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Adverse effects of aortic backward waves in a group of African Ancestry

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Adverse Effects of Aortic Backward Waves in a Group of African Ancestry.

Moekanyi Jeffrey Sibiya

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ABSTRACT

Although brachial blood pressure (BP) is a well-recognized risk factor for predicting cardiovascular events, aspects of aortic BP may enhance risk prediction. Pulse pressure (PP) is amplified from the aorta to peripheral arteries and variations in differences between brachial and aortic PP (PP amplification) are determined by factors that influence either the aortic forward (Pf) or backward (Pb)(reflected) pressure waves. Although aortic Pb may be more important than Pf in mediating cardiovascular risk, the best approach to assessing backward wave function (augmentation pressures [Pa] and index [AIx] or wave separation analysis); the relative impact of aortic Pb versus Pf on cardiovascular damage; and whether the ability of aortic-to-brachial PP amplification (PPamp) to add to risk prediction reflects backward or forward wave effects, is uncertain.

In the present thesis I therefore first assessed in 808 community participants whether gender influences relations between Pa or AIx and left ventricular mass (LVM), a well-accepted end-organ measure. Aortic haemodynamics were determined using radial applanation tonometry and SphygmoCor software and LVM from echocardiography. In men, both AIx derived from Pa/central aortic PP (Pa/PPc) ($p<0.01$) and AIx derived from the second peak/first peak (P_2/P_1) of the aortic pulse wave ($p<0.0005$) were associated with LVM. In contrast, in women neither AIx derived from Pa/PPc ($p=0.08$) nor AIx derived from P_2/P_1 ($p=0.17$) were associated with LVM. Both the strength of the correlations ($p<0.001$ and $p<0.0005$) and the slope of the AIx-LVM relationships ($p=0.001$ and $p<0.0005$) were greater in men as compared to women. Therefore, in the present study I show that AIx is independently associated with LVMI in men, but not in women.

I subsequently evaluated whether in women, measures of aortic systolic pressure augmentation (Pa or AIx) underestimate the effects of reflected waves on cardiovascular risk or whether Pb plays little role in cardiovascular risk prediction. In the same community sample I therefore evaluated sex-specific contributions of reflected (Pb and the reflection index [RI]) versus augmented (Pa and AIx) pressure wave indices to

variations in PPc (n=1185, 65.0% women), and LVM (n=793, 64.9% women). Aortic Pb and Pf were determined using wave separation analysis. In both women and in men, independent of confounders, RI and Pb contributed more than Pf, whilst Pa and AIx contributed less than incident wave pressure (Pi) to variations in PPc ($p<0.0001$ for comparison of partial r values). In both men and in women Pb contributed more than Pf ($p<0.05$) to variations in LVM. Although in men Pa (partial $r=0.33$, $p<0.0001$) contributed to a similar extent as Pi ((partial $r=0.34$, $p<0.0001$) to variations in LVMI, in women Pa (partial $r=0.05$, $p=0.36$) failed to contribute to LVM, whilst Pi was significantly associated with LVM (partial $r=0.30$, $p<0.0001$). Similar results were obtained with AIx as opposed to Pa in the regression models. Therefore, in both women and in men, Pb is more closely associated with PPc and LVM than Pf, but indices of aortic pressure augmentation markedly underestimate these effects, particularly in women.

As the relative impact of aortic Pb as compared to Pf on cardiovascular damage independent of brachial BP is uncertain, in 1174 participants from a community sample I subsequently assessed the relative impact of Pb and Pf on variations in LVM (n=786), aortic pulse wave velocity (PWV)(n=1019), carotid intima-media thickness (IMT)(n=578), transmitral early-to-late LV diastolic velocity (E/A)(n=779) and estimated glomerular filtration rate (eGFR)(n=1174). Independent of mean arterial pressure and confounders, PPc and both Pb and Pf were associated with end-organ measures or damage ($p<0.05$ to <0.0001). With adjustments for brachial PP and confounders, Pb remained directly associated with LVM (partial $r=0.10$, $p<0.01$), PWV (partial $r=0.28$, $p<0.0001$), and IMT (partial $r=0.28$, $p<0.0001$), and inversely associated with E/A (partial $r=-0.31$, $p<0.0001$) and eGFR (partial $r=-0.14$, $p<0.0001$). Similar relations were noted with the presence of end-organ damage ($p<0.05$ to <0.0001). In contrast, with adjustments for brachial PP and confounders, Pf no longer retained direct relations with LVM, PWV, and IMT or inverse relations with E/A and eGFR. Adjustments for Pb, but not Pf diminished brachial PP-independent relationships between PPc and end-organ measures. Thus, although both Pf and Pb contribute to end-organ measures and damage, independent of brachial

BP, the impact of aortic BP is accounted for largely by Pb.

PPamp is independently associated with cardiovascular outcomes. However, the aortic functional change most likely to account for this effect is uncertain. In 706 community participants I subsequently aimed to identify the aortic functional change that accounts for relations between PPamp and LVM. In multivariate models with the inclusion of brachial PP, 1/PPamp (partial $r=0.12$, $p<0.005$), Pb (partial $r=0,09$, $p<0.05$), and aortic PWV (partial $r=0.09$, $p<0.05$) were independently associated with LVMI. Similarly, in multivariate models with the inclusion of brachial PP, 1/PPamp ($p<0.005$), Pb ($p<0.01$), and aortic PWV ($p<0.01$) were independently associated with LV hypertrophy (LVH). With adjustments for Pb, the brachial PP-independent relationships between 1/PPamp and LVMI or LVH were abolished ($p>0.08$ for both). However, adjustments for PWV failed to modify brachial PP-independent relations between 1/PPamp and LVMI or LVH. Hence, independent relations between PPamp and LVM or LVH are largely accounted for by Pb.

In conclusion, in the present thesis I show that the use of augmented pressures underestimates the impact of reflected pressure wave effects on end-organs, particularly in women; that brachial BP-independent relations between aortic BP and end organs is determined largely by Pb and that relations between PPamp and end organ measures is largely accounted for by Pb. These findings add to our understanding of the adverse effects of aortic functional changes on the cardiovascular system and suggest cost-effective approaches to add to risk prediction.

DECLARATION

I declare that this is my own unaided work. It is being submitted for the degree of Doctor of Philosophy in the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg. The work contained in this thesis has not been submitted for any degree or examination in this University, or any other University.

.....

Moekanyi Jeffrey Sibiya

..... day of ……., 2017

I certify that the studies contained in this thesis have the approval of the Committee for Research in Human Studies of the University of the Witwatersrand, Johannesburg. The ethics approval numbers are M02-04-72 and renewed as M07-04-69, M12-04-108 and M10-11-46.

……...

Moekanyi Jeffrey Sibiya

.....day of ……., 2017

.....	.....
Gavin R. Norton (supervisor)	Angela J. Woodiwiss (supervisor)
Date.....	Date.....

.....

Elena Libhaber (supervisor)

Date.....

Dedication:
For my parents,
Samuel Olifile and Iris Batshabile
Sibiya

PUBLICATIONS AND PRESENTATIONS ARISING FROM THE THESIS

Publications

1) **Sibiya** MJ, Norton GR, Hodson B, Redelinghuys M, Maseko MJ, Majane OHI, Libhaber E, Woodiwiss AJ. Gender-specific contribution of aortic augmentation index to variations in left ventricular mass index in a community sample. Hypertension Research 2014;37:1021-1027.
2) **Sibiya** MJ, Woodiwiss AJ, Booysen HL, Raymond A, Millen AME, Maseko MJ, Majane OHI, Sareli P, Libhaber E, Norton GR. Reflected rather than forward wave pressures account for brachial pressure-independent relations between aortic pressure and end-organ changes in an African community. J Hypertens 2015;33: 2083-20290.
3) **Sibiya** MJ, Norton GR, Booysen HL, Tade G, Libhaber CD, Ballim I, Sareli P, Woodiwiss AJ. Aortic backward waves rather than stiffness account for independent associations between pulse pressure amplification and left ventricular mass in a young-to-middle aged sample. J Am Soc Hypertens (under review).
4) Booysen HL, Woodiwiss AJ, **Sibiya** MJ, Hodson B, Raymond A, Libhaber E, Sareli P, Norton GR. Indexes of aortic pressure augmentation markedly underestimate the contribution of reflected waves toward variations in aortic pressure and left ventricular mass. Hypertension 2015;65:540-546.
5) Bursztyn M, Norton GR, Ben-Dov IZ, Booysen HL, **Sibiya** MJ, Sareli P, Woodiwiss AJ. Aortic pulse pressure amplification imputed from simple clinical measures adds to the ability of brachial pressure to predict survival. Am J Hypertens 2016;29:754-762.

Oral presentations

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2) **Sibiya** MJ, Norton GR, Hodson B, Redelinghuys M, Maseko MJ, Majane OHI, Libhaber E, Woodiwiss AJ. Gender-Specific Contribution of Aortic Augmentation Index to Variations in Left Ventricular Mass Index in a Community Sample. Stroke and Hypertension Congress, Durban, 2014.
3) **Sibiya** MJ, Woodiwiss AJ, Booysen HL, Raymond A, Millen AME, Maseko MJ, Majane OHI, Sareli P, Libhaber E, Norton GR. Reflected rather than forward wave pressures account for brachial pressure-independent relations between aortic pressure and end-organ changes in an African community. 41st Conference of the Physiology Society of Southern Africa (PSSA), University of the Witwatersrand & University of Johannesburg, held in Parys, 2015.

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1) **Sibiya** MJ, Norton GR, Maseko MJ, Majane OHI, Woodiwiss AJ. Relative Contribution of Aortic Forward and Augmented Pressures to the Impact of Aortic Pulse Pressure on Carotid Intima-Media Thickness in a Community Sample. Annual Scientific Meeting and Exposition of The American Society of Hypertension. New York, United States of America, 2014.
2) **Sibiya** MJ, Norton GR, Hodson B, Redelinghuys M, Maseko MJ, Majane OHI, Libhaber E, Woodiwiss AJ. Gender-Specific Contribution of Aortic Augmentation Index to Variations in Left Ventricular Mass Index in a Community Sample. Faculty of Health Sciences Research Day & Postgraduate Expo. University of the

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4) **Sibiya** MJ, Woodiwiss AJ, Booysen HL, Tade G, Libhaber CD, Ballim I, Sareli P, Norton GR. Which Indexes of Aortic Function Best Add to Brachial Pulse Pressure Associations with End-Organ Changes Independent of Pulse Wave Velocity in a Group of African Ancestry? Stroke and Hypertension Congress, Misty Hills, 2016.

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STATEMENT OF CONTRIBUTION TO DATA COLLECTION AND ANALYSIS

I contributed to the collection of all data with the assistance of a qualified nurse and several research assistants. I contributed toward the development of the database and I analysed the data with the support of my supervisors.

LIST OF ABBREVIATIONS

AIx	augmentation index
AP	augmentation pressure
BMI	body mass index
BP	blood pressure
CAFE	Conduit Artery Function Evaluation
CHD	coronary heart disease
CI	confidence interval
Cm	centimeter
DBP	diastolic blood pressure
DM	diabetes mellitus
E/A	transmitral early-to-late LV diastolic velocity
EF	ejection fraction
eGFR	estimated glomerular filtration rate
F(t)	flow wave
GBD	global burden of disease
GTF	generalized transfer function
g/m^2	gram per $meter^2$
$g/m^{1.7}$	gram per $meter^{1.7}$
$g/m^{2.7}$	gram per $meter^{2.7}$
$h^{1.7}$	$height^{1.7}$
HbA1C	glycated haemoglobin
HDL	high density lipoprotein
HIV	human immunodeficiency virus
IMT	carotid intima-media thickness
ISH	isolated systolic hypertension

kg	kilogram
kg/m²	kg per meter²
LV	left ventricular
LVED	LV end diastolic
LVEDD	LV end diastolic diameter
LVEDV	LV end diastolic volume
LVESD	LV end systolic diameter
LVESV	LV end systolic volume
LVH	LV hypertrophy
LVM	left ventricular mass
LVMI	left ventricular mass index
LVMI-BSA	LVM indexed for body surface area
m^2	meter²
m/sec	meter per second
MAP	mean arterial pressure
MHz	megahertz
ml/min	milliliter per minute
mls/min	milliseconds per minute
mm	millimeter
mm Hg	millimetres of mercury
mmol/l	millimole per litre
mmol/day	millimoles per day
mV	millivolts
n	number (sample size)
Na+/K+	sodium-to-potassium ratio
NCD-RisC	NCD Risk Factor Collaboration
P_1	central (aortic) forward component pressure
P_2	central (aortic) backward component pressure

P(t)	measured pressured wave
Pa	augmentation Pressure
Pb	backward wave pressure
Pf	forward wave pressure
Pi	incident Wave Pressure
PPb	brachial pulse pressure
PPc	central aortic pulse pressure
PP	pulse pressure
Pty. Ltd.	proprietary limited
p value	probability value
PWT	posterior wall thickness
PWV	pulse wave velocity
r	partial correlation coefficients
RI	reflected wave index
RM	reflected wave magnitude
RWT	relative wall thickness
SAS	statistical analyses software
SBP	systolic blood pressure
SBPc	central aortic systolic BP
SD	standard deviation
SEM	standard error of the mean
SPC-301	sphygmocor-301
Statistics SA	statistics South Africa
WHO	World Health Organization
Zc	characteristic impedance

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PREFACE

Cardiovascular disease is the leading cause of morbidity and mortality globally and a major cause of mortality in South Africa. Although several well-established risk factors may be employed to risk predict, these may only account for a portion of the overall cardiovascular risk. A major cause of cardiovascular disease is hypertension and hypertension is thought to be the major risk factor for cardiovascular events in South Africa. Although brachial blood pressure (BP) is a well-recognised predictor of cardiovascular events and target for drug therapy, there is increasing evidence that several factors that contribute to aortic BP may add to risk prediction. However, the relative role of these variables beyond brachial BP is uncertain.

The present thesis is motivated by a need to better understand those aortic functional changes that contribute toward variations in target organ measures in a community of African ancestry in South Africa. These studies were performed with the hope that this information will provide a guide to how to best enhance risk prediction beyond conventional cardiovascular risk factors, including brachial BP, using simple, easy to measure and cost-effective approaches to aortic function measurements. Importantly, in the present thesis I assessed relations between aortic function and target organ measures, rather than cardiovascular outcomes (hard end points) as in South Africa 50% of death certificates indicate “natural causes” rather than a specific cause of death. In this regard, it is well accepted that several end-organ measures including left ventricular hypertrophy, carotid indices of atheroma, an index of large artery stiffness, and measures of renal function predict outcomes beyond conventional risk factors. These end-organ measures are therefore assumed to represent effective intermediate phenotypes to hard end-point.

The present thesis is written as a series of semi-independent chapters, each with its own introduction, methods, results and discussion section. The thesis begins with a review chapter which highlights the current understanding and controversies in the field and leads the reader through a series of arguments in support of conducting the studies

described in the present thesis. Furthermore, the present thesis concludes with a summary chapter which consolidates the findings of each chapter and underscores the novelty of the findings by placing the studies in the context of our present understanding of the field. In support of the present thesis, the data presented in chapters 2 and 3 have been published in the journals *Hypertension Research* (Sibiya et al 2014), and *Hypertension* (Booysen et al 2015) respectively, the data presented in chapter 4 in the *Journal of Hypertension* (Sibiya et al 2015), and the data in chapter 5 has received favourable reviews from the *Journal of the American Society of Hypertension* (Sibiya et al 2017, under review).

CHAPTER 1

INTRODUCTION:

Current Understanding of the Role of Aortic Pulse Pressure and the Determinants Thereof in Cardiovascular Disease

1.1 Introduction

Cardiovascular disease constitutes a group of disorders of the heart and blood vessels which often share similar risk factors. These disorders mainly include cerebrovascular disorders or stroke (ischaemic and haemorrhagic), ischaemic heart disease including myocardial infarction, heart failure, peripheral arterial disease and renal failure. As identified in the Global Burden of Disease (GBD 2015) study, cardiovascular disease is a major cause of global mortality and morbidity (Roth et al 2015, GBD 2015), where in 2013 cardiovascular disease contributed to 32% (17 million) of the more than 54 million deaths recorded world-wide. The GBD study was a comprehensive study that accounted for outcomes based on both death registrations, as well as verbal autopsies, and determined mortality for 240 diseases from 188 countries globally from the year 1990 to 2013. Of the four major categories of non-communicable diseases (diabetes mellitus, cardiovascular disease, cancer and chronic obstructive lung disease) cardiovascular disease was noted to be the most common cause of death compared to the other three categories (Roth et al 2015).

The GBD study (2015) was limited by the fact that data from low income or developing countries was not readily available. Economic challenges leading to a lack of education and malnutrition play a major role in the epidemiology of non-communicable disease. Therefore, understanding the burden of non-communicable diseases in developing countries is of critical importance. It is essential to note that approximately 80% of cardiovascular deaths in the year 2005 occured in low-to-middle income countries (Mendis et al 2007). When comparing mortality rates between high and low income countries using age standardized methods, the mortality rate attributable to cardiovascular disease in low income countries decreased from 381 per 100 000 people in 1990 to 332 per 100 000 in the year ending 2013 (13% decline) whilst in high income countries, the mortality rate decreased from 283 per 100 000 people in 1990 to 160 per 100 000 in the year ending 2013 (43% decline) (Roth et al 2015). Thus, the decline in

mortality rate from cardiovascular disease was markedly worse for low as compared to high income countries. Moreover, there was a significant increase in the number of deaths attributed to cardiovascular disease in low income countries from 7.2 million to 12 million (66% increase) in the year ending 2013 (Roth et al 2015). This marks a striking increase over a two-decade period. In 2013, cardiovascular disease caused approximately a million deaths sub-Saharan Africa (Mensah et al 2015). These data suggest that the burden of cardiovascular disease is far greater in developing nations rather than economically developed countries. Why is cardiovascular disease becoming more important in developing countries?

An epidemiologic transition is thought to exist in developing nations. Whilst previously diseases of poverty, malnutrition and infectious diseases were the main causes of morbidity and mortality, this spectrum of disease is now changing into diseases of lifestyle. In Africa, the burden of non–communicable disease is attributed to cardiovascular disease (Mocumbi 2013). Although people in Africa present with traditional risk factors for cardiovascular disease, the condition is exacerbated by the scourge of infectious disease. In Africa, especially, sub- Saharan Africa, the high rate of human immunodeficiency virus infections, which for several reasons increases the prevalence of conventional risk factors and may itself have direct effects on the cardiovascular system, has complicated the management of cardiovascular risk factors (Mocumbi et al 2012, Temu et al 2015). In sub-Saharan Africa the low doctor-to-patient ratio and scarcely resourced healthcare systems as noted by the World Health Origination (WHO) add to the threat of inadequate healthcare provision.

In 2007 and 2008 greater than 19.4% of deaths in South Africa were from cardiovascular disease. This represents a similar burden of disease as that given for the leading reported cause of death, which is tuberculosis (21.8%) (Statistics SA 2010). Age-adjusted mortality rate attributable to cardiovascular disease in South Africa indicates the range to be between 250-to-325 per 100 000 people in the year 2013 (GBD 2015). As with other developing countries, this is higher than developed nations. These figures

represent similar figures of reported deaths as those given in 2003/2004 (Statistics SA 2006) and are in-line with the WHO prediction that during the period 2006 to 2015, deaths from non-communicable diseases will increase by more than 24% in Africa, and that a substantial portion of families with heart disease will experience catastrophic expenditure which will drive families below the poverty line (Zarocostas 2010). These figures are also in-line with WHO predictions that by 2020, 69% of diseases in developing countries such as South Africa will be non-communicable diseases, of which the greatest burden will derive from cardiovascular disease (Zarocostas 2010, Boutayeb 2006).

1.1.1 Hypertension as cause of cardiovascular disease

Of all the risk factors for cardiovascular disease, which include hypertension, diabetes mellitus, dyslipidaemia, obesity, smoking, and alcohol consumption, most population attributable risk for cardiovascular events is determined by hypertension (Steyn et al 2005, Rayner et al 2010, Huang et al 2013, Park et al 2015). As an important example of such a study conducted in those of African ancestry, in The Atherosclerosis Risk in Communities Study which evaluated a large multi-center and biracial community-based cohort; diabetes mellitus and hypertension accounted for most of the risk for cardiovascular disease (Cheng et al 2014). It is not only blood pressure values over presently accepted thresholds of 140/90 mm Hg that predict risk. Indeed, there is considerable evidence that blood pressure values over a lower range predict risk and that this is noted irrespective of age, gender, ethnicity, or follow-up duration and that the impact of blood pressure on risk prediction in the pre-hypertensive range was unaffected by adjustments for comorbidities (Huang et al 2013). In this regard, the high population attributable risk of hypertension and pre-hypertension may be explained by the fact that of all of the cardiovascular risk factors, the prevalence rate of hypertension and pre-hypertension is by far the highest. Importantly however, it should be acknowledged that

hypertension is strongly associated with other risk factors and these risk factors often precede the development of hypertension. Indeed, those with pre-hypertension have at least one other cardiovascular risk factor (Greenlund et al 2004).

1.1.2 Differences in hypertension prevalence rates between populations.

There are considerable differences in the prevalence of hypertension in developed and developing countries. In this regard, in population-based measurement surveys from 200 countries of 19.1 million participants 18 years and above, when compared to most countries in most continents, based on age-standardized blood pressure the prevalence of hypertension was noted to be the highest in sub-Saharan Africa and South Asia when it used to predominately affect high-income countries or regions (NCD-RisC [NCD Risk Factor Collaboration] 2017). In this survey, age-standardized adult mean blood pressure remained virtually unchanged between the years 1975 to 2015 in men, whilst a slight decrease of blood pressure in women was noted. The cause of hypertension in different populations may vary and this may contribute to variations in the prevalence rate of hypertension between communities. For example, in African populations salt sensitivity may be a more important cause of hypertension than in alternative populations and hence prevalence rates may depend more on the average salt intake of a community (Maseko et al 2006). Socio-economic status also determines the prevalence of hypertension in various populations. High income population groups tend to have a lower prevalence of hypertension as compared to low income populations and this may be attributed to a greater ability to afford healthier foods, a better understanding of what healthier foods are or higher levels of activity (Yusuf et al 2011).

1.1.3 Half of cardiovascular deaths may not be accounted for by conventional risk factors

Previous studies have estimated that about 50% of cardiovascular deaths or events may not be accounted for by conventional risk factors (Yusuf et al 2004, Chockalingam et al 2000, Yusuf et al 2001). More recently however, some studies have reported that when taken together, conventional risk factors account for approximately 90% or more of cardiovascular risk (Ôunpuu et al. 2001, Yusuf et al 2004, McQueen et al 2008, O'Donell et al 2010a, O'Donell et al 2010b, O'Donell et al 2016). However, these studies (Ôunpuu et al 2001, Yusuf et al 2004, McQueen et al 2008, O'Donell et al 2010a, O'Donell et al 2010b, O'Donell et al 2016) are case-control studies and in none of these studies did the authors indicate how they avoided a selection bias in the control groups. In these studies (Ôunpuu et al 2001, Yusuf et al 2004, McQueen et al 2008, O'Donell et al 2010a, O'Donell et al 2010b, O'Donell et al 2016) controls were convenience samples including the use of hospital patients who had not had a cardiovascular event. Moreover, in these studies (Ôunpuu et al 2001, Yusuf et al 2004, McQueen et al 2008, O'Donell et al 2010a, O'Donell et al 2010b, O'Donell et al 2016) the authors failed to indicate whether the control samples showed risk factor profiles comparable with randomly selected population or community samples from which the cases were derived. Hence, it is likely that the results are in-part attributed to population stratification. Thus, these studies have not hampered the search for biomarkers of cardiovascular risk beyond conventional risk factors.

1.2 Aortic as opposed to brachial blood pressure in risk prediction

In the present thesis I studied the possibility of measures of aortic blood pressure (BP) adding to risk prediction beyond brachial BP and additional cardiovascular risk factors. Hence, in the present chapter I will provide a critical review of the current evidence supporting or refuting a role of aortic function (with a focus on aortic BP measurements) in risk prediction. Central to an understanding of why aortic BP was

considered as a measurement that may add to risk prediction is the landmark findings of a more important role of brachial systolic as opposed to diastolic BP in risk prediction.

1.2.1 Why has the emphasis moved from diastolic to systolic BP in risk prediction?

The presence of hypertension is diagnosed on the basis of a raised brachial artery systolic or diastolic BP. However, risk prediction using brachial BP measurements has over the years changed from a focus on diastolic BP (DBP) to that of systolic BP (SBP). In this regard, the most important risk factor for cardiovascular disease, that is advancing age, is associated with linear increases in SBP across the adult lifespan, whilst DBP increases during early to mid-life and then begins to decline during old age (Franklin et al 1999). Importantly, the Framingham Heart Study showed that SBP is a stronger predictor of cardiovascular risk than DBP in older persons (Kannel et al 1971). Moreover, several observational studies subsequently reported on a direct relationship between SBP and cardiovascular risk whilst an inverse relationship was noted between DBP and cardiovascular risk (Franklin et al 1999, Benetos et al 2000, Staessen et al 2000). Nevertheless, when predicting risk, DBP is now recognized as being more important than brachial SBP in those younger than 45 years of age (Chobanian et al 2003, Mancia et al 2007), but this has been suggested to be attributed to the overestimation of aortic SBP with brachial SBP measurements in this age group (McEniery et al 2008).

With the recognition of a more important role for brachial SBP than DBP in cardiovascular risk prediction, the question has arisen as to whether SBP measured at the brachial artery is the best SBP measurement for risk prediction? In this regard, through amplification of BP from the aorta to the brachial artery (see later discussion for the mechanisms), aortic SBP may be considerably lower than brachial SBP whilst DBP is similar in the aorta and the brachial artery. As it is hypothesized that the BP in the aorta rather than the brachial artery is more likely to be responsible for end-organ damage, it is

possible that brachial SBP may not be an adequate surrogate of the BP thought to produce cardiovascular damage. Hence, in the following sections of this chapter I will discuss the differences in the determinants of aortic and brachial BP and the evidence for or against a role for aortic as opposed to brachial BP or their determinants as the better measures of end-organ damage. I will simultaneously highlight the missing evidence which prompted me to perform the studies conducted in the present thesis.

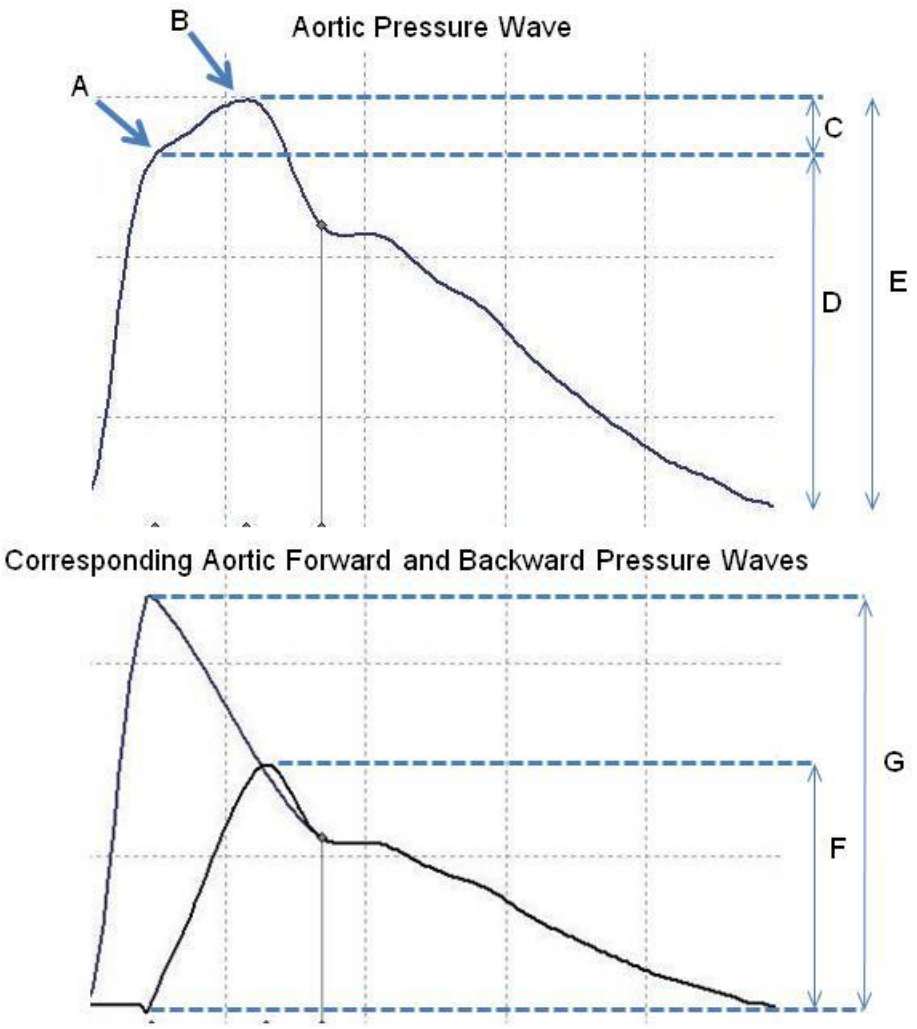
1.2.2 Central aortic BP is lower than brachial BP

Aortic SBP is generally lower than brachial SBP because of the higher stiffness (and hence impedance) of more peripheral arteries as compared to the aorta (Nichols et al 2011). In other words the pulse is amplified from the aorta to the brachial artery because the aorta is an elastic artery whilst peripheral arteries are less compliant. This difference in stiffness occurs because peripheral arteries are muscular with a relatively small radius, whilst the aorta is a distensible conduit (high quantity of elastic tissue) and has a much wider radius. Importantly, there is little difference between DBP in the aorta as compared to peripheral arteries and hence the main distinction between aortic and brachial BP is in the difference between SBP and DBP, that is, the main difference between aortic and brachial BP is in the pulse pressure (PP). Hence, differences between brachial and aortic BP are often referred to as PP amplification. What are the factors that determine aortic as opposed to brachial PP and hence PP amplification?

1.2.3 Determinants of aortic versus brachial PP

Although during youth and early adulthood the aorta represents a highly elastic conduit, with ageing and with the effects of several risk factors (hypertension, smoking, diabetes mellitus, dyslipidaemia and chronic inflammation), the aorta becomes stiffer. As the aorta stiffens, aortic pressures are enhanced during aortic ejection when blood is

pumped into a stiffer conduit. Increasing stiffness of the aorta with age and cardiovascular risk factors involves destruction of elastic tissue, increases in aortic collagen content and changes in the properties of collagen (e.g. increased collagen cross-linking as may occur with enhanced glycosylation of collagen in diabetes mellitus or in conditions where lysyl oxidase activity [the enzyme responsible for cross-linking of collagen] increases) (Nichols et al 2011). Importantly, the magnitude of the pressure waveform generated when blood is ejected into a stiffer aorta (the aortic forward pressure wave, Figure 1.1) is determined largely by two factors. In this regard, the forward wave pressure increases with an enhanced stroke volume which in-turn increases with increments in left ventricular contractility and the Frank-Starling effect (improved ventricular filling causing a greater force of contraction). In addition, the forward wave pressure is also augmented by aortic impedance, which increases as the aorta stiffens. Across the adult lifespan whilst aortic stiffness may increase, especially with the ageing process, the stiffness of peripheral arteries in the upper limb increases to a lesser degree (Nichols et al 2011). Hence, with ageing and disease, it is proposed that as aortic BP increases, BP in peripheral arteries increases far less and hence brachial BP begins to approximate aortic BP (Nichols et al 2011, McEniery et al 2008). Indeed, on average, brachial BP increases by 25 mm Hg between the ages of 20–80 years, whilst central aortic BP increases by 40 mm Hg over this same age range (Vlachopoulos & O'Rourke 2000). Thus, with increasing age, and with more cardiovascular risk factors, aortic BP increases far more than brachial BP and PP amplification decreases. Hence, increases in aortic BP in excess of brachial BP and a reduced PP amplification may be surrogate indices of an increased aortic stiffness that occurs with advancing age and the presence of cardiovascular risk factors. Consequently, it has been proposed that either aortic BP or PP amplification may be better indices than brachial BP, or at least indices that add to the ability of brachial BP to predict cardiovascular events.



A: First Systolic Shoulder

B: Second Systolic Shoulder

C: Augmentation Pressure (Pa)

D: Incident Wave Pressure (Pi)

E: Central Aortic Pulse Pressure (PPc)

F: Backward Wave Pressure (Pb)

G: Forward Wave Pressure (Pf)

Augmentation Index (AIx) = Pa/PPc

Wave Reflection Magnitude (RM) = Pb/Pf

Figure 1.1 Aortic pressure wave (upper panel) as determined by the combined effect of the aortic forward (Pf) and aortic backward (Pb) pressure waves (lower panel). Definitions of various measures of arterial pulse wave analysis are also shown. The figure shows actual data obtained from SphygmoCor recordings.

To recapitulate, a higher brachial as compared to aortic BP (PP amplification) is attributed to the differences in stiffness between the distensible aorta and stiff peripheral arteries (brachial). Thus, decreases in PP amplification are attributed in-part to increases in aortic stiffness with lesser increases in peripheral artery stiffness. However, variations in aortic backward wave pressure (Figure 1.1) also determine the variability of PP amplification. In this regard, pressure waves travelling down arteries encounter reflection points which may occur at innumerable sites in the arterial bed (Nichols et al 2011). These reflection points are generated by discontinuities in the arterial tree produced by branch points, changes in wall structure and tapering of vessels. Increases in tapering of vessels may occur with vasoconstriction of either arterioles or of more proximal vessels. At these sites pressure waves are reflected back and return to the ascending aorta. Summation of reflected waves derived from multiple reflection points results in a single backward wave returning to the aorta.

The backward wave may return sufficiently early that the pressure generated by this wave (Pb) adds to the pressure generated by the forward wave (Pf) and hence Pb augments aortic SBP (Figure 1.1). In this regard, two pressure waves appear in the aorta and the peak of the backward wave (second systolic shoulder) appears as the peak of the aortic pressure wave (Figure 1.1). In contrast, the peak of the forward wave approximates the inflection point of the first systolic shoulder and appears as a lower value than the peak of the backward wave (Figure 1.1). Hence, in the aorta, although the backward wave is of smaller amplitude than the forward wave, the backward wave clearly contributes to peak aortic SBP. However, the aortic backward wave appears in a different form in the brachial pressure wave.

As with the aorta, in the brachial artery two pressure waves are also generated, and these include a percussion wave (first systolic shoulder), which largely reflects the effect of blood flow generated by aortic Pf, and a later tidal wave (second systolic shoulder), which largely reflects aortic backward wave pressures (Figure 1.2). In contrast to what occurs in the aorta however, where the backward wave clearly adds to peak

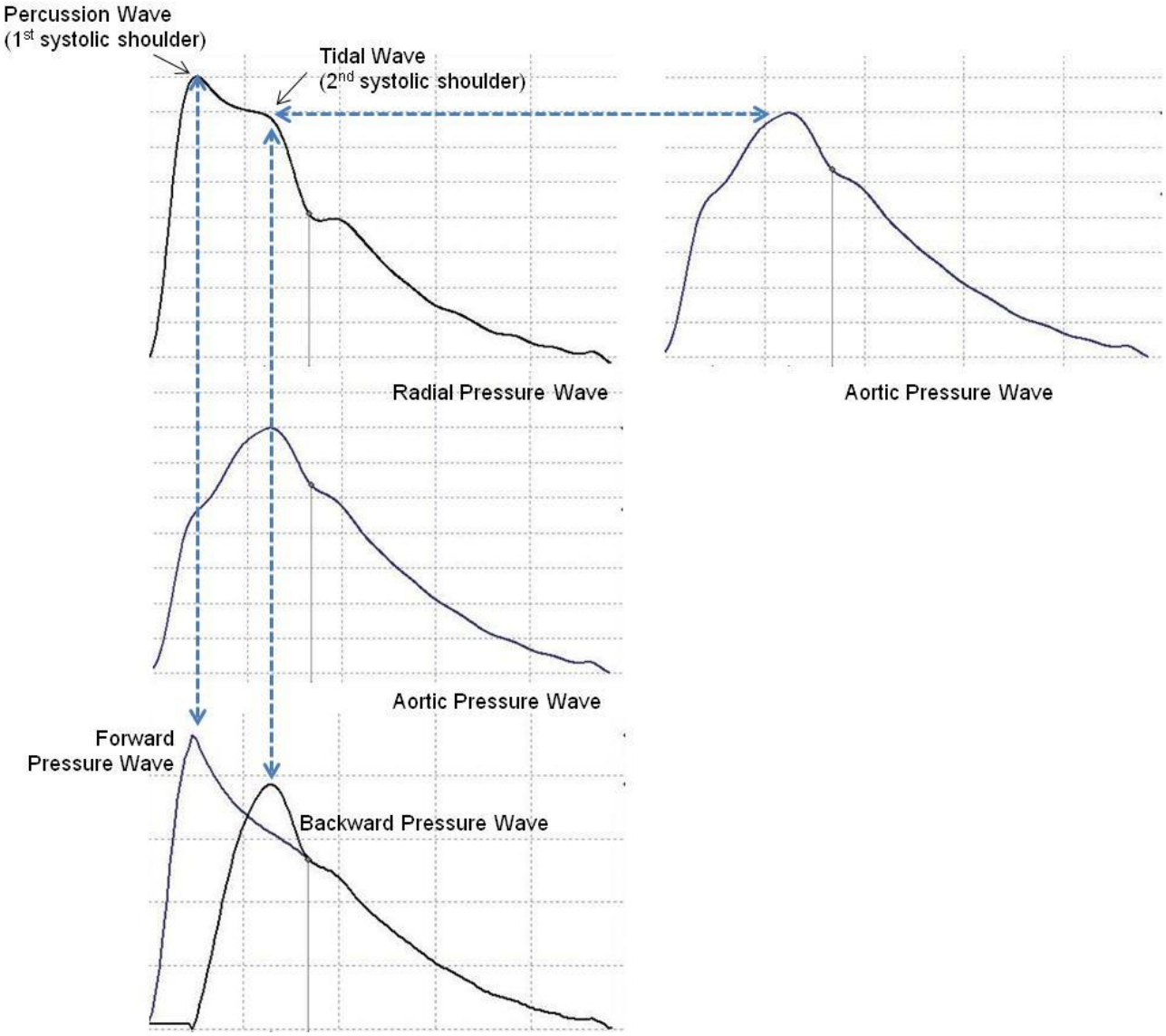


Figure 1.2. The contribution of aortic forward and aortic backward waves to aortic and radial (approximate of brachial) pulse waves. The dashed lines show temporal alignment of 1st and 2nd systolic shoulders (left panels) and alignment of the magnitude (left versus right panels) of pressure waves. The figure shows actual data obtained from SphygmoCor recordings.

aortic pressures, in peripheral e.g. brachial) arteries the backward wave (second systolic shoulder) appears as a lower value than the forward wave (the percussion wave is larger than the tidal wave), and hence makes little contribution to brachial pressures. Because SBP is considered to be the maximum pressure generated in the brachial artery, the pressure generated by the forward wave (percussion wave) is therefore recorded as SBP, whilst the pressures generated largely by backward waves (the tidal wave) are not recorded (Figure 1.2).

With aging, because backward wave pressures (Pb) begin to increase from as early as 20-30 years of age, brachial SBP increases less than aortic SBP from early adult life to old age. This is because brachial SBP only detects the peak of the percussion wave which is driven by the forward wave pressure (Pf) (Figure 1.3). In contrast, aortic SBP increases more than brachial SBP as aortic SBP is determined by both Pf and Pb (Figure 1.3). With advanced age, Pb may be sufficiently large that peak brachial SBP reflects either Pf or Pb (Figure 1.3) (Nichols et al 2011). Under these circumstances peak brachial BP closely approximates the peak of Pb and PP amplification is close to 0. Hence, variations in differences between aortic and brachial BP and in PP amplification may not only be attributed to differences in stiffness between the distensible aorta and stiff peripheral arteries, but also to the effects of age on wave reflection. Importantly, unlike aortic stiffness, which only increases to any marked extent from age 50 to 60 years, the aortic reflected wave begins to increase from age 20 years. Hence, although aortic pressures are lower than brachial pressures because of differences in stiffness between these vascular beds, peak brachial SBP in most adults, especially the young and in middle-aged adults, largely ignores the impact of Pb on aortic BP (tidal wave) and assesses mainly the impact of Pf (percussion wave) (Figure 1.2).

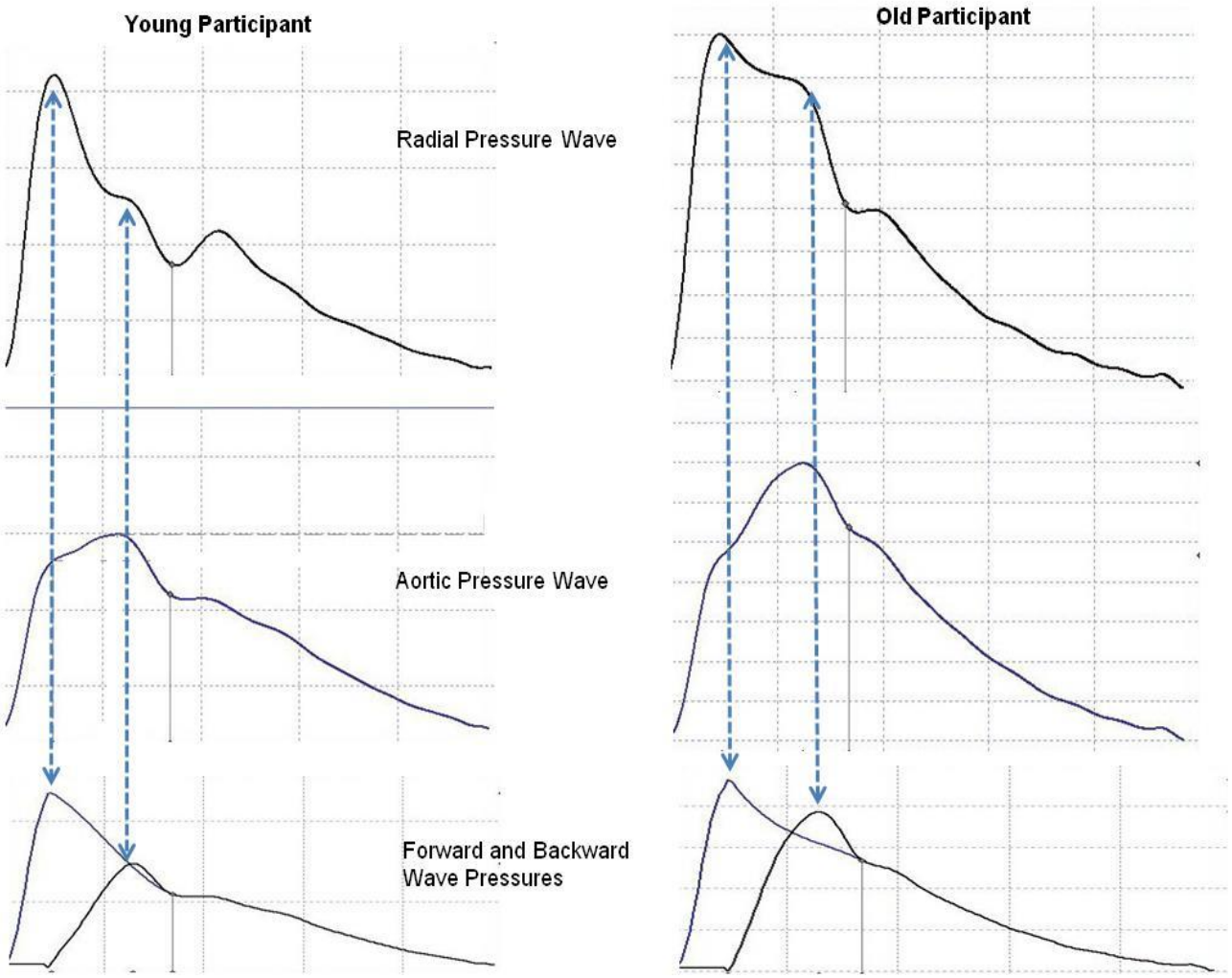


Figure 1.3. Age effects on aortic and radial artery pressure waves (which approximate brachial pressure waves). The figure shows changes in the combined effect of the aortic forward and aortic backward waves on pressure waveforms with age. The dashed line show how the forward and backward pressure waves contribute to radial and aortic pressure waves in a young and an old participant. The figure shows actual data obtained from SphygmoCor recordings.

1.2.4 Aortic versus brachial BP in risk prediction and associations with end-organ changes

Over the past two-to-three decades a number of simple and reliable approaches to aortic BP measurement have become commercially available. Several studies employing these approaches support the view that aortic BP is associated with cardiovascular end-organ measures better than or independent of brachial BP (Boutouyrie et al 1999, Covic et al 2000, (Safar et al 2002, Williams et al 2006, Wang et al 2009, Benetos et al 2010, Roman et al 2010, Wohlfahrt et al 2012, Benetos et al 2012, Neisius et al 2012, Norton et al 2012, Regnault et al 2012) and this topic has been extensively reviewed by Roman and Devereux (2014). Moreover, a recent meta-analysis provides evidence to show that aortic SBP or PP is more strongly associated with end-organ measures than brachial SBP or PP (Kollias et al 2016). However, the results of the relative role of aortic versus brachial BP in cardiovascular risk prediction are more contradictory.

A number of studies have demonstrated that aortic BP predicts cardiovascular outcomes better than or independent of brachial BP (Safar et al 2002, Williams et al 2006, Roman et al 2007, Jankowski et al 2008, Pini et al 2008, Roman et al 2009, Wang et al 2009, Benetos et al 2010, Benetos et al 2012, Regnault et al 2012). These findings were reported in patients with end-stage renal disease (Safar et al 2002), in patients undergoing coronary angiography (Jankowski et al 2008), in the elderly (Pini et al 2008), and in the general population (Roman et al 2007, Roman et al 2009). In contrast, however, in female hypertensives, brachial, but not central aortic BP was reported to predict cardiovascular outcomes (Dart et al 2006). Moreover, in a meta-analysis of these studies (Vlachopoulos et al 2010), the comparative ability of aortic versus brachial BP to cardiovascular risk predict did not achieve significance, although a trend for a better effect was noted for aortic as compared to brachial PP ($p=0.057$). This meta-analysis (Vlachopoulos et al 2010) however, excluded data from the The Conduit Artery Function Evaluation (CAFE) study (and obviously other later studies) which also reported on relations between aortic versus brachial BP and cardiovascular outcomes (Williams et al 2006) as well as a study conducted in Taiwan which

had not as yet been published at the time of the meta-analysis (Wang et al 2009) which similarly demonstrated an enhanced ability of aortic as compared to brachial BP in risk prediction. Moreover, this meta-analysis (Vlachopoulos et al 2010) was criticized for the inclusion of data from the study which failed to show relations between aortic BP whilst brachial BP did (Dart et al 2006). This criticism was based on the possibility that aortic BP values had not been adequately calibrated in that study (Dart et al 2006). Nevertheless, the Framingham Heart Study, which similarly had not been published at the time of the meta-analysis, demonstrated that neither aortic SBP or PP, nor PP amplification offered an ability to risk predict beyond brachial BP (Mitchell et al 2010a). However, in the Framingham Heart Study, little difference between aortic and brachial BP (PP amplification) was noted across the adult lifespan (Mitchell et al 2010b) and hence the chances of demonstrating a better or independent ability of aortic BP to risk predict than brachial BP were low. Although several subsequent and more contemporary studies also failed to show that aortic SBP or PP adds much to risk prediction beyond brachial SBP or PP, at the same time these studies demonstrated that PP amplification does add to risk prediction (Benetos et al 2010, Regnault et al 2012, Benetos et al 2012, Chirinos et al 2012, Bursztyn et al 2016). Hence, it is possible that PP amplification rather than aortic BP is more likely to act as a useful biomarker of risk prediction beyond brachial BP measurements.

Because of the inconsistencies in the ability of aortic BP and even PP amplification (in the Framingham Heart Study) to predict risk beyond brachial BP, the focus has shifted to the question of the importance of the factors which determine differences between aortic and brachial BP in risk prediction. As indicated in previous discussion there are two possible determinants of the differences in aortic and brachial SBP and PP and these include increases in aortic stiffness and increases in aortic backward waves. As the role of aortic stiffness as indexed using aortic pulse wave velocity (PWV) is now a well-established risk factor for cardiovascular events beyond brachial BP (Vlachopoulus et al 2010, Ben-Sehlomo et al 2014), further work on this topic is unlikely to significantly add to this field. However, as will be discussed there is still considerable uncertainty as to the role of aortic backward waves

in risk prediction. Hence, in the present thesis I have focused my efforts on evaluating the role of aortic backward waves as determinants of cardiovascular end-organ measures.

1.3 Role of aortic backward versus forward waves

In the following section I will discuss the methods of assessing aortic backward wave function; the evidence to support a particularly important role of aortic backward waves in groups of African ancestry, and the evidence to either support or refute a role for aortic backward waves in cardiovascular risk prediction or in associations with end-organ measures beyond brachial BP. In doing so I will highlight the unanswered areas in the field which prompted me to perform the studies conducted in the present thesis.

1.3.1 Approaches to assessing aortic backward wave function

Figure 1.1 shows the two approaches to assessing aortic reflected wave (backward wave) function. In this regard, aortic reflected waves have mainly been determined by evaluating the extent to which aortic systolic pressure is augmented by reflected waves and is derived from the difference between peak systolic pressure and the inflection point on the first systolic shoulder of the aortic pulse. This is called augmented pressure (Pa). Augmented pressure is expressed as a proportion of aortic pulse pressure and this is called augmentation index (AIx). Augmentation index as opposed to Pa is often employed to assess reflected wave function in order to avoid calibration errors (errors in calibration will appear in both the numerator and the denominator and hence will largely be eliminated by expressing the data as a ratio or proportion) and to demonstrate the relative importance of the backward (reflected) wave versus the forward wave. The latter argument is based on the fact that the portion of aortic PP that is not determined by the reflected wave will obviously be determined by the forward wave. To avoid negative values in younger persons (when backward wave pressures appear as a lower value than forward wave pressures), aortic augmentation index

is sometimes calculated as aortic SBP/pressure at the first systolic shoulder of the aortic pressure wave x 100.

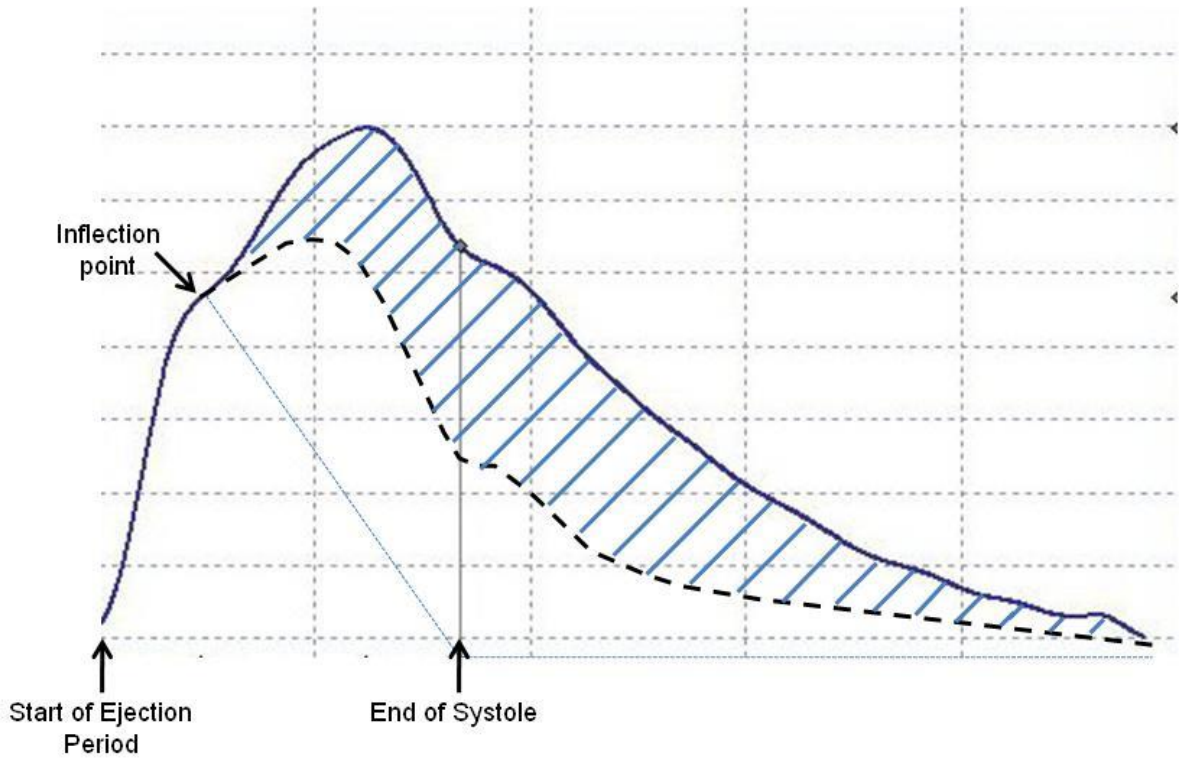
In addition to the use of aortic augmentation pressures or index, aortic backward waves can be separated from forward waves using “wave separation analysis” to produce two distinct waveforms illustrated in the lower panel of Figure 1.1. From these waveforms, the peak pressure generated by the forward (Pf) and backward (Pb) waves can be determined and the relatively greater role of the aortic backward wave is sometimes identified as the ratio of Pb to Pf (reflected wave magnitude [RM] or the reflection coefficient). The backward and forward waveforms may be separated using simultaneous aortic pressure and flow measurements (Westerhof et al 2006). The following formula is used to calculate Pf and Pb:

$$Pf(t)=[P(t) + Zc \bullet F(t)]/2$$

$$Pb(t)=[P(t) – Zc \bullet F(t)]/2$$

where P(t) is the measured pressured wave, F(t) is the flow wave, and Zc is characteristic impedance of the proximal aorta (Westerhof et al 2006). Characteristic impedance (Zc) is derived from the 4th to 7th harmonic (Westerhof et al 2006). In the calculation of Pb and Pf, Zc • F appears, where Zc is a ratio of (P/F). Therefore the product of Zc • F is independent of flow calibration (Westerhof et al 2006).

As simultaneous pressure and flow waveforms are laborious to acquire and are therefore unlikely to ever be used for risk prediction at a primary healthcare level, “assumed” aortic flow waves have been employed for wave separation analysis. This approach to “wave separation” analysis is depicted in Figure 1.4. The aortic flow wave is assumed to either be a triangular waveform or to assume a single “physiological” waveform shape (Kips et al 2009, Westerhof et al 2006). The more readily usable approach is to assume that the flow wave is



Thick Solid Line: Measured Pressure Wave
Thick Dashed Line: Forward Wave Pressure (Measured Pressure Wave – Pressure at Same Time Point in Triangular Waveform)
Fine Dotted Line: Triangular Waveform
Shaded Area: Backward Wave Pressure

Figure 1.4. Approach to separating aortic forward and backward pressure waves using an assumed triangular aortic flow wave. (Modified from Mitchell 2006).

triangular in shape. From comparisons against actual flow measurements, it was noted that one can approximate a flow waveform using a triangulation technique (Westerhof et al 2006). To apply a triangular flow waveform all that is required is the identification of the start, peak and end of the aortic flow (Westerhof et al 2006). As indicated in Figure 1.4, the start is at the beginning of the ejection period, the peak occurs at the inflection point of the first systolic shoulder or at 30% of the ejection time, and the end of flow is at the dicrotic notch where the aortic valve closes. The three points of the triangle are placed at these points (Figure 1.4) and the forward and backward waves determined as shown in Figure 1.4. As the aortic flow wave is often not a precise triangle, a better approach to wave separation analysis may be the use of a “physiological waveform”, which represents the average aortic flow waveform for a particular community (Kips et al 2009). Indeed, relationships between aortic backward waves derived from actual aortic flow waves and “physiological waveforms” may be stronger than relationships between aortic backward waves derived from actual aortic flow waves and “triangular waveforms” (Kips et al 2009). However, this approach assumes that every person has the same flow waveform shape, which is obviously not the case.

1.3.2. Aortic backward waves and pulse pressure.

The debate as to the factors that contribute most to increases in aortic PP with age is still ongoing. In this regard, the misconception that aortic stiffness is the main determinant of age-related increases in aortic PP is still propagated. However, as previously indicated aortic pulse wave velocity, a gold-standard measure of aortic stiffness only increases to any significant degree from around age 50 years, whilst aortic PP begins to increase from early adulthood (Hodson et al 2016, McEniery et al 2008, Mitchell et al 2010b). In contrast to significant increases in aortic stiffness occurring from only around 50 years of age, aortic backward wave pressures increase from early adulthood (20-30 years of age) and closely track age-related increases in aortic PP (Hodson et al 2016, Namasivayam et al 2009). A number of studies indicate that across the adult age range, as compared to aortic forward

wave pressures (or incident wave pressures) reflected waves, assessed from either indices of pressure augmentation, or from wave separation analysis, dominate age-related increases in aortic pressure (McEniery et al 2008, Namasivayam et al 2009, Cecelja et al 2009, Booysen et al 2015) and that reflected waves account for increases in aortic pressure in hypertension (Sibiya et al 2015). Hence, there is significant evidence that aortic backward waves are more important than forward waves in contributing toward increases in aortic PP. However, the contribution of aortic backward waves to increases in aortic PP may be more important in some as compared to other ethnic groups. What is the evidence to suggest an ethnic-specific effect on aortic backward waves?

It is well recognized that groups of African ancestry have a higher prevalence of salt sensitivity. Recently, our group have demonstrated an independent relationship between the ratio of urinary sodium to potassium derived from 24-hour urinary samples, and aortic augmented pressures or augmentation index and hence aortic pulse pressure (Redelinghuys et al 2010), thus suggesting a relationship between salt intake and aortic reflected wave function. This may explain the markedly higher aortic augmentation indexes noted in this ethnic group as compared to alternative populations around the world (Chirinos et al 2011). The possibility that there may be an ethnic-specific effect of aortic backward waves is underscored by the fact that unlike in may studies, aortic forward waves have been demonstrated to contribute far more to age-related increases in aortic PP than aortic backward waves in the Framingham Heart Study (Mitchell et al 2010b). However, in that study (Mitchell et al 2010b) a very high proportion of participants were receiving antihypertensive therapy and it is now well-recognized that antihypertensive agents produce marked decreases in aortic backward waves and the relationship between backward and forward wave pressures (see section1.3.6).

1.3.3 Aortic pressure augmentation in risk prediction and associations with end-organ measures

Several earlier studies demonstrated that aortic backward (reflected) waves, as determined from indices of pressure augmentation (Pa or AIx) are associated with cardiovascular damage (Hashimoto et al 2007, Hashimoto et al 2006, Weber et al 2006, Westerbacka et al 2005, Sibiya et al 2014), and predict cardiovascular outcomes (Chirinos et al 2005, London et al 2001, Ueda et al 2004, Weber et al 2005) independent of brachial BP. A meta-analysis of these and other outcome driven studies provides clear evidence that indices of pressure augmentation predict outcomes beyond brachial BP (Vlachopoulos et al 2010). Hence, based on measures of aortic pressure augmentation, aortic reflected waves were considered to be an important determinant of aortic pressure effects on cardiovascular damage independent or beyond brachial BP. However, the Framingham Heart Study failed to show that indices of aortic pressure augmentation predict outcomes independent of brachial BP (Mitchell et al 2010). Further, all of the earlier studies suggesting an important role for aortic wave reflection in mediating cardiovascular damage (Hashimoto et al 2007, Hashimoto et al 2006, Weber et al 2006, Westerbacka et al 2005, Chirinos et al 2005, London et al 2001, Ueda et al 2004, Weber et al 2005) employed Pa or AIx as a measure of wave reflection. As shown in Figure 1.1, the obvious error which may be introduced when assessing wave reflection with indices of pressure augmentation is that the point where the forward wave peaks and the reflected wave begins is obscure. Indeed, reflected wave pressures derived from wave separation analysis are considerably higher than that reported from Pa. The use of Pa or AIx as measures of aortic wave reflection have recently been criticized (Davies et al 2010, Cheng et al 2012, Hughes et al 2013, Fok et al 2014a, Torjesen et al 2014, Schultz et al 2013). In this regard, several studies suggest that many factors other than the magnitude of the aortic backward wave influence Pa and AIx (Cheng et al 2012, Fok et al 2014a, Torjesen et al 2014, Schultz et al 2013) and hence these measures may be poor indices of wave reflection. Indeed, there may be a weak relationship between the magnitude of the reflected wave and Pa or AIx with increases in aortic reservoir function, the timing or magnitude of the Pf or incident (Pi) wave pressures (aortic PP- [Pressure at the first systolic shoulder of the aortic pressure wave-DBP]) (Figure 1.1), and left ventricular systolic function playing a more

important role than wave reflection in contributing to variations in Pa and AIx (Davies et al 2010, Cheng et al 2012, Hughes et al 2013, Fok et al 2014a, Torjesen et al 2014, Schultz et al 2013). Furthermore, there is some evidence that whilst reflected wave magnitude derived from wave separation analysis is independently associated with cardiovascular events, augmentation index is not (Chirinos et al 2012) and that adjustments for augmented pressures and augmentation index do not influence the independent relationship between wave-separation analysis-derived backward wave pressures and cardiovascular events (Wang et al 2010). However, both augmentation index and the reflected wave magnitude have also been demonstrated to independently predict cardiovascular events (Weber et al 2012). Hence, there is considerable controversy as to whether relations between Pa or AIx and end-organ measures or cardiovascular outcomes reflect an impact of backward waves or alternative factors that influence Pa or AIx.

An impact of gender on Pa or AIx is well-recognised. In this regard, women have a higher AIx than men (Hughes et al 2013, Mitchell et al 2010b), but these differences may be attributed to factors unrelated to the magnitude of aortic wave reflection (Hughes et al 2013, Mitchell et al 2010a). Indeed, gender-specific effects on AIx in women of the Framingham Heart Study were attributed to increases in forward wave peak width, slope of the backward pressure wave, and forward wave amplitude, but not backward wave amplitude (Torjesen et al 2014). Whether these other factors (forward wave peak width, slope of the backward pressure wave, and forward wave amplitude) contribute as much as backward wave amplitude to cardiovascular damage is unknown. Hence, the impact of AIx on cardiovascular damage in women may not be as strong as that in men. Indeed, while AIx predicts outcomes in men, similar relationships may be diminished in women (Wang et al 2010). Nevertheless, in that study (Wang et al 2010) unadjusted relationships between AIx and end-organ changes were no different in women as compared to men. However, multivariate adjusted relationships between AIx and end-organ changes were not reported on (Wang et al 2010). To clarify whether gender influences relationships between AIx and cardiovascular end-organ changes, *in the present thesis I aimed to compare the association between AIx and left*

ventricular mass index (LVMI) in men and women in a large, community-based sample and to evaluate whether these effects are attributed to differences in backward wave pressures effects. These data are described in chapters 2 and 3 of the present thesis and have been published in the journals *Hypertension Research* (Sibiya et al 2014) and in-part in the journal *Hypertension* (Booysen et al 2015).

1.3.4 Relative contribution of aortic backward versus forward waves as determined using wave separation analysis to cardiovascular risk and end-organ measures.

As there is significant evidence to suggest that the use of aortic Pa or AIx are inadequate indices of aortic backward wave function, the question arises as to the relative contribution of aortic forward and backward waves, as determined using wave separation analysis, to cardiovascular end-organ measures and events. In the past few years, several studies have described an association of reflected waves (Pb or the reflected wave index-RI) derived from wave separation analysis with end-organ changes (Wang et al 2010, Weber et al 2012) or an ability of Pb or RI (or reflected wave magnitude-RM) to risk predict beyond brachial BP (Wang et al 2010, Weber et al 2012, Chirinos et al 2012, Zamani et al 2014). In this regard, in 1272 normotensive and untreated hypertensives, over an average of 15 years of follow-up, an increased wave reflection predicted cardiovascular mortality (n=64 events) in both men and women (Wang et al 2010). However, the extent to which the forward wave also contributed to cardiovascular end-organ changes and events was uncertain. In this regard, these authors (Wang et al 2010) showed that forward wave pressures were also predictive of events and similar relations between aortic forward wave pressures and end-organ measures as those noted between aortic backward wave pressures and end-organ measures were noted, but they failed to adjust for confounders or brachial BP. Further, in 725 patients undergoing coronary angiography, over an average of 3.83 years of follow-up, backward, but not forward wave pressures independently predicted cardiovascular events (n=139 events) (Weber et al 2012). However, again the extent to which the forward wave also contributed to

cardiovascular end-organ changes was uncertain (Weber et al 2012). In this regard, these authors (Weber et al 2012) also showed equivalent relations between aortic forward wave pressures and end-organ measures as those noted between aortic backward wave pressures and end-organ measures. In addition, in 5960 participants of a multi-ethnic community sample followed for an average of 7.61 years, the reflective wave magnitude was predictive of cardiovascular events and heart failure (n=281 events) (Chirinos et al 2012), but in this study it was uncertain as to whether the forward wave also predicted events. Nevertheless, in this same multi ethnic study, analysis of a much larger cohort of 6814 participants followed for 9.8 years, the backward, but not the forward wave was independently associated with all-cause mortality (n=617 events) (Zamani et al 2014). In contrast to the ability of several groups to show independent relations between aortic backward waves and outcomes, neither backward wave pressures nor the reflected wave index were independently associated with outcomes in the Framingham Heart study (Cooper et al 2014). Nevertheless, as pointed out in previous sections, a high proportion of the participants of the Framingham Study were receiving antihypertensive therapy, and as will be discussed in section 1.3.6, antihypertensive agents reduce aortic backward wave pressures. Consequently, aortic backward waves in the Framingham Heart Study failed to contribute as much as aortic forward waves to age-related increases in aortic PP as did aortic forward wave pressures (Mitchell et al 2010b).

In summary, despite the evidence in favor of aortic backward waves derived from wave separation analysis contributing to end-organ changes and cardiovascular risk (Wang et al 2010, Weber et al 2012, Chirinos et al 2012, Zamani et al 2014), whether forward wave pressures also associate with cardiovascular damage independent of brachial BP, and the relative contribution of forward wave and backward wave pressures to the brachial BP-independent relationship between PPc and cardiovascular damage is uncertain. This is particularly important for relations between the backward and forward wave components of aortic pulse pressure and end-organ measures. As highlighted above, the two studies which previously described these relations (Wang et al 2010, Weber et al 2012) failed to provide convincing evidence of a stronger brachial BP-independent relationship between aortic

backward as opposed to forward wave pressures and end-organ measures. Hence, as part of the present thesis *I aimed to assess in a community of African ancestry whether brachial BP-independent associations between Pb, Pf or both and end-organ measures or damage occur and whether brachial BP-independent associations between PPc and cardiovascular end-organ measures or damage are accounted for by an impact of Pb, Pf or both*. These data are described in chapter 4 of the present thesis and have been published in the *Journal of Hypertension* (Sibiya et al 2015).

1.3.5 Relative contribution of aortic backward versus forward waves to the impact of PP amplification on cardiovascular risk.

As indicated in the aforementioned discussion, PP amplification is determined by a greater stiffness of peripheral arteries as compared to the central aorta. However, as also indicated in previous sections the age-associated decline in PP amplification that occurs in most individuals is attributed to two factors. These include an increased aortic stiffness so that the aortic stiffness approximates or even becomes greater than peripheral arterial stiffness. The consequence is that whilst aortic PP increases markedly with age, peripheral arterial PP increases to a lesser extent for a given increase in age. In addition, age-related increases in aortic backward wave pressures occur, and these increases are reflected mainly in increases in the peak of the aortic pulse, but do not contribute as much to the peak of the peripheral arterial pulse (see section 1.2.3 for explanation). Importantly, as previously indicated, because aortic backward wave pressures increase markedly from young adulthood, whilst aortic stiffness only begins to significantly increase from 50-60 years of age, age-related decreases in PP amplification are mainly attributed to increases in aortic backward wave pressures (Hodson et al 2016).

As summarized in section 1.2.4 of the present chapter, PP amplification has on several occasions been shown to predict cardiovascular risk (Benetos et al 2010, Regnault et al 2012, Benetos et al 2012, Chirinos et al 2012, Bursztyn et al 2016). Importantly, these

associations have frequently been demonstrated in studies where aortic PP was imputed from simple clinical measures (Benetos et al 2010, Bursztyn et al 2016). Hence, PP amplification can be determined using approaches which cost little and hence are ideal for resource-limited settings. Because age-related increases in aortic backward waves are largely responsible for age-related decreases in PP amplification, we hypothesize that the mechanism responsible for associations between PP amplification and cardiovascular risk is mainly attributed to age-related increases in aortic backward wave pressures. However, no study has assessed whether increases in aortic stiffness or backward waves account for the brachial BP-independent association between PP amplification and cardiovascular end-organ changes. As one of the key end-organ changes that occur in response to aortic haemodynamic loads is left ventricular hypertrophy (LVH), as part of the present thesis *I therefore aimed to determine first whether PP amplification adds to brachial BP in associations with LV mass index (LVMI) and LVH in a large randomly selected community-based sample of largely young-to-middle aged participants. I further aimed to assess whether this relationship can be accounted for either by aortic stiffness as indexed by PWV, and/or by aortic backward wave function.* These data are shown in chapter 4 of the present thesis and have been accepted for publication in the *Journal of the American Society of Hypertension* (Sibiya et al 2017).

1.3.6 Antihypertensive effects on aortic forward and backward waves and PP amplification

As summarized in the preceding discussion there is still considerable uncertainty as to the role of PP amplification and aortic backward waves in mediating cardiovascular damage, whilst the gold-standard measure of aortic stiffness, PWV, is now recognized as a measure that will enhance risk prediction beyond brachial BP (Vlachopoulus et al 2010, Ben-Shlomo et al 2014). It is therefore important to understand whether current antihypertensive therapy modifies aortic stiffness and hence forward wave pressures, aortic backward wave pressures and/or PP amplification. Several antihypertensive drug classes have been

demonstrated to reduce aortic PP in-part through decreases in wave reflection, as indexed using Pa or AIx (Agabiti-Rosei et al 2007, Manisty et al 2012, Williams et al 2006, Miyashita et al 2010, Jiang 2007, Vinereanu et al 2014, Agnoletti et al 2013). Whether antihypertensive effects on aortic PP are mainly through reductions in Pb is nevertheless uncertain with a meta-analysis (Manisty et al 2012) and a large recent study (Agnoletti et al 2013) demonstrating little effect on AIx. In this regard vasodilator agents may also reduce Pf by decreasing distending pressures and hence aortic stiffness without altering vascular structure (McDonald's 2011). Moreover, diuretic agents may decrease Pf by reducing stroke volume. Thus, decreases in Pf rather than Pb may be the main mechanism of antihypertensive drug effects on aortic PP. However, if aortic backward waves and consequent decreases in PP amplification are central to mediating cardiovascular damage, it is important to first identify the role of these indices of aortic function and then to detect those antihypertensive agents that best modify these indices. Hence, in the present thesis I focused my efforts on contributing to our understanding of the role of aortic backward waves and PP amplification on end-organ measures.

1.4 Aims

In the present thesis, I therefore aimed to:

1) compare the association between AIx and left ventricular mass index (LVMI) in men and women in a large, community-based sample and to evaluate whether these effects are attributed to differences in backward wave pressures effects. These data are described in chapters 2 and 3 of the present thesis and have been published in the journals *Hypertension Research* (Sibiya et al 2014) and in-part in the journal *Hypertension* (Booysen et al 2015).

2) assess in a community of African ancestry whether brachial BP-independent associations between Pb, Pf or both and end-organ measures or damage occur and whether brachial BP-independent associations between PPc and cardiovascular end-organ measures or damage are accounted for by an impact of Pb, Pf or both. These data are described in chapter 3 of the present thesis and have been published in the *Journal of Hypertension* (Sibiya et al 2015).

3) whether PP amplification adds to brachial BP in associations with LV mass index (LVMI) and LVH in a large randomly selected community-based sample of largely young-to-middle aged participants. I further aimed to assess whether this relationship can be accounted for either by aortic stiffness as indexed by PWV, and/or by aortic backward wave function. These data are shown in chapter 4 of the present thesis and have been accepted for publication in the *Journal of the American Society of Hypertension* (Sibiya et al 2017).

CHAPTER 2

Gender-Specific Contribution of Aortic Augmentation Index to Variations in Left Ventricular Mass Index in a Community Sample of African Ancestry.

This chapter has been published as follows

Moekanyi J Sibiya, Gavin R Norton, Bryan Hodson, Michelle Redelinghuys, Muzi J Maseko, Olebogeng HI Majane, Elena Libhaber, Angela J Woodiwiss. Gender-specific contribution of aortic augmentation index to variations in left ventricular mass index in a community sample of African ancestry. *Hypertension Research* 2014;37:1021-1027

2.1 **Abstract**

Although indices of aortic augmentation derived from radial applanation tonometry are independently associated with adverse cardiovascular effects, whether these relationships are influenced by gender is uncertain. I compared the brachial BP-independent contribution of augmentation index (AIx) to variations in left ventricular mass index (LVMI) in a community sample of 808 participants, 283 of whom were men. Aortic haemodynamics were determined using radial applanation tonometry and SphygmoCor software and LVMI from echocardiography. In men, both AIx derived from aortic augmentation pressure/central aortic pulse pressure (AP/PPc) (partial r=0.17, β-coefficient±SEM=0.55±0.20, p<0.01) and AIx derived from the second peak/first peak (P_2/P_1) of the aortic pulse wave (partial r=0.21, β-coefficient±SEM=0.42±0.12, p<0.0005) were associated with LVM indexed to body surface area (LVMI-BSA). In contrast, in women neither AIx derived from AP/PPc (partial r=-0.08, β-coefficient±SEM=-0.20±0.11, p=0.08) nor AIx derived from P_2/P_1 (partial r=-0.06, β-coefficient±SEM=-0.07±0.05, p=0.17) were associated with LVMI-BSA. Both the strength of the correlations (p<0.001 and p<0.0005 with z-statistics) and the slope of the AIx-LVMI relationships (p=0.001 and p<0.0005) were greater in men as compared to women. The lack of relationship between AIx and LVMI was noted in both premenopausal (n=285)(AP/PPc vs LVMI-BSA, partial r=0.01, p=0.95, P_2/P_1 vs LVMI-BSA, partial r=0.02, p=0.77), and postmenopausal (n=240)(AP/PPc vs LVMI-BSA, partial r=-0.06, p=0.37, P_2/P_1 vs LVMI-BSA, partial r=-0.03, p=0.64) women. Similar differences were noted in the relationships between AIx and LVM indexed to height$^{2.7}$ in men and women. In conclusion, radial applanation tonometry-derived AIx may account for less of the variation in end organ changes in women as compared to men.

Key words: Central aortic augmented index, left ventricular mass index, gender.

2.2 **Introduction**

Although pulse pressure (PP) measured at the brachial artery is closely correlated with central PP (PPc), PPc may be considerably lower than in brachial arteries (Aviolo et al 2009, Agabiti-Rosei et al 2007). The factors that determine aortic PP differ markedly from those that determine brachial PP. In this regard, aortic PP is augmented by changes in aortic reservoir function, the timing or magnitude of both the forward and reflected waves, and left ventricular systolic function (Aviolo et al 2009, Agabiti-Rosei et al 2007, Davies et al 2010, Cheng et al 2012, Hughes et al 2013). Several studies have demonstrated that indices of aortic pressure augmentation predict cardiovascular events (London et al 2001, Ueda et al 2004, Weber et al 2005, Chirinos et al 2005, Wang et al 2010, Chirinos et al 2012, Vlachopoulos et al 2010), or are associated with end-organ damage independent of or better than brachial blood pressure (BP) (Hashimoto et al 2006, Hashimoto et al 2007, Weber et al 2006, Westerbacka et al 2005). As indices of aortic pressure augmentation may be derived from simple, and highly reproducible tonometric assessments of the radial artery, these indices are attractive additions to routine risk prediction. However, some studies (Vlachopoulos et al 2010, Mitchell et al 2010a, Hayashi et al 2014) including the Framingham Heart Study (Mitchell et al 2010a), have failed to show similar relations between indices of aortic augmentation and cardiovascular outcomes. The factors that determine whether indices of aortic pressure augmentation predict cardiovascular damage therefore require identification.

The impact of gender on aortic augmentation index (AIx) (augmentation pressure/aortic pulse pressure), is well-recognised. In this regard, women may have a higher AIx than men (Hughes et al 2013, Mitchell et al 2010b), but these differences may be attributed to factors unrelated to aortic wave reflection (Hughes et al 2013). Hence, the impact of AIx on cardiovascular damage in women may not be as strong as that in men. Indeed, while AIx predicts outcomes in men, similar relationships may be diminished in women (Wang et al 2010). Nevertheless, in that study (Wang et al 2010) unadjusted

relationships between AIx and end-organ changes were no different in women as compared to men. However, multivariate adjusted relationships between AIx and end-organ changes were not reported on (Wang et al 2010). To clarify whether gender influences relationships between AIx and cardiovascular end-organ changes, the aim of the current chapter is to compare the association between AIx and left ventricular mass index (LVMI) in men and women in a large, community-based sample. In this regard, LVMI and the regression thereof with antihypertensive therapy are well-recognised independent predictors of cardiovascular outcomes (Casale et al 1986, Levy et al 1990, Koren et al 1991, Levy et al 1994, Verdecchia et al 1996, Ghali et al 1998, Devereux et al 2004, Okin et al 2004).

2.3 **Methods**

2.3.1 Study group.

The present study was conducted according to the principles outlined in the Helsinki declaration. The Committee for Research on Human Subjects of the University of the Witwatersrand approved the protocol (approval number: M02-04-72 and renewed as M07-04-69 and M12-04-108). Participants gave informed, written consent. The present study design has previously been described (Norton et al 2008, Woodiwiss et al 2009, Redelinghuys et al 2010). Briefly, 808 participants from randomly recruited families of black African descent (Nguni and Sotho chiefdoms) with siblings older than 16 years from the South West Township of Johannesburg, South Africa, and with central haemodynamic measurements and high quality echocardiograms were studied.

*2.3.2 Clinical, demographic and anthropometric measurements***.**

A standardized questionnaire was administered to obtain demographic and clinical data (Norton et al 2008, Woodiwiss et al 2009, Redelinghuys et al 2010). Height and weight

were measured using standard approaches and participants were identified as being overweight if their body mass index (BMI) was ≥25 kg/m^2 and obese if their BMI was ≥30 kg/m^2. High quality BP measurements were obtained by a trained nurse-technician using a standard mercury sphygmomanometer (Woodiwiss et al 2009). Korotkoff phases I and V were employed to identify systolic and diastolic BP respectively and care was taken to avoid auscultatory gaps. Hypertension was defined as a mean systolic/diastolic BP≥140/90 mm Hg or the use of antihypertensive medication. Laboratory blood tests of renal function, liver function, blood glucose, haematological parameters, and percentage glycated haemoglobin (HbA_{1C}) were performed. Diabetes mellitus (DM) or abnormal blood glucose control was defined as the use of insulin or oral hypoglycaemic agents or an HbA_{1C} value greater than 6.1%. Menopause was confirmed with measurements of follicle stimulating hormone concentrations.

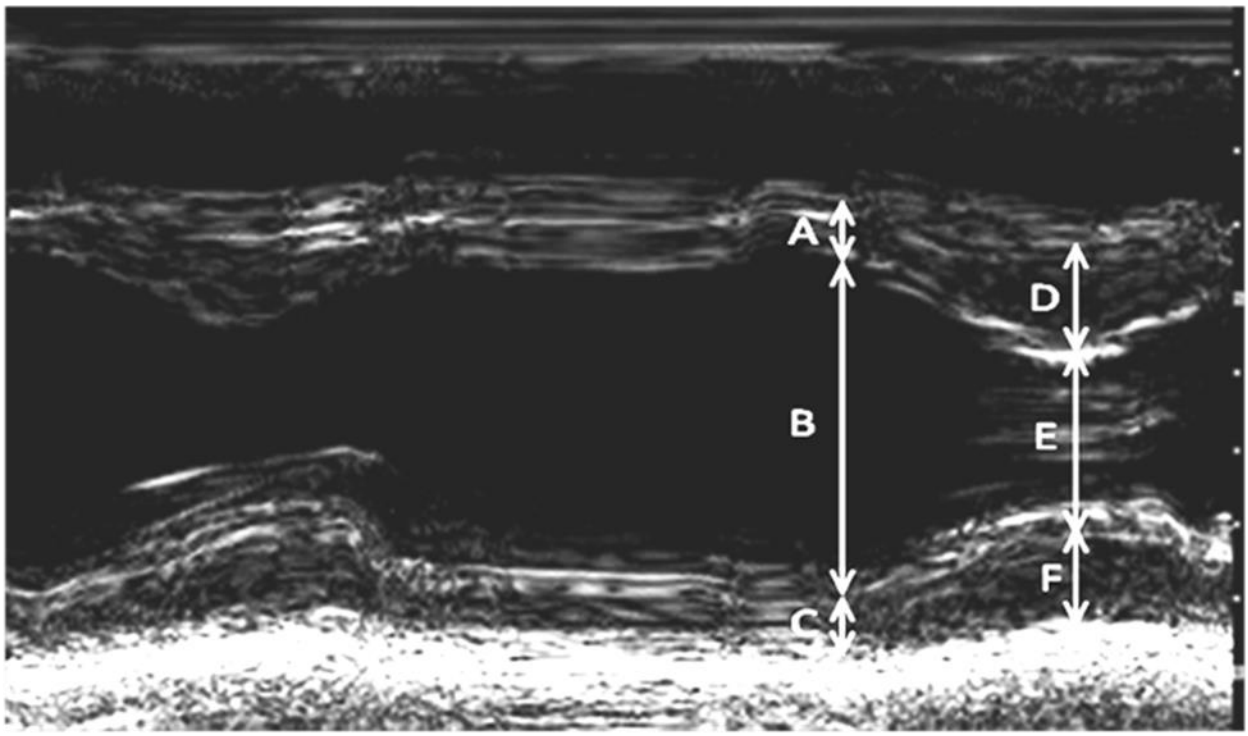
2.3.4 Pulse wave analysis.

Central aortic systolic BP (SBPc), PPc and AIx were estimated using techniques previously described (Redelinghuys et al 2010, Norton et al 2012). Briefly, after participants had rested for 15 minutes in the supine position, arterial waveforms at the radial (dominant arm) pulse were recorded by applanation tonometry during an 8-second period using a high-fidelity SPC-301 micromanometer (Millar Instrument, Inc., Houston, Texas) interfaced with a computer employing SphygmoCor, version 6.21 software (AtCor Medical Pty. Ltd., West Ryde, New South Wales, Australia). The pulse wave was calibrated by manual measurement (auscultation) of brachial BP taken immediately before the recordings. The peripheral pressure waveform was converted into a central aortic waveform using a validated generalized transfer function incorporated in SphymoCor software. Recordings where the systolic or diastolic variability of consecutive waveforms exceeded 5% or the amplitude of the pulse wave signal was less than 80 mV were discarded. All measurements were made by a single experienced trained technician unaware of the clinical history of the participants and

with a low degree of intra-observer variability and a high degree of reproducibility (Redelinghuys et al 2010, Norton et al 2012). Central aortic PP was determined as the difference between SBPc and diastolic BP (DBP). Augmented pressure (AP) was determined using SphygmoCor software and identified as the difference between PPc and the first systolic shoulder of the aortic pulse wave. Aortic AIx was determined as AP/aortic PP (AP/PPc) expressed as a percentage. To avoid obtaining negative aortic AIx values in young participants, AIx was also determined as the pressure at the second systolic peak of the aortic pulse wave/the pressure at the first systolic peak of the aortic pulse wave (P_2/P_1) expressed as a percentage (Chirinos et al 2011).

2.3.5 Echocardiography.

Left ventricular end diastolic internal diameter and septal (anterior wall) and posterior wall thickness were determined from transthoracic two-dimensional targeted M-mode echocardiographic images obtained in the parasternal long-axis as previously described (Norton et al 2008, Woodiwiss et al 2009, Norton et al 2012). Variables were analysed according to the American Society of Echocardiography convention (Sahn et al 1978). All measurements were recorded and analysed off-line by experienced investigators (CDL and AJW) who were unaware of the clinical data of the participants and whom had a low degree of inter- and intra-observer variability (Norton et al 2008, Woodiwiss et al 2009, Norton et al 2012). Only M-mode images of acceptable quality were analysed (see Figure 2.1). In this regard, acceptable quality was considered to exist when appropriate visualization of both the right and the left septal surfaces occurred and where the endocardial surface of the septal and posterior wall were clearly visible when imaging at the optimal angle of incidence (perpendicular to the posterior wall) and close to the mitral leaflets. Left ventricular mass (LVM) was determined using a standard formula (Devereux et al 1986) and indexed (LVMI) to height$^{2.7}$ (LVMI-ht$^{2.7}$) and to body surface area (LVMI-BSA). Left ventricular relative wall thickness (RWT) was defined as (LV anterior + posterior wall thickness at end diastole)/LV



A: Left Ventricular Septal Wall Thickness at End Diastole

B: Left Ventricular End Diastolic Diameter

C: Left Ventricular Posterior Wall Thickness at End Diastole

D: Left Ventricular Septal Wall Thickness at End Systole

E: Left Ventricular End Systolic Diameter

F: Left Ventricular Posterior Wall Thickness at End Systole

Figure 2.1. Example of an M-mode echocardiographic image obtained in the parasternal long-axis of the heart. M-mode images were used to determine left ventricular end diastolic internal diameter and septal and posterior wall thickness dimensions.

end diastolic diameter. LVH was identified as an LVMI-BSA>95 g/m^2 for women and >115 g/m^2 for men. Concentric LV remodelling was identified as a RWT ≥0.42, and eccentric LVH as a RWT<0.42 with an increased LVMI-BSA.

2.3.6 Statistical analysis.

For database management and statistical analysis, SAS software, version 9.1 (SAS Institute Inc., Cary, NC) was employed. To determine relationships between PPc or AIx and LVMI, multivariate linear regression analysis was performed. To determine relationships between AIx and concentric LV remodelling, LVH or eccentric LVH in sex-specific groups, multivariate logistic regression analysis was performed. In multivariate models adjustments were made for the impact of brachial BP (PP, systolic BP [SBP] or mean arterial pressure [MAP]), age, body weight, body height (for LVMI-BSA), the presence of diabetes mellitus or an HbA_{1C}>6.1%, treatment for hypertension, regular tobacco use, and regular alcohol intake. To determine probability values, further adjustments for non-independence of family members was performed using non-linear regression analysis (mixed procedure as defined in the SAS package). To ensure that relationships occurred independent of the use of antihypertensive therapy, sensitivity analysis was conducted in participants not receiving antihypertensive therapy. Regression coefficients were compared with z statistics.

2.4 **Results**

2.4.1 Characteristics of the participants.

The clinical and demographic characteristics of women and men are shown in Table 2.1. 1.9% of participants had a history of cardiovascular disease. Importantly, 45.2% of participants with hypertension were not receiving therapy. Moreover, 35.4% of all participants and 28.0% of participants not receiving antihypertensive therapy had uncontrolled

hypertension. 19.1% of participants had concentric LV remodelling, and 17.3% had LVH (7.1% concentric and 10.2% eccentric LVH). More women than men had concentric LV remodelling, but a similar proportion had LVH, with no differences noted in the proportion with concentric and eccentric LVH (Table 2.1). Women had a higher AIx than men, but PPc was similar in men and women (Table 2.1).

2.4.2 *Relationships between aortic BP and LVMI independent of brachial BP in gender-specific groups*.

Aortic pulse pressure (PPc) was related to LVMI independent of MAP in both men and women (Table 2.2, Figure 2.2). However, the strength of the relations (partial r) was greater in men than in women (Table 2.2). In men, but not in women PPc was related to

Table 2.1. Characteristics of the study sample.

	Men (n=283)	Women (n=525)	p-value
Age (years)	43.0±19.0	45.3±17.5	=0.09
Body mass index (kg/m^2)	25.9±16.1	32.6±13.6	<0.0001
Body weight (kg)	71.9±17.6	80.2±29.2	<0.0001
Body height (m)	168.5±8.7	157.4±7.1	<0.0001
% obese	17.7	56.6	<0.0001
Regular tobacco (% subjects)	33.6	4.8	<0.0001
Regular alcohol (% subjects)	33.2	12.4	<0.0001
% with DM or HbA_{1C}>6.1%	21.2	28.4	<0.05
% women postmenopausal	-	45.7	-
% hypertensive	40.3	45.3	=0.17
% treated for hypertension	15.6	30.7	<0.0001
% hypertensives controlled to target BP[#]	28.1	39.1	<0.05
% of all with uncontrolled BP[##]	38.9	33.5	=0.14
Pulse rate (beats/min)	62±12	68±11	<0.0001
Conventional SBP/DBP (mm Hg)	131±22/85±13	128±23/83±13	=0.07/<0.05
Conventional pulse pressure (mm Hg)	45.9±18.0	44.5±15.3	=0.26
Central SBP (mm Hg)	121±22	120±23	=0.29
Central pulse pressure (PPc) (mm Hg)	35.9±17.1	35.7±14.1	=0.90
Aortic augmentation index (AP/PPc)[†] (%)	23.9±12.8	28.8±12.5	<0.0001
Aortic augmentation index (P_2/P_1)[††] (%)	135±22	145±25	<0.0001
Left ventricular mass index (g/m$^{2.7}$)	40.4±14.8	42.3±15.1	=0.07
Left ventricular mass index (g/m^2)	82.8±34.4	72.1±27.7	<0.0001
Left ventricular relative wall thickness	0.38±0.08	0.39±0.08	<0.05
Concentric LV remodelling (%)	14.8	21.3	<0.05
Concentric LV hypertrophy (%)	7.4	6.9	=0.77
Eccentric LV hypertrophy (%)	8.5	11.1	=0.25

Data are expressed as mean±SD or proportions. Data were compared with Chi-squared analysis or a Student's unpaired t-test. DM, diabetes mellitus; HbA_{1C}, glycosylated haemoglobin; BP, blood pressure; SBP, systolic BP; DBP, diastolic BP; AP, aortic augmentation pressure; LV, left ventricular. [†](Augmentation pressure/aortic pulse pressure) x 100, [††](Pressure at the second systolic peak of the aortic pulse wave/Pressure at the first systolic peak of the aortic pulse wave) x 100. [#]indicates conventional SBP/DBP<140/90 mm Hg. [##]indicates conventional SBP/DBP≥140/90 mm Hg.

Table 2.2. Brachial blood pressure-independent relations between central aortic pulse pressure (PPc) and left ventricular mass (LVM) index in men and women from a community sample.

	Men			Women		
Adjustments	n=	partial r* (95% CI)	p-value	n=	partial r* (95% CI)	p-value
PPc vs LVM indexed to body surface area						
* + brachial SBP	283	0.25 (0.14 to 0.36)	<0.0001	525	0.05* (-0.03 to 0.14)	=0.23
* + brachial PP	283	0.14 (0.02 to 0.25)	<0.05	525	0.02 (-0.07 to 0.10)	=0.71
* + brachial MAP	283	0.27 (0.16 to 0.38)	<0.0001	525	0.13* (0.04 to 0.21)	<0.005
PPc vs LVM indexed to height$^{2.7}$						
* + brachial SBP	283	0.27 (0.16 to 0.38)	<0.0001	525	0.06* (-0.03 to 0.14)	=0.18
* + brachial PP	283	0.18 (0.06 to 0.29)	<0.005	525	0.02* (-0.07 to 0.11)	=0.65
* + brachial MAP	283	0.29 (0.18 to 0.39)	<0.0001	525	0.11* (0.02 to 0.19)	<0.05

SBP, systolic blood pressure; PP, pulse pressure, OR, odds ratio. *Adjustments are for age, body weight, height (for LVM indexed for BSA), the presence of diabetes mellitus or an HbA1c>6.1%, pulse rate, treatment for hypertension (in all participants), regular tobacco use, and regular alcohol intake and brachial BP as indicated. Probability values are derived after further adjustments for the non-independence of family members. *p<0.05 for comparison of r values between men and women using z-statistics.

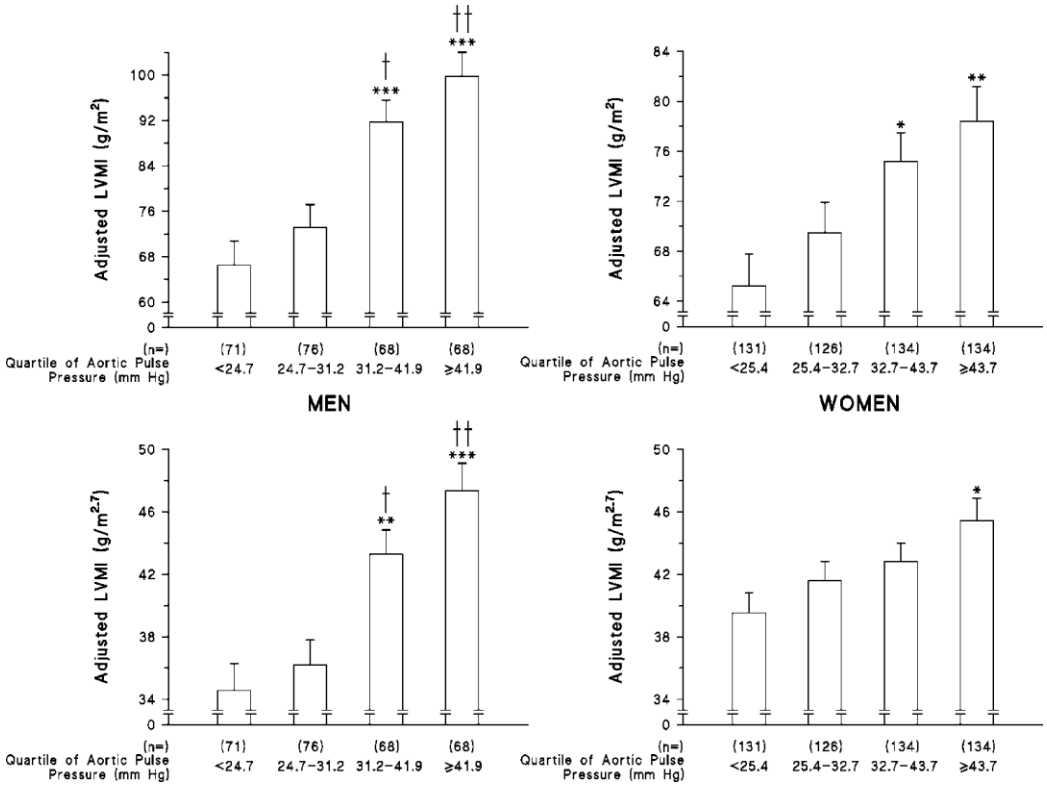


Figure 2.2. Multivariate adjusted left ventricular mass indexed for body surface area (BSA) (LVMI in g/m^2) or height$^{2.7}$ (LVMI in g/m$^{2.7}$) across quartiles of central aortic pulse pressure in men and women from a community sample. Adjustments are for age, mean arterial pressure, body weight, body height (for LVM indexed for BSA), the presence of diabetes mellitus or an HbA_{1C}>6.1%, pulse rate, treatment for hypertension, regular tobacco use, and regular alcohol intake. Probability values are derived after further adjustments for the non-independence of family members. p for trend effects: LVM indexed for BSA; men, p<0.0001, women, p<0.005; , LVM indexed for height$^{2.7}$; men, p<0.0001, women, p<0.05. See Table 2 for comparison of relationships between men and women. *p<0.05, **p<0.01, ***p<0.0001 vs quartile1, †p<0.01, ††p<0.0005 vs quartile 2.

LVMI independent of confounders and brachial PP and SBP (Table 2.2). However, no differences were noted in the strength (partial r values, Table 2, p=0.09 using z-statistics) or slopes (β-coefficients, p=0.06) of the brachial PP adjusted PPc-LVMI-BSA relations in men versus women. In contrast to the brachial BP-independent relations between PPc and LVMI in men, SBPc was not related to LVMI-BSA independent of brachial SBP or PP in men (p=0.36-0.38) or brachial SBP in women (p=0.43). Moreover, SBPc was not related to LVMI-$ht^{2.7}$ independent of brachial SBP or PP in men (p=0.07-0.73) or brachial SBP in women (p=0.68). These brachial BP-independent relations between PPc or SBPc and LVMI were largely reproduced in participants not receiving antihypertensive therapy and in pre- and post-menopausal women (data not shown).

2.4.3 Gender-specific relationships between AIx and LVMI.

On bivariate analysis, AIx was associated with LVMI in both men (p<0.0001 for all) and women (p<0.05 to p<0.0001). However, the relationship between AIx (P_2/P_1) and LVM indexed to BSA was stronger in men (r=0.28, 95% CI=0.16 to 0.38, p<0.0001) as compared to women (r=0.11, 95% CI=0.02 to 0.19, p<0.05)(p<0.05 for comparison of relationships using z-statistics). Furthermore, men showed a trend for a stronger AIx (AP/PPc)-LVM indexed for BSA relationship (p=0.05 for comparison of relationships) and for a stronger AIx (P_2/P_1)-LVM indexed for $height^{2.7}$ relationship (p=0.05 for comparison of relationships) than women.

On multivariate regression analysis independent of MAP and alternative confounders, AIx was associated with LVMI in men, but not in women (Table 2.3, Figure 2.3). Moreover, the strength (partial r values) and the slope (β-coefficients) of the relationships between AIx and LVMI were greater in men as compared to women (Table 2.3). Independent relationships between AIx and LVMI were noted in neither pre-, nor postmenopausal women (Table 2.3).

Table 2.3. Brachial blood pressure-independent relations between aortic augmentation indices and left ventricular mass indexed to body surface area (LVMI-BSA) or height$^{2.7}$ (LVMI-ht$^{2.7}$) in men and in women from a community sample.

	n=	partial r (95% CI)*	β-coefficient±SEM	p-value
Augmentation index (AP/PPc)† vs LVMI-BSA				
Men	283	0.17‡ (0.05 to 0.28)	0.55±0.20#	<0.01
Women	525	-0.08 (-0.16 to 0.01)	-0.20±0.11	=0.08
Premenopausal women	285	0.01 (-0.11 to 0.12)	0.01±0.14	=0.95
Postmenopausal women	240	-0.06 (-0.19 to 0.07)	-0.18±0.21	=0.37
Augmentation index (P_2/P_1)†† vs LVMI-BSA				
Men	283	0.21‡ (0.10 to 0.32)	0.42±0.12#	<0.0005
Women	525	-0.06 (-0.14 to 0.03)	-0.07±0.05	=0.17
Premenopausal women	285	0.02 (-0.10 to 0.14)	0.02±0.08	=0.77
Postmenopausal women	240	-0.03 (-0.16 to 0.10)	-0.04±0.09	=0.64
Augmentation index (AP/PPc)† vs LVMI-ht$^{2.7}$				
Men	283	0.19‡ (0.07 to 0.30)	0.25±0.08#	<0.005
Women	525	-0.04 (-0.13 to 0.04)	-0.05±0.06	=0.34
Premenopausal women	285	0.09 (-0.02 to 0.21)	0.09±0.06	=0.12
Postmenopausal women	240	-0.09 (-0.21 to 0.04)	-0.15±0.12	=0.19
Augmentation index (P_2/P_1)†† vs LVMI-ht$^{2.7}$				
Men	283	0.23‡ (0.11 to 0.34)	0.18±0.05#	=0.0001
Women	525	-0.04 (-0.13 to 0.04)	-0.03±0.03	=0.32
Premenopausal women	285	0.09 (-0.02 to 0.21)	0.05±0.03	=0.12
Postmenopausal women	240	-0.07 (-0.20 to 0.05)	-0.06±0.05	=0.26

*Adjustments are for age, mean arterial pressure, body weight, height (for LVM indexed for BSA), the presence of diabetes mellitus or an HbA_{1C}>6.1%, pulse rate, treatment for hypertension, regular tobacco use, and regular alcohol intake. Probability values are derived after further adjustments for the non-independence of family members. †(Augmentation pressure/aortic pulse pressure) x 100, ††(Pressure at the second systolic peak of the aortic pulse wave/Pressure at the first systolic peak of the aortic pulse wave) x 100. ‡p<0.005 vs partial r value for women. #p<0.005 vs β-coefficient for women.

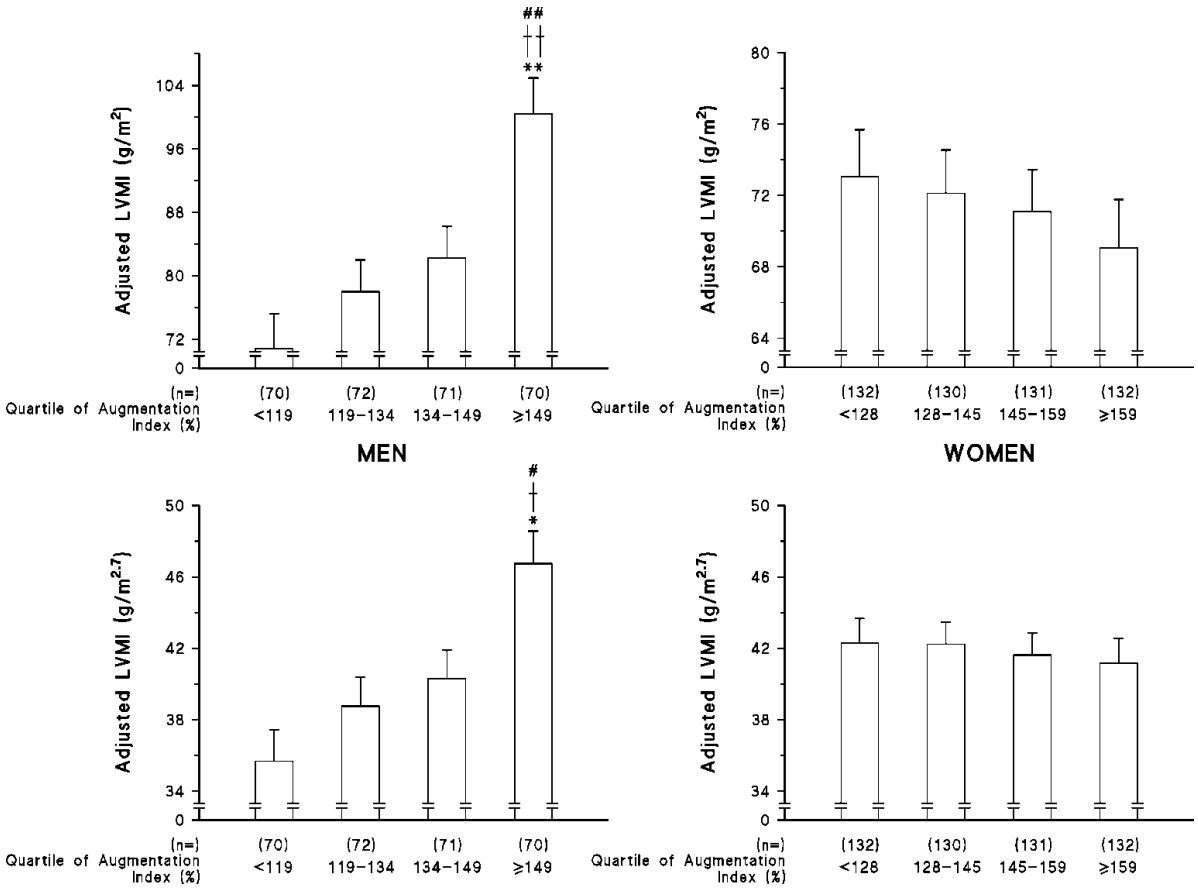


Figure 2.3. Multivariate adjusted left ventricular mass indexed for body surface area (BSA) (LVMI in g/m^2) or $height^{2.7}$ (LVMI in $g/m^{2.7}$) across quartiles of aortic augmentation index ([Pressure at the second systolic peak of the aortic pulse wave/Pressure at the first systolic peak of the aortic pulse wave] x 100) in men and women from a community sample. Adjustments are for age, mean arterial pressure, body weight, body height (for LVM indexed for BSA), the presence of diabetes mellitus or an HbA_{1C}>6.1%, pulse rate, treatment for hypertension, regular tobacco use, and regular alcohol intake. Probability values are derived after further adjustments for the non-independence of family members. p for trend effects: LVM indexed for BSA; men, p<0.0005, women, p=0.17; , LVM indexed for $height^{2.7}$; men, p=0.0001, women, p=0.32. See Table 2 for comparison of relationships between men and women. *p<0.001, **p<0.0005 vs quartile1, †p<0.05, ††p<0.005 vs quartile 2, $^{\#}$p<0.05, $^{\#\#}$p<0.01 vs quartile 3.

In participants not receiving antihypertensive therapy, an independent relationship between AIx (P_2/P_1) and LVMI-BSA was noted in men (n=239, partial r=0.16, p<0.05), whilst no relationship between AIx and LVMI-BSA was noted in women (n=364, partial r=-0.02, p=0.76)(p<0.05 for comparison using z-statistics). Moreover, in participants not receiving antihypertensive therapy, a trend for an independent relationship between AIx (P_2/P_1) and LVM indexed for height$^{2.7}$ was noted in men (partial r=0.13, p=0.05), whilst no relationship between AIx and LVM indexed for height$^{2.7}$ was noted in women (partial r=-0.003, p=0.96).

2.4.4 Relationships between AIx and LV remodelling or LVH.

In neither men (AIx [AP/PPc], Odds ratio=1.029, Wald statistics=2.31, p=0.13; AIx [P_2/P_1], Odds ratio=1.013, Wald statistics=1.70, p=0.19) nor in women (AIx [AP/PPc], Odds ratio=0.99, Wald statistics=0.65, p=0.42; AIx [P_2/P_1], Odds ratio=1.00, Wald statistics=0.001, p=0.98), was AIx independently associated with LVH (concentric + eccentric) (Table 4). No relations between AIx and concentric LV remodelling or AIx and the type of LVH (eccentric versus concentric) were noted in either men or women (data not shown).

2.5 **Discussion**

The main finding of the present study is that in a large, community-based sample, AIx was associated with LVMI in men, but not in women. Although there is considerable debate as to the factors that determine AIx (Davies et al 2010, Cheng et al 2012, Hughes et al 2013), this does not detract from the evidence provided from several studies demonstrating that AIx is associated with cardiovascular damage beyond brachial BP (London et al. 2001, Ueda et al 2004, Weber et al 2005, Chirinos et al 2005, Wang et al 2010, Chirinos et al 2012, Vlachopoulos et al 2010, Hashimoto et al 2007, Hashimoto et al 2006). However, as in some studies AIx does not predict cardiovascular outcomes (Vlachopoulos et al 2010, Mitchell et al 2010a, Hayashi et al 2014) the possible factors that influence this relationship require

identification. In this regard, although AIx predicts outcomes in men, similar relationships may be diminished in women (Wang et al 2010). The present study provides support for a decrease in the relationship between AIx and end-organ damage in women as compared to men. This is in contrast to the comparable unadjusted relations previously demonstrated between AIx and LVMI or alternative end-organ changes between men and women in a large community-based study (Wang et al 2010). However, whether in that study (Wang et al 2010) similar relations between AIx and end-organ changes were also noted in men and women after multivariate adjustments is unclear (Wang et al 2010).

Previous studies that have demonstrated that AIx derived from radial applanation tonometry is independently associated with LVM reduction, or LVH, (Hashimoto et al 2007, Hashimoto et al 2006) were not statistically powered to report on whether these associations were sex-specific. Interestingly however, in both studies 70% or more of study participants were men (Hashimoto et al 2007, Hashimoto et al 2006). Hence, both of these studies (Hashimoto et al 2007, Hashimoto et al 2006) may reflect a dominant impact of AIx on LVMI in men.

An explanation for the gender-specific impact on relations between AIx and LVMI noted in the present study, or between AIx and cardiovascular outcomes in a previous study (Wang et al 2010), requires consideration. In this regard, in contrast to what was previously thought, AIx is not an appropriate index of wave reflection (Davies et al 2010, Cheng et al 2012, Hughes et al 2013). Rather, unlike more suitable indices of wave reflection, AIx may be influenced by aortic reservoir function (Davies et al 2010), left ventricular systolic function (Cheng et al 2012), as well as height and female gender (Davies et al 2010). Some of these factors may have little impact on cardiovascular risk. Indeed, measures of reflective wave function are better risk markers than AIx (Wang et al 2010, Mitchell et al 2010a). Alternatively, although aortic PP is associated with cardiovascular damage, reflective wave function may contribute little toward the impact of aortic PPc on cardiovascular damage in women. Indeed, in a large, community-based study, both AIx and the reflection index predicted cardiovascular outcomes in men, but not in women (Wang et al 2010). Hence,

further studies are required to establish whether the sex-specific relations between AIx and LVMI or alternative end-organ changes are attributed to the poor relationship between AIx and reflective wave function (Davies et al 2010, Cheng et al 2012, Hughes et al 2013), or to the lack of impact of reflective waves on end-organ changes in women as compared to men.

Several differences were noted between men and women in the present study, differences which may account for the sex-specific effects of AIx on LVMI. In this regard, more women than men were obese or had diabetes mellitus or an abnormal HbA1c and hence obesity or diabetes mellitus may play a more important role than BP in mediating increases in LVMI in women. In addition, although a similar proportion of men and women were hypertensive, fewer hypertensive men were receiving antihypertensive medication. Hence, the sensitivity to detect an impact of AIx on LVMI may have been greater in men than in women.

The clinical implication of the present study is that when considering the contribution of central aortic haemodynamic measurements as predictors of cardiovascular damage, AIx may serve as an appropriate predictor in men, but not in women. Hence, in women, either aortic BP *per se* may be a better aortic haemodynamic index to predict damage beyond brachial BP, or wave separation analysis may be required to identify the impact of reflective waves on cardiovascular damage.

The limitations of the present study are as follows: First, the cross-sectional nature of the study precludes conclusions being drawn regarding cause and effect. Second, in the present study calibration of the radial waveform from brachial BP measurements ignores amplification of BP from brachial to radial arteries. Hence, aortic pressures are likely to have been underestimated using the current approach. Third, because the present study was community-based, only a small proportion of participants had LVH. Hence, we were not statistically powered to show sex-specific relations between AIx and LVH. Thus, further studies are necessary in untreated hypertensives to evaluate whether the relationship between AIx and LVH is sex-specific. Last, the present study was conducted in one ethnic group. Hence further studies in communities of alternative ethnic origins are required.

In conclusion, in the present study I show that despite an independent relationship between aortic BP and LVMI in both men and women, AIx is independently associated with LVMI in men, but not in women. These data suggest that AIx may not be an appropriate predictor of the extent of cardiovascular end-organ changes in women.

CHAPTER 3

The Relationship Between Aortic Reflected Waves, Derived From Wave Separation Analysis, and Aortic Pulse Pressure or Left Ventricular Mass Index is Not Gender-Specific

This chapter has been published as a component of the following paper:

Hendrik L Booysen, Angela J Woodiwiss, **Moekanyi J Sibiya**, Bryan Hodson, Andrew Raymond, Elena Libhaber, Pinhas Sareli, Gavin R Norton. Indexes of aortic pressure augmentation markedly underestimate the contribution of reflected waves toward variations in aortic pressure and left ventricular mass. *Hypertension* 2015;65:540-546

3.1 **Abstract**

Although indices of aortic wave reflection enhance risk prediction, the extent to which measures of aortic systolic pressure augmentation (augmented pressures [Pa] or augmentation index [AIx]) underestimate the effects of reflected waves on cardiovascular risk in women is uncertain. From a community sample (age>16 years) I therefore evaluated sex-specific contributions of reflected (backward wave pressures [Pb] and the reflection index [RI]) versus augmented (Pa and AIx) pressure wave indices to variations in central aortic pulse pressure (PPc) (n=1185, 65.0% women), and left ventricular mass index (LVMI [n=793, 64.9% women]). Aortic haemodynamics and LVMI were determined using radial applanation tonometry (SphygmoCor) and echocardiography. In both women and in men, independent of confounders, RI and Pb contributed more than forward wave pressures (Pf), whilst Pa and AIx contributed less than incident wave pressure (Pi) to variations in PPc ($p<0.0001$ for comparison of partial r values). In both men and in women Pb contributed more than Pf ($p<0.05$ for comparison of r values) to variations in LVMI. Although in men Pa (partial $r=0.33$, $p<0.0001$) contributed to a similar extent as Pi (partial $r=0.34$, $p<0.0001$) to variations in LVMI, in women Pa (partial $r=0.05$, $p=0.36$) failed to contribute to LVMI, whilst Pi was significantly associated with LVMI (partial $r=0.30$, $p<0.0001$). Similar results were obtained with AIx as opposed to Pa in the regression models. In conclusion, the contribution of aortic backward wave pressures to variations in aortic PP and LVMI is similar in women as it is in men; in both women and in men indices of aortic pressure augmentation markedly underestimate the contribution of aortic backward wave pressures to variations in LVMI; and in women this effect is sufficiently marked that augmentation indices are unrelated to LVMI.

Key words: Central blood pressure, aortic pulse pressure, reflected waves, augmentation index, left ventricular mass index.

3.2 **Introduction**

Although pulse pressure (PP) measured at the brachial artery is closely correlated with central aortic PP (PPc), PP may be considerably higher in brachial arteries as compared to the aorta (Aviolo et al 2009, Agabiti-Rosei et al 2007). A key determinant of PPc is an increase in aortic wave reflection, which enhances backward wave pressures (Pb) and hence augments aortic systolic blood pressure (BP) if returning to the ascending aorta sufficiently early (Aviolo et al 2009, Agabiti-Rosei et al 2007). An enhanced aortic wave reflection is thought to be a major cause of cardiovascular damage. Indeed, several studies have demonstrated that aortic augmented pressures (Pa), and augmentation index (AIx), indexes of wave reflection, are associated with cardiovascular outcomes (London et al 2001, Ueda et al 2004,Weber et al 2005, Chirinos et al 2005, Davies et al 2010, Vlachopoulos et al 2010, Cheng et al 2012) and end-organ damage (Hashimoto et al 2007, Hughes et al 2013, Hashimoto et al 2006, Fok et al 2014a, Weber et al 2006, Torjesen et al 2014, Westerbacka et al 2005, Sibiya et al 2014) independent of brachial BP. However, more recently the use of Pa or AIx as indexes of wave reflection in risk prediction has been challenged (Davies et al 2010, Cheng et al 2012, Hughes et al 2013).

Marked overlap between aortic forward and reflected waves may confound Pa and AIx and hence these measures may be poor indexes of wave reflection (Davies et al 2010, Cheng et al 2012, Hughes et al 2013). Indeed, there is a weak relationship between the magnitude of the reflected wave and Pa or AIx, and increases in aortic reservoir function, the timing or magnitude of the forward (Pf) or incident (Pi) wave pressures, and left ventricular systolic function may play a more important role than wave reflection in contributing to variations in Pa and AIx (Davies et al 2010, Cheng et al 2012, Hughes et al 2013). More recent studies have therefore focused on the role of reflected waves (Pb and reflected wave index-RI), as determined using wave separation analysis, as independent determinants of age-related increases in PPc or cardiovascular damage (Wang et al 2010, Chirinos et al 2012, Weber et al 2012, Mitchell et al 2010b). However, in these studies (Wang et al 2010,

Chirinos et al 2012, Weber et al 2012, Mitchell et al 2010b) the extent to which Pb or RI are more closely associated with PPc or cardiovascular damage than Pa or AIx is uncertain. In this regard in these studies, relations with end-organ damage were not adjusted for confounders (Wang et al 2010, Chirinos et al 2012, Weber et al 2012); discrepancies in the index of wave reflection that was better associated with end-organ damage beyond forward wave pressures were noted (Wang et al 2010, Chirinos et al 2012, Weber et al 2012); and forward wave pressure rather than Pb was reported to be the main determinant of PPc in a community sample with a high prevalence of well-controlled BP values (Mitchell et al 2010b). In the previous chapter and recently reported on (Sibiya et al 2014), I have demonstrated that Pa and AIx associate with left ventricular mass index (LVMI) and left ventricular hypertrophy (LVH) in men, but not in women. However, in that study (Sibiya et al 2014, chapter 2), I did not have access to wave separation analysis to determine the actual relationship between aortic reflected (backward) waves and LVMI. As the manufacturer of the measurement system that I employed to determine aortic function (SphygmoCor) has recently developed the software to perform wave separation analysis, in the present study I aimed to determine whether the lack of association between Pa or AIx and LVMI or LVH can be attributed to a lack of impact of aortic backward waves on aortic PP or LVMI, or because Pa and AIx are poor indices of backward wave effects in women as opposed to men.

3.3 **Methods**

3.3.1 Study group.

The present study was conducted according to the principles outlined in the Helsinki Declaration. The Committee for Research on Human Subjects of the University of the Witwatersrand approved the protocol (approval number: M02-04-72 and renewed as M07-04-69 and M12-04-108). Participants gave informed, written consent. The present study design has previously been described (Norton et al 2008, Woodiwiss et al 2009, Redelinghuys et al

2010, Norton et al 2012). Briefly, 1185 participants from families of black African descent (Nguni and Sotho chiefdoms) with siblings older than 16 years with central haemodynamic measurements were randomly recruited from the South West Township (SOWETO) of Johannesburg, South Africa. In a sub-study, 793 participants had LVMI determined using echocardiography.

*3.3.2 Clinical, demographic and anthropometric measurements***.**

For details see section 2.3.2

3.3.3 Pulse wave analysis.

For further details see section 2.3.4. Aortic Pb and Pf were determined using SphygmoCor software which separates the aortic waveform using a triangular flow wave (Westerhof et al 2006). In the present study we did not employ a “physiological aortic flow waveform” approach to wave separation analysis as in a pilot study conducted in 26 participants, the previously described physiological aortic flow waveform did not closely approximate aortic flow waveforms in the present community sample. Moreover, a wide variety of aortic flow waveforms were identified in the 26 participants studied, precluding the possibility of identifying a single “representative waveform” which could be used for wave separation analysis. Reflected wave index (RI) was determined as previously described (Hughes et al 2013). Aortic augmented pressure (Pa) was determined using SphygmoCor software and identified as the difference between SBPc and the first systolic peak of the aortic pulse wave. Incident wave pressure (Pi) was defined as PPc-Pa. To avoid obtaining negative aortic AIx values in young participants, AIx was determined as the pressure at the second systolic peak of the aortic pulse wave/the pressure at the first systolic peak of the aortic pulse wave expressed as a percentage.

3.3.4 Echocardiography.

For details see section 2.3.5 Acceptable quality of images was considered to exist when appropriate visualization of both the right and the left septal surfaces occurred and where the endocardial surface of the septal and posterior wall were clearly visible when imaging at the optimal angle of incidence (perpendicular to the posterior wall) and close to the mitral leaflets. Left ventricular mass was determined using a standard formula (Devereux et al 1986) and indexed (LVMI) to body surface area (LVMI-BSA) or height$^{1.7}$ (LVMI-ht$^{1.7}$). Left ventricular hypertrophy (LVH) was identified as an LVMI-BSA>95 g/m^2 for women and >115 g/m^2 for men. Stroke volume was evaluated from the difference between LV end diastolic and systolic volumes determined using the Z-derived method (de Simone et al 1996).

3.3.5 Statistical analysis.

For database management and statistical analysis, SAS software, version 9.1 (SAS Institute Inc., Cary, NC) was employed. To determine relationships multivariate regression analysis was performed with appropriate adjustments. Adjustments included in multivariate models were those correlated with central hemodynamic variables or LVMI in bivariate analysis. To assess the relative contribution of incident and augmented waves to variations in PPc, in stepwise regression analysis, Pi and AIx were included in multivariate models. AIx rather than Pa was included in the same regression model with Pi to avoid the confounding effect of forward wave amplitude on the amplitude of the augmented wave (Mitchell et al 2010b). To determine probability values, further adjustments for non-independence of family members was performed using non-linear regression analysis (mixed procedure as defined in the SAS package). To ensure that relationships occurred independent of the use of antihypertensive therapy, sensitivity analysis was conducted in participants not receiving antihypertensive therapy. Regression coefficients were compared with z statistics.

3.4 **Results**

3.4.1 Characteristics of the participants.

The clinical and demographic characteristics of the participants are shown in Table 3.1. 1.9% of participants had a history of cardiovascular disease. Importantly, a high proportion (45.9%) of participants had hypertension, and 47.2% of hypertensives were not receiving therapy. Moreover, 36.4% of all participants and 60.6% of participants receiving antihypertensive therapy had uncontrolled hypertension. Of the participants with echocardiography, 17% had LVH. Although of a similar age, women were more obese, had a higher prevalence of DM, and a higher pulse rate, but regularly smoked or consumed alcohol less, and more were receiving antihypertensive therapy than men. Women had higher values for indices of wave reflection (Pb, RI, Pa and AIx).

3.4.2 Age-related increases in aortic hemodynamics.

In multivariate-adjusted models, including adjustments for mean arterial pressure (MAP), all aortic haemodynamic parameters were independently associated with age (Table 3.2). In both men and in women the association between age and Pa was stronger (partial r) than the association between age and Pi (Table 3.2). However, in men the strength (partial r) of the association between age and either aortic forward or backward wave pressures was similar, whilst in women the association between age and aortic backward wave pressures was stronger than the association with forward wave pressures (Table 3.2).

Table 3.1. Characteristics of the study sample.

Characteristics	All (n=1185)	Women (n=771)	Men (n=414)
% Female	65.0	-	-
Age (years)	44.3±18.3	44.8±17.6	43.3±19.4
Body mass index (kg/m^2)	29.6±8.1	32.0±8.2***	24.9±5.2
% Obese	43.3	57.8***	16.2
Regular tobacco (% subjects)	15.2	5.8***	32.7
Regular alcohol (% subjects)	20.9	13.6***	34.6
% with DM or HbA1c>6.1%	25.8	28.8**	20.3
% Hypertensive	45.9	45.9	45.8
% Treated for hypertension	24.2	28.1***	16.7
% Hypertensives controlled to target BP	20.8	24.9***	12.7
% of all with uncontrolled BP	36.4	34.5	39.9
Pulse rate (beats/min)	66±12	68±11***	63±11
Brachial SBP/DBP (mm Hg)	130±22/84±13	129±23*/83±13**	131±21/85±12
Brachial pulse pressure (mm Hg)	46±16	44±16	46±18
Brachial mean arterial pressure (mm Hg)	100±16	100±17	101±15
Central aortic SBP (mm Hg)	120±23	119±23	122±23
Central aortic pulse pressure (PPc) (mm Hg)	35±15	35±14	35±17
Aortic forward wave pressure (Pf) (mm Hg)	24±9	24±9*	25±9
Aortic reflected wave pressure (Pb)(mm Hg)	17±8	17±8	17±9
Aortic reflected wave index	0.16±0.06	0.16±0.06	0.15±0.06
Aortic augmented pressure (Pa)	11±8	11±8**	10±8
Aortic Pi	25±9	24±8**	26±10
Aortic augmentation index (AIx) (%)	142±25	146±26***	135±23
Stroke volume (mls)(n)	63±17 (793)	60±17*** (515)	67±17 (278)
Left ventricular mass index (g/m^2)(n)	76±31 (793)	72±29*** (515)	82±33 (278)
Left ventricular mass index (g/m$^{1.7}$)(n)	67±24 (793)	67±24 (515)	68±25 (278)

Data expressed as mean ± SD or proportions. DM, diabetes mellitus; HbA_{1C}, glycosylated haemoglobin; BP, blood pressure; SBP, systolic BP; DBP, diastolic BP; Pi=PPc-Pa. *p<0.05,**p<0.005, ***p<0.0005 versus men.

Table 3.2 Multivariate adjusted relations between age and central aortic hemodynamics in sex-specific categories in a group of African ancestry (n=1185).

Age versus	Estimate (mm Hg)* (±SEM)	partial r (95% CI)	p-value
	Women (n=771)		
Forward wave pressure (Pf)	0.27±0.06	0.15 (0.08 to 0.22)	<0.0005
Reflected wave pressure (Pb)	0.94±08	0.39 (0.32 to 0.44)†	<0.0001
Reflected wave index (RI=Pb/Pf)	120±10	0.41 (0.35 to 0.47)	<0.0001
Aortic Pi	0.40±0.07	0.21 (0.14 to 0.28)	<0.005
Aortic augmented pressure (Pa)	1.17±0.08	0.44 (0.38 to 0.49)†	<0.0001
Aortic augmentation index (AIx)	0.20±0.02	0.30 (0.24 to 0.37)	<0.0001
Stroke volume (n=515)	0.06±0.04	0.07 (-0.01 to 0.16)	=0.09
	Men (n=414)		
Forward wave pressure (Pf)	0.46±0.09	0.24 (0.15 to 0.33)	<0.0001
Reflected wave pressure (Pb)	1.30±0.10	0.24 (0.15 to 0.33)	<0.0001
Reflected wave index (Pb/Pf)	169±12	0.57 (0.50 to 0.63)	<0.0001
Aortic Pi	0.46±0.09	0.26 (0.16 to 0.34)	<0.0001
Aortic augmented pressure (Pa)	1.47±0.10	0.57 (0.51 to 0.64)†	<0.0001
Aortic augmentation index (AIx)	0.45±0.04	0.52 (0.45 to 0.59)	<0.0001
Stroke volume (n=278)	0.07±0.06	0.07 (-0.04 to 0.19)	=0.22

CI, confidence intervals; Pi=Aortic pulse pressure-Pa. *β-coefficient (slope) of the relations. Pi=aortic pulse pressure-Pa. Adjustors are mean arterial pressure, body height, body weight, pulse rate, diabetes mellitus or an HbA1c>6.1%, regular smoking and regular alcohol intake. †p<0.0001 for comparisons of partial r values with Pf.

3.4.3 Relative independent contribution of reflected versus forward waves to variations in PPc.

When included in separate models (Table 3.3) or in the same multivariate stepwise models (Figure 3.1), in both women and in men a stronger relationship was noted between RI and PPc or Pb and PPc than between Pf and PPc or AIx and PPc. In contrast, in both women and in men a stronger relationship was noted between Pi and PPc, than between Pa and PPc (Table 3.3) or between AIx and PPc (Table 3.3, Figure 3.1). In both women and in men with RI and AIx in the same multivariate model, a distinctly stronger relationship was noted between RI and PPc than between AIx and PPc (Figure 3.1). Similar findings were noted in participants not receiving antihypertensive therapy (Table 3.4). Stroke volume was modestly correlated with PPc ($r=0.20$, $p<0.0001$). With the inclusion of stroke volume in multivariate models, similar differences between aortic hemodynamic-PPc relations were noted (Table 3.5).

3.4.4 Comparison of independent relations between aortic hemodynamics and LVMI.

In both men and in women Pb was more closely associated with LVMI than Pf (Figure 3.2). In a multivariate model in women with Pb and Pf in the same model, Pb (partial $r=0.32$, CI=0.22 to 0.40, $p<0.0001$), but not Pf (partial $r=0.02$, CI=-0.06 to 0.10, $p=0.59$) was independently associated with LVMI. Similarly, in a multivariate model in men with Pb and Pf in the same model, Pb (partial $r=0.34$, CI=0.22 to 0.45, $p<0.0001$), but not Pf (partial $r=0.02$, CI=-0.10 to 0.13, $p=0.75$) was independently associated with LVMI. In contrast however, in men Pa showed similar associations with LVMI as did Pi and in women Pi, but not Pa was independently associated with LVMI (Figure 3.2). In addition, RI was more closely associated with LVMI than AIx in both men and in women (Figure 3.2). Importantly, although the relations between Pa or AIx and LVMI were stronger in men than in women ($p=0.01$ to 0.0001 for comparison of r values) (Figure 3.2), these differences were not attributed to

Table 3.3 Independent relationships between aortic hemodynamics and central aortic pulse pressure (PPc) in women versus men of African ancestry.

	Women (n=771)		Men (n=414)	
PPc vs	partial r (CI)*	p value	partial r (CI)*	p value
Pb	0.97 (0.90 to 1.04)[†]	<0.0001	0.92 (0.82 to 1.02)[†]	<0.0001
Pf	0.80 (0.73 to 0.87)	<0.0001	0.75 (0.65 to 0.85)	<0.0001
Pa	0.88 (0.81 to 0.95)	<0.0001	0.90 (0.80 to 1.00)	<0.0001
Pi	0.90 (0.83 to 0.97)[#]	<0.0001	0.94 (0.84 to 1.04)[#]	<0.0001
RI	0.88 (0.81 to 0.95)[$]	<0.0001	0.86 (0.76 to 0.96)[$]	<0.0001
AIx	0.02 (-0.05 to 0.09)	=0.46	0.34 (0.24 to 0.44)	<0.0001

CI, confidence intervals. See tables 1 and 2 for further abbreviations. *Adjustors are age, mean arterial pressure, body height, body weight, pulse rate, diabetes mellitus or an HbA1c>6.1%, regular smoking and regular alcohol intake. [†]p<0.0001 for comparisons of partial r values with Pf, [#] p<0.05, [##]p<0.005 for comparisons of partial r values with Pa, [$]p<0.0001 for comparisons of partial r values with AIx (z-statistics).

Table 3.4 Independent relationships between aortic hemodynamics and central aortic pulse pressure (PPc) in women and men of group of African ancestry not receiving antihypertensive therapy.

PPc vs	Women (n=554)		Men (n=342)	
	partial r (CI)*	p value	partial r (CI)*	p value
Pb	0.97 (0.89 to 1.05)†	<0.0001	0.89 (0.78 to 0.99)†	<0.0001
Pf	0.83 (0.75 to 0.91)	<0.0001	0.70 (0.59 to 0.81)	<0.0001
Pa	0.85 (0.77 to 0.93)	<0.0001	0.90 (0.79 to 1.01)	<0.0001
Pi	0.88 (0.80 to 0.96)$^{\#}$	<0.0001	0.94 (0.83 to 1.05)$^{\#\#}$	<0.0001
RI	0.88 (0.80 to 0.96)$^{\$}$	<0.0001	0.83 (0.72 to 0.94)$^{\$}$	<0.0001
AIx	-0.01 (-0.09 to 0.08)	=0.84	0.33 (0.22 to 0.44)	<0.0001

CI, confidence intervals. See tables 1 and 2 for further abbreviations. *Adjustors are age, mean arterial pressure, body height, body weight, pulse rate, diabetes mellitus or an HbA1c>6.1%, regular smoking and regular alcohol intake. †p<0.0001 for comparisons of partial r values with Pf, $^{\#}$p<0.05,$^{\#\#}$p<0.0005 for comparisons of partial r values with Pa, $^{\$}$p<0.0001 for comparison of partial r values with AIx (z-statistics).

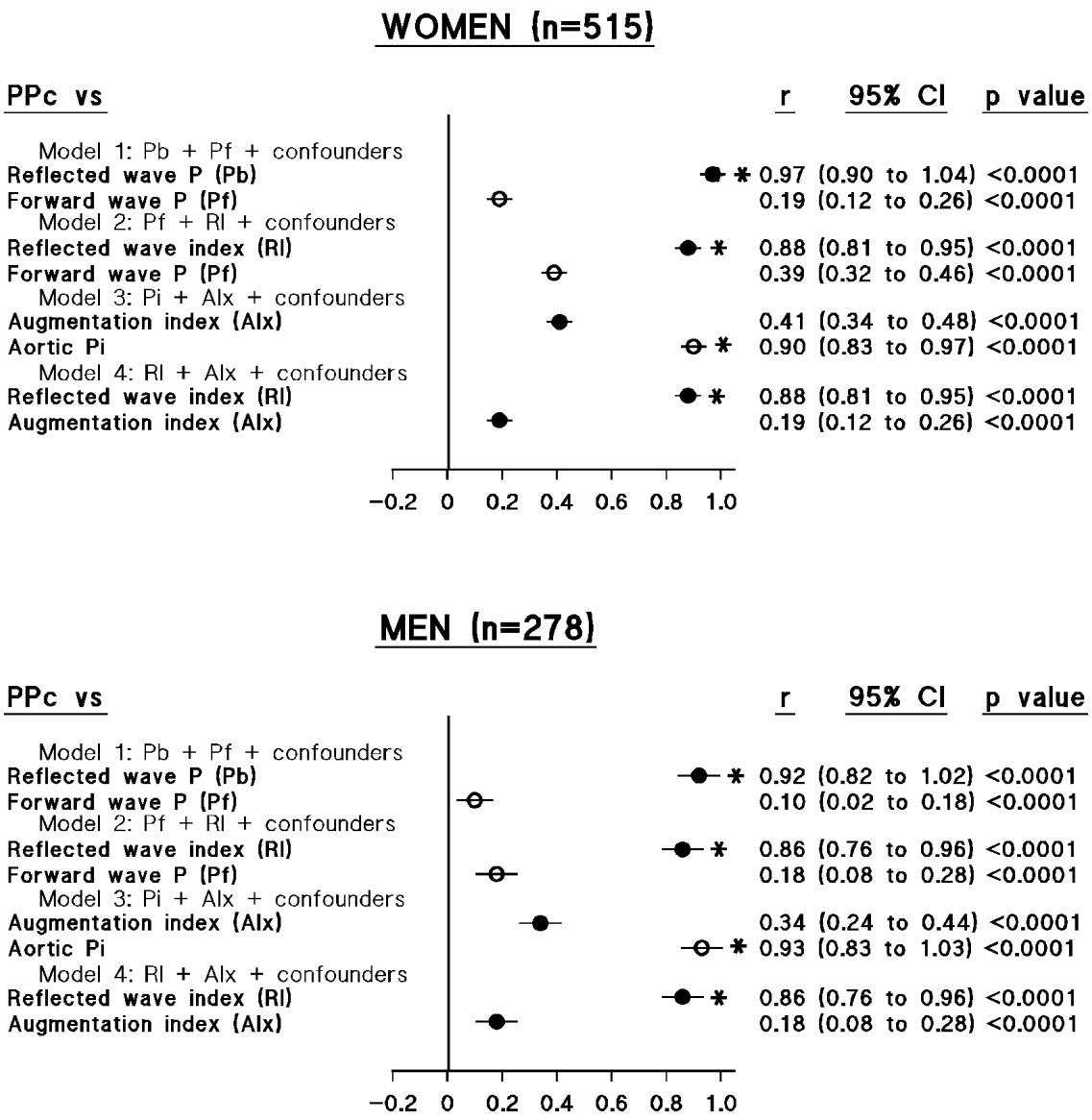


Figure 3.1. Relative contribution of aortic hemodynamic variables to variations in central (aortic) pulse pressure (PPc) in sex-specific groups in a group of African descent. Closed circles indicate indexes of wave reflection; open circles indicate indexes of forward or incident wave pressures. Data show multivariate adjusted correlation coefficients (partial r) derived from stepwise regression analysis with Pf and Pb (model 1), Pf and RI (model 2), Pi and AIx (model 3), or RI and AIx (model 4) + confounders included in the same regression models. Potential confounders included in the model are age, mean arterial pressure, body height, body weight, pulse rate, diabetes mellitus or an HbA1c>6.1%, regular smoking and regular alcohol intake. Those factors not independently associated with PPc were forced into the model. Pi=Aortic pulse pressure-Pa. *p<0.0001 for comparisons of partial r values with Pf or AIx (z-statistics).

Table 3.5. Impact of adjustments for stroke volume (SV) on the independent relationships between indexes of aortic wave reflection and central aortic pulse pressure (PPc) in women and men of African ancestry.

PPc vs	Women (n=515)				Men (n=278)			
SV adjusted	Before		After		Before		After	
	partial r (CI)*	p value	partial r (CI)*	p value	partial r (CI)*	p value	partial r (CI)*	p value
Pb	0.97 (0.88 to 1.05)†	<0.0001	0.97 (0.88 to 1.05)†	<0.0001	0.89 (0.77 to 1.01)†	<0.0001	0.89 (0.77 to 1.01)†	<0.0001
Pf	0.78 (0.69 to 0.86)	<0.0001	0.78 (0.69 to 0.86)	<0.0001	0.69 (0.57 to 0.81)	<0.0001	0.69 (0.57 to 0.81)	<0.0001
Pa	0.86 (0.77 to 0.94)	<0.0001	0.86 (0.77 to 0.94)	<0.0001	0.91 (0.79 to 1.03)	<0.0001	0.91 (0.79 to 1.03)	<0.0001
Pi	0.90 (0.81 to 0.99)$^{\#\#}$	<0.0001	0.90 (0.81 to 0.99)$^{\#\#}$	<0.0001	0.95 (0.83 to 1.07)$^{\#}$	<0.0001	0.95 (0.83 to 1.07)$^{\#}$	<0.0001
RI	0.87 (0.78 to 0.95)$^{\$}$	<0.0001	0.87 (0.78 to 0.95)$^{\$}$	<0.0001	0.84 (0.72 to 0.96)$^{\$}$	<0.0001	0.84 (0.72 to 0.96)$^{\$}$	<0.0001
AIx	-0.04 (-0.12 to 0.04)	=0.19	-0.03 (-0.12 to 0.05)	=0.26	0.46 (0.34 to 0.58)	<0.0001	0.46 (0.34 to 0.58)	<0.0001

CI, confidence intervals. See tables 1 and 2 for further abbreviations. