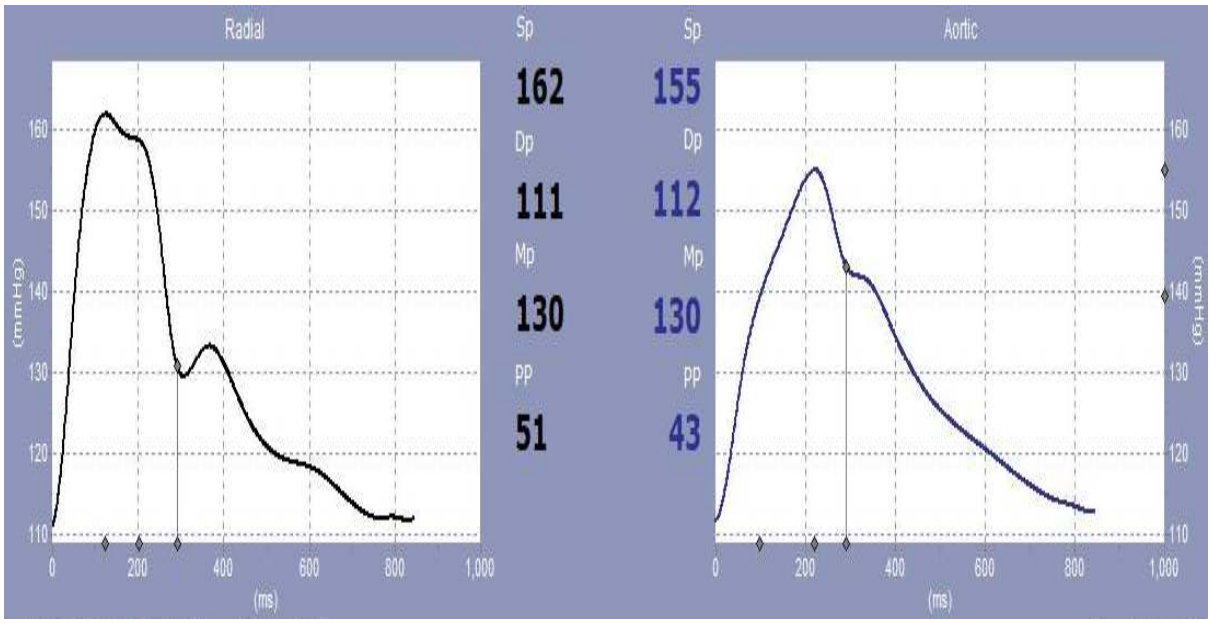

Figure 2.2: Peripheral pressure waveform converted into a central aortic waveform using a validated generalized transfer function incorporated in SphygmoCor software. Sp, systolic blood pressure; Dp, diastolic blood pressure; Mp, mean arterial pressure; PP, pulse pressure. x-axis represents timing in (ms) and y-axis represents pressure in (mmHg).

difference between aortic PP and the pressure at the inflection point of the first systolic shoulder-diastolic BP as determined by SphygmoCor software.

2.7 Aortic Velocity Flow Wave

At the same time as central aortic pressures were recorded using radial applanation tonometry as described above, echocardiographic measurements were obtained by an experienced observer (Professor Angela Woodiwiss) with the participants in the left lateral decubitus position using an Acuson SC2000 Diagnostic ultrasound system (Siemens Medical Solutions, USA, Inc.) equipped with a standard linear array transducer (1-4 MHz frequency range) and electrocardiogram (Figure 2.3). Aortic velocity waveforms were obtained in the apical five-chamber view and aortic diameter measurements were obtained just proximal to the aortic leaflets in the long axis parasternal view. The largest diameter recorded in early systole was employed to construct the flow waveform (Mitchell et al., 2010) (Figure 2.4). Aortic flow waveforms were generated from aortic velocity and diameter measurements. Taking care to avoid any overshoot of the image, the leading (outer) edge or the most dense, or brightest, portion of the spectral image of the velocity waveform was outlined using graphics software (SanteDicom Viewer 6.0 Freeware) and using aortic diameter measurements employed to construct a flow waveform (Figure 2.5). Aortic flow at each time point along the velocity wave, was calculated from the aortic velocity x aortic root area (3.142 x [aortic root diameter/2]^2). Peak aortic flow (peak Q) was determined at peak velocity. Aortic velocity and diameter were also employed to determine the time to the peak of aortic flow, ejection duration (ED) and stroke volume using standard approaches (Mitchell et al., 2010). In this regard, time to the peak of flow was determined from the foot to the peak of the velocity wave, ED from the duration of the velocity wave from foot to foot and stroke volume (SV)

Figure 2.3: Acuson SC2000 Diagnostic ultrasound system (Siemens Medical Solutions, USA, Inc.) equipped with a standard linear array transducer and electrocardiogram. A is the standard linear array transducer; B are the electrocardiogram leads.

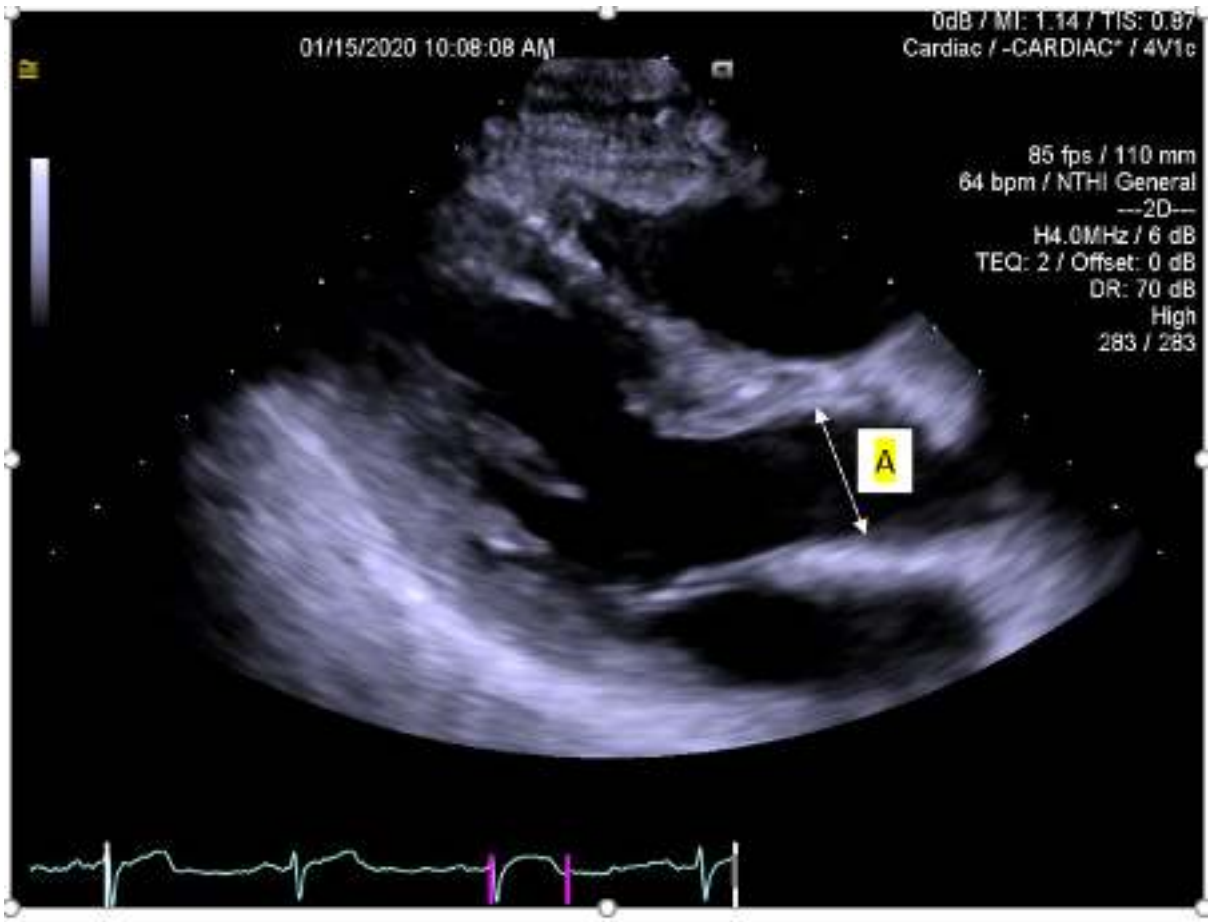

Figure 2.4: Aortic diameter measurements obtained just beyond the aortic root at the tip of the aortic valves when in the open position in the outflow tract in the parasternal long axis view. A is Aortic root diameter in systole.

