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DETERMINATION OF CHARACTERISTIC IMPEDANCE IN A RETROSPECTIVE COHORT OF CORONARY ARTERY DISEASE IN SOUTH AFRICA

Danelle Els

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, 2024

Declaration

I, Danelle Els, declare that this dissertation is my own unaided work. It is being submitted for the Degree in Masters of Science in Medicine at the University of the Witwatersrand, Johannesburg. The work done in this dissertation has not been submitted for any Degree or examination in this University or any other University.



……

(Signature of candidate)

……4…… day of ……November…… 2024 in ……Johannesburg……...

I certify that the studies contained in this dissertation have been approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, Johannesburg. The ethics approval number is M21-01-34.



……

…….



Vernice R. Peterson (Supervisor 1)

Date: …4 November 2024…….

Ferande Peters (Supervisor 2)

Date: …...4 November 2024……

Dedication

I dedicate this work to my parents, Justus and Elize, who have supported me unconditionally throughout my studies. I would also like to extend my gratitude to all my mentors for their continued support. This dissertation is in memory of a great mentor, Professor Gavin Norton. I would also like to dedicate this work to my late grandfather, who always showed interest in my work.

Presentations

The following **oral** presentations have arisen from this work:

- "Marked Increases in Proximal Aortic Characteristic Impedance and hence Forward Wave Pressures Beyond Brachial Blood Pressure in Patients with Angiographic Proven Coronary Artery Disease."- Danelle Els, Ferande Peters, Eitzaz Sadiq,*Ravi Naran, Taalib Monareng,* Talib Abdool-Carrim,* Ismail Cassimjee,* Girish Modi,* Gavin R Norton, Angela J Woodiwiss, Vernice Peterson. Southern African Hypertension Society Biennial Congress, 16 - 18 September 2022, Gauteng. (**Third Prize- Lionel Opie Award**)
- "Marked Increases in Proximal Aortic Characteristic Impedance and hence Forward Wave Pressures Beyond Brachial Blood Pressure in Patients with Angiographic Proven Coronary Artery Disease."- Danelle Els, Ferande Peters, Eitzaz Sadiq,*Ravi Naran, Taalib Monareng,* Talib Abdool-Carrim,* Ismail Cassimjee,* Girish Modi,* Gavin R Norton, Angela J Woodiwiss, Vernice Peterson. Wits School of Physiology Research Day, 13 September 2023, Gauteng.
- "Marked Increases in Proximal Aortic Characteristic Impedance and hence Forward Wave Pressures Beyond Brachial Blood Pressure in Patients with Angiographic Proven Coronary Artery Disease."- Danelle Els, Ferande Peters, Eitzaz Sadiq,*Ravi Naran, Taalib Monareng,* Talib Abdool-Carrim,* Ismail Cassimjee,* Girish Modi,* Gavin R Norton, Angela J Woodiwiss, Vernice Peterson. SAHS 2nd NextGen Virtual Spring School, 12 October 2023, Gauteng.

Publications

The work done in my Master's project contributed to the manuscript below:

"**Aortic Characteristic Impedance-Induced Increases in Forward Wave but Not Central Arterial Pulse Pressure Beyond Brachial Blood Pressure in Coronary Artery Disease."** Authors: Vernice R Peterson, Danelle Els, Eitzaz Sadiq, Ravi Naran, Taalib Monareng, Talib Abdool-Carrim, Ismail Cassimjee, Girish Modi, Gavin R Norton, Ferande Peters, Angela J Woodiwiss. This manuscript was submitted to the Journal of Hypertension in November 2023.

Abstract

The relationship between coronary artery disease (CAD) and proximal aortic stiffness-induced increases in central arterial forward wave pressures (Pf) is uncertain. Using central pressure and aortic velocity and diameter measurements, we compared aortic characteristic impedance (Zc) (n=71) and central arterial pressure wave morphology (n=189) in patients with CAD to central arterial function in 210 age- and sex-matched controls from a community study. The results showed that Zc was markedly increased in patients with CAD compared to community controls ($p<0.0001$). In addition, after adjustment for mean arterial pressure and aortic root diameter, the early systolic pressures generated by the product of peak aortic flow (Q) and Zc (P_{QxZc}) and Pf were markedly increased in patients with CAD as compared to controls ($p<0.0001$). This increase in Pf was accounted for by an enhanced P_{QxZc} at peak PPc rather than increases in re-reflected wave pressures. Further adjustments for either brachial PP or systolic blood pressure (SBP) showed that higher Pf values were retained in the CAD patients ($p<0.05$, $p<0.01$, $p<0.0001$). After adjusting for conventional risk factors, peak central aortic PPc was higher in patients with CAD as compared to controls ($p<0.05$, $p<0.005$, $p<0.0001$). However, after adjusting for brachial SBP and confounders, central aortic PPc did not differ between the groups. Thus, increases in stiffness-associated proximal aortic Zc in patients with CAD translate into marked increases in Pf, but not peak PPc beyond brachial BP. These findings suggest that pulsatile load responsible for CAD is beyond brachial BP and poorly indexed by peak PPc.

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I would like to thank my supervisors, Dr Vernice R. Peterson and Professor Ferande Peters, for their continued support, patience and guidance. I would also like to extend my gratitude to Professor Angela J. Woodiwiss and Professor Gavin R. Norton for giving me guidance and great advice. Lastly, I would like to thank my parents for giving me the foundation to achieve this dream.

Table of Contents

Declaration ii
Dedication iii
Presentations iv
Publications iv
Abstract v
Acknowledgements vi
List of Figures ix
List of Tables xi
Abbreviations xii
CHAPTER 1: INTRODUCTION 1
1.1 Introduction 2
1.2 Altered Aortic Function in CAD 3
1.3 Pulse Pressure in CAD 4
1.4 Determinants of Central Aortic Pulse Pressure 8
1.5 Arterial Stiffness 12
1.6 Study Rationale 14
1.7 Aims 15
CHAPTER 2: METHODS 16
2.1. Ethical Approval 17
2.2. Study Design and Participants 17
2.3. Clinical, Demographic and Anthropometric Measurements 18
2.4. Arterial Haemodynamic Assessment 18
2.5. Aortic Velocity Flow Wave 21
2.6. Aortic Pressure Wave Separation 21
2.7. Data Analysis 28
CHAPTER 3: RESULTS 29
3.1 Participant Characteristics 30
3.2 Comparison of Haemodynamic Variables Between Participants with CAD and Controls Before the Adjustments for Confounders 30
3.3. Comparison of Haemodynamic Variables Between Patients with CAD and The Community Sample After Adjusting for Confounders 33

3.4 Relative Contribution of Central Arterial Functional Changes Versus Conventional Risk Factors in Association with CAD....34
CHAPTER 4: DISCUSSION....44
4.1 Summary of Findings....45
4.2 Novelty of The Present Study....45
4.3 Central Pulse Pressure and CAD....46
4.3.1 Forward Wave Pressures....46
4.3.2 Backward Wave Pressures....47
4.3.3 The Effect of Age on Forward and Backward Wave Pressures....47
4.4 Arterial Stiffness in CAD....48
4.5 Clinical Implications....51
4.6 Potential limitations....51
4.7 Future studies....52
4.8 Conclusion....52
References....54
APPENDICES....72
Appendix 1: Ethics....73
Appendix 2: Turnitin Report (Plagiarism Report)....75

List of Figures

CHAPTER 1: INTRODUCTION.....1

Figure 1.1 An illustration of the pressure wavefom's amplication from the aorta to the radial artery (McEniery *et al.*, 2014).....6

Figure 1.2 Aortic pressure wave determined by the combine effect of the aortic forward (Pf) and aortic backward (Pb) pressure wave.....10

CHAPTER 2: METHODS 16

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). 19

Figure 2.2 Peripheral (radial) pressure waveform (left panel) converted into a central (aortic) pressure waveform (right panel) using the generalised transfer function incorporated in SphygmoCor software.....20

Figure 2.3 Cardiac ultrasound device, Philips CX-50 Compact Xtreme System (2009) used to obtain aortic velocity waveforms.....23

Figure 2.4 Aortic velocity waveforms (lower panel) obtained in the apical five-chamber view (upper panel) of the heart 24

Figure 2.5 Aortic diameter measurements obtained just proximal to 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 (Mitchell *et al.*, 2010b). A) aortic root diameter in systole and B) ECG 25

Figure 2.6 Illustration of the paring of the aortic pressure waveform and the aortic flow waveform (Q) which is the product of aortic velocity and area (Motau *et al*., 2018).....26

Figure 2.7 Wave separation analysis was performed using the approach of (Westerhof *et al.,* 2009).....27

CHAPTER 3: RESULTS.....29

Figure 3.1 Comparison of multivariate adjusted brachial pulse pressure (PPb) in those with angiographic coronary artery disease (CAD) as compared to age- and sex-matched community participants (CON).....35

Figure 3.2 Comparison of multivariate adjusted brachial systolic blood pressure (SBPb, panels A and B) and central systolic blood pressure (SBPc, panels C and D) in those with

angiographic coronary artery disease (CAD) as compared to age- and sex-matched community participants (CON). 36

Figure 3.3 Impact of adjustments for brachial pulsatile pressures (PPb, SBPb) on comparison of multivariate adjusted central pulse pressure (PPc) in those with angiographic coronary artery disease (CAD) as compared to age- and sex-matched community participants (CON). 37

Figure 3.4 Impact of adjustments for brachial pulsatile pressures (PPb, SBPb) on comparison of multivariate adjusted forward wave pressure (Pf phys. and Pf act.) in those with angiographic coronary artery disease (CAD) as compared to age- and sex-matched community participants (CON). 38

Figure 3.5 Impact of adjustments for brachial pulsatile pressures (PPb, SBPb) on comparison of multivariate adjusted backward wave pressure (Pb phys. and Pb act.) and re-reflected pressure (Pre-reflect) in those with angiographic coronary artery disease (CAD) as compared to age- and sex-matched community participants (CON). 39

Figure 3.6 Impact of adjustments for brachial pulsatile pressures (PPb, SBPb) on comparison of multivariate adjusted peak PQxZc (panel A) and PQxZc at PPc (panel B) in those with angiographic coronary artery disease (CAD) as compared to age- and sex-matched community participants (CON). 40

Figure 3.7 Impact of adjustments for brachial pulsatile pressures (PPb, SBPb) on comparison of Multivariate adjusted Zc (panel A), aortic diameter (panel C), aortic flow (Q) (panel D) and the impact of further adjustments for aortic diameter on Zc (panel B) in those with angiographic coronary artery disease (CAD) as compared to age- and sex-matched community participants (CON). 41

List of Tables

CHAPTER 3: RESULTS.....29

Table 3.1 General participant characteristics for patients with angiographically proven CAD compared to age- and sex-matched community samples (Controls) 31

Table 3.2 Comparison of unadjusted haemodynamic values between age- and sex-matched community participants (controls) and patients with CAD.....32

Table 3.3 Relative contribution of central arterial functional changes versus conventional risk factors in association with CAD.....42

Abbreviations

AF	Atrial fibrillation
BMI	Body mass index
BP	Blood pressure
BSA	Body surface area
CAD	Coronary artery disease
CHD	Coronary heart disease
cm	centimetres
CO	Cardiac output
CON	Community participants
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DM	Diabetes mellitus
ED	Ejection duration
HR	Heart rate
HT	Hypertension
kg	kilogram
kg/m^2	kilogram(s) per meters square
LV	Left ventricle
LVOT	Left ventricular outflow tract
m^2	meters squared
MAP	Mean arterial pressure
MHz	Megahertz
mmHg	Millimetres of Mercury
m/s	meters per second
ml/s	millimetres per second
Pa	Augmented pressure
Pb	Aortic backward wave pressure
Pf	Aortic forward wave pressure
Pf act.	Actual aortic forward wave pressure
Pf phys.	Physiological aortic forward wave pressure
PP	Pulse pressure
PPb	Brachial pulsatile pressure

PPc	Central pulse pressure
Preflect	Reflected wave pressure
PWA	Pulse wave analysis
PWV	Pulse wave velocity
P_{QxZc}	Peak flow
Q	Aortic flow
SBP	Systolic blood pressure
SBPb	Brachial systolic blood pressure
SBPc	Central systolic blood pressure
SV	Stroke volume
SVR	Systemic vascular resistance
TAC	Total arterial compliance
Zc	Characteristic impedance

CHAPTER 1: INTRODUCTION

1.1 Introduction

Globally, cardiovascular disease (CVD) is the primary cause of death and a major factor in reduced life expectancy. It encompasses a number of cardiac and vascular conditions (Mensah *et al*., 2019). In 2017, it was estimated that 330 million years of life were lost due to CVD, with 17.8 million deaths expected (Mensah *et al*., 2019). The number of CVD fatalities globally has increased by 12.5% during the past decade (Joseph *et al*., 2017). While the death rate from cardiovascular disease (CVD) has decreased in several developed nations, an unsettling rise in CVD rates has been reported in low- and middle-income nations (Pieters *et al*., 2017). Coronary artery disease (CAD), which accounts for 45% of all fatalities in Europe, is the most prevalent form of CVD (Gaudio *et al*., 2020) and the most common cause of death globally (Malakar *et al*., 2019). Premature death from CAD causes more years of life lost than the combined amount of time lost to lung, colon, breast, and prostate cancers (Duggan *et al*., 2022).

The cardiovascular condition known as CAD is brought on by atherosclerotic plaque occlusion of the coronary arteries (Malakar *et al*., 2019). The primary causes of CVD in Sub-Saharan Africa are reported to be cardiomyopathy, hypertension, and rheumatic heart disease, and the incidence rates for CVD were 60 per 100,000 in 1990 (Akinkugbe, 1990; Okrainec *et al*., 2004). Although CAD has historically been uncommon among South Africans, research has shown an increased prevalence of CAD, particularly in urban areas, due to urbanisation (Pieters *et al*., 2017). One of the primary risk factors for both cerebrovascular illness and CAD is hypertension (Okrainec *et al*., 2004). In addition, CAD is the most typical consequence for people with hypertension of all ages (Hajar, 2017). By 2025, 77.1 million women and 73.6 million men in sub-Saharan Africa are expected to develop hypertension, with urbanisation being a key contributing factor to this increased prevalence (Kearney *et al*., 2005). With the increased burden of CVD on the South African population and economy, little is known about the pathophysiological mechanisms and clinical manifestations related to hypertension-induced CAD in South Africa. Thus, it is important to identify and understand the haemodynamic mechanisms associated with changes in aortic pulse pressure in CAD to best improve clinical outcomes. Therefore, in the subsequent sections of my introduction, I will introduce the altered aortic function that presents in CAD, followed by the potential impact of changes in haemodynamic mechanisms in CAD. In addition, I will discuss the haemodynamic determinants of central aortic pulse pressure. This section will be followed by a discussion on arterial stiffness and characteristic impedance in the context of CAD.

1.2 Altered Aortic Function in CAD

Coronary artery disease is caused by atherosclerosis or atherosclerotic occlusions of the coronary arteries (Malakar *et al*., 2019). Atherosclerosis affects the conduit function of the arteries by forming plaque that impedes blood flow through the arteries (London & Pannier, 2010). Moreover, atherosclerosis is a multifaceted disease that promotes the hardening of artery walls (Mehta *et al*., 1998). In addition, atherosclerotic plaque development can result from injury after minor damage to the coronary artery wall (Kop, 1997). Understanding the mechanisms related to the development of CAD and the elements affecting the prognosis of patients with CAD is crucial for early diagnosis and individualised therapy. In the last ten years, research has shown a number of risk factors that contribute to the development of CAD, including age, obesity, smoking, dyslipidemia, diabetes mellitus, and hypertension (Kannel, 1961; Okrainec *et al*., 2004; Mahalle *et al*., 2014; Ghebre *et al*., 2016; Duggan *et al*., 2022). Despite efforts to avoid and treat these risk factors, the prognosis is still poor and the prevalence of CAD is still high (Collet *et al*., 2019; Kim & Weber, 2021). Hence, a better understanding of CAD and its risk factors is required.

Coronary artery disease is linked to arterial stiffness and has a predictive value for coronary thrombosis and heart failure (Ikonomidis *et al*., 2015). The structural alterations that occur due to stiffening of coronary arteries may enhance the already atherogenic local haemodynamic environment, supporting the development of atherosclerotic plaque (Chatzizisis & Giannoglou, 2007). When atherosclerotic plaque forms in the coronary artery, blood flow is obstructed, which causes a mismatch between myocardial oxygen demand and supply and increasing stiffness (Malakar *et al*., 2019). Research shows that arterial stiffness is a significant predictor of unfavorable cardiovascular events beyond traditional risk variables, including CAD-related morbidity and mortality (Mattace-Raso *et al*., 2006; Ikonomidis *et al*., 2015).

In a healthy, normal-functioning heart, the aorta allows for substantial distension during systole because the arterial wall contains a high percentage of elastin fibers. Due to the elastic recoil or spring-like capability of the heart, blood is forced forward through the arterial tree during diastole, ensuring a smooth unidirectional flow of blood (Quinn *et al*., 2014; Bell & Mitchell, 2015). Blood travels to the capillaries as the heart contracts, stretching the spring and storing a portion of the stroke volume (Adenwalla *et al*., 2017). The distensibility of the aortic spring affects the pulsatile haemodynamics of the heart (Hashimoto, 2017). Hence, as the aorta stiffens in CAD, central pulse pressure widens, resulting in increased left ventricular afterload in

systole (Hashimoto, 2017). Therefore, the heart must work harder during systole and will not recoil, thus reducing blood flow to capillaries and reducing filling of the ventricle during diastole (Bell & Mitchell, 2015; Adenwalla *et al*., 2017; Hashimoto, 2017). Atherosclerosis is more likely to occur when haemodynamic variables such as low wall shear rate, wall shear stress, and disrupted blood flow are present. Therefore, it is necessary to investigate the effect of cardiac afterload, aortic stiffness and other aortic pulsatile haemodynamics in individuals with CAD to enhance our understanding and gain deeper insights. Hence, in the subsequent section, I will discuss the current literature on PP in CAD.

1.3 Pulse Pressure in CAD

According to physiological principals, there are several of very distinct divisions within the field of haemodynamics, which deal with physical phenomena connected to blood pressure and flow (Secomb, 2016). The term "haemodynamics" is a fundamental concept in medicine, commonly used to describe measurements of cardiovascular function such as arterial pressure or cardiac output (Secomb, 2016). The relationship between the left ventricle and the peripheral arterial tree influences central or aortic haemodynamics (Li *et al*., 2017). Heart disease is still largely attributed to disagreements on the relative contributions of brachial and central arterial blood pressure (BP). Mean arterial pressure (MAP) and pulse pressure (PP) are the two components of blood pressure that can be separated (Motau *et al*., 2018). Small resistance vascular function and cardiac output characterise the steady component (Kim & Weber, 2021). As opposed to this, the pulsatile component is mostly dictated by major artery compliance, which is the opposite of stiffness, left ventricular (LV) ejection, and the intensity and speed of reflected waves that result from slow variations in the impedance to flow at arterial bifurcation sites (Phan *et al*., 2016). Thus, PP is amplified from the central to the peripheral pulse (Vlachopoulos *et al*., 2011). Moreover, peak central arterial PP (PPc) in the aorta is determined by the sum of both forward (Pf) and backward (Pb) travelling pressure waves, the latter which are derived from reflections off distal arterial sites; however, peripheral wave reflections do not influence peak PP in the brachial artery (Vlachopoulos *et al*., 2011).

Blood flow in the arteries exhibits a number of distinct properties from a haemodynamic view: (i) due to the oscillation between the ejection and filling phases during the cardiac cycle, it is extremely pulsatile, (ii) because artery walls are elastic and flexible, changes in pressure during the cardiac cycle cause changes in arterial diameter that vary over time, (iii) the cardiac pulse spreads along arteries as a wave due to the interaction of pulsatile flow and compliant channels

and (iv) arteries feature intricate structures, including branching, tapering, curvature, and regional changes in diameter. In pathological conditions, such as when aneurysms, stenoses, or atherosclerotic plaques form, these geometrical properties may change (Secomb, 2016).

The compliance of the arteries cause the transmission of the cardiac pressure pulse to move gradually along the vessels as a traveling wave rather than being immediately transmitted to all areas of the arterial system (Secomb, 2016; Kim & Weber, 2021). In essence, a negative pressure gradient is created at the leading edge of an artery as a pulse of increased pressure moves along it. This gradient causes the blood to move quicker, thus resulting in a spatial gradient of flow rate, with a brief part of the vessel experiencing a higher flow rate entering it than exiting it (Laurent *et al*., 2003; Secomb, 2016). Consequently, the pulse propagates because the vessel needs to expand. The technique allows a pulse wave to propagate in the opposite direction because it reflects the principal wave that the left ventricle produces during systole. The velocity at which these waves propagate depends on the ratio of the wall's elastic stiffness to the fluid's inertia (Secomb, 2016; Kim & Weber, 2021). The peripheral arteries stiffen and narrow as blood moves away from the aorta, which causes the upper portion of the waveform to narrow and become more pronounced. The upstroke of the waveform is influenced by rising systolic pressure while mean and diastolic arterial pressure remain constant (PP amplification) (McEniery *et al.*, 2014) (see Figure 1.1). Therefore, the dual function of arteries is to transport blood to the periphery and to reduce pressure pulsations brought on by irregular ventricular contraction (Mitchell, 2004). Left ventricular (LV) ejection produces a pressure waveform that goes down the arterial tree and modifies the pressure wave (Roman *et al.*, 2009). The clinical significance of central blood pressure stems from the fact that aortic diastolic pressure determines coronary artery perfusion. In contrast, systolic pressure indicates the interaction between left ventricular ejection and arterial load (Shenouda *et al*., 2021).

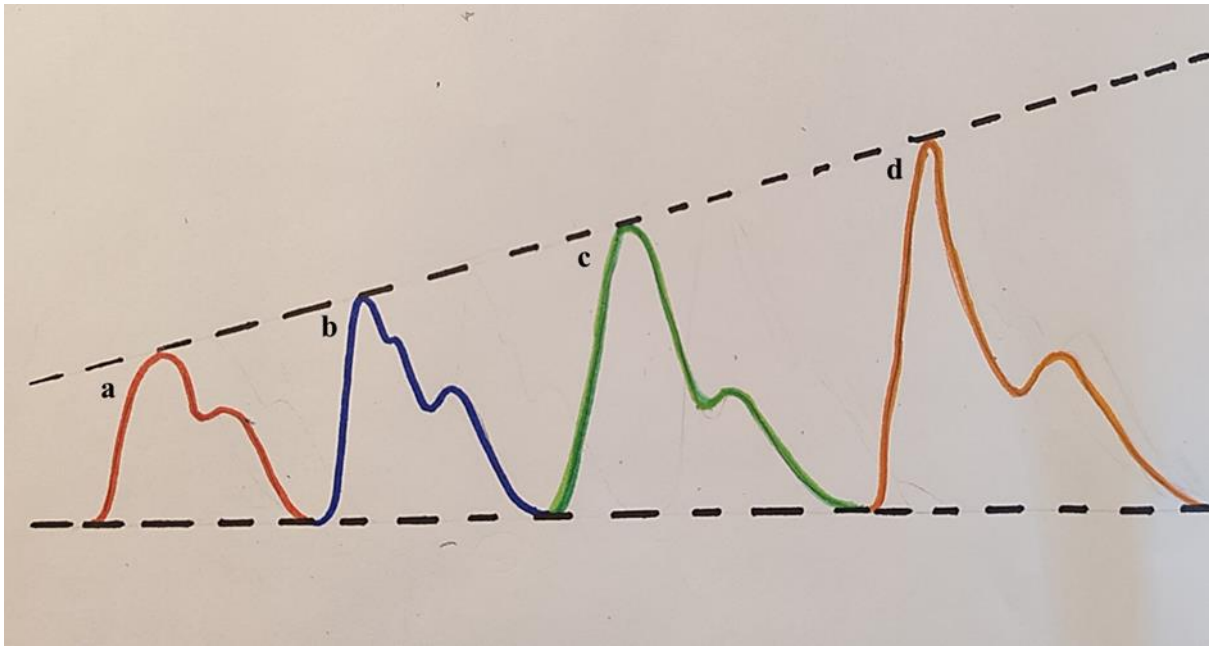

Figure 1.1 An illustration of the pressure waveform's amplification from the aorta to the radial artery (McEniery *et al.*, 2014), a; aorta (red), b; carotid (blue), c; brachial (green) and d; radial (orange).

Unfavorable central aortic pressure characteristics, such as elevated cardiac afterload and lowered diastolic endocardial perfusion pressure, are caused by the stiffening of the arteries as a result of the loss of the "Windkessel function" and decreased arterial wall elasticity (Blacher & Safar, 2005). The early return of the reflected wave due to arterial stiffness causes an increase in central aortic systolic and pulse pressure, but not in peripheral brachial systolic or pulse pressure (Hashimoto & O'Rourke, 2008). Research suggests a substantial correlation between cardiovascular death and morbidity and arterial stiffness's effects on central blood pressure, which are measured using a brachial cuff (Millasseau *et al*., 2003; Hashimoto & O'Rourke, 2008). The connection between the components of blood pressure and the size of the aortic root is a topic of significant controversy (Mitchell *et al.*, 2003; Vasan, 2008).

A study of 96 CAD patients who underwent treadmill exercise tests showed that patients with established CAD had many wave reflections approaching the ischemia threshold earlier, leading to clinical consequences (Kingwell *et al*., 2002). Although increased systolic blood pressure (SBP), rather than diastolic blood pressure (DBP), has been more strongly correlated with an increased risk of cardiovascular events, in CAD patients, high SBP and low DBP are secondary to increased arterial stiffness (Chirinos *et al*., 2005). Moreover, the association between coronary atherosclerosis and pulsatile haemodynamics/arterial stiffness may be explained by the fact that the two conditions share similar risk factors, such as age and other conventional cardiovascular risk factors (Kim & Weber, 2021). Therefore, it is essential to identify changes that occur in central PP in CAD.

According to Weber *et al*. (2012), the primary cause of the age-related rise in central PP throughout a person's life is the risk of CAD and cardiovascular (CV) risk scores. Aortic PP was a more powerful predictor of CAD presence than SBP or DBP in multivariate analyses. However, aortic pulsatility (ratio of PP to mean BP) was not more discriminant than PP itself in men with CAD (Danchin, 2004). The arterial pulse wave seen in arterial beds distal to the aorta, affected by stiffness, plaque rupture, or stenosis, differs from the central aortic pulse wave. The wave reflections that contribute to distal arterial PP are obtained from local vascular beds, whereas central arterial wave reflections that determine PPc are the total of waves derived from a range of arterial sites, typically near the aorta (Baksi *et al*., 2016). While peak PPc may not accurately reflect the pulsatile load on artery beds that have been damaged by plaque rupture or stenosis, Pf in the proximal aorta, transferred to distal arterial sites, causes the pressure wave in aortic branches affected by plaque rupture or stenosis (Vlachopoulos *et al*., 2011). Therefore, while peak PPc may not determine arterial events beyond brachial BP, Pf

could predict cardiovascular risk beyond brachial BP in CAD. Hence, further studies need to be done to assess PPc and its determinants in patients with CAD.

1.4 Determinants of Central Aortic Pulse Pressure

According to the theory of flow propagation, during ventricular systole, a forward pressure wave, also known as the incident wave, is produced (Safar *et al*., 1996). This wave travels through the viscoelastic aortic tube until it reaches zones of impedance mismatch or branch points, where it can be reflected as a backward pressure wave (Mitchell & Pfeffer, 1999; Vasan, 2008). When the dynamic vascular load is considered, the lower frequency components of reflected pressure waves that move more quickly tend to amplify the incident pressure waves at the aortic opening (Pepine *et al*., 1978). When forward and backward traveling pressure waves are added together, pulse pressure is produced (Li *et al.*, 2017). A graded increase in impedance to flow amplifies PP the central to the peripheral pulse (Vlachopoulos *et al*., 2011). Moreover, peak PPc in the aorta is determined by the sum of both Pf and Pb travelling pressure waves, the latter which are derived from reflections off distal arterial sites; however, peripheral wave reflections do not influence peak PP in the brachial artery (Vlachopoulos *et al*., 2011). Left ventricular ejection produces a pressure waveform that goes down the arterial tree and modifies the pressure wave (Roman *et al.*, 2009). The upper part of the wave narrows and becomes more noticeable as it moves away from the aorta, while the peripheral arteries stiffen and decrease in radius (Figure 1.2). PP amplification increases systolic pressure while maintaining a steady diastolic and mean arterial pressure (McEniery *et al.*, 2014).

In addition to central systolic pressure, the waveforms of the central aortic pressure provide important prognostic information. Aortic pressure waveforms can be divided into Pf- and Pb components using pressure-flow equations and wave separation techniques (Figure 1.3) (Kips *et al.*, 2009; Westerhof *et al.*, 2009; Safar *et al.*, 2011; Shenouda *et al.*, 2021). Various characteristics of the arterial affect these two components of central pulse pressure. Specifically, the elastic properties and impedance of the arterial system primarily affect the Pb, while the mechanical properties of the core elastic arteries dictate the Pf (Nichols & Singh, 2002; Armstrong *et al*., 2021). According to Nichols & Singh (2002), the peak Pf pressure corresponds to the first systolic shoulder of the aortic pressure wave, whereas the peak Pb pressure represents the peak aortic pressure. While the elastic and impedance attributes of the arterial shape the Pb, the mechanical properties of the central elastic arteries govern the Pf (Nichols & Singh, 2002). Importantly, resistance accounts for only a portion of stress on the

heart, as the heart pumps intermittently rather than continuously. Input impedance further clarifies this load by illustrating the relationship between the oscillatory and constant components of pressure and flow waves in the aorta (O'Rourke, 2002). Factors such as the inertia of blood flow and the elasticity, viscosity, and morphology of arteries also play a significant role in determining impedance (O'Rourke, 2002). Increased impedance due to heightened arterial stiffness can lead to elevated pressure levels.

Aortic pressure is a more reliable predictor of cardiovascular events than brachial blood pressure because it measures the LV's systolic pressure during diastole, which controls coronary perfusion (Agabiti-Rosei *et al.*, 2007). However, when the aorta and major elastic-type arteries stiffen under pathological conditions—which are mainly explained by the effects of aging and vascular system illnesses like hypertension—aortic pressures increase because blood is pushed into a stiffer conduit during aortic ejection. Increased aortic and arterial stiffness increases forward and reflected wave transmission, which causes the reflected wave to enter the aorta earlier and increases pressure in late systole. As a result, the aortic pressure wave's enhancement demonstrates wave reflection (Cho *et al.*, 2013). Reduced aortic distensibility causes the raised pressure to be followed by a greater systolic pressure increase and a smaller diastolic pressure increase (O'Rourke, 2002).

Wave separation analysis is a technique that helps combine two types of waves that occur in the arterial tree to create the pressure waveform that is recorded at any location. Left ventricular ejection produces the Pf, while various sites of resistance, including bifurcations and heart returns, reflect the Pb (Avolio *et al*., 2009; Kips *et al*., 2009; Nelson *et al*., 2010; Li *et al*., 2017; Shenouda *et al*., 2021). The amplitude of Pf is influenced by several factors, such as cardiac contractility, left ventricular afterload, and ventricular filling (Frank-Starling effect). These factors also play a role in determining aortic flow (Q), the amount of blood pumped by the heart with each beat (stroke volume); therefore, in turn, it affects the SBP and PP (Vlachopoulos *et al*., 2011). The aorta acts as a cushion during ventricular ejection and produces minimum flow resistance in a pulsatile system when there are no reflected waves, thanks to its elasticity and width. This phenomenon is known as characteristic impedance (Zc). The aorta is highly compliant when young but becomes stiffer with age (Mitchell *et al*., 2010b; Wang *et al*., 2010; Vlachopoulos *et al*., 2011).

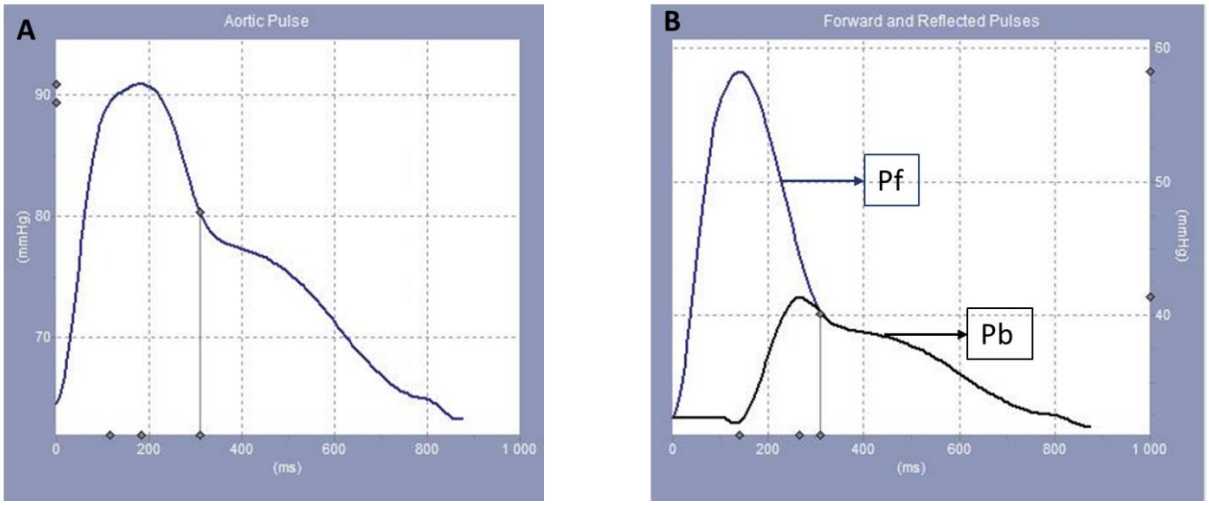

Figure 1.2 Aortic pressure wave as determined by the combined effect of the aortic forward (Pf) and aortic backward (Pb) pressure waves. Left panel (A) indicate the aortic pressure wave and the right panel (B) indicate the Pf and Pb components of the aortic pressure wave. The x-axis represents time (ms) and the y-axis represents pressure (mmHg).

Therefore, the relationship between aortic characteristic impedance and stiffness with age has implications for arterial stiffness and its clinical surrogates.

The concept of Zc is crucial to the theory of haemodynamics. It is a widely used measure of pulse wave velocity and proximal arterial stiffness (Lee & Oh, 2010; Chirinos, 2012; Chirinos *et al.*, 2019). Estimates of Zc can be calculated using dynamic pressure and flow data recorded simultaneously utilising techniques based on frequency or time domain analysis (Qureshi *et al.*, 2018). Most input impedance analysis applications approximate the Zc to evaluate the behaviour of vascular stiffness (Hametner *et al.*, 2015; Qureshi *et al.*, 2018). The aortic flow (Q) and Zc product (PQxZc) is assumed to be the main force behind the forward pressure wave. However, the maximum pressure produced by Q x Zc typically occurs well before peak Pf at a location near the first systolic shoulder of the pressure wave (just before the inflection point). As a result, it is evident that Pf has an excess of pressure that neither Q nor Zc can account for. In this sense, wave re-reflection is responsible for the extra pressure in the forward wave (Phan *et al.*, 2016). Wave re-reflection happens when backward-moving waves return to the proximal aorta and reflect forward, increasing the pressure of the forward waves (Vlachopoulos *et al.*, 2011; Phan *et al.*, 2016). The magnitude of the reflected wave is believed to be related to the magnitude of the original wave through Newton's first and third laws of motion (Vlachopoulos *et al.*, 2011; Phan *et al.*, 2016). Significantly, when wave re-reflection is taken into consideration, the pressure generated by the combination of Q and Zc is significantly outweighed by the pressure generated by the sum of the pressure generated by the backward travelling pressure wave and re-reflected waves at the time point when maximal PP occurs. As a result, the pressure produced by the product of Q and Zc is overshadowed by the contribution of reflected waves to the peak PP. In other words, aortic augmentation pressure (Pa), originates from a rise in aortic PP brought on by an early return of aortic Pb in the cardiac cycle, underestimates the overall contribution of wave reflection to aortic PP while Pf overestimates the effect of Q and Zc on aortic PP. Increases in Zc and pulse wave velocity (PWV) that accompany aortic stiffening raise pulse pressure and aid in the development of systolic hypertension (Bell & Mitchell, 2015). Significantly, structural modifications to the proximal aorta that affect its stiffness and diameter are what cause increases in Zc (Mmopi *et al.*, 2020). Furthermore, changes in Zc brought on by age, specifically, cause an increase in systemic vascular resistance (SVR) (Segers *et al.*, 2007). It is important to note that SVR are determined by the length of the blood vessels, the diameter of the vessels, and the viscosity of the blood within them (Trammel & Sapra, 2020). Hypertension is one of the most common conditions

that can disrupt normal SVR (Trammel & Sapra, 2020). Damage to blood vessel walls in CAD impairs the blood vessels' capacity to expand or contract in response to hemodynamic changes. This injury frequently results in an excessive amount of resistance (SVR) within the vessel, which either worsens the damage or stops blood flow to that vascular area (Gjøvaag *et al.*, 2016; Trammel and Sapra, 2020). Despite evidence of changes in SVR in CAD, there is limited data on arterial stiffness assessed through Zc in CAD; hence, further investigation is needed.

1.5 Arterial Stiffness

The first recognisable stage of atherosclerosis development has been identified as the onset of physiological abnormalities in endothelial function. Furthermore, the discovery of the genetic factors and signalling pathways that contribute to the formation of atherosclerosis have improved and provided insight on the early stages of vascular disease development (Liao & Farmer, 2014). Arterial stiffening is caused by the gradual loss of the elastic matrix and the ongoing deposition of various proteins, including collagen (Falk, 2006). Numerous techniques can be used to measure arterial stiffness, which has been used as a prognostic indicator outside of the conventional risk factor classification framework and associated with a greater risk of developing atherosclerosis (Liao & Farmer, 2014).

A notable degree of elastic rebound in the aorta serves as a physiological mechanism to sustain forward flow during diastole. The vascular system becomes less flexible as we age, leading to gradual stiffness. The ageing process alters the arterial media, which is a combination of vascular smooth muscle cells and variable degrees of elastic tissue (Liao & Farmer, 2014). Furthermore, as people age, the intima made up of the elastic lamina and endothelial cells—progressively changes. Several anatomical and functional changes that gradually take place over time affect the variable degree of aortic stiffness with ageing. Shearing forces and various local atherogenic variables cause the arteries to change in structure and function, resulting in increased luminal diameter and aortic stiffness(O'Rourke & Nichols, 2005) .

Arterial stiffness and its clinical surrogates, measured by PWV and pulse wave analysis (PWA), have emerged as well-known concepts in cardiovascular risk classification (Mahmud & Feely, 2003; Hametner *et al.*, 2013). The most widely used non-invasive markers and key hemodynamic measures of aortic stiffness are local or Zc and PWV. However, Zc is more sensitive to changes in lumen diameter than PWV is (Vasan *et al*., 1995; Chirinos *et al.*, 2019; Mynard *et al.*, 2020). Studies show that PWV is frequently used to aid in the diagnosis of heart failure, CAD, and other CVDs (Palatini *et al.*, 2011; Cho *et al.*, 2013; Said *et al.*, 2018; Stoka

et al., 2018; Ikonomidis *et al.*, 2019). Using PWV, numerous clinical investigations have demonstrated a correlation between CAD and measurements of arterial stiffness and wave reflections (Nakayama *et al.*, 2000; Philippe *et al.*, 2002; Guray *et al.*, 2005; Kim & Weber, 2021). Unfortunately, there is little literature on Zc in CAD, and when it does exist, it mostly discusses other diseases, such as systolic hypertension, without addressing CAD (Hametner *et al.*, 2013; Ikonomidis *et al.*, 2019). Hence, for my study, I will only focus on using the PWA to calculate Zc.

Pulse wave analysis is a simple, non-invasive method extensively employed in epidemiological and interventional research (Wilkinson *et al.*, 2002; Vlachopoulos *et al.*, 2010; Stoner *et al.*, 2012) to obtain measures of central arterial pressures and wave reflection (Müller *et al.*, 2018; DuPont *et al.*, 2019). Since it offers helpful details on PP and Zc about the mechanical properties of the arterial tree (Stoner *et al.*, 2012; Weber *et al.*, 2012). An effective method for assessing endothelial function is PWA, which also provides valuable insights into the mechanical properties of the arterial tree and the heart-blood vessel interaction (Stoner *et al*., 2012). Important details concerning central systolic pressure, pulse pressure, and central augmentation can be obtained by analysing the pulse waveform (Shirwany & Zou, 2010). Pulse wave analysis is used to record the radial pulse wave and central arterial pressure and is considered the "gold standard" method of applanation tonometry (Doupis *et al.*, 2016). Traditional methods involve placing a tonometry probe on the skin over the radial artery and applying pressure to applanate (flatten) the artery, which produces a signal that roughly represents arterial pressure (Butlin & Qasem, 2017). A generalised transfer function creates the matching central arterial waveform (Stoner *et al*., 2012). The SphygmoCor system, a widely available non-invasive device is commonly used in clinical practice and derives pressure PWA from the shape of the arterial pressure pulse. Pulse wave analysis recordings permit the construction of the wave contour of the ascending aorta. Analysis of this central curve provide shape characteristics and cardiac function i.e., vascular stiffness. A study by Weber *et al.* (2004), identified a significant correlation between early wave reflections and signs of increased arterial stiffness derived from non-invasive PWA and the existence and, to some extent, severity of CAD (Weber *et al.*, 2012). Through wave separation analysis, pressure can be divided into two directions: forward from the left ventricle toward the arterial tree's periphery and backwards from the arterial tree toward the ventricle (Fok *et al.*, 2014). The physiological flow waveform, proposed by Kips *et al.* (2009), results in more accurate flow waveforms, allowing for more precise derivation of flow wave reflection indices (Shenouda

et al., 2021). However, the application of various flow waveforms to accurately calculate Zc, using PWA as a surrogate for arterial stiffness, has never been assessed in individuals with CAD; hence the findings from this study will contribute to further understanding.

1.6 Study Rationale

An increase in the stiffness of major arteries is one of the first indications of atherosclerosis, which is known as arterial stiffness. The amplification of the arterial pulse from the aorta to the brachial pulse is dampened by the increase in stiffness, which increases central arterial impedance more than peripheral arterial impedance (Vlachopoulos *et al.*, 2011). Consequently, brachial BP is thought to be limited as a surrogate of aortic stiffness-induced increases in aortic impedance to flow and hence BP. Nonetheless, despite a clear ability of indexes of aortic stiffness to predict cardiovascular risk beyond brachial BP (Mitchell *et al.*, 2010a; Vlachopoulos *et al.*, 2011; Ben-Shlomo *et al.*, 2014), peak PPc has demonstrated a limited (Vlachopoulos *et al*., 2010), or no ability to predict risk independent of brachial BP (Mitchell *et al.*, 2010a). However, while peak PPc may not predict risk beyond brachial BP, the role of Pf as a risk predictor beyond both brachial PP and peak PPc, is uncertain. These measurements could provide comprehensive insights into the external afterload that the left ventricle faces and unveil detail about the physical condition of the arteries (Nichols *et al.*, 1977). A notable study found that higher pulse wave velocity was associated with 48% increased relative risk of cardiovascular events (Aatola *et al*.,2010). In South Africa, hypertension is a prevalent cause of CAD, necessitating investigation of whether Pf can predict the risk of arterial events beyond brachial BP, specifically in the context of CAD. Furthermore, an observational study by Kaess *et al*. (2012) showed that in people who had previously been normotensive, a significant increase in both forward wave amplitude and arterial stiffness correlated with a heightened risk of developing hypertension among previously normotensive individuals; however, no data currently exists regarding the risk of developing CAD. Given these findings, arterial stiffness may serve as key assessment toll for patients at high risk for CAD. Furthermore, the use of PWA can help identify structural and functional changes in the arterial wall. Currently, these measures are employed in both cardiovascular risk prediction clinics and research settings (Mackenzie *et al*., 2002), offering valuable insights into the potential relationships between arterial stiffness and CAD. However, no studies have assessed whether a relationship exists between angiographically proven CAD and aortic characteristic impedance and Pf beyond both brachial PP and PPc. Therefore, in this study, we aimed to retrospectively assess central

haemodynamic changes in patients with angiographically proven CAD compared to age- and sex-matched community participants from South Africa.

1.7 Aims

The aims of this MSc are:

1. To retrospectively determine characteristic impedance (Zc) using non-invasive measures (SphygmoCor and echocardiography) in patients with angiographically documented CAD.
2. To determine the relationship between Zc and the extent of CAD in patients with angiographically documented CAD.
3. To determine whether arterial stiffness associated increases in forward wave pressures are enhanced beyond brachial or peak central arterial blood pressure in CAD.

CHAPTER 2: METHODS

2.1. Ethical Approval

This retrospective study was conducted according to the guidelines outlined in the Helsinki Declaration. Ethics approval for the protocol was obtained from the University of the Witwatersrand Human Research Ethics Committee (approval number: M210136).

2.2. Study Design and Participants

Data were obtained from 189 patients from different ethnic groups with CAD who underwent cardiac catheterisation and angiography at the Life Flora Hospital over the past 3-4 years. The 189 participants were in the full adult age range (>18-99) and from different ethnic groups. Briefly, angiographic severity of coronary lesions was determined by quantitative coronary angiography. The number of severely blocked arteries, extensive involvement of the left main coronary artery, broad impairment of left ventricular function, or ventricular aneurysm, are the most crucial criteria in the prognosis of CAD (Proudfit *et al.*, 1978). The number of epicardial vessels determined the extent of coronary lesions involved, e.g., 1- single vessel disease, 2- multivessel disease or 3- more vessels involved. Consecutive patients undergoing coronary angiography with angiographically proven CAD (>60% stenosis of at least one coronary artery) (n=189) were recruited for the study. For the purpose of this study, data was extracted from the clinical records archived at the West Rand Cardiovascular Centre, with permission of the attending physician. Aortic function was assessed in all patients with CAD using wave separation analysis assuming a physiological flow wave (Kips *et al.*, 2009). In 71 patients with high quality velocity assessments in the LV outflow tract (echocardiography), aortic function was also assessed using paired pressure and flow wave analysis. Data obtained in patients with angiographically proven CAD were compared with data acquired from 210 age- and sex-matched randomly recruited community participants living in the Southwest Township (SOWETO) of Johannesburg, South Africa, using the population census figures of 2001. Patients or participants who presented with arterial fibrillation were excluded from the study due to irregular pressure waveforms. Other exclusion criteria for this study include incomplete data, poor-quality assessments and patients with previous diagnoses of cardiac failure or kidney disease.

2.3. Clinical, Demographic and Anthropometric Measurements

A standardised health questionnaire was used to collect demographic and clinical information. Anthropometric measurements were performed by a nurse to determine each participant's weight and height. Standard approaches were used to calculate body mass index (BMI) from the height and weight obtained on admission. Diabetes mellitus was defined based on the usage of insulin or other oral hypoglycaemic medication. A nurse used an accredited oscillometric blood pressure monitor (HBP-1300, Tateishi Electric Manufacturing Company, Kyoto, Japan) to take high-quality office brachial blood pressure (BP) readings while the patient was in the supine position and after five minutes of rest. Recordings made using the oscillometric device were utilized to calibrate recordings made using the SphygmoCor device. The mean of 5 measurements obtained at least 30 seconds apart was taken as office BP. Standard cuffs with an inflatable bladder of 22 cm long by 12 cm wide were used for oscillometric blood pressure measurements, with the exception of cases where the arm circumference was greater than 31 cm, in which case bigger cuffs measuring 31 x 15 cm were utilized. Mean office BP ≥140/90 mmHg or taking antihypertensive medication were both considered to be indicators of hypertension.

2.4. Arterial Haemodynamic Assessment

Central arterial pressure wave forms were collected at the time of the cardiac catheterisation procedure in all of the patients. Peripheral pressure waveforms were recorded noninvasively from the radial artery at the wrist (non-dominant arm), using applanation tonometry during an 8 second period with a high-fidelity micromanometer (Miller Instrument, Inc., Houston, Texas). The micromanometer was interfaced with a computer using SphygmoCor, version 9 (AtCor Medical Pty. Ltd., West Ryde, New South Wales, Australia) (Figure 2.1). The radial artery is flattened by applying pressure with a probe to the skin, which produces a signal that approximates arterial pressure (Stoner *et al*., 2012). After 20 sequential radial pressure waveforms had been acquired, a validated generalized transfer function, incorporated in SphygmoCor software, was used to generate the corresponding central aortic pressure waveform (Figure 2.2) (Chen *et al.*, 1997; Pauca *et al.*, 2001). Transfer functions are mathematical entities that are used to characterize a system in terms of the relationship between input and output signals (Avolio *et al.*, 2009).

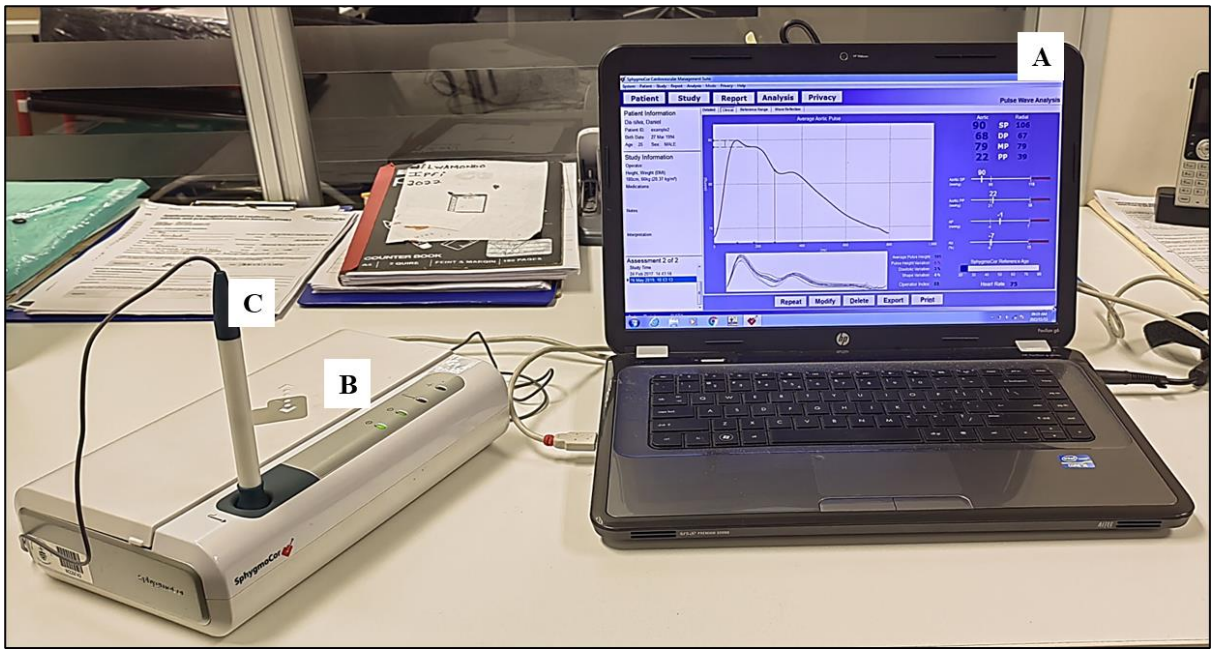

Figure 2.1 SphygmoCor system interfaced with a computer employing SphygmoCor, version 9.0 software (AtCor Medical Pty. Ltd., West Ryde, New South Wales, Australia). A) The computer with which the SphygmoCor device is interfaced with, B) the SphygmoCor device and C) the applanation tonometer.

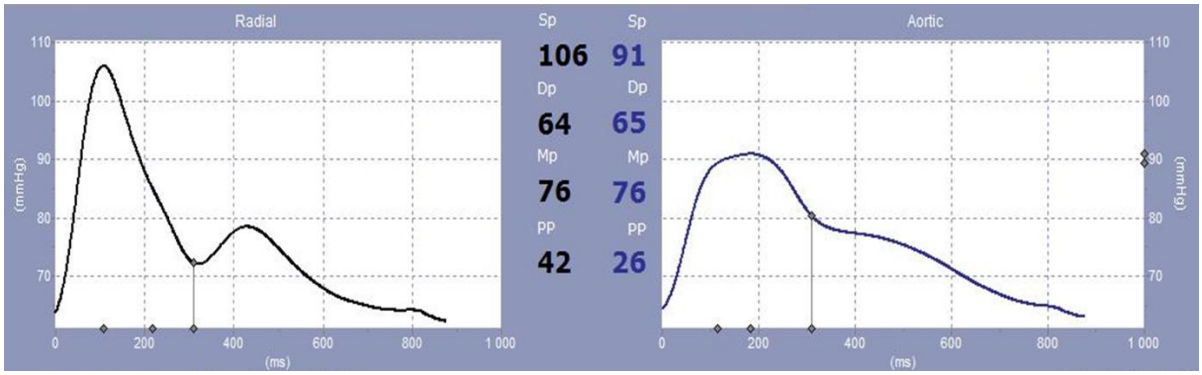

Figure 2.2 Peripheral (radial) pressure waveform (left panel) converted into a central (aortic) pressure waveform (right panel) using the generalised transfer function incorporated in SphygmoCor software. Sp, systolic blood pressure; Dp, diastolic blood pressure; Mp, mean arterial pressure; PP, pulse pressure. The x-axis represents time (ms) and the y-axis represents pressure (mmHg).

2.5. Aortic Velocity Flow Wave

While central aortic pressures were recorded, as described in section 2.4 above, echocardiographic measurements were collected by an experienced technician using a Philips CX- 50 cardiac ultrasound machine equipped with a standard cardiac phased array transducer (1-4 MHz) (Figure 2.3). With the patient in the left decubitus position, aortic velocity waveforms were obtained in the apical five-chamber view (Figure 2.4). Aortic diameter measurements were obtained just proximal to the aortic leaflets in the long axis parasternal view (Mitchell *et al.*, 2010b). The largest diameter recorded in early systole was employed to construct the flow waveform (Figure 2.5). To generate an aortic flow waveform, 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 ultrasound graphics software (SanteDicom Viewer 6.0 Freeware) and using aortic diameter measurements, to construct a flow waveform. To determine aortic flow (Q) at each time point along the velocity wave, Q was calculated as aortic velocity at each time point 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 peak of aortic flow, ejection duration (ED) and stroke volume (SV) using standard approaches. A recording was discarded if the pulse wave signal's amplitude was less than 80 mV (derived from an algorithm including average pulse height, pulse height variation, diastolic variation, and the maximum rate of rise of the peripheral waveform), or the systolic or diastolic variability of successive waveforms exceeded 5%. Central aortic pulse pressure (PPc) was determined as the difference between aortic systolic BP (SBP) and aortic diastolic BP (DBP).

2.6. Aortic Pressure Wave Separation

Wave separation analysis was performed using the approach of Westerhof *et al.* (2009) where the start and the end of the aortic flow waveform is aligned with the end of diastole (start of systole) and the dicrotic notch (incisura) on the aortic pressure waveform respectively. Assuming that there is no flow during diastole, the beginning and end of the flow wave are lined up with the beginning (foot of the upstroke of the aortic pressure wave) and end of systole (dicrotic notch) on the aortic pressure waveform form. Two approaches were used to separate the aortic pressure wave into its component waves. Firstly, I used a physiological flow wave form (Kips *et al.*, 2009). Secondly, I paired each patient's actual flow waveform obtained using echocardiography as described in section 2.5 above.

In order to calculate aortic characteristic impedance, the aortic flow waveform was paired with the central arterial pressure waveform by aligning the foot (t0) of the signal averaged aortic waveforms with the start of the aortic flow waveform (Motau *et al.*, 2020). The point at which flow achieves 95% of its peak (tQ95) was identified. The corresponding pressure change between t0 and tQ95 was determined. Characteristic impedance (Zc) was calculated in the time domain as change in pressure/change in flow from the foot (t0) of the pulse wave up until 95% of peak aortic flow (Q) (tQ95) (Figure 2.6) (Segers *et al.*, 2007; Mitchell *et al.*, 2010b; Motau *et al.*, 2018). The pressure wave generated by Q was subsequently determined by calculating the product of Q and Zc (P_{QxZc}) over multiple time points from the foot of the flow wave to the dicrotic notch (Chirinos *et al.*, 2012). To determine the impact of increases in peak Q to PPc, peak P_{QxZc} was identified. The use of a pressure waveform generated from the product of Q and Zc rather than relying on Pf to identify the impact of changes in Q, excludes the possibility of errors inherent in the use of Pf which includes pressures generated by wave re-reflection. Using Zc values and flow and pressure waves, wave separation analysis was performed based on the following formulae to identify forward and backward wave pressure: Forward wave pressure = [(aortic PP + QxZc)/2] and backward wave pressure = [(aortic PP – QxZc)/2] (Murgo *et al.*, 1980; Westerhof *et al.*, 2006). An example of the forward and backward waveforms is given in Figure 2.7. Central aortic PP (PPc) was determined as the difference between aortic systolic and diastolic BP derived from SphygmoCor software. Peak forward (Pf) and backward (Pb) wave pressures were determined from wave separation analysis (Motau *et al.*, 2020). In addition, re-reflected wave pressures and the combined impact of wave reflection on aortic PP (reflected + re-reflected wave pressures) (Figure 2.7) were determined. To do this I calculated the contribution of wave reflection ($P_{reflect}$) and re-reflection ($P_{re\text{-}reflection}$) to peak PPc as the difference between peak aortic PPc and Pf ($P_{reflect}$) and the difference between Pf and P_{QxZc} at peak PPc ($P_{re\text{-}reflect}$) (Phan *et al.*, 2016).

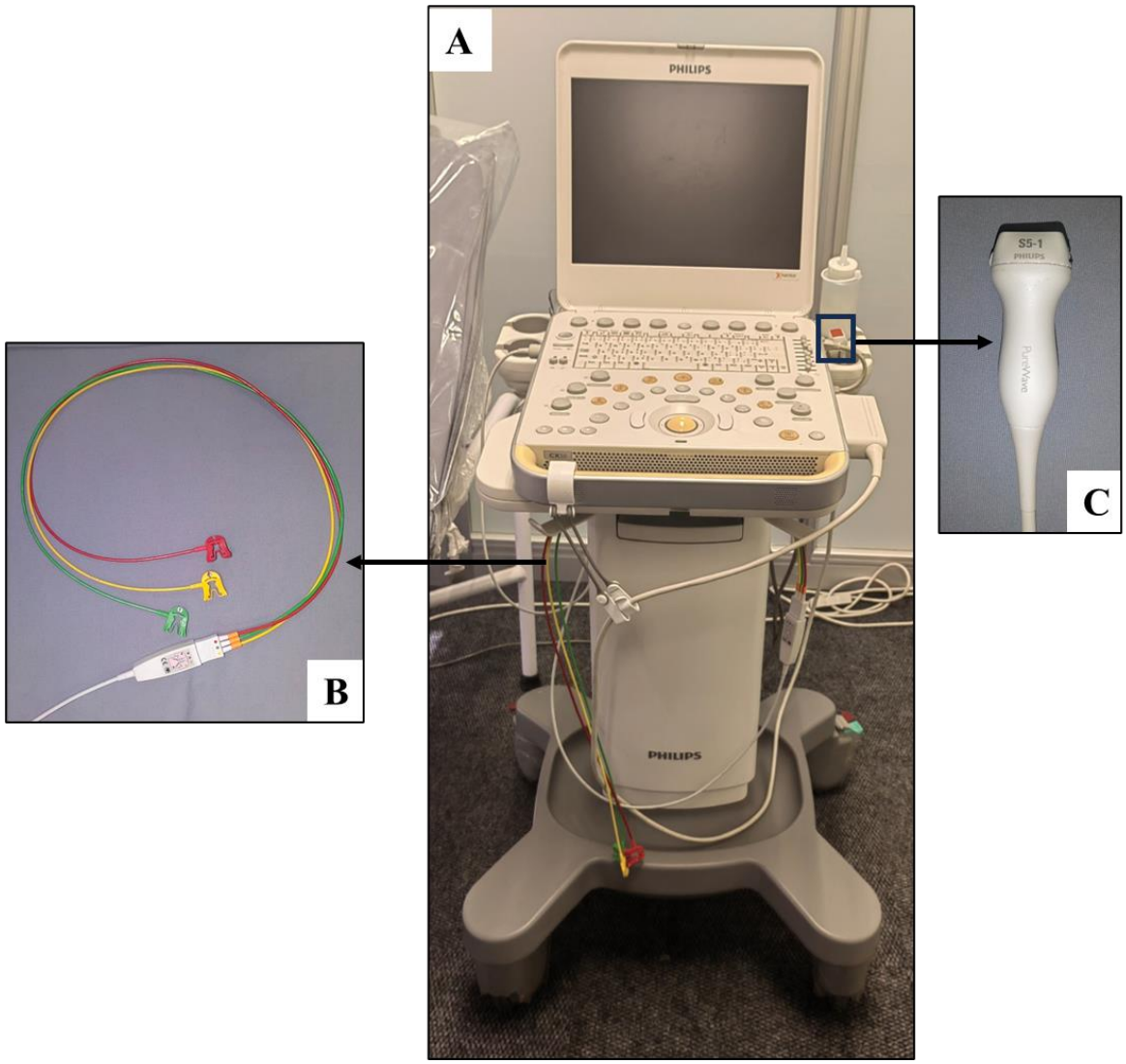

Figure 2.3 Cardiac ultrasound device, Philips CX-50 Compact Xtreme System (2009) used to obtain aortic velocity waveforms. The ultrasound device was equipped with a standard cardiac transducer (1-4MHz) and electrocardiogram. A) Philips ultrasound machine, B) the ECG leads and C) the standard cardiac transducer.

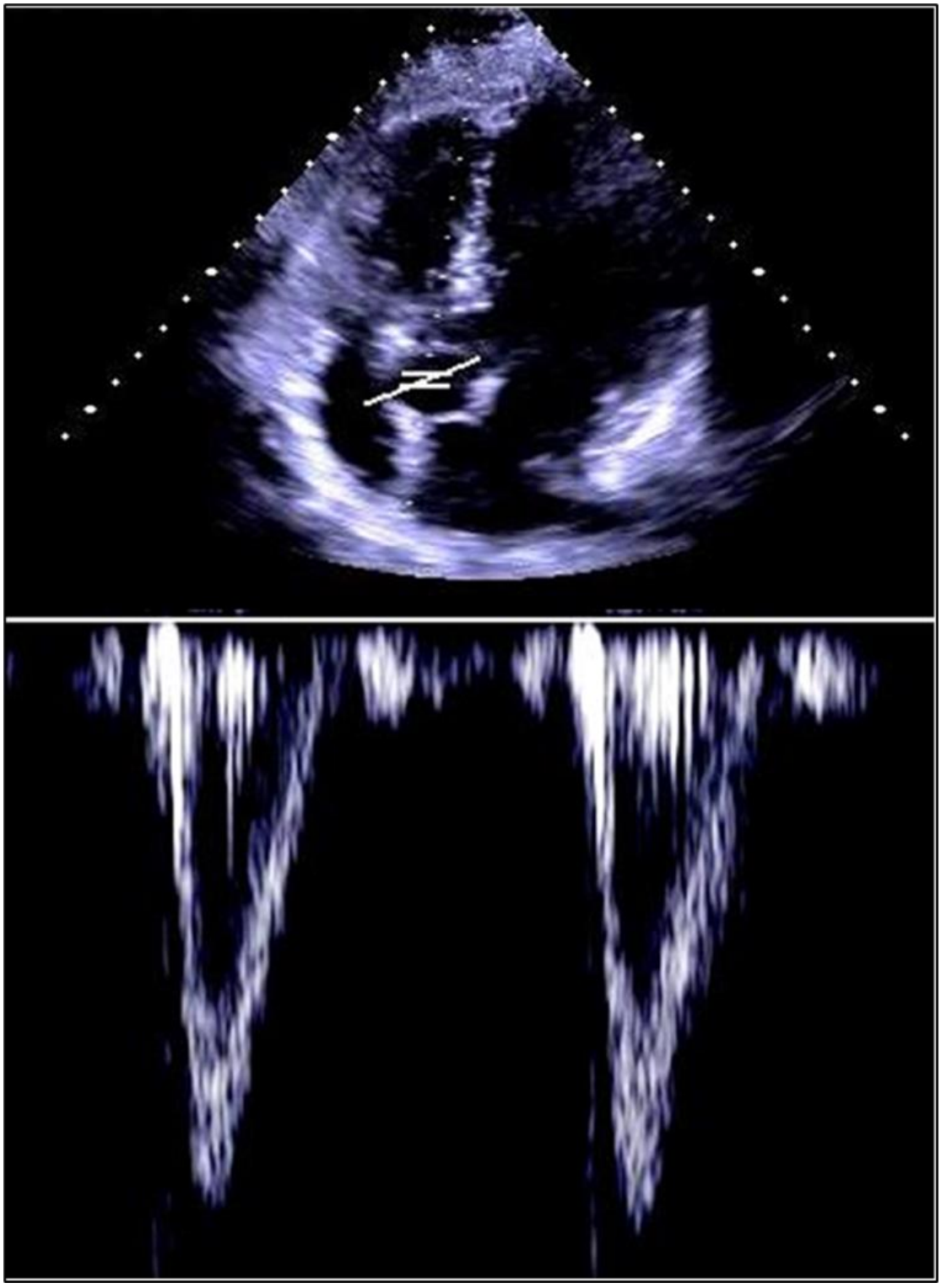

Figure 2.4 Aortic velocity waveforms (lower panel) obtained in the apical five-chamber view (upper panel) of the heart.

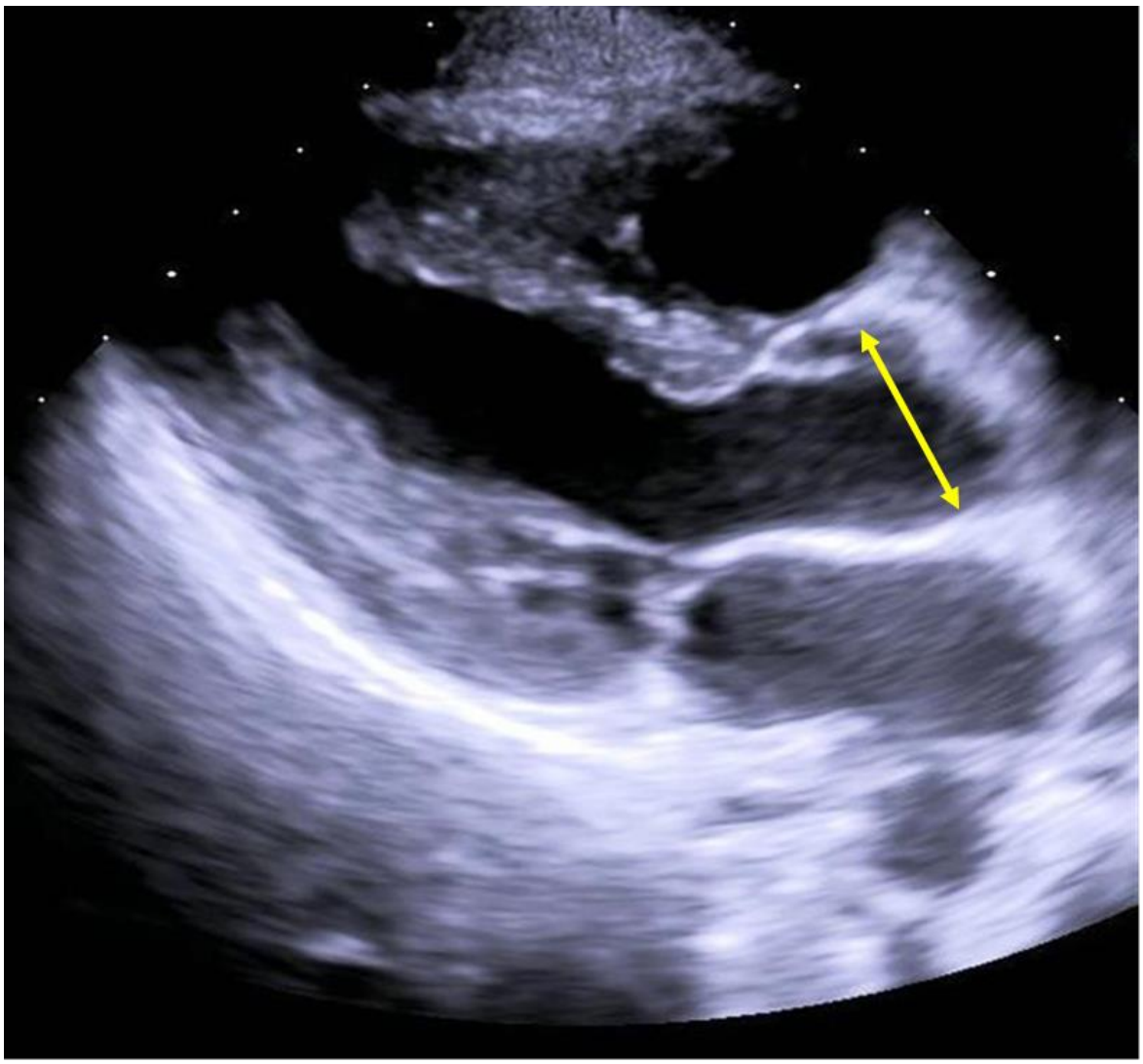

Figure 2.5 Aortic diameter measurements obtained just proximal to the aortic root at the tip of the aortic valves (yellow arrow) when in the open position in the outflow tract in the parasternal long axis view (Mitchell *et al.*, 2010b).

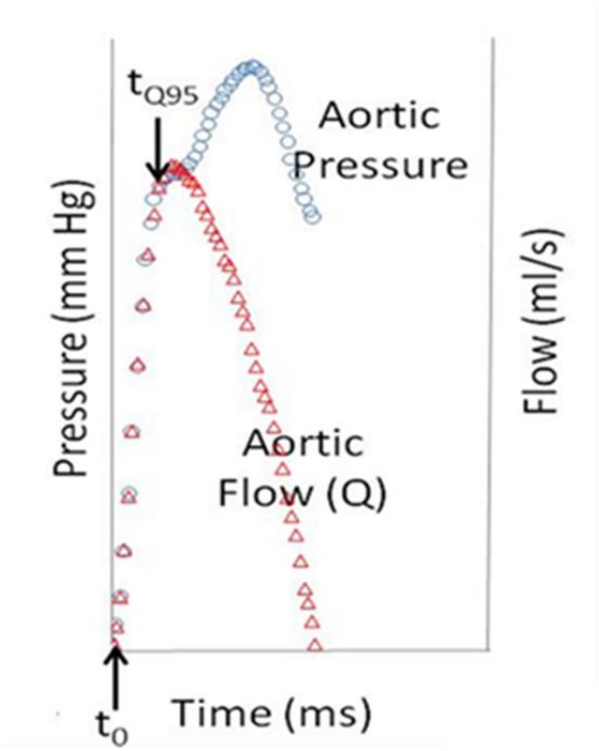

Figure 2.6 Illustration of the paring of the aortic pressure waveform and the aortic flow waveform (Q) which is the product of aortic velocity and area (Motau *et al*., 2018). t0, foot of the signal averaged aortic waveform and the start of the aortic flow waveform, t95, the point at which flow achieves 95% of its peak.

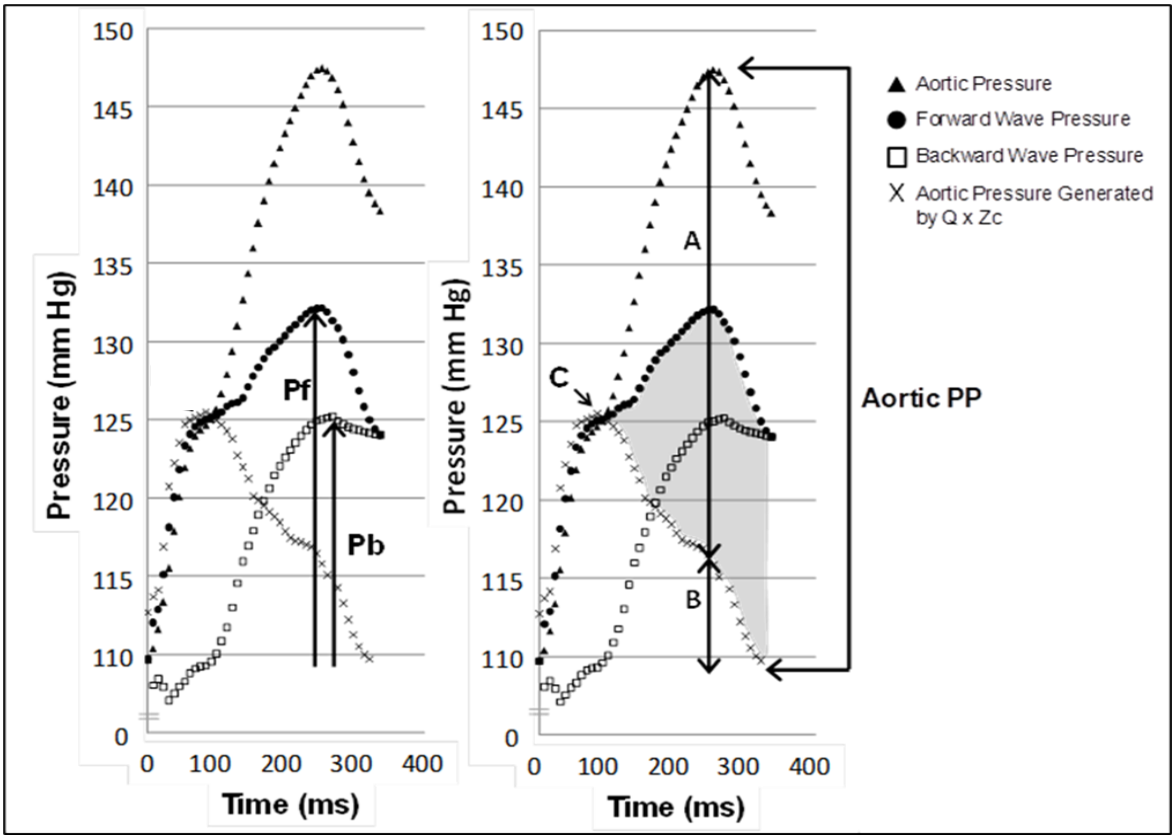

Figure 2.7 Wave separation analysis was performed using the approach of Westerhof *et al.* (2009). The wave components of aortic pulse pressure (PP) superimposed on the aortic pressure wave. Pb, backward wave pressure; Pf, forward wave pressure. A) reflected + re-reflected wave pressures; B) pressures generated by the product of aortic flow (Q) and characteristic impedance (Zc) at peak PP; C) maximum pressure generated by the product of Q and Zc (Max P_{QxZc}). Shaded area, re-reflected wave.

2.7. Data Analysis

Database management and statistical analysis was performed using SAS software, version 9,4 (SAS Institute Inc., Cary, NC). Continuous variables were expressed as means ± SD. Dichotomous variables are expressed as proportions or percentages. Comparisons of unadjusted data between the patients with CAD and the community participants (controls) were made using an unpaired t-test. Multiple logistic regression analysis was performed to determine the independent relations between haemodynamic variables and CAD. Adjustments were for age, sex, BMI, HR, treatment for hypertension, MAP, diabetes mellitus and smoking. As brachial pulsatile pressures (PPb and SBPb) differed between the two groups, comparisons of central arterial haemodynamic variables were further adjusted for either PPb or SBPb. Comparisons of Zc between the two groups were further adjusted for aortic root diameter which differed between the two groups and impacts on Zc. Multivariate linear regression analysis was used to evaluate the independent relationships between brachial PP and various components of proximal aortic function, including Zc and the presence of CAD. Factors included in the models were age, sex, BMI, MAP, HR, smoking, hypertension and diabetes mellitus. A p value <0.05 was considered significant.

CHAPTER 3: RESULTS

3.1 Participant Characteristics

The characteristics of the study patients with CAD (whole sample, n=189, and CAD patients with high quality aortic velocity assessments in the LV outflow tract, n=71) compared to age- and sex-matched community participants (controls) are shown in Table 3.1. The participants with CAD were predominantly middle to older age (mean age over 60 years) and 2/3 of the participants were males. The patients with CAD had marginally higher BMI than the age- and sex-matched community participants. Furthermore, more of the CAD patients were hypertensive. As the majority of CAD patients with hypertension were being treated (96%) as compared to only 55% of the community participants with hypertension, the mean blood pressure values (particularly DBP and MAP) were lower in the patients with CAD. More of the CAD patients had diabetes mellitus compared to the control group. No differences in heart rate were noted between the groups. Importantly, no differences in demographic or clinical features were noted in the CAD patients with versus without high quality aortic velocity assessments in the LV outflow tract.

3.2 Comparison of Haemodynamic Variables Between Participants with CAD and Controls Before the Adjustments for Confounders

Table 3.2 shows the comparison of the haemodynamic variables between the groups before adjustments for confounders. Pulse pressure (PP), both brachial (PPb) and central (PPc) were greater in patients with CAD. Similar to brachial SBP (Table 3.1), central SBP was lower in patients with CAD. Hence, the greater PPb and PPc are likely to be due to the lower DBP in patients with CAD (Table 3.1), rather than increases in SBP. The increases in pulsatile pressures (PPb and PPc) in patients with CAD were accompanied by greater Pf (irrespective of how determined), peak P_{QxZc} and P_{QxZc} at PPc in the CAD patients when compared to the control group. Reflected wave pressure (Pb, irrespective of how determined), did not differ between the groups and re-reflected pressure was lower in patients with CAD compared to controls. The lower re-reflected wave pressure was probably due to the lower DBP in patients with CAD (Table 3.1). Although Q did not differ between the groups. Zc was markedly increased, and aortic diameter reduced.

Table 3.1 General participant characteristics for patients with angiographically proven CAD compared to age- and sex-matched community samples (Controls)

Variable	**Controls (n=210)**	**CAD (n=189)**	**CAD (n=71) †**
Age (years)	62.5±11.4	64.2±11.6	63.5±11.5
Sex (% male)	61.4	69.8	73.2
Body mass index (kg/m²)	28.4±6.7	29.9±6.4*	29.5±6.7
% Hypertensive	69.5	88.9**	90.1*
% Treated hypertension	38.6	85.2**	88.7**
% Diabetes mellitus	21.0	36.5*	38.0*
% Regular smokers	20.5	28.0	25.4
Brachial SBP (mm Hg)	137±21	132±23*	134±21
Brachial DBP (mm Hg)	86±13	73±14**	74±13**
Brachial MAP (mm Hg)	105±15	93±16**	94±16**
Heart rate (beats/min)	68±13	70±14	69±15

Data expressed as mean±SD or proportions. CAD, angiographic coronary artery disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure. † Indicates CAD patients with high quality aortic velocity assessments in the LV outflow tract. * $p<0.05$, ** $p<0.0001$ vs controls. There is no difference between all CAD patients and the cohort of CAD patients with high quality aortic velocity assessments.

Table 3.2 Comparison of unadjusted haemodynamic values between age- and sex-matched community participants (controls) and patients with CAD

Variable	Controls (n=210)	CAD (n=189)	CAD (n=71) †
Brachial PP (PPb) (mmHg)	50.4±14.6	58.5±18.1**	60.4±14.7**
Central PP (PPc) (mmHg)	41.7±14.0	45.7±17.0*	47.0±14.7*
Central SBP (mmHg)	129±21	120±23**	122±21*
Forward wave pressure (Pf) phys. (mmHg)	30.0±9.0	35.2±11.7**	36.7±10.2**
Pf act. (mmHg)	30.2±9.5	-	37.2±10.4**
Backward wave pressure (Pb) phys. (mmHg)	15.1±5.6	15.2±6.3	15.1±5.2
Pb act. (mmHg)	15.3±4.8	-	14.2±5.4
Re-reflected wave pressure (mmHg)	14.0±6.1	-	11.6±5.9*
Peak P_{QxZc} (mmHg)	28.3±7.7	-	35.1±9.0**
P_{QxZc} at PPc (mmHg)	13.2±6.3	-	23.8±9.0**
Characteristic impedance (Zc) (dynes.s/cm^5)	84.9±45.9	-	171.1±112.9**
Aortic diameter (cm)	2.66±0.44	-	2.30±0.47**
Peak aortic flow (Q) (ml/s)	375±149	-	369±194

Data expressed as mean±SD. CAD, angiographic coronary artery disease. † Indicates CAD with high quality aortic velocity assessments in the LV outflow tract. Phys., physiological waveform; act., actual waveform. Peak P_{QxZc}, pressure generated by the product of aortic flow (Q) and characteristic impedance to flow (Zc); P_{QxZc} at PPc, pressure generated by the product of aortic flow (Q) and characteristic impedance (Zc) at the peak of PPc. *$p<0.05$, ** $p<0.0001$ vs controls. There is no difference between CAD and CAD with high quality aortic velocity assessments.

3.3. Comparison of Haemodynamic Variables Between Patients with CAD and The Community Sample After Adjusting for Confounders

Brachial pulse pressure (PPb) was markedly increased in patients with CAD compared to controls after the adjustment for confounders (Figure 3.1). After adjusting for confounders, including MAP and the treatment for hypertension, both brachial and central SBP were markedly increased in participants with CAD compared to the community participants (controls) (Figure 3.2).

Figure 3.3 shows the comparisons of central pulse pressures between the groups after the adjustments for confounders. Central pulse pressure (PPc) was elevated in the patients with CAD compared to the community participants. However, after further adjustments for brachial pulsatile pressures (either PPb or SBPb), the differences were abolished. Hence, the increased PPc in the patients with CAD was due to the higher brachial BP in this group.

Figure 3.4 shows the comparison of forward wave pressures between the groups after adjustments for confounders. Forward wave pressure (Pf, irrespective of how determined) was increased in patients with CAD compared to community participants. Furthermore, after additional adjustments for brachial pulsatile pressures (either PPb or SBPb), the increase in Pf remained. Hence, the increased Pf in the patients with CAD was independent of increases in brachial pulsatile pressures.

In patients with CAD, (Pb) were either increased (when determined using the physiological wave form) or no different (when determined using the actual flow wave form) compared to the age- and sex-matched community participants after adjusting for confounders (Figure 3.5). However, after further adjusting for brachial pulsatile pressures (PPb or SBPb), Pb in the patients with CAD was either no different from that in the community participants or was in fact reduced (Figure 3.5). Similarly, reflected wave pressures ($P_{re\text{-}reflected}$) were not different between the groups after adjustments, and were reduced in the patients with CAD compared to community participants after further adjusting for brachial pulsatile pressures (PPb and SBPb) (Figure 3.5).

Both peak P_{QxZc} and P_{QxZc} at PPc were elevated in patients with CAD compared to community participants after adjustments for confounders (Figure 3.6). The increases in peak P_{QxZc} and P_{QxZc} at PPc in the CAD group compared to the community participants, remained after further adjusting for brachial pulsatile pressures (PPb and SBPb) (Figure 3.6).

After adjusting for confounders Zc remained increased in patients with CAD compared to community participants (Figure 3,7 panel A). Furthermore, the increased Zc in the patients with CAD was only partly explained by their smaller aortic diameter (Figure 3.7 panel C). Further adjustments for aortic diameter, although reducing the mean value of Zc in the patients with CAD, did not abolish the differences in Zc between the patients with CAD and the community participants (Figure 3.7 panel B). As aortic flow (Q) did not differ between the groups (Figure 3.7 panel D), the increased peak P_{QxZc} (Figure 3.6 panel A) and P_{QxZc} at PPc (Figure 3.6 panel B) in patients with CAD compared to community participants are explained by the dramatic increases in Zc in the patients with CAD.

3.4 Relative Contribution of Central Arterial Functional Changes Versus Conventional Risk Factors in Association with CAD

Table 3.3 shows the relative contribution of each of the central hemodynamic functional changes (in separate models) versus the conventional risk factors including brachial PP in their association with CAD. In the model with PPb, the conventional risk factors that were positively associated with CAD were PPb, the presence of HT and male gender and elevated HR. Central PP (PPc) was not positively associated with CAD beyond brachial PP. In comparison, Pf (irrespective of whether determined using physiological flow or actual flow), was positively associated with CAD independent of brachial PP and conventional risk factors. Importantly, the magnitude of the contribution of Pf to CAD was similar to that of hypertension. Peak P_{QxZc} was also positively associated with CAD independent of brachial PP and conventional risk factors and the magnitude of the contribution of peak P_{QxZc} to CAD was similar to that of hypertension. In addition to Pf and peak P_{QxZc}, Zc was positively associated with CAD independent of brachial PP and conventional risk factors. Importantly, the magnitude of the contribution of Zc was more than double that of PPb (in the same model) and greater than that of either Pf or peak P_{QxZc}. Furthermore, the inclusion of Zc in the models abolished the relationships between Pf (actual flow) and CAD (standardized β-coefficient±SEM =0.120±0.093, p=0.199) and between peak P_{QxZc} and CAD (standardized β-coefficient±SEM=0.091±0.081, p=0.264).

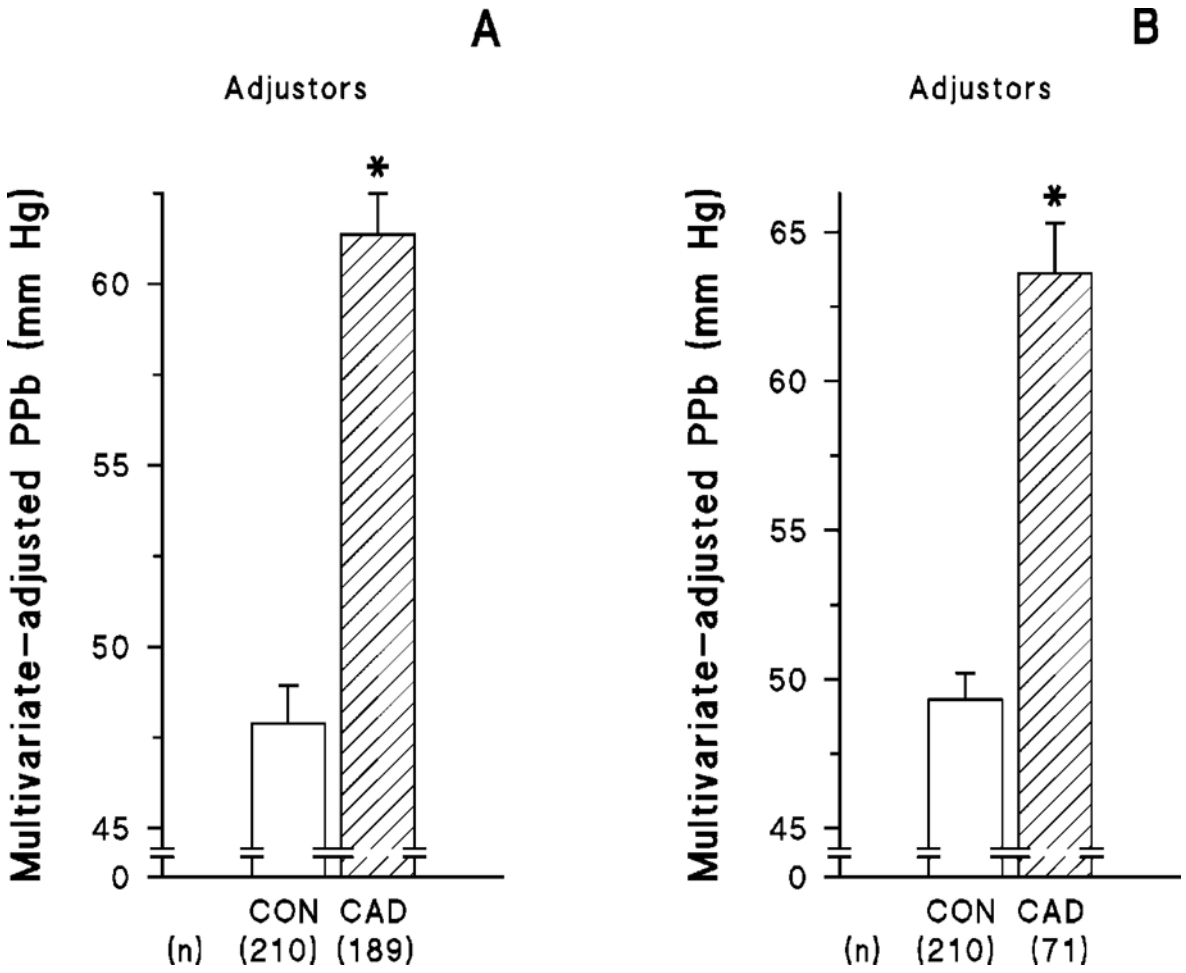

Figure 3.1 Comparison of multivariate adjusted brachial pulse pressure (PPb) in those with angiographic coronary artery disease (CAD) as compared to age- and sex-matched community participants (CON). Left panel (A) indicates all participants with CAD. Right panel (B) indicates CAD patients with high aortic velocity assessments. *$p<0.0001$ versus control group. Adjustments are for age, sex, BMI, HR, treatment for hypertension, MAP, diabetes mellitus and smoking.

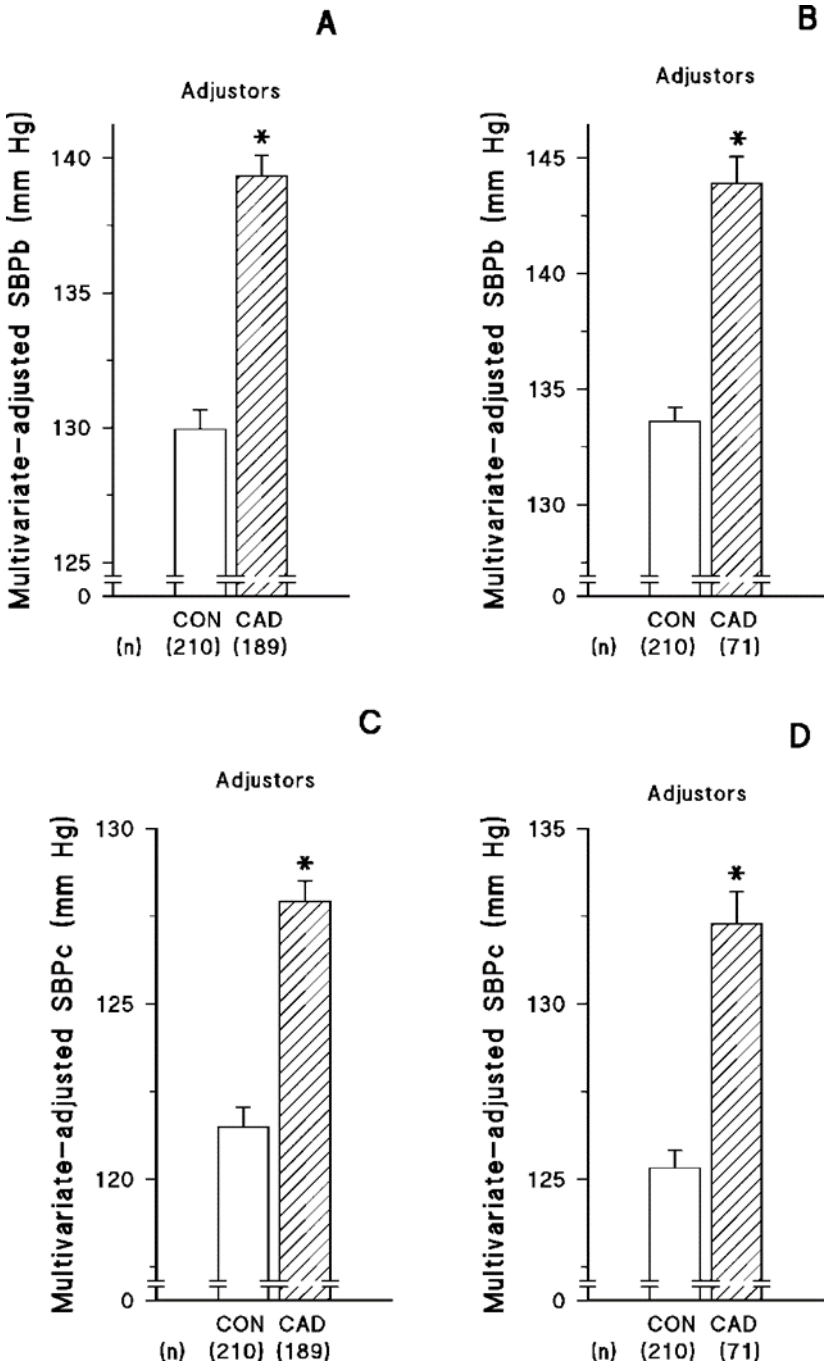

Figure 3.2 Comparison of multivariate adjusted brachial systolic blood pressure (SBPb, panels A and B) and central systolic blood pressure (SBPc, panels C and D) in those with angiographic coronary artery disease (CAD) as compared to age- and sex-matched community participants (CON). Left panels (A, C) indicate all patients with CAD. The right panels (B, D) indicate CAD patients with high aortic velocity assessments. *$p<0.0001$ versus control group. Adjustments are for age, sex, BMI, HR, treatment for hypertension, MAP, diabetes mellitus and smoking.

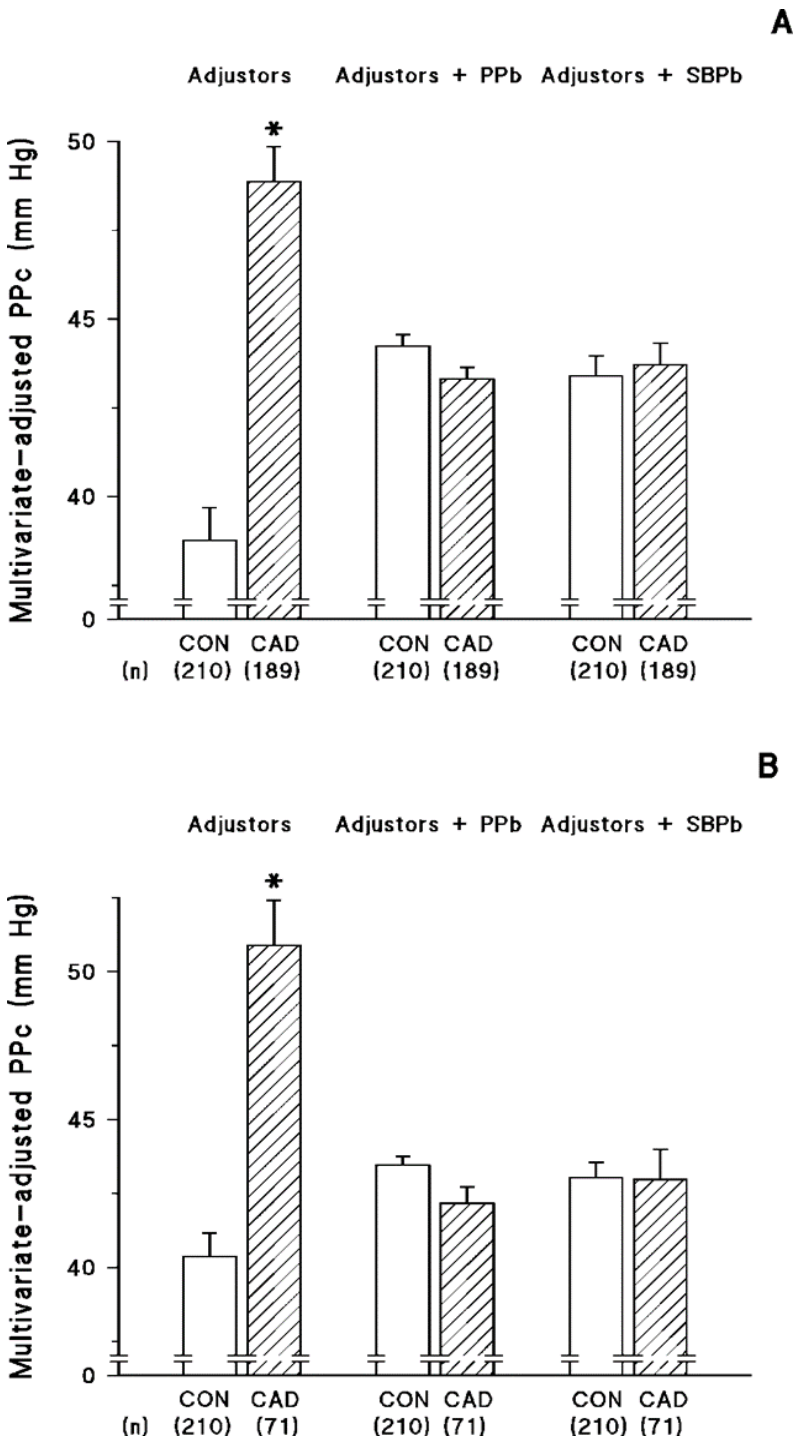

Figure 3.3 Impact of adjustments for brachial pulsatile pressures (PPb, SBPb) on comparison of multivariate adjusted central pulse pressure (PPc) in those with angiographic coronary artery disease (CAD) as compared to age- and sex-matched community participants (CON). Top panel (A) indicates all patients with CAD. Lower panel (B) indicates CAD patients with high aortic velocity assessments. *$p<0.0001$ versus control group. Adjustments are for age, sex, BMI, HR, treatment for hypertension, MAP, diabetes mellitus and smoking, plus further adjustments for brachial pulse pressure (PPb) and systolic blood pressure (SBPb) as indicated.

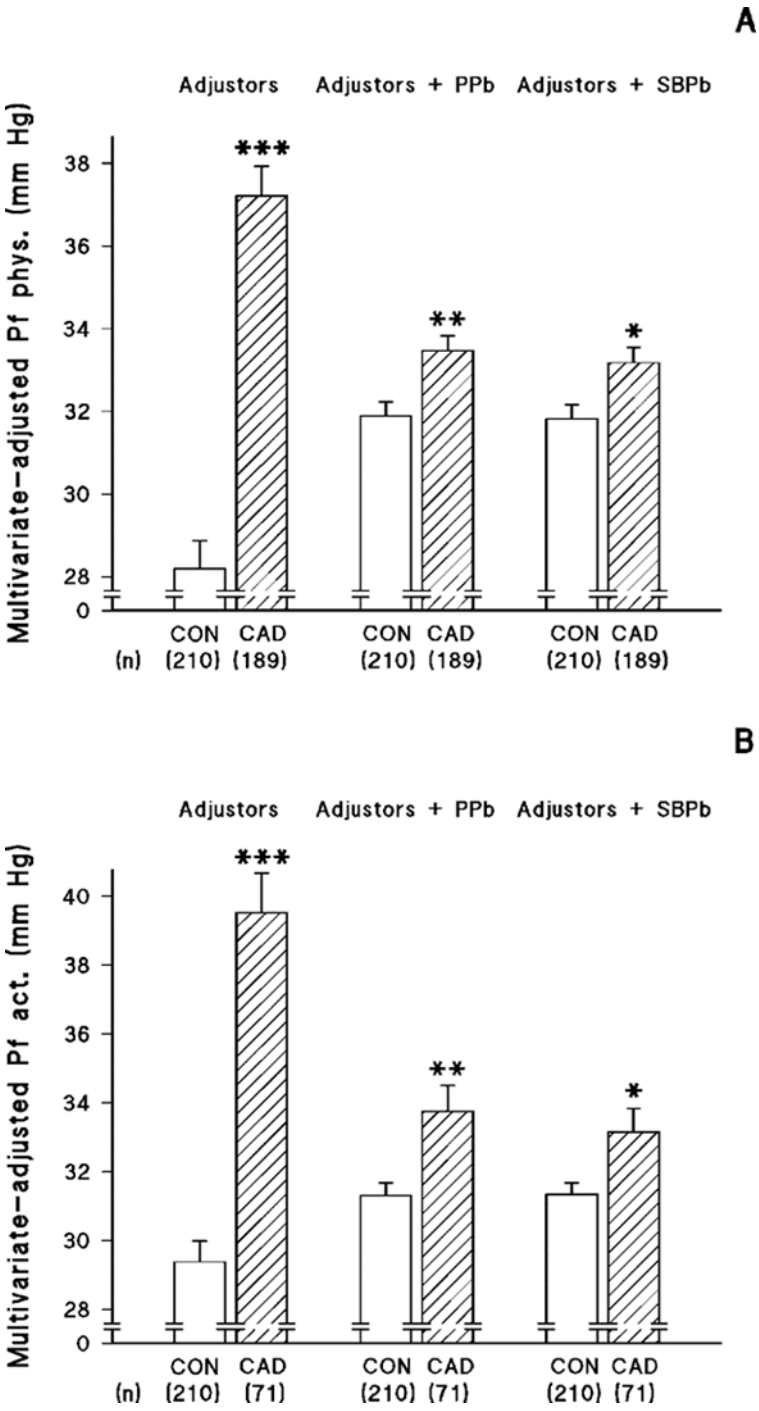

Figure 3.4 Impact of adjustments for brachial pulsatile pressures (PPb, SBPb) on comparison of multivariate adjusted forward wave pressure (Pf phys. and Pf act.) in those with angiographic coronary artery disease (CAD) as compared to age- and sex-matched community participants (CON). Top panel (A) indicates all patients with CAD. Lower panel (B) indicates CAD patients with high aortic velocity assessments. *p<0.05, **p<0.01, ***p<0.0001 versus control group. Adjustments are for age, sex, BMI, HR, treatment for hypertension, MAP, diabetes mellitus and smoking, plus further adjustments for brachial pulse pressure (PPb) and systolic blood pressure (SBPb) as indicated.

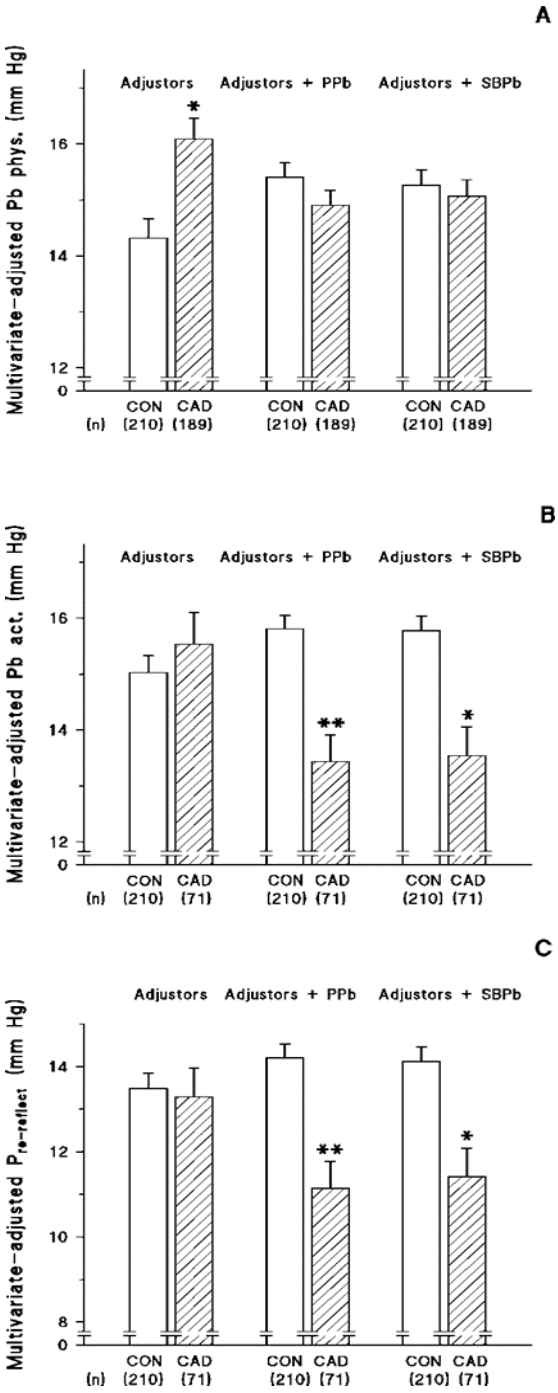

Figure 3.5 Impact of adjustments for brachial pulsatile pressures (PPb, SBPb) on comparison of multivariate adjusted backward wave pressure (Pb phys. and Pb act.) and re-reflected pressure ($P_{re\text{-}reflect}$) in those with angiographic coronary artery disease (CAD) as compared to age- and sex-matched community participants (CON). Top panel (A) indicates all patients with CAD. Lower and middle panels (B, C) indicate CAD patients with high aortic velocity assessments. *$p<0.005$, **$p<0.0001$ versus control group. Adjustments are for age, sex, BMI, HR, treatment for hypertension, MAP, diabetes mellitus and smoking, plus further adjustments for brachial pulse pressure (PPb) and systolic blood pressure (SBPb) as indicated.

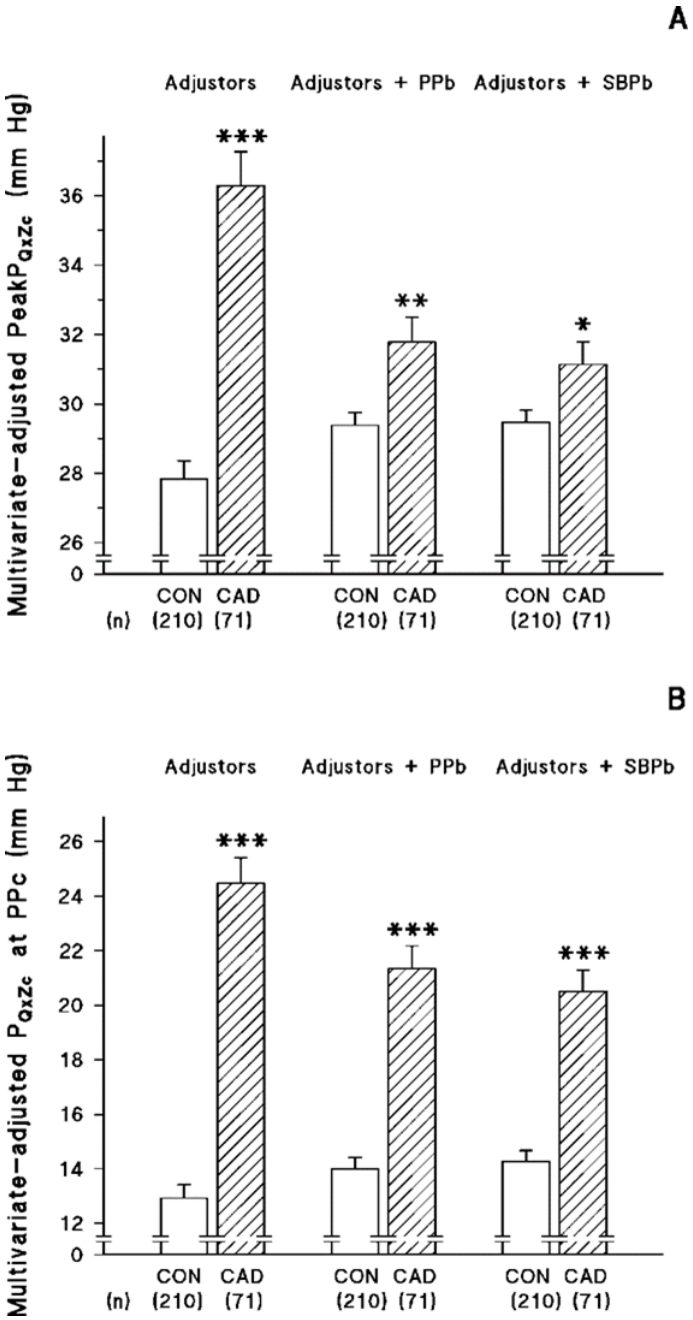

Figure 3.6 Impact of adjustments for brachial pulsatile pressures (PPb, SBPb) on comparison of multivariate adjusted peak PQxZc (panel A) and PQxZc at PPc (panel B) in those with angiographic coronary artery disease (CAD) as compared to age- and sex-matched community participants (CON). Both panels indicate CAD patients with high aortic velocity assessments. *p<0.05, **p<0.005, ***p<0.0001 versus control group. Adjustments are for age, sex, BMI, HR, treatment for hypertension, MAP, diabetes mellitus and smoking, plus further adjustments for brachial pulse pressure (PPb) and systolic blood pressure (SBPb) as indicated.

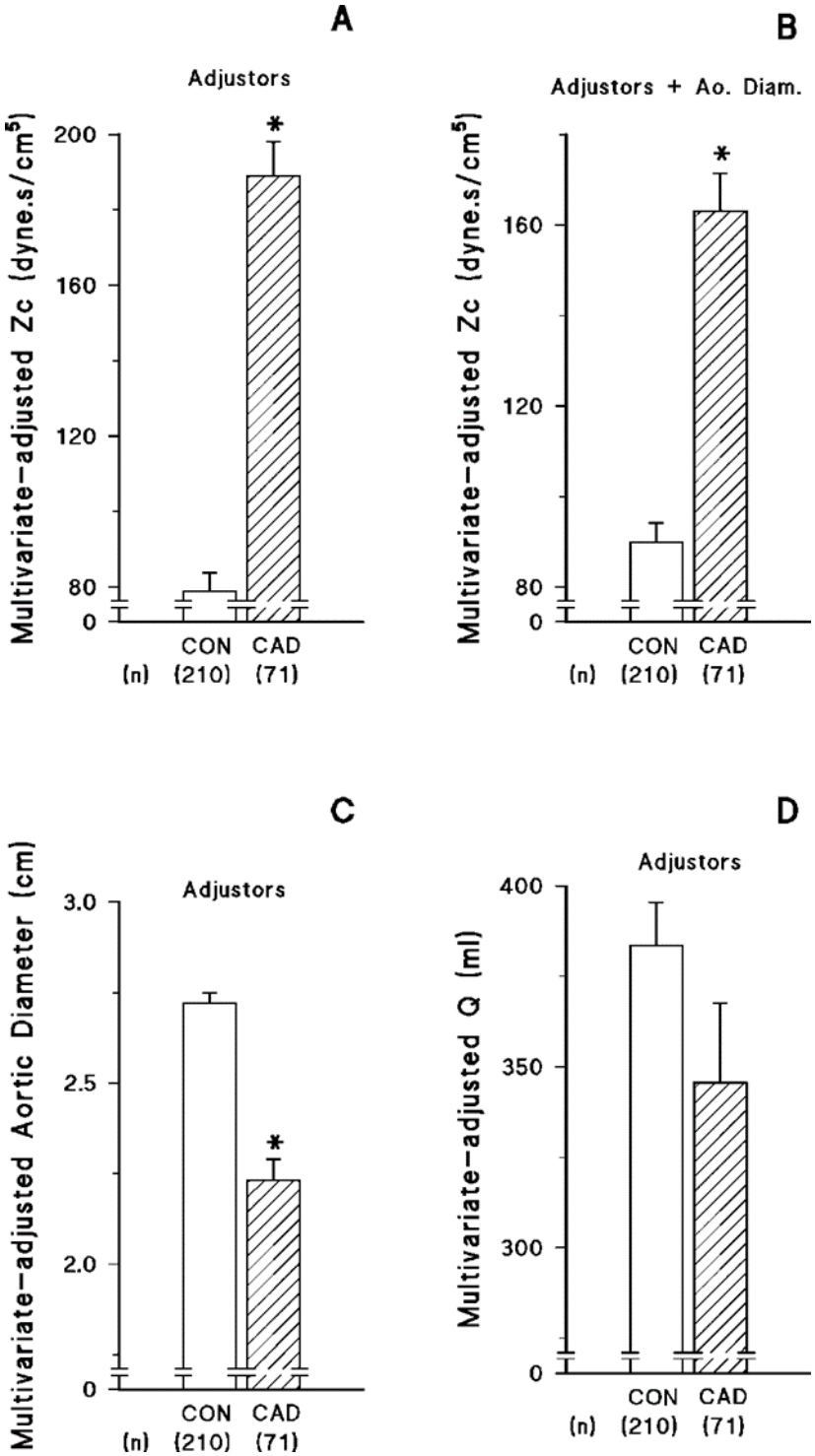

Figure 3.7 Impact of adjustments for brachial pulsatile pressures (PPb, SBPb) on comparison of Multivariate adjusted Zc (panel A), aortic diameter (panel C), aortic flow (Q) (panel D) and the impact of further adjustments for aortic diameter on Zc (panel B) in those with angiographic coronary artery disease (CAD) as compared to age- and sex-matched community participants (CON). All panels indicate CAD patients with high aortic velocity assessments. * $p<0.0001$ versus control group. Adjustments are for age, sex, BMI, HR, treatment for hypertension, MAP, diabetes mellitus and smoking.

Table 3.3 Relative contribution of central arterial functional changes versus conventional risk factors in association with CAD

CAD vs → **in model**		**PPc (n=189)**	**Pf phys. (n=189)**	**Pf act. (n=71)**	**Peak P_{QxZc} (n=71)**	**Zc (n=71)**
Brachial PP (PPb)	**0.378±0.059*** **	0.758±0.172***	0.102±0.105	0.142±0.104	0.167±0.093	0.156±0.058**
Central PP (PPc)	-	**-0.434±0.186***	-	-	-	-
Pf	-	-	**0.272±0.103****	**0.275±0.101****	-	-
Peak P_{QxZc}	-	-	-	-	**0.255±0.087****	-
Zc	-	-	-	-	-	**0.458±0.056*** **
HT	0.259±0.058***	0.255±0.057***	0.268±0.044***	0.268±0.057***	0.265±0.057***	0.260±0.051***
DM	0.053±0.052	0.045±0.052	0.027±0.042	0.040±0.052	0.033±0.052	0.050±0.047
Smoking	0.073±0.053	0.097±0.053	0.110±0.042**	0.068±0.052	0.072±0.052	0.065±0.048
Age	-0.103±0.055	-0.066±0.057	-0.035±0.044	-0.109±0.055*	-0.106±0.054*	-0.093±0.050

Sex (male)	0.144±0.054**	0.122±0.055*	0.147±0.043**	0.138±0.055*	0.123±0.054*	0.161±0.049**
BMI	0.019±0.053	0.001±0.053	0.057±0.042	0.021±0.053	0.011±0.053	0.051±0.048
MAP	-0.507±0.056***	-0.449±0.061***	-0.543±0.044***	-0.516±0.055***	-0.497±0.055***	0.477±0.050***
HR	0.126±0.053*	0.052±0.061	0.187±0.043***	0.147±0.053**	0.128±0.052*	0.082±0.047

β-coeff., standardized β-coefficient. * $p<0.05$, ** $p<0.01$, *** $p<0.0001$ vs controls. PPb, brachial pulse pressure; PPc, central pulse pressure; Pf, forward wave pressures determined from wave separation analysis using a physiological flow wave (Pf phys.) and an actual wave (Pf act.); Peak P_{QxZc}, pressure generated by the product of aortic flow (Q) and characteristic impedance to flow (Zc); HT, hypertension; DM, diabetes mellitus; BMI, body mass index; MAP, mean arterial pressure; HR, heart rate. The contributions of central arterial functional changes are shown in bold type. Adjustments are for age, sex, BMI, smoking, DM, HR and MAP.

CHAPTER 4: DISCUSSION

4.1 Summary of Findings

In the current study, I evaluated the degree to which increases in Pf are independently linked with CAD beyond brachial BP, although peak aortic PPc is not, through increases in proximal aortic stiffness. The major finding of this case-control study was that the proximal aorta is stiffer in patients with established CAD. Thus, I demonstrated that proximal aortic Zc, independent of aortic root diameter and additional confounders, is significantly increased in individuals with angiographically documented CAD, supporting the idea that increases in proximal aortic stiffness are noticeable. According to these findings, the aberrant aortic pressure-flow relationship and elevated Pf in CAD patients may be caused by an anomaly in proximal aortic diameter. In contrast, no variations in PP were found beyond brachial BP and did not contribute to age-related increases in PP since backward wave pressures were not raised. Furthermore, CAD was linked to aortic Pf but not brachial or aortic PP due to a significant prevalence of modifiable traditional risk factors that were unaffected by distending pressures (MAP) or additional confounders. Importantly, CAD was not associated with aortic Pb.

4.2 Novelty of The Present Study

Although a previous study has demonstrated relationships between Zc-induced increases in Pf, not peak PPc beyond brachial BP in stroke and CLI patients (Motau *et al.*, 2020), no studies to date have investigated this in patients with CAD. According to Motau *et al.* (2020), increases in Zc result in improved forward-moving pressure waves (Pf), independent of brachial blood pressure, via increases in the pressure produced by the product of aortic flow (Q) and Zc (P_{QxZc}) (Motau *et al.*, 2020). Moreover, Zc effects beyond aortic root diameter, which are linked to elevated stiffness in the proximal aorta in stroke and CLI patients, partially explain the association between P_{QxZc} and small vessel or atherosclerotic end organ measurements (Motau *et al.*, 2020). Therefore, the present study is the first to provide evidence to demonstrate that Zc-dependent increases in Pf, but not peak PPc are associated with CAD beyond brachial BP (PP or SBP). Notably, the increases in Pf beyond brachial BP were far more striking in patients with CAD than in the study done by Motau *et al.* (2020). Thus, an increase in PP is not necessarily because of central SBP; instead, an increase in PP is accompanied by an increase in Pf and an increase in P_{QxZc} due to Zc and small diameter rather than Q.

4.3 Central Pulse Pressure and CAD

While measures of aortic stiffness have provided an apparent ability to predict cardiovascular events beyond brachial BP (Vlachopoulos *et al.*, 2010; Ben-Shlomo *et al.*, 2014) central aortic BP, which is strongly determined by aortic stiffness, does not (O'Rourke *et al.*, 2002; Mitchell *et al.*, 2010a; Vlachopoulos *et al.*, 2010). Hence, pressure and flow waves at every point in the arterial tree are the total of waves that move from the heart in the direction of the periphery (forward waves) and waves that move from peripheral arteries in the direction of the heart (backward or reflected waves) (Van de Vosse & Stergiopulos, 2011). Therefore, in the subsequent sections I will discuss the components of central pulse pressure.

4.3.1 Forward Wave Pressures

The Pf is influenced by the pattern of ventricular ejection and aortic stiffening (Safar *et al.*, 1996). According to a recent study, wave re-reflection, which is dependent on the amplitude of the backward (reflected) pressure wave, is the cause of the excess pressure produced by increases in forward wave pressures (Phan *et al.*, 2016). However, in my study, wave re-reflection was no different in the CAD patients compared to the community sample; in fact, wave re-reflection was decreased in the CAD patients following additional brachial pulsatile pressure adjustment. Though peak central arterial blood pressure does not correlate with risk variables or predict events beyond brachial blood pressure, it is noteworthy that increases in forward travelling pressure waves caused by aortic stiffness are linked to end-organ measurements or risk factors (Cooper *et al.*, 2015; Motau *et al.*, 2018; Motau *et al.*, 2020; Motau *et al.*, 2021). In contrast, the arterial wave generated in the arterial beds that contribute to arterial events is derived from Pf generated in the central aorta. The present study revealed that a higher Pf was linked to increases in pulsatile pressures ($p<0.0001$), and increased Pf in patients with CAD was independent of increases in brachial pulsatile pressures. Thus, Pf is positively associated with CAD. Consequently, Pf may be the central arterial pressure measurement that predicts arterial events beyond brachial PP; although further studies are needed.

Furthermore, an increase in Pf amplitude implies that elevated central and peripheral systolic and pulse pressure with advancing age in healthy individuals is primarily caused by increases in Pf and central arterial stiffness rather than reflected wave amplitude (Mitchell *et al.*, 2004). This has significant implications for the ageing population, as increases in systolic and pulse

pressures have been linked to cardiovascular events (O'Rourke 1982). In addition, a study conducted by Mitchell *et al.* (2010a) shows that Pf is responsible for the recognised rapid increase in systolic pressure and PP with ageing. Moreover, the Pf amplitude increases with advancing age and Pb remains the same (Mitchell *et al.*, 2010a).

4.3.2 Backward Wave Pressures

After encountering the forward pressure wave and falling on it, the reflected wave proceeds retrogradely toward the heart, creating an augmented or summated pressure wave (Vasan, 2008; Van de Vosse & Stergiopulos, 2011; Gao *et al.*, 2016). Furthermore, studies investigating central haemodynamics in a African community sample of uncontrolled hypertension have shown a substantial link between Pb and central PP, proving that Pb is a main predictor of PP (Booysen *et al.*, 2015; Sibiya *et al.*, 2015). Pb has also been proven to impact the form of the forward travelling arterial wave (Nichols & Singh, 2002; Weber *et al.*, 2012; Booysen *et al.*, 2015). In comparison, the findings from my study indicate that while the backward pressure waves do interact with the Pf, they do not significantly alter central pulse pressure in CAD patients, which is contrary wave behaviours in the aforementioned community samples. This discrepancy can be attributed to CAD patients exhibiting a diminished occurrence of wave reflections, likely due to lower diastolic blood pressure from lessened vasoconstriction (Wesseling *et al*., 1985).

In the present study, the CAD group was observed to have a reduced Pb following adjustment for brachial pulsatile pressures which may partly be due to widespread use of antihypertensive medication, which exerts vasodilatory effects. Consequently, the influence of Pb is moderated thus diminishing the direct impact on central elastic arteries but profoundly affecting peripheral muscle arteries. These effects lead to reductions in systolic and pulse pressures, a lowering of left ventricular afterload, and a diminution in the magnitude of wave reflections (Safar *et al.*, 1996; Nichols, 2005; Duprez & Cohn, 2006; Nichols *et al.*, 2006; Vasan, 2008; Weber *et al.*, 2012), all of which carry significant implications for cardiovascular health of patients with CAD.

4.3.3 The Effect of Age on Forward and Backward Wave Pressures

In both ageing and hypertensive populations, a loss of elasticity or compliance commonly occurs leading to inefficient blood flow. The inefficient blood flow results in most of the stroke volume being transported distally during systole, with little to no blood flow during diastole (Lilly *et al.*, 2014). This reduced suppleness accelerates with conditions such as CAD and can

lead to the development of various other cardiovascular complications thus highlighting the importance of monitoring cardiovascular disease progression. Studies have demonstrated that the amplitude of the forward pressure wave is the primary correlate of both the late increase in pulse pressure after the age of 50 and the central and peripheral pulse pressures at any age (Mitchell *et al.*, 2010b). If the rise in the amplitude of the forward wave is greater than the decrease in the wave reflections, such as when the wave reflections remain steady or diminish, the reflected wave amplitude would escalate (Mitchell *et al.*, 2010a). In my study the mean age of the CAD group was over 60 and although age- and sex-matched to the community sample, this data thus validates the increase in Pf with age, affirming the connection between advancing age and increased pulse wave amplitude. Brachial artery stiffness tends to rise disproportionately more with age than central arterial stiffness, increasing central PP and decreasing peripheral PP augmentation (Avolio *et al.*, 1985; Kelly & Fitchett, 1992; Lakatta, 1993; Mitchell *et al.*, 2004; Benetos *et al.*, 2010). Moreover, direct measurements of pulsatile haemodynamics in systolic hypertensive patients revealed that higher PP was linked to a narrower aortic root diameter and increased characteristic impedance (Lam *et al.*, 2010) which supports my study findings on CAD. There is strong evidence that as people age, the stiffening of the aorta causes aortic SBP to approximate brachial SBP (McEniery *et al.*, 2014). Hence, brachial SBP rather than DBP more closely relates to cardiovascular damage. Therefore, in the present study, after the adjustments for confounders were made, both brachial and central SBP were markedly elevated.

4.4 Arterial Stiffness in CAD

In the early stages of systole, before the reflected pressure wave returns, characteristic impedance serves as an indicator of the pressure produced by a certain flow waveform in the proximal aorta (Mitchell & Pfeffer, 1999). Increases in the proximal aortic characteristic impedance to flow (Zc; resistance to flow in a pulsatile system in the absence of reflected waves) multiply the aortic flow (Q) to produce these pressures (Segers *et al.*, 2007; Phan *et al.*, 2016). Modifications to the proximal aorta's structure that affect its stiffness and diameter cause increases in Zc. The amplitude of the forward wave will be high if Zc is excessively high, according to Bell & Mitchell, (2015). In my study, aortic flow (Q) did not differ between the groups. Therefore, the increase in peak P_{QxZc} and P_{QxZc} at PPc can mainly be explained by the dramatic increases in Zc in CAD. In addition to this, the marked increase in Zc can be explained by the smaller aortic diameters in the CAD group. Further adjusting for the diameter, although

reducing the mean value of Zc, the differences in Zc between the groups were not abolished. Therefore, Zc is positively associated with CAD but is also greater than PPb, Pf and peak PQxZc.

In hypertensives, central arteries have been shown to have increased stiffness, whereas peripheral arteries have been shown to have normal or reduced stiffness (Avolio *et al.*, 1985; Nichols *et al.*, 1986; Hayoz *et al.*, 1992; Laurent *et al.*, 1993). Strong evidence suggests that patients with systolic hypertension and CAD may have unusually small aorta diameters based on an assessment of the factors influencing aortic root diameter in Framingham Heart Study participants (Vasan *et al.*, 1995). Additionally, these researchers showed an inverse relationship between brachial PP and SBP and aortic root diameter when assessed as a continuous variable (Vasan *et al.*, 1995). Hence, in my study, this may be the case, as most of the CAD patients were hypertensive; it can be supported by the fact that stiffness is increased due to the smaller aortic diameters and the dramatic increase in Zc.

A higher aortic Zc results in higher aortic forward wave pressures (Pf), which lessens the impedance mismatch between the aorta and farther-reaching arteries and enhances the pulsatile load. This procedure enables a greater pulsatile energy transfer into these vessels (Mitchell *et al.*, 2010a; Hashimoto & Ito, 2010; O'Rourke *et al.*, 2010). It is thought that vascular injury is caused by increased pulsatile load, which is the transfer of pulsatile energy to the cerebral, coronary, or lower limb circulation, which in turn is linked to coronary artery disease and stroke (Motau *et al.*, 2020).

In my study, compared to the control group, CAD patients had a significantly higher Zc due to a reduced diameter and increased stiffness, which affects cardiac function. The heart has to work harder in systole and does not recoil in diastole because of the increased stiffness. The heart is working against a higher workload because of the smaller diameter, but smaller diameter does not explain all of Zc. The increased workload of the heart is also due to intrinsic stiffness because of the loss of elastic tissue and an increased collagen content (Bell & Mitchell, 2015). Moreover, the stiffening of the arteries causes unfavourable central aortic pressure characteristics, such as elevated cardiac afterload and lowered diastolic endocardial perfusion pressure (Blacher & Safar, 2005).

The present study assessed the role of Zc-induced increases in Pf beyond brachial BP in patients over the middle and older age range, rather than at a younger adult age. This was due to the

fact that in South Africa, CAD rarely develops over the course of a younger adult life and is still extremely rare among South Africans (Walker *et al.*, 2002). Consideration of the Zc in relation to mean aortic blood pressure and age in our subjects suggests that these two factors may account for the relatively high characteristic impedances in individuals with coronary disease. In hypertensive men, increased Zc was caused by a smaller aortic diameter; there was no change in aortic stiffness at the same mean brachial pressure (Laurent & Boutouyrie, 2007). Consequently, the CAD group were hypertensive and of male gender, which is supported by the study done by Laurent & Boutouyrie (2007).

Characteristic impedance has a strong inverse relation with aortic diameter (Laurent & Boutouyrie, 2007; Bell & Mitchell, 2015; Ikonomidis *et al.*, 2019). Furthermore, after additional adjustments for aortic root diameter in the current study, Zc remained elevated in the CAD group, confirming that Zc has a strong inverse relation with aortic diameter. A mismatch between aortic flow and area is indicated by a higher Zc (Ye *et al.*, 2015). Regarding this, earlier research carried out in different groups imply that Q might even be reduced, seen in this CAD study, a result of higher flow resistance in a pulsatile system (Zc) (Mitchell *et al.*, 2008). Therefore, if Zc is applied, flow will be altered because of the narrowing and tapering of the vessels, which affect flow and therefore will result in an increase in the workload of the heart. This confirms the effect of CAD on vascular impedance and flow in this study.

The recoil of the spring aids diastole and filling of the heart (Laurent & Boutouyrie, 2007; Bell & Mitchell, 2015; Adenwalla *et al.*, 2017). The extensibility of the aortic spring affects how the heart works. It will be more difficult for the heart to contract in systole if the aorta is stiff due to an elevated Zc, as seen in my study with CAD. Because of this, the heart must work harder during systole and will not recoil and reduce the flow to capillaries (fill as much during diastole) (Bell & Mitchell, 2015; Adenwalla *et al.*, 2017). Diastolic pressure drops while systolic pressure rises (Westerhof *et al.*, 1972; Vlachopoulos *et al.*, 2011).

The above-mentioned mechanisms further add to the reduction in flow as a consequence of CAD in the current study. Cardiovascular damage is determined by pulsatile haemodynamic effects beyond steady-state pressures, which are caused by multiple aortic alterations resulting from modifiable traditional risk factors (Motau *et al.*, 2018). Additionally, a decrease in vascular ventricular coupling was found in CAD from a study done by (Fitzpatrick *et al.*, 2018). Moreover, this will result a decrease in cardiac efficiency and an overall decrease in CV performance (Patterson *et al.*, 2021) in the CAD patients from the current study. In this regard,

an increased aortic stiffness enhances aortic Zc and thus Pf, as seen in this study. Higher Zc, but not peak flow, was linked to a higher risk of incident CVD events in and additional study that looked at important factors influencing Pf amplitude (Cooper *et al.*, 2015). Indeed, an increase in Q would be beneficial as an increased Q translates into an increased flow through the coronary arteries. However, in this study the increase in QxZc was not due to Q but due to the markedly increased Zc in the CAD group.

4.5 Clinical Implications

Several studies have suggested that utilising peak aortic central SBP or PP in addition to brachial blood pressure measures may not be effective in replacing or supplementing risk prediction (O'Rourke, 2002; Mitchell *et al.*, 2010b; Vlachopoulos *et al.*, 2010). However, it remains unclear whether Pf pressures can enhance risk prediction for arterial incidents beyond brachial blood pressure. While several studies (Cooper *et al.*, 2015; Motau *et al.*, 2018; Motau *et al*., 2020; Motau *et al*., 2021) suggest that this may be the case, alternative studies (Wang *et al.*, 2010; Chirinos *et al.*, 2012; Weber *et al.*, 2012) have reported on a small number of incidents or a lack of ability for Pf pressures to anticipate events (Wang *et al.* 2010) and (Weber *et al.* 2012) or where heart failure was the dominant event (Chirinos *et al.*, 2012). Furthermore, studies have shown that CAD patients exhibit significant increases in stiffness compared to controls. Thus, aortic stiffness associated with Pf is enhanced beyond brachial or peak central arterial BP in CAD. However, by reducing arterial stiffness, it is possible to achieve selective and long-term reduction of brachial and, more importantly, central SBP and PP. Therefore, these findings support the need for intense brachial BP reduction in CAD.

4.6 Potential limitations

Although this study provides valuable insights into our understanding, the findings should be interpreted with consideration of several limitations. Firstly, the study excluded patients with atrial fibrillation as PWA could not be accurately performed on these individuals. Secondly, the community cohort may not have undergone a CT or an angiographic exam to exclude coronary artery disease as most of the participants were seen at primary healthcare clinics, which relied on a referral approach. In addition, the data collected relied on participants self-reporting previous history and these individuals may or may not have known whether they had CAD. Further to this, no interval data was acquired after patients had their coronary angiogram or CT, therefore no information is available on whether they subsequently needed PCI or stent.

Thirdly, patients with fistulas were also excluded due to the diminished radial blood flow which compromised the integrity of the PWA waveforms. Fourthly, conducting echocardiography posed challenges in individuals with narrow intercostal rib spaces. In addition, due to the nature of the angiogram procedure, patients were in supine position, which meant some patients were non-echogenic. Furthermore, the absence of comprehensive lipid profiles for all patients meant that dyslipidemia could not be reliably factored into the statistical analysis. Lastly, due to the small sample size and ethnic heterogeneity, it is not possible to preclude definitive causal inferences consequently, further research is needed to confirm these findings.

4.7 Future studies

Although controversy regarding the potential use for Pf pressures to strengthen risk prediction beyond brachial measurements remains, my study findings suggest that patients with CAD present with a marked increase in aortic stiffness, with associated Pf being more pronounced than elevations in brachial or central arterial blood pressure. Nevertheless, future studies need to consider heterogeneity of the cohort, to ensure CAD was eliminated from the control group. Furthermore, given the scarcity of research on central haemodynamics and its underlying factors in patients with CAD, there is a need for comprehensive research examining various components of central PP and Zc, Q or P_{QxZc} in CAD. Moreover, as my study was retrospective in design, future studies should not only confirm the selection of techniques used to assess Zc in CAD patients but prospective studies should be designed to include non-invasive techniques such as cardiac magnetic resonance imaging (MRI) and coronary computed tomography angiography (CCTA) for real-time imaging (Marano *et al.*, 2020; Liao *et al.*, 2024). These tools would allow for correlation with Zc to refine prognostic assessments and tailor treatment for patients with CAD, as previously highlighted (Leta *et* al., 2004; Ridgway, 2010; Ohyama *et al.*, 2018). Furthermore, future studies identifying the drivers of Zc alterations in CAD are paramount. Thus, understanding the mechanisms linked to the implication of Zc is crucial in guiding future novel therapeutic approaches which would reduce Zc and consequent afterload in patients with CAD.

4.8 Conclusion

In conclusion, this study provides evidence of significant increases in stiffness-associated proximal aortic Zc in patients diagnosed with CAD. This results in a central artery pulsatile burden that is significantly higher than what brachial blood pressure measurements can predict. While peak central pulse pressure is produced, aortic Pf pressures are the more accurate

measurement in a CAD cohort. These findings suggest that the pulsatile load responsible for CAD is not measured well by central pulse pressure and extends beyond brachial blood pressure. The results above provide new insight into the significance of conduit artery function in the aetiology and management of CAD. Furthermore, this study has shown that reducing arterial stiffness makes it possible to achieve a selective and long-term reduction of brachial and, more importantly, central SBP and PP. The central circulation, composed of the aortic pressures, is a more clinically relevant measurement than peripheral pressures when considering the risk development and progression of vascular disease. Furthermore, I have shown that most of the faster increase in pulse pressure after midlife can be attributed to fluctuations in forward wave amplitude. Based on the proximal aorta's peak flow and characteristic impedance, this is the main hemodynamic correlate of pulse pressure over the adult age range. As a result, variations in the relative wave reflection only slightly affect pulse pressure variability, whereas changes in central wave reflection timing have little effect. Therefore, in conclusion, increases in stiffness-associated proximal aortic Zc in patients with CAD translate into marked increases in Pf but not peak PPc beyond brachial BP. Therefore, the pulsatile load responsible for CAD is beyond brachial BP and poorly indexed by peak PPc.

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APPENDICES

Appendix 1: Ethics

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research and Innovation)

TO: Professor F Peters, Ms D Els, et al
School of Physiology
Cardiovascular Pathophysiology and Genomics RU
Medical School
University

E-mail: Vernice.Petersen@wits.ac.za

CC: Supervisor: Dr V Petersen and Professor F Peters
<Ferande.Peters@wits.ac.za>
and <HREC-Medical Research Office@wits.ac.za>

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

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

DATE: 2021/05/31

REF: R14/49

PROTOCOL NO: **M210136** (This is your ethics application reference number. Please quote it in all enquiries, oral or written, relating to this study.)

PROJECT TITLE: *Arteriosclerotic aortic functional changes in cardiac pathology across the full adult lifespan in South Africa*

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 Government funding of the University.

M:\Work\2020\Iain\0007\Clearscan.wpd

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R49 Professor F Peters, Ms D Els, et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M210136

NAME: (Principal Investigator)	Professor F Peters, Ms D Els, et al
DEPARTMENT:	School of Physiology Cardiovascular Pathophysiology and Genomics RU Medical School University
PROJECT TITLE:	*Arteriosclerotic aortic functional changes in cardiac pathology across the full adult lifespan in South Africa*
DATE CONSIDERED:	2021/01/29
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr V Petersen and Professor F Peters
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2021/05/31

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

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

I/we fully understand the conditions under which I am/we are authorized 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 submit details 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 when the study was initially reviewed. In this case, the study was initially reviewed in January and therefore reports and re-certification will be due in the month of January each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator

Date

Appendix 2: Turnitin Report (Plagiarism Report)

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ORIGINALITY REPORT

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