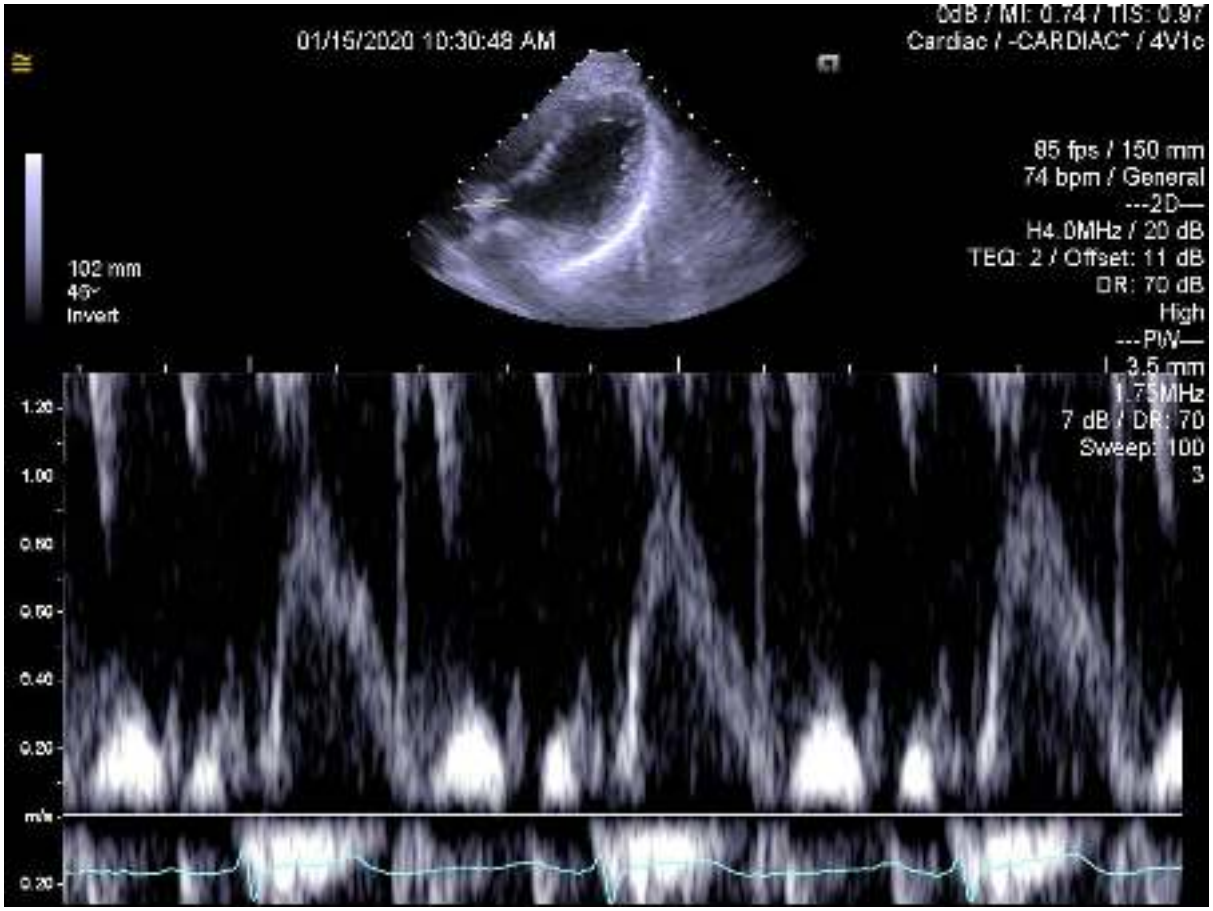

Figure 2.5: Velocity waveforms in the apical five-chamber view.

from the velocity-time integral x aortic root area.

2.8 Aortic Forward and Backward Pressure Wave Separation

Wave separation analysis was performed using the approach of Westerhof et al (2009), where the start and end of the aortic flow waveform is aligned with end of diastole (start of systole) and the incisura (dicrotic notch) on the aortic pressure waveform respectively (Figure 2.6). Wave separation analysis was performed based on the following formulae: Forward wave pressure= ((Pc + QxZc)/2) and Backward wave pressure= ((Pc – QxZc)/2) (Murgo et al., 1981; Westerhof et al., 2006), where Zc is characteristic impedance and Q is flow. Zc was calculated in the time domain as change in pressure/change in flow from the foot of the pulse wave up until 95% of peak flow (Segers et al., 2017; Mitchell et al., 2010). An example of the forward and backward pressure waveforms derived from these analyses is given in Figure 2.6. Central aortic PP (PPc) was determined as the difference between aortic systolic and the diastolic BP derived from SphygmoCor software. Peak forward (Pf) and backward (Pb) wave pressures were determined from wave separation analysis. In addition, re-reflected wave pressures (Figure 2.6) and the combined impact of wave reflection on aortic PP (reflected + re-reflected wave pressures (Figure 2.6) were determined. Reflected wave magnitude (RM), the Pf-independent measure of reflected wave function, was calculated as Pb/Pf and expressed as a percentage.

2.9 Aortic Stiffness

Carotid-femoral pulse wave velocity (PWV) was determined as an index of aortic stiffness (Laurent et al., 2001; Smulyan et al., 2016). Pulse wave velocity was determined from

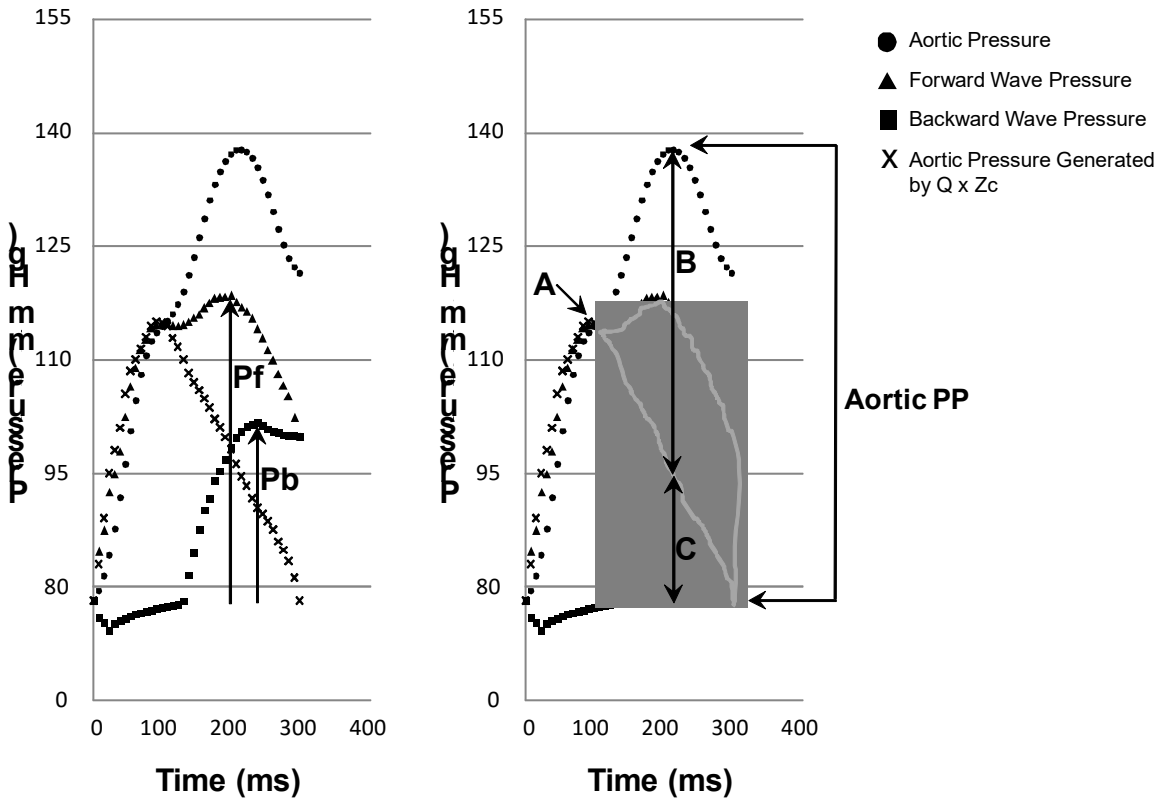

Figure 2.6: Wave separation analysis was performed using the approach of Westerhof et al (2009). The figure shows wave components of aortic pulse pressure (PP) superimposed on the aortic pressure wave. Pb, backward wave pressure; Pf, forward wave pressure; A, maximum pressure generated by the product of Q and Zc (Max P_{QxZc}); B, reflected + re-reflected wave pressures; C, pressure generated by the product of aortic flow (Q) and characteristic impedance (Zc) at peak PP (PQxZc at peak PPc); shaded area, re-reflected wave.

sequential waveform measurements at carotid-femoral and carotid-radial sites respectively using applanation tonometry device and SphygmoCor software (Figure 2.7 and Figure 2.8). The time delay in the pulse waves between the carotid-femoral and carotid-radial sites was identified using an electrocardiograph-derived R wave as a fiducial point. Pulse transit time was obtained from the average of 10 consecutive beats. The distance which the pulse wave travels was assessed as the difference between the distance from the femoral sampling site to the suprasternal notch, and the distance from the carotid sampling site to the suprasternal notch. In addition, the distance of wave travel was estimated from 80% of the direct distance between the carotid and femoral sampling site.

2.10 Cardiac Data

Systemic hemodynamic values were determined from systemic vascular resistance (SVR), stroke volume (SV), cardiac output (CO), HR and mean arterial pressure (MAP) assessments, where MAP was determined from SphygmoCor software, assuming that right atrial pressure=0 mm Hg. CO was determined from the product of SV and HR, SVR was calculated from MAP and CO (MAP=SVR x CO), assuming right atrial pressure = 0 mm Hg, and SV was determined from aortic velocity time integral (VTI) and diameter measurements in the aortic outflow tract (LVOT) using a standard formula: SV= LVOT VTI × cross sectional area of the LVOT (Tan et al., 2017).

Left ventricular (LV) dimensions were acquired through 2D guided M-mode echocardiography in the parasternal long axis view of the LV, as per guidelines (Sahn et al., 1978). In order to obtain M-Mode images in the long axis of the LV, a sample bar was positioned at right angles to the LV posterior wall and interventricular septal wall (IVS) as close to the mitral valve as possible such that the mitral valve is omitted from the M-Mode

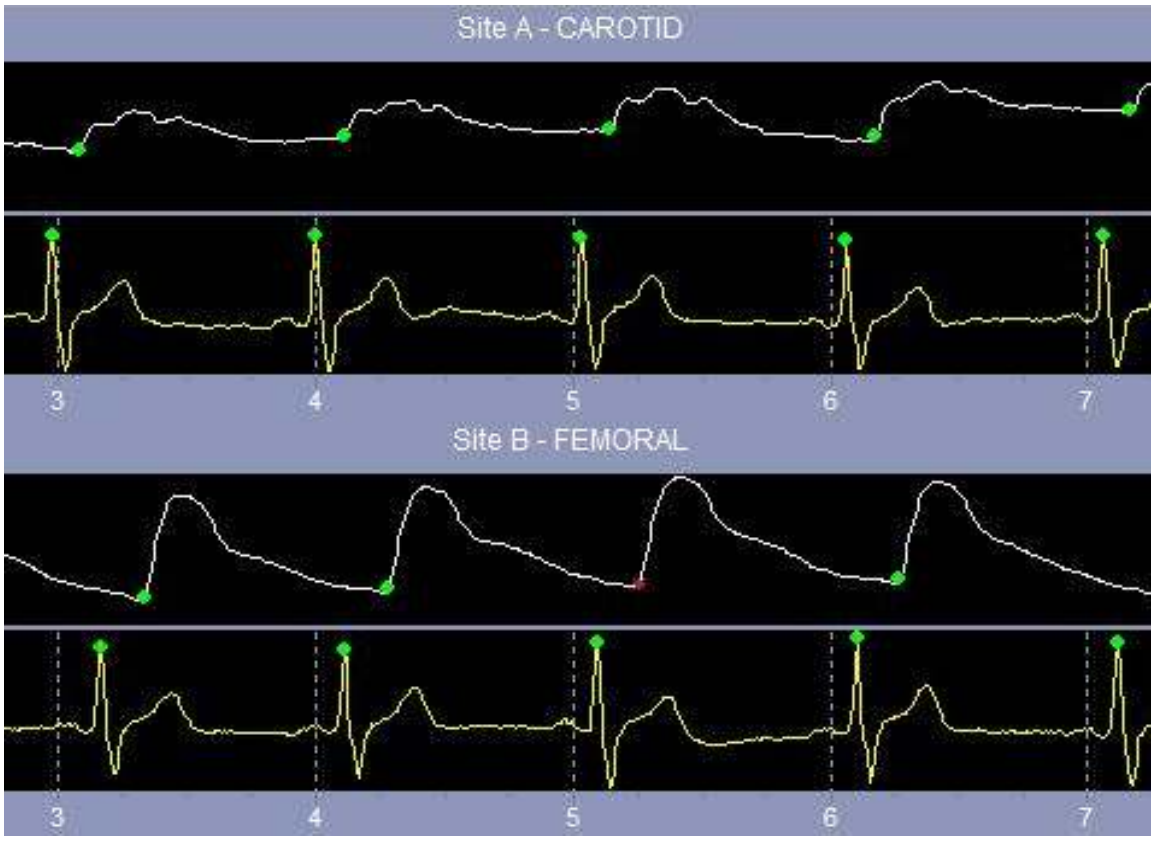

Figure 2.7: Pulse wave velocity was determined from sequential waveform measurements at the carotid-femoral site using the applanation tonometry device and SphygmoCor software. Red lines refer to the timing between the electrical events and arterial pressure changes in the carotid as well as the femoral arterial sites which was used to calculate PWV.

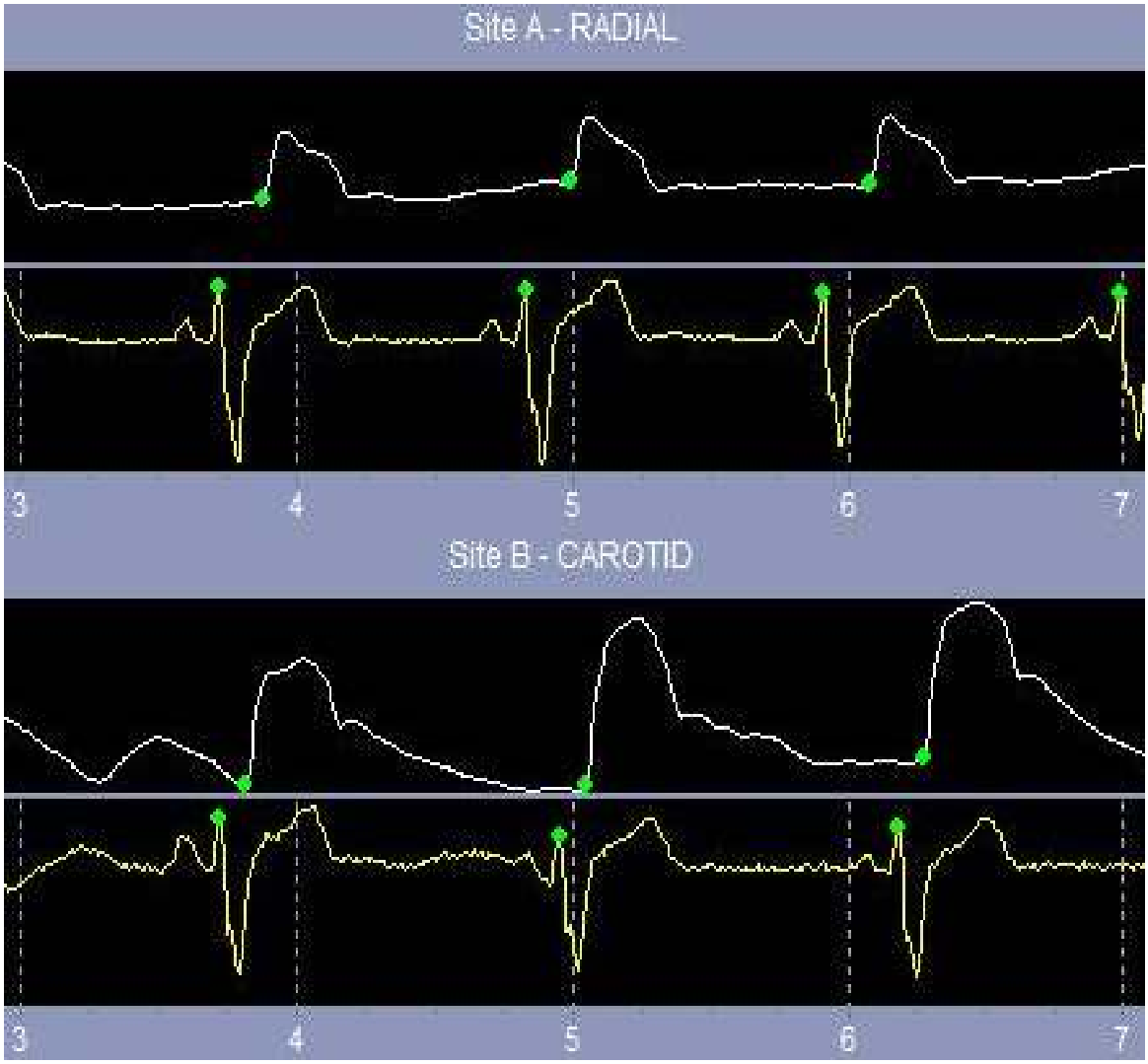

Figure 2.8: Pulse wave velocity determined from sequential waveform measurements at carotid-radial site using applanation tonometry device and SphygmoCor software. Red lines refer to the timing between the electrical events and arterial pressure changes in the radial as well as the carotid arterial sites which is used to calculate PWV.

recording. Interventricular septal wall thickness in systole and diastole (IVSs; IVSd), left ventricular inner diameter in systole and diastole (LVIDs; LVIDd) and left ventricular posterior wall thickness (LVPW) in systole and diastole (LVPWs; LVPWd) were measured (Figure 2.9). Left ventricular end diastolic volume (EDV) and LV ejection fraction (EF) were determined from the biplane Simpson approach. Mitral valve flow velocity was determined using pulsed doppler through 2D guided echocardiography according to guidelines (Kalmanson et al., 1977; Thuillez et al., 1980). In order to obtain the relationship between early and late diastolic filling (E/A ratio), the doppler sample volume, at its smallest length (5 to 7 mm), was placed perpendicular to flow and above the leaflets of the mitral valve within the LV in the apical four chamber view (Quinones et al., 2002) (Figure 2.10). Lateral tissue Doppler myocardial velocity (lateral e') and septal tissue doppler myocardial velocity (septal e'), which refer to early longitudinal velocity of the myocardial lateral wall and septum respectively, were obtained at the level of the mitral annulus through 2D guided echocardiography in the apical four chamber view as per guidelines (Rokey et al., 1985). In this case, the sample volume was placed in the lateral wall or the septum of the myocardium (Figure 2.11). Through the use of mitral valve flow velocity and the average of lateral and septal tissue doppler myocardial velocity, E/e' ratio was obtained in order to assess left ventricular filling pressures. Data were expressed as E/A, e'/a' and the E/e' ratio (an index of LV filling pressures).

2.11 Statistical Analysis

Statistical analyses and database management was performed with SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA). Data was expressed as proportions or mean±SD. All the data collected was parametric and met the criteria of normal distribution. An unpaired t test

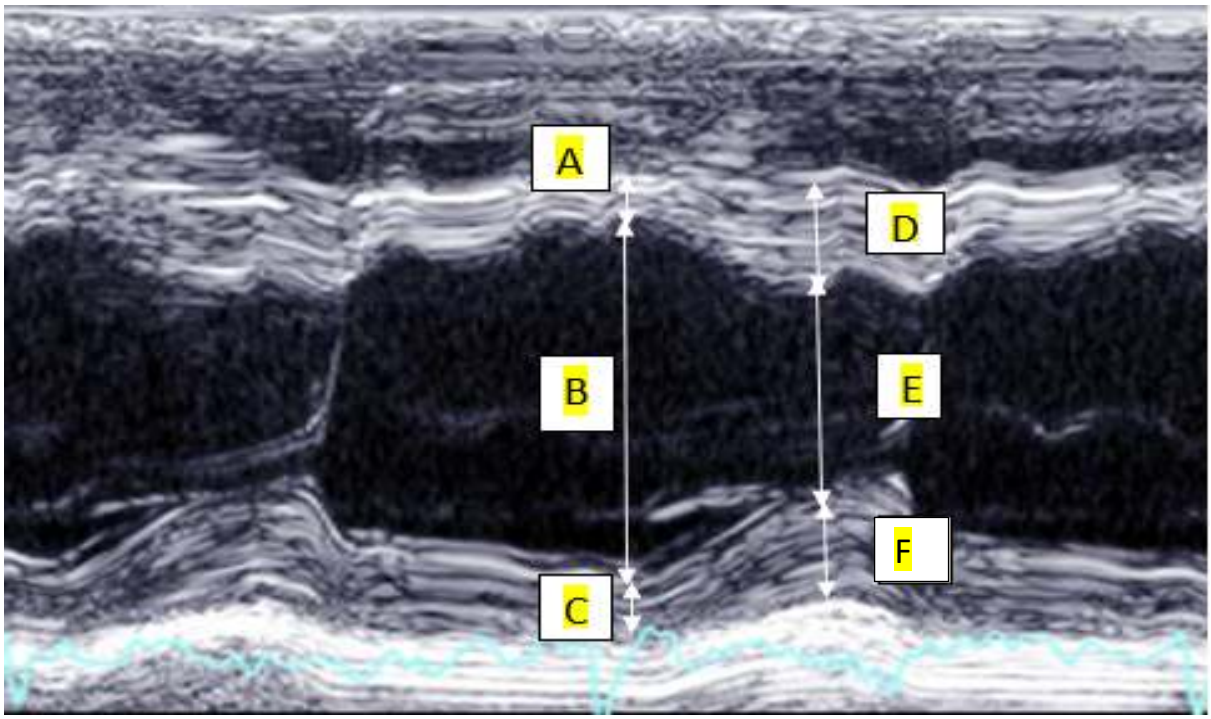

Figure 2.9: Two-Dimensional M-mode guided echocardiographic view. A is the interventricular septal wall thickness in diastole (IVSd), B is the left ventricular inner diameter in diastole (LVIDd), C is the left ventricular posterior wall thickness in diastole (LVPWd), D is the interventricular septal wall thickness in systole (IVSs), E is the left ventricular inner diameter in systole (LVIDs), F is the left ventricular posterior wall thickness in systole (LVPWs).

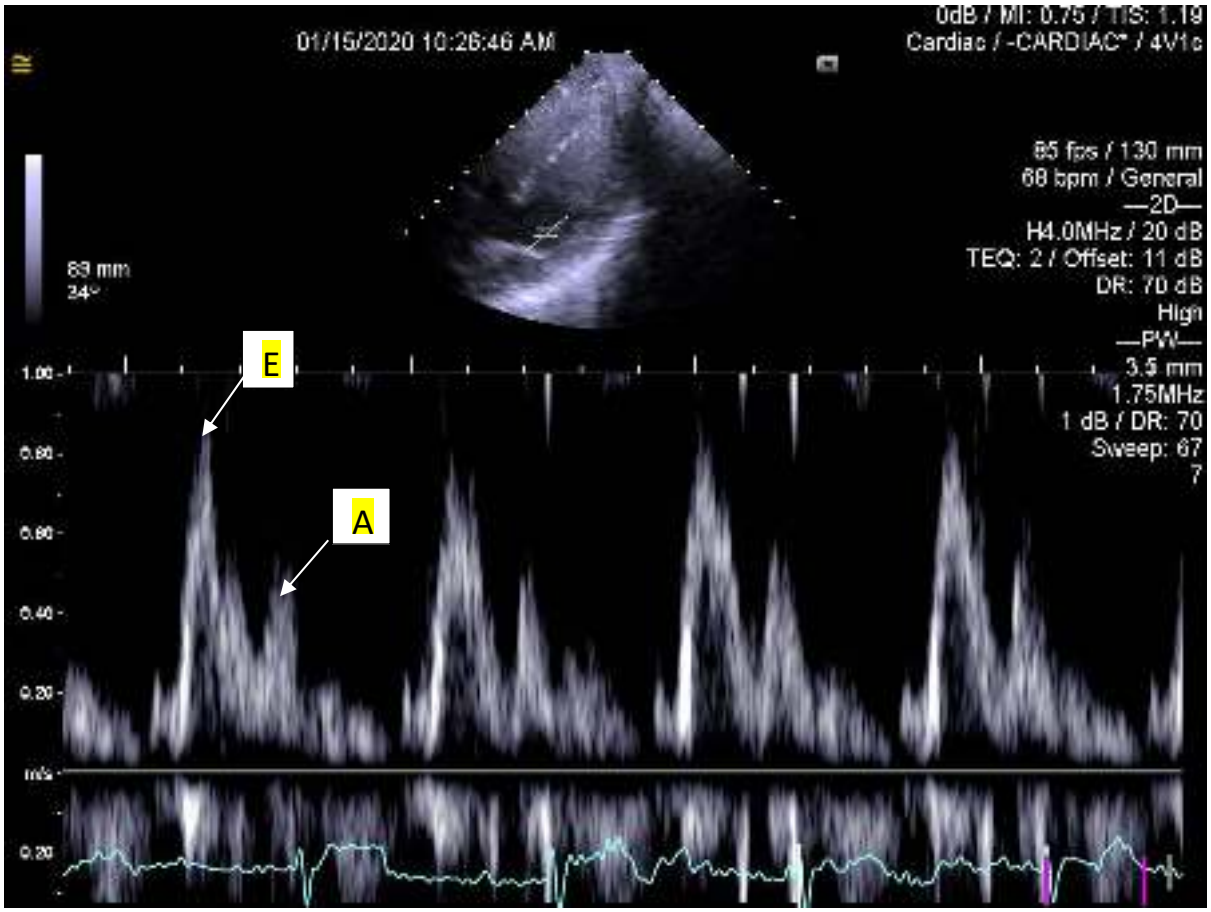

Figure 2.10: Mitral valve flow velocity using pulsed doppler through 2D guided echocardiography. E is early diastolic filling velocity; A is late diastolic filling velocity as a result of atrial contraction.

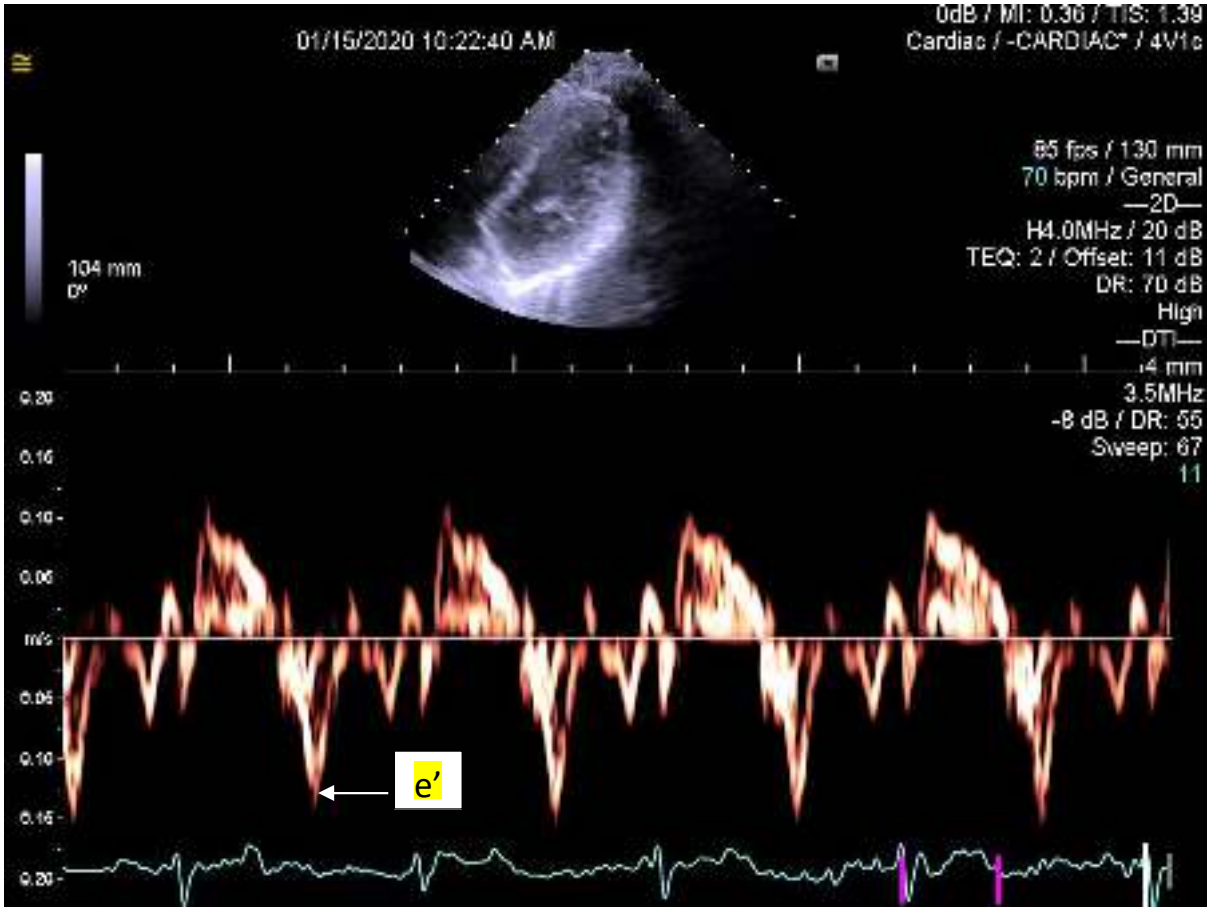

Figure 2.11: Septal Tissue doppler Myocardial Velocity. e' is the early longitudinal velocity of the myocardial septum.

was performed to compare the unadjusted means for various haemodynamic parameters and wave components before versus immediately after acute activity. Bivariate relationships were determined using Pearson's correlations. To determine the relative contribution of TPR and Zc to SV at rest, immediately after acute activity and the change in SV with acute activity, multivariate adjusted regression analysis was performed with SV as the outcome variable and with both TPR and Zc in the models. No other factors were included in the models. Comparisons of partial r values were made using Z statistics, whereby Fisher's r to Z transformation was performed and Z scores were compared (also termed Steiger's Z test). An unpaired t test was performed to compare the unadjusted means for various haemodynamic parameters and wave components in the participants with high (high PWV) versus low aortic stiffness (low PWV). The relative contributions of TPR and Zc to SV at rest, immediately after acute activity and the change in SV with acute activity, were performed separately in each of these subgroups (high PWV, low PWV) using multivariate adjusted regression analysis with SV as the outcome variable and with both TPR and Zc in the models. Comparisons of partial r values were made using Z statistics. To determine the impact of TPR compared to Zc on the change in SV with acute activity, multivariate adjusted analysis of covariance was performed. To achieve statistical power at 95% with a two-sided α value of <0.01 a sample size of 36 was required, as calculated from a mean difference and standard deviation of 15.94±15.00 ml/bt based upon significant changes in stroke volume previously reported (Higginbotham et al., 1986).

CHAPTER 3: RESULTS

3.1 Characteristics

Table 3.1 shows the general characteristics of the study sample and the different classes of antihypertensive agents employed in the participants. The majority of the participants were women. They were mostly overweight or obese and of middle age. Most of the participants were receiving diuretics, calcium channel blockers and angiotensin-converting enzyme inhibitors. The majority were receiving three (39.3%) or four (23.2%) classes of antihypertensive agents, with only 26.8% receiving two or less antihypertensive agents and 10.7% receiving five or more antihypertensive agents. 60.7% of the participants had blood pressure values controlled to target (<140/90 mm Hg). The mean carotid-femoral pulse wave velocity was 8.14±2.84 m/sec and the mean carotid-radial pulse wave velocity was 6.94±1.83 m/sec.

3.2 Changes in General Haemodynamics with Acute Activity

Table 3.2 compares the general haemodynamics before versus immediately after acute activity. Both brachial systolic and diastolic blood pressure increased with acute activity. Hence no change in brachial pulse pressure was noted. Heart rate, stroke volume and hence cardiac output increased and total peripheral resistance and ejection duration decreased with acute activity.

3.3 Changes in Central Aortic Haemodynamics with Acute Activity

Table 3.3 shows the impact of acute activity on central aortic haemodynamics. No changes in aortic systolic or pulse pressure were noted. Similarly, aortic forward and reflected

Table 3.1 Characteristics of the study sample.

Variable	
Sample size	56
% men (n)	35.7 (20)
Age (years)	56.9±12.8
Body mass index (kg/m^2)	33.0±8.0
% Overweight/Obese	28.6/55.3
% Antihypertensive medication (%)	
Diuretics (n)	83.9 (47)
Calcium channel blockers (n)	82.1 (46)
ACE Inhibitors (n)	58.9 (33)
Beta blockers (n)	39.3 (22)
Alpha blockers (n)	7.1 (4)
Hydralazine	14.3 (8)
Methyldopa	7.1 (4)
Aldactone	3.6 (2)
Losartan	7.1 (4)

Data expressed as mean±SD, % and (n). ACE-inhibitors indicates angiotensin converting enzyme inhibitors.

Table 3.2 General Haemodynamic Parameters at Rest and Immediately After Acute Activity.

Parameter	Rest	Acute Activity	p-value
Peripheral SBP (mmHg)	140±18	145±22	<0.05
Peripheral DBP (mmHg)	79±9	83±11	<0.005
Peripheral PP (mmHg)	60±14	62±16	=0.44
Heart rate (beats/min)	65±12	68±13	=0.0001
SV (ml/beat)	128±43	161±68	=0.0001
CO (l/min)	8±3	11±5	<0.0001
TPR (mmHg/l/min)	14±5	12±5	<0.005
MAP (mmHg)	101±11	105±14	<0.02
Ejection duration (msec)	325±28	320±29	<0.005

Data expressed as mean±SD. CO, cardiac output; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; SBP, systolic blood pressure; SV, stroke volume; TPR, total peripheral resistance.

Table 3.3 Central Aortic Haemodynamic Parameters at Rest and Immediately After Acute Activity.

Parameter	Rest	Acute Activity	p-value
Aortic SBP (mmHg)	130±17	134±19	=0.12
Aortic PP (mmHg)	50±13	50±14	=0.88
Pf (mmHg)	33.6±7.6	35.4±10.4	=0.16
Pb (mmHg)	24.6±7.9	23.6±7.8	=0.24
Aortic Pa (mm Hg)	16.3±7.3	15.3±8.9	=0.25
Aortic AIx (%)	148±27	140±21	<0.001
Aortic RM (mm Hg)	73±15	68±17	<0.005
Aortic flow (Q) (ml/s)	432±147	503±164	<0.02
Zc (dynes.s/cm^5)	82.6±37.0	81.3±43.0	=0.85
Max P_{QxZc} (mm Hg)	33.5±8.1	34.2±8.8	=0.32
P_{QxZc} at peak PPc (mm Hg)	17.8±6.3	19.2±6.9	=0.13

Data expressed as mean±SD. Pa, augmentation pressure; Pb, backward wave pressure; Pf, forward wave pressure; PP, pulse pressure; PPc, aortic pulse pressure; P_{QxZc}, compression wave pressure; Q, flow; RM, reflection magnitude (Pb/Pf); SBP, systolic blood pressure; Zc, characteristic impedance.

(backward) wave pressures, the magnitude of the compression wave pressure (max P_{QxZc}), and P_{QxZc} at peak aortic PP were not changed. However, augmentation index and reflection magnitude (Pb/Pf) were decreased after acute activity (HR effect). Aortic flow was increased with no changes in characteristic impedance, or compression wave pressures.

3.4 Changes in Cardiac Function with Acute Activity

Table 3.4 shows baseline cardiac function and the impact of acute activity on cardiac function. Importantly, no participants had an EF which was less than 40% either at rest or during acute activity. Increases in left ventricular filling volume (LV EDV) were noted with acute activity; but there were no changes in left ventricular end systolic volume (LV ESV), EF or midwall fractional shortening (FS). Hence, the increases in aortic flow (Q) and SV noted with acute activity was accompanied by increases in left ventricular filling volume but not with changes in cardiac systolic function. In addition, increases in peak aortic velocity and aortic root diameter noted with acute activity accompanied the exercise-induced increases in Q and SV. Left ventricular diastolic function as indexed by E/A was decreased with acute activity; however this effect was attributed to changes in HR as no differences were noted before versus after activity with adjustments for HR (E/A before: 1.02±0.29, E/A after: 0.99±0.29, p=0.65). Acute activity had no impact on LV filling pressures as indexed by LV E/e'.

3.5 Determinants of Stroke Volume at Rest

Table 3.5 shows the bivariate relationships between various haemodynamic or cardiac

Table 3.4 Cardiac Parameters at Rest and Immediately After Acute Activity.

	Rest	Acute Activity	p-value
LV EDD (cm)	4.8±0.8	5.0±0.9	<0.05
LV ESD (cm)	3.4±0.8	3.5±0.9	=0.15
LV EDV (ml)	107±34	117±46	<0.05
LV ESV (ml)	46±19	49±21	=0.10
LV EF (%)	58±9	59±10	=0.68
LV midwall FS (%)	30±8	30±8	=0.70
E/A	1.03±0.30	0.98±0.30	<0.05
E/e’	6.94±2.39	6.90±2.51	=0.90
Vmax (cm/s)	96.8±22.3	104.3±24.7	<0.05
VTI (cm)	22.7±5.2	24.3±6.3	<0.05
AoR diameter (mm)	27.9±4.3	29.3±4.7	<0.05

Data expressed as mean±SD. AoR, aortic root; E/A, early to late transmitral velocity; EDD, end diastolic diameter; EDV, end diastolic volume; E/e’, early transmitral velocity / velocity of myocardial tissue lengthening in early diastole; EF, ejection fraction; ESD, end systolic diameter; ESV, end systolic volume; FS, fractional shortening; LV, left ventricular; VTI, aortic velocity time integral; Vmax, maximal aortic velocity.

Table 3.5. Bivariate Relationships with Stroke Volume at Rest and Immediately After Acute Activity.

	Rest		Acute Activity	
	r	p-value	R	p-value
HR	-0.061	=0.65	-0.091	=0.51
LV EDV	0.109	=0.42	0.305	=0.022
LV EF	-0.264	=0.05	-0.304	=0.023
E/A	0.125	=0.36	0.101	=0.46
E/e’	-0.006	=0.97	0.034	=0.81
Vmax	0.255	=0.06	0.478	=0.0002
VTI	0.445	=0.0007	0.631	<0.0001
AoR diameter	-0.405	=0.002	0.691	<0.0001
Zc	-0.499	<0.0001	-0.682	<0.0001
TPR	-0.795	<0.0001	-0.774	<0.0001
MAP	0.034	=0.80	-0.055	=0.69

AoR, aortic root; E/A, early to late transmitral velocity; EDV, end diastolic volume; E/e’, early transmitral velocity / velocity of myocardial tissue lengthening in early diastole; EF, ejection fraction; HR, heart rate; LV, left ventricular; MAP, mean arterial pressure; TPR, total peripheral resistance; VTI, aortic velocity time integral; Vmax, maximal aortic velocity; Zc, characteristic impedance.

parameters and SV at rest. TPR, Zc, aortic root diameter and EF were associated with SV at rest, and the strongest determinants of SV at rest were Zc and TPR. Importantly, the Pearson's correlation coefficient was stronger for TPR than for Zc ($p<0.05$). Moreover, when TPR and Zc were in the same regression model, the relationship between Zc and SV was markedly reduced whereas that between TPR and SV was unchanged (Figure 3.1). In addition, the relationship between TPR and SV was stronger than the relationship between Zc and SV (Figure 3.1).

3.6 Determinants of Stroke Volume Immediately After Acute Exercise

Table 3.5 shows the bivariate relationships between various haemodynamic or cardiac parameters and SV immediately after acute exercise. TPR, Zc, aortic root diameter, EDV and EF were associated with SV after acute exercise, and the strongest determinants were aortic root diameter, Zc and TPR. Importantly, when TPR and Zc were in the same regression model, the relationship between Zc and SV was no longer significant whereas that between TPR and SV remained highly significant (Figure 3.1). In addition, the relationship between TPR and SV was stronger than the relationship between Zc and SV (Figure 3.1). The increase in SV with acute activity was associated with resting Zc independent of activity-induced decreases in TPR. However, the relationship between Zc and change in SV was not as strong as that between changes in TPR and SV (Figure 3.1).

3.7 Determinants of Stroke Volume at Rest and Immediately After Acute Exercise in Patients with High Compared to Low Aortic Stiffness

Table 3.6 shows the characteristics of the patients with high compared to low aortic stiffness.

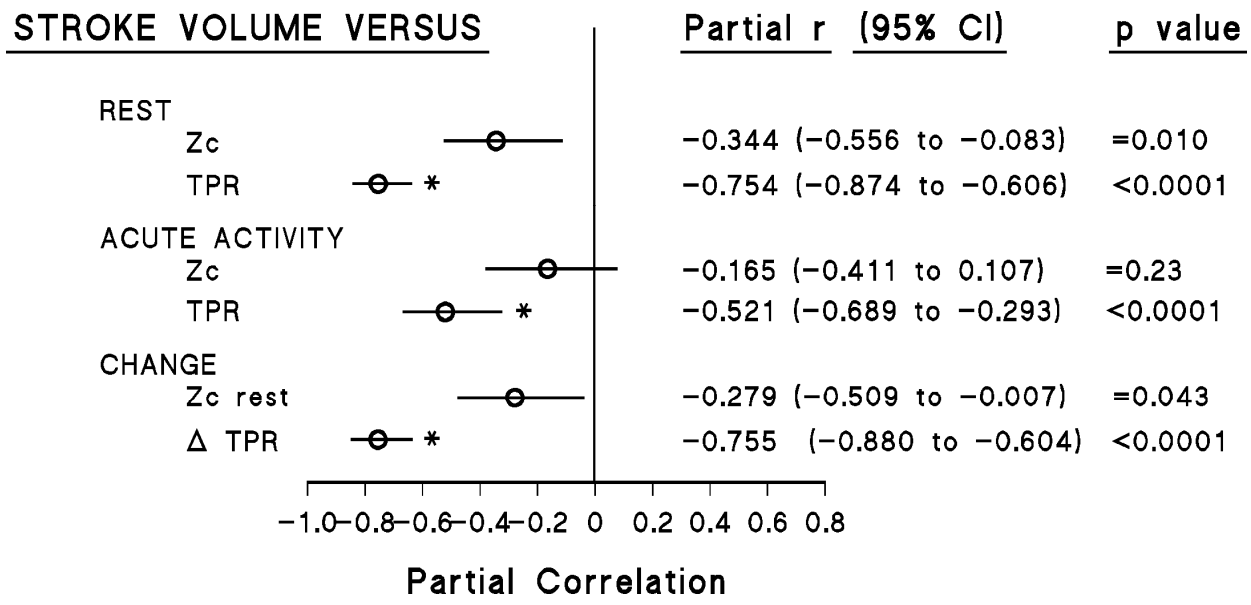

Figure 3.1. Relative Contribution of Characteristic Impedance (Zc) and Total Peripheral Resistance (TPR) to Stroke Volume at Rest and Immediately After Acute Activity. Δ, change in; *$p<0.05$ versus relationship between Zc and SV.

Only carotid-femoral PWV differed between the two groups. Figure 3.2 shows the relative impact of Zc and TPR on SV when in the same regression model in patients with low aortic stiffness (carotid-femoral PWV<7.7 [median]) compared to patients with high aortic stiffness (carotid-femoral PWV≥7.7 [median]). In patients with low aortic stiffness, only TPR was associated with SV either at rest or after acute activity. In comparison, in patients with high aortic stiffness, both Zc and TPR were associated with SV at rest. However, the relationship between SV and TPR was stronger than that between SV and Zc. Moreover, in patients with high aortic stiffness, only TPR was associated with SV after acute activity.

3.8 The Comparative Impact of TPR and Zc on Stroke Volume Response to Acute Activity

Figure 3.3 shows the mean values of stroke volume at rest and immediately after acute activity before and after adjustments for either TPR or Zc. The adjustment for TPR marked reduced the difference between SV at rest compared to after acute activity, whereas the adjustment for Zc had little effect.

Table 3.6 Characteristics and Haemodynamic Parameters at Rest and During Acute Activity in Patients with Low Compared to High Aortic Stiffness.

Parameter	Low PWV (n=29)	High PWV (n=27)	p-value
Age (years)	56.3±11.9	57.4±14.0	=0.75
Sex (% women)	72.4	55.6	=0.27
BMI (kg/m^2)	34.5±8.3	30.6±6.3	=0.052
PWV (m/s)	6.2±1.2	10.0±2.7	<0.0001
REST			
Peripheral SBP (mm Hg)	137±20	142±15	=0.30
Peripheral DBP (mm Hg)	79±9	80±10	=0.52
Peripheral PP (mm Hg)	59±15	62±13	=0.39
Aortic SBP (mm Hg)	129±19	132±14	=0.51
Aortic PP (mm Hg)	49±14	50±12	=0.78
SV (ml/beat)	126±41	129±45	=0.79
TPR (mmHg/l/min)	13.9±5.1	14.0±5.8	=0.94
Zc (dynes.s/cm^5)	82.0±36.0	83.3±38.8	=0.90
HR (beats/min)	64.3±11.2	65.6±12.5	=0.68
ACUTE ACTIVITY			
Peripheral SBP (mm Hg)	143±24	146±19	=0.68
Peripheral DBP (mm Hg)	84±11	82±11	=0.65
Peripheral PP (mm Hg)	60±17	64±15	=0.39
Aortic SBP (mm Hg)	134±22	133±16	=0.77

Aortic PP (mm Hg)	49±16	49±12	=0.99
SV (ml/beat)	162±75	160±62	=0.91
TPR (mmHg/l/min)	11.9±5.8	11.2±4.8	=0.62
Zc (dynes.s/cm^5)	79.6±40.1	79.4±32.1	=0.98
HR (beats/min)	68.0±12.5	68.3±13.1	=0.93

Data expressed as mean±SD. BMI, body mass index; DBP, diastolic blood pressure; HR, heart rate; PP, pulse pressure; PWV, pulse wave velocity; SBP, systolic blood pressure; SV, stroke volume; TPR, total peripheral resistance; Zc, aortic characteristic impedance. Low PWV=PWV<7.7 (median) and high PWV=PWV≥7.7 (median).

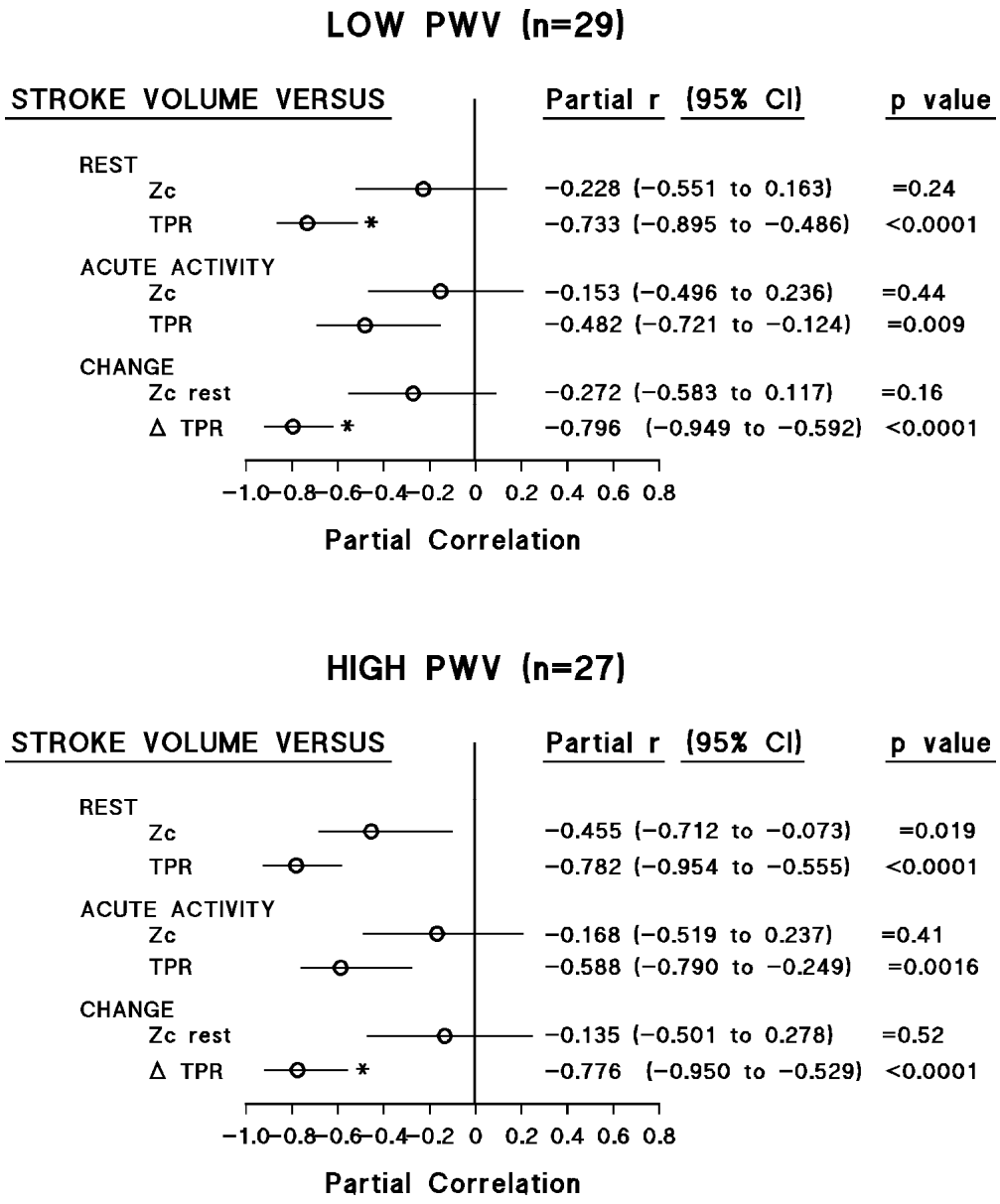

Figure 3.2. Relative Contribution of Characteristic Impedance (Zc) and Total Peripheral Resistance (TPR) to Stroke Volume at Rest and Immediately After Acute Activity in Patients with High Aortic Stiffness (carotid-femoral pulse wave velocity [PWV] ≥7.7[median]) versus Low Aortic Stiffness (carotid-femoral PWV<7.7). Δ, change in; *p<0.05 versus relationship between Zc and SV.

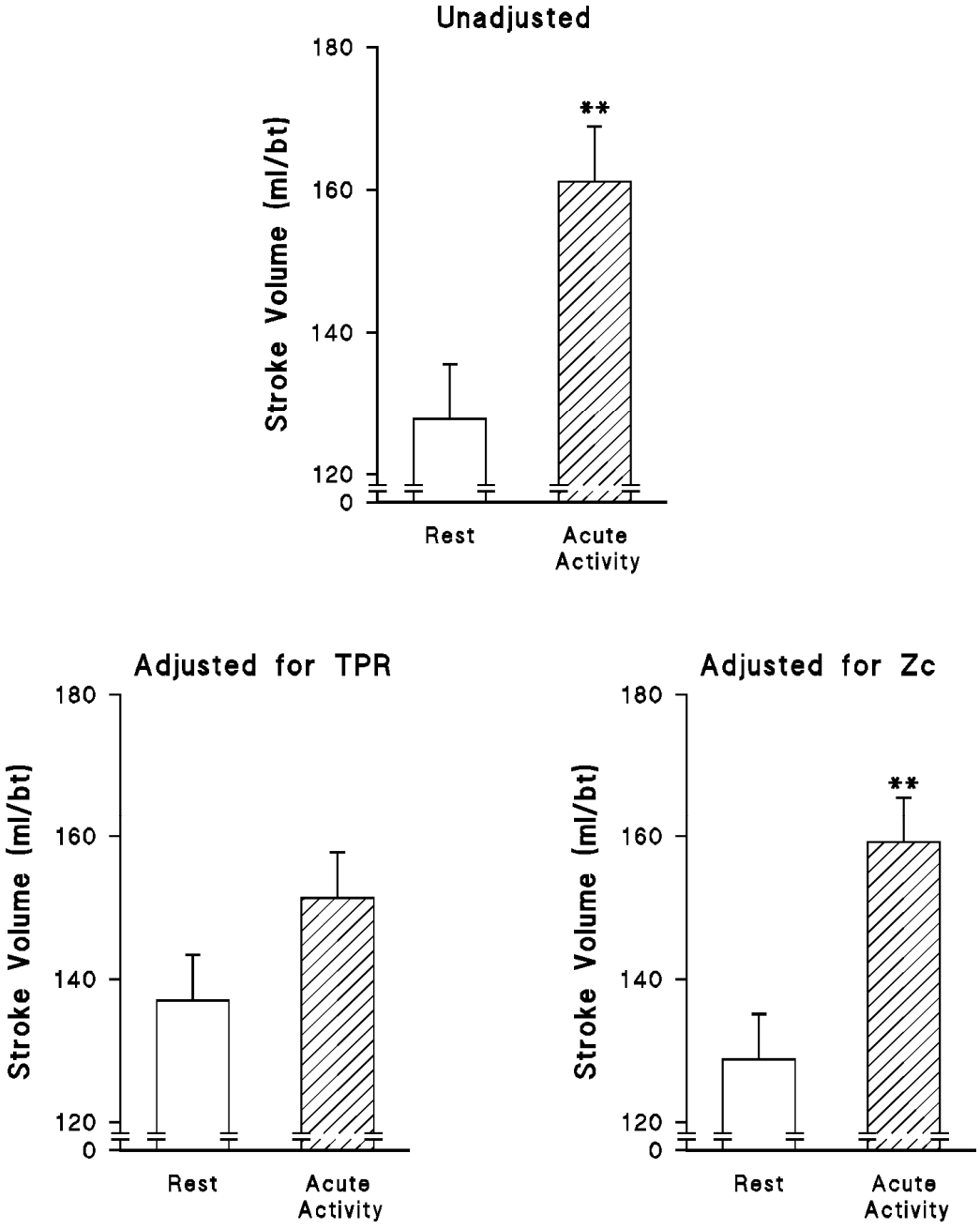

Figure 3.3. Stroke Volume at Rest and Immediately After Acute Activity Before and After Adjustments for Either TPR or Zc. **p<0.0005 versus rest.

CHAPTER 4: DISCUSSION

4.1 Summary of Findings

The main findings of the present study are as follows. In middle aged or elderly severe or refractory hypertensives with largely controlled blood pressure values (or blood pressure values only marginally above threshold values) whilst on antihypertensive medication, but with a high mean aortic pulse wave velocity (aortic stiffness); I evaluated the relative contribution of vascular changes to the ability to generate and increase stroke volume with modest physical activity. In this regard, I show that although characteristic impedance in the proximal aorta was inversely and independently associated with resting stroke volume, as well as with increases in stroke volume with exercise, that the principle determinant of exercise-induced increases in stroke volume was the extent to which systemic vascular resistance decreased with modest exercise. Importantly, increases in stroke volume with modest physical activity did not occur in parallel with increases in ejection fraction, but did occur in conjunction with increases in left ventricular end diastolic volume (Frank-Starling effect). Although peak aortic flow increased with physical activity, this was insufficient to translate into an enhanced pulse pressure and hence the adverse effects of characteristic impedance on stroke volume could not be accounted for by load-induced effects on left ventricular function. Rather, they are likely accounted for by the resistance to flow in a pulsatile system generated by characteristic impedance (Q=PP/Zc). Although systemic vascular resistance decreased with exercise, diastolic blood pressure increased with physical activity, an effect accounted for by increases in cardiac output. Hence, cardiac output-induced increases in wall stress at the peak of isovolumic contraction, which corresponds with diastolic blood pressure and a high volume in the left ventricle (the same volume as at end diastole), may have contributed to preventing increases in ejection fraction with physical activity.

4.2 Novelty of the Present Study

The present study is the first to evaluate the relative impact of proximal aortic Zc versus SVR as determinants of increases in systemic blood flow with physical activity in human participants. In this regard, a number of studies have reported on relationships between oxygen consumption and aortic PWV (Vaitkevicius et al., 1993; Boreham et al., 2004; Fernberg et al., 2017; Gando et al., 2010; Tanisawa et al., 2015; Alves et al., 2018; Sung et al., 2018). Importantly, all of these studies speculated on possible mechanisms that explain these relations including a possibility that aortic stiffness reduces SV or CO increases with exercise. Nevertheless, one small (n=19) study reported that acute decreases in PWV produced by the calcium channel blocker verapamil, were associated with both an increased SV and oxygen consumption during submaximal exercise (Chen et al., 1999). However, this effect could have readily been explained by the impact of the calcium channel blocker on SVR. Nevertheless, in patients with dilated cardiomyopathy peak oxygen consumption was reported to be inversely correlated with PWV and positively correlated with SV (Bonapace et al., 2003). Similarly, in patients with non-ischaemic dilated cardiomyopathy an increased PWV was noted to be associated with both a decreased peak oxygen consumption and LV systolic function (Patrianakos et al., 2009). Moreover, in patients with HFpEF, total arterial compliance and CO reserve were reduced during submaximal exercise compared to hypertensive controls, despite similar MAP (Reddy et al., 2017). Moreover, in these same patients, inorganic nitrite-induced increases in total arterial compliance during submaximal exercise were accompanied by improvements in CO during submaximal exercise (Reddy et al., 2017). Nevertheless, these effects are likely explained by an impact on vascular tone rather than by the effects of resistance to flow in the proximal aorta in a pulsatile system (Zc). Despite the evidence to suggest that aortic stiffness may contribute toward a reduced SV and

CO during exercise, there are no human studies that have evaluated the aortic changes that may account for these relations, and that is an increased resistance to flow in a pulsatile system (Zc). In this regard, I provide the first evidence to show that in a group well recognised as being at risk for marked increases in aortic stiffness, that through increases in Zc, aortic stiffness may indeed limit SV changes during physical activity. The caveat is nevertheless that this effect is minimal in comparison to the impact of exercise on SVR and that PWV has little role to play in explaining these relations.

4.3 Comparison with Animal Studies

Previous animal-based studies have evaluated the impact of alterations in aortic function on SV, CO or EF. In this regard, an artificially created increase in aortic stiffness has been demonstrated to decrease EF (Urschel et al., 1968), an effect thought to be mediated by an increased afterload to the LV. In contrast however, the present study does not show relations between Zc and EF, and hence this effect described in dogs may be attributed to extreme changes in aortic stiffness. Nevertheless, in an alternative study also conducted in dogs, in elderly dogs, physical exercise was noted to increase Zc and decrease TPR, the consequence being that no increase in SV was noted with exercise (Yin et al., 1981). In comparison, in younger dogs, the same levels of incremental aerobic physical exercise (treadmill running) resulted in no change in Zc, but a similar decrease in TPR as the older dogs and hence an increase in SV was noted (Yin et al., 1981). Although oxygen consumption was not assessed in this study, all except for one of the young dogs, but none of the old dogs could complete the period of extreme exercise. In keeping with that study (Yin et al., 1981), in the present study I note that even modest physical activity resulted in increases in SV and CO and that Zc was inversely associated with these increases.

4.4 Cardiac Responses to Exercise

In the present study I show that increases in SV with physical activity occurred without associated increments in EF. Rather, increases in SV were accounted for by increases in LV filling volumes (LVEDV) and hence through a Frank-Starling effect. The increased filling volumes may be explained by vasodilator effects (vasodilator metabolites in skeletal muscle or sympathetic-induced β_2-adrenoreceptor activation) with concomitant increases in venous return. Alternatively, skeletal muscle contraction may promote an enhanced venous return (through an impact of the muscle pump). However, this is an unlikely explanation as the intensity of physical activity was low. The inability of EF to increase with exercise may be explained by the low levels of exercise with only a limited sympathetic response (the heart rate increase was very modest). Alternatively, as highlighted in the introductory chapter, hypertensives show a reduced exercise-induced increase in EF and thus CO as compared to healthy individuals (Stratton et al., 1994; Paolillo et al., 2018; Austin et al., 2010; Bonapace et al., 2003) effects most likely mediated by a reduced cardiac performance caused by long-standing hypertension. Through the associated cardiac hypertrophy that often accompanies hypertension, an increase in myocardial oxygen demand-to-supply ratio may further limit physical activity associated increases in cardiac function (EF) (Alves et al., 2018). As also highlighted in the introductory chapter, age similarly has a marked effect on the cardiac response to physical activity and in the present study, the mean age (57 years) reflects a predominantly middle-aged to elderly cohort. Advancing age in healthy individuals is sufficient to cause a decline in EF and CO in those performing supine physical activity (Stratton et al., 1994). Despite SV responses to physical activity being similar, the elderly tend to augment SV through increases in cardiac filling (increases in LV end diastolic volume) but without any significant changes in EF, while the young rely on increases in EF

without the need for LV volume expansion (Stratton et al., 1994; Yin et al., 1981). Importantly, in the present study the increase in HR was too modest to have limited the SV response to physical activity (when SV increases depend on LV filling, high HR will limit filling and hence increases in SV) (Vieira et al., 2016; Stratton et al., 1994).

4.5 Could the Limited Increase in EF be Accounted for by Aortic Dysfunction?

As highlighted in the introductory chapter, decreases in aortic compliance (increased stiffness) may make a marked contribution to cardiac energetic cost at a given SV (Bonapace et al., 2003; Theoleyre et al., 2016). In this regard, the main role of the aorta is to buffer pressure and flow generated by the LV and hence to maintain a low LV load, which in turn modulates LV dynamics as well as coronary perfusion (Bonapace et al., 2003; Pierce, 2017). With respect to effects on LV load, as indicated in the introduction to this dissertation, an increased aortic stiffness creates a resistance to flow in a pulsatile system (Zc) and this enhances Pf and central aortic pressures in early systole while ejection occurs. A reduction in proximal aortic distensibility as accompanied by advancing age and hypertension therefore causes increases in PP and SBP (afterload). As afterload increases, wall stress in the heart is enhanced and myocardial oxygen demand increases. This limits the ability to generate sufficient oxygen required for increases in EF and hence SV with exercise. With respect to effects on coronary flow, a stiff aorta reduces flow during diastole (elastic recoil is reduced) and hence DBP, which in turn limits coronary perfusion (which occurs during diastole) (Bonapace et al., 2003). Thus, a mismatch between oxygen demand and supply is the consequence and increases in EF and hence SV with exercise are reduced. Thus, a possible reason why EF failed to increase with physical activity in the present study is because of the presence of a stiffer aorta impeding increases in EF and hence SV. Importantly however, no

inverse relations between EF and PP or SBP were noted. Thus, load-induced effects on the LV are unlikely to explain the lack of increases in EF with physical activity. However, as comparisons with healthy controls of a similar or younger age were not made in the present study, I am unable to identify whether the central cause of the inability to increase EF with physical activity can be attributed to the low levels of physical activity performed, a reduced cardiac performance or through an impact of aortic stiffness on afterload.

4.6 Explanation for Relations Between Zc and SV in Exercise

Although the inability of physical activity to increase EF in the present study may be mediated not only by low levels of exercise performed, but also by increases in afterload generated by an enhanced aortic stiffness, afterload effects cannot explain the relationship between Zc and SV. Indeed, physical activity-induced increases in SV were independent of EF, and rather determined by Frank-Starling effects. The most likely explanation for inverse relations between Zc and SV are that increases in Zc generate a resistance to aortic flow (Q) during ventricular ejection which limits the ability to increase SV when EF fails to increase with exercise. Similarly, because increments in SV were not associated with an enhanced EF during physical activity, inverse relationships between SVR and SV are also most likely to be accounted for simply by the effects of SVR on resistance to flow. Nevertheless, I cannot discount an impact of SVR on SV in-part through afterload effects on the LV, as DBP increased in response to increments in CO. This will indeed increase LV wall stress at end isovolumic contraction when filling volumes are highest and hence the ratio between wall thickness and radius (h/r) is the lowest.

4.7. Exercise Intensity

As indicated in the aforementioned sections, in the present study the level of physical activity performed was low as participants were asked to exercise only at comfortable levels. The low levels of physical activity are evidenced by the fact that increases in HR were modest at best. Thus, whether SV increases at higher intensities of exercise are driven by Zc as strongly as SVR changes drive SV increases is unknown and requires further study. Importantly however, it is unlikely that physical activity in elderly or hypertensive participants will be at a particularly high level and hence the present study may reflect what normally occurs in such patients. In this regard, although guidelines are clear on the frequency and duration of exercise that should be performed to gain the benefits of BP lowering, they are unclear as to how low the intensity of exercise can be to produce benefits to BP reduction. In this regard, there is little point in advocating interventions which only have benefit if unacceptable levels of associated discomfort occur. Of importance, recent evidence suggests that moderate or high intensity physical activity in hypertensives has little or no more benefit to outcomes displayed with low levels of activity (walking) (Joseph et al., 2019), and the latter may be more consistent with that performed by participants in the present study.

4.8 Clinical Implications

The present study suggests that at low intensity physical activity, aortic stiffness is unlikely to markedly limit the increases in SV and CO necessary to generate comfortable activity. In this regard, the impact is largely driven by SVR changes. These data would suggest that exercise prescription of low intensity activity may not necessarily be limited in elderly hypertensives or hypertensives with more advanced vascular pathology (with marked increases in aortic

stiffness). Nevertheless, vascular (vasodilator) responses to very low levels of physical activity may change over time with habitual activity. Hence, whether Zc contributes more and SVR less to increasing levels of activity requires further study. Importantly, the marked contribution of SVR and the contribution of changes in SVR during physical activity to increases in SV and CO with activity suggests that pharmacological agents with vasodilator properties are critical to ensuring that exercise prescription is closely adhered to in hypertensives. As a high proportion of the present cohort of participants were receiving a number of agents with vasodilator properties, further studies are required in participants receiving agents with more modest effects on vascular properties (some diuretic agents). However, through autoregulatory changes even diuretic agents may produce most of their benefits on BP through an impact on SVR and hence the type of agent received may be of little consequence.

4.9. Limitations

There are several limitations of the present study that warrant consideration and many have already been alluded to in aforementioned sections. These include the small sample size as well as limited intensity of the physical activity performed and the evaluation of participants receiving several antihypertensive agents in combination. This was largely necessary to ensure that participants with advanced aortic functional changes were studied who are generally more frail and carry several comorbidities, thus limiting their capacity to safely perform physical activity and a need to ensure that their BP was well-managed at the time. Additional limitations include the lack of measurement of oxygen consumption which was difficult to perform at the same time as capturing difficult echocardiographic and central arterial functional data. Hence, I cannot comment on whether SV changes did indeed

translate into a limited ability to consume oxygen. However, SV is a well-accepted determinant of oxygen consumption. As indicated in aforementioned sections a group of age and sex-matched healthy participants was not studied, largely because most persons who are of this age have aortic dysfunction and hence obtaining those without would have been self-limiting. Moreover, matching levels of physical activity between cases and controls without performing oxygen consumption measurements would not have been possible. However, the aim of the study was to determine the relative impact of several measures of resistance to flow (Zc versus SVR) to physical activity-induced increases in SV, an aim which does not require a control group. A further limitation is that I could not assess haemodynamic function during exercise as echocardiography and applanation tonometry is only accurate in a stationary person. Hence, all measures were acquired immediately after exercise and the time after exercise that these data were acquired would have varied from participant to participant depending on several factors (e.g. echogenicity). Additional limitations include the fact that calibration of the radial pulse waveform was determined from brachial BP measurements which ignores amplification from brachial to radial arteries. However, a similar error would have been produced before and after exercise.

4.10 Conclusions

In conclusion, my study shows that in the middle-aged or elderly with severe or refractory hypertension with blood pressure controlled as a result of antihypertensive therapy, characteristic impedance and total peripheral resistance were inversely proportional to mild activity-induced increases in stroke volume. However, the principal determinant of mild activity-induced increases in stroke volume was a decrease in total peripheral resistance. These data highlight the fact that modest physical activity is unlikely to be limited by

variations in aortic stiffness noted to occur in middle-aged to elderly hypertensives. Whether higher levels of physical activity are limited by aortic stiffness requires further study.

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Appendix A: Ethical clearance certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG	HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research & Post Graduate Affairs)

TO: Mr DDS Fernandes et al
School of Physiology
Medical School
University

E-mail: 722797@students.wits.ac.za

CC: Supervisor: Professor AJ Woodiwiss and Dr V Petersen
<Angela.Woodiwiss@wits.ac.za>
and <HREC-Medical.ResearchOffice@wits.ac.za>

FROM: Iain Burns
Human Research Ethics Committee (Medical)
Tel: 011 717 1252

E-mail: Iain.Burns@wits.ac.za

DATE: 01/10/2018

REF: *R14/49*

PROTOCOL NO: **M180897** *(This is your ethics application study reference number. Please quote this reference number in all correspondence relating to this study)*

PROJECT TITLE: *Impact of physical activity on wave refection in treated refractory hypertensives*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to the Government funding of the University.

MSWorks2000/Iain0007/Clearscan.wps

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Mr DDS Fernandes et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M180897

NAME: (Principal Investigator)	Mr DDS Fernandes et al
DEPARTMENT:	School of Physiology Medical School University
PROJECT TITLE:	Impact of physical activity on wave refection in treated refractory hypertensives
DATE CONSIDERED:	Ad hoc
DECISION:	Approved unconditionally
CONDITIONS:	Sub-study under M170271
SUPERVISOR:	Professor AJ Woodiwiss and Dr V Petersen
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	01/10/2018

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on 3rd floor, Philip V Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

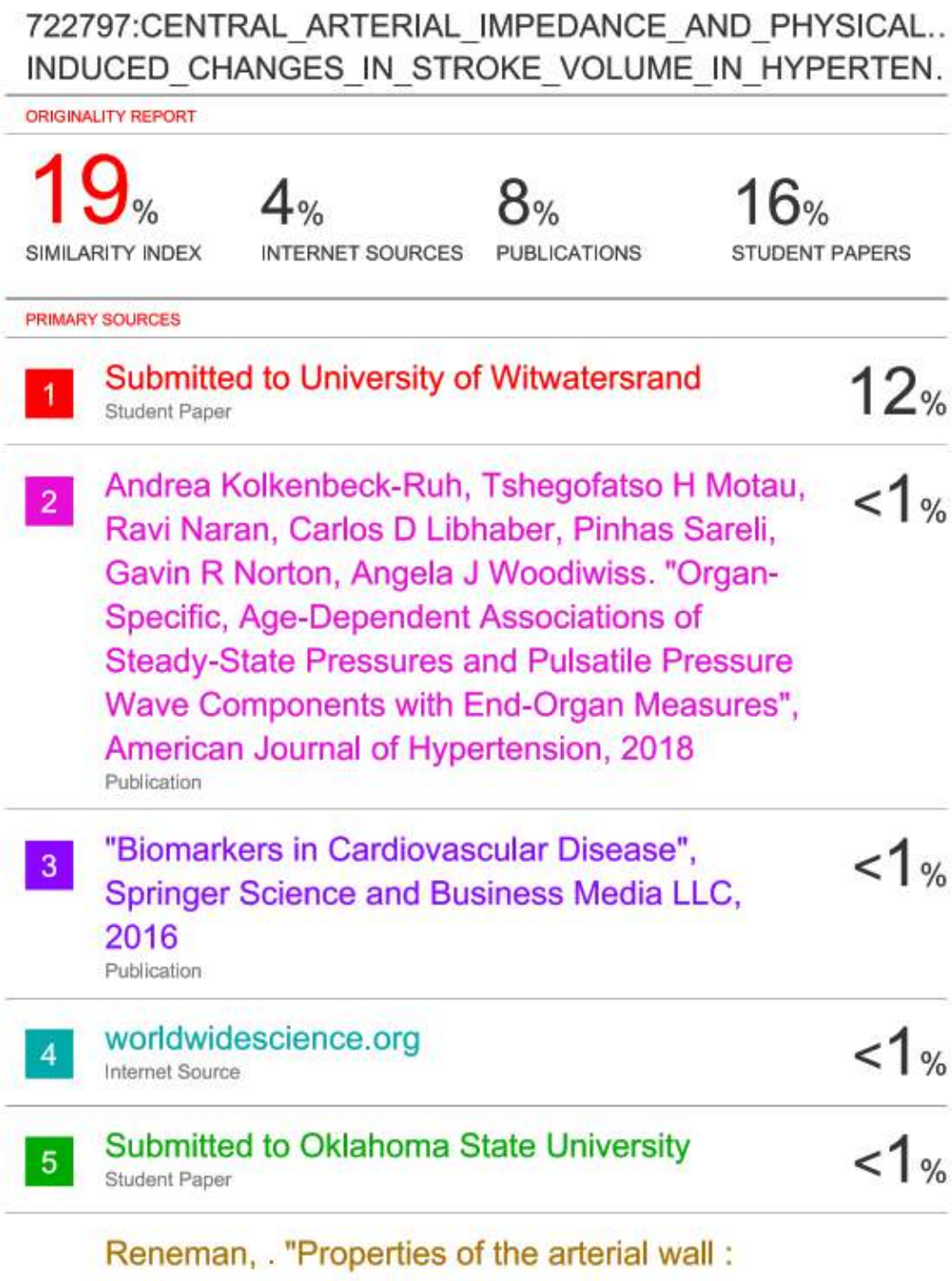
I/We fully understand the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to resubmit to the Committee. I agree to submit a yearly progress report. When a funder requires annual re-certification, the application date will be one year after the date of the meeting when the study was initially reviewed. In this case, the study was initially reviewed in August and will therefore reports and re-certification will be due early in the month of August each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

30/03/2020
Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix B: Plagiarism Report



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ORIGINALITY REPORT

19%	4%	8%	16%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Submitted to University of Witwatersrand Student Paper	12%
2	Andrea Kolkenbeck-Ruh, Tshegofatso H Motau, Ravi Naran, Carlos D Libhaber, Pinhas Sareli, Gavin R Norton, Angela J Woodiwiss. "Organ-Specific, Age-Dependent Associations of Steady-State Pressures and Pulsatile Pressure Wave Components with End-Organ Measures", American Journal of Hypertension, 2018 Publication	<1%
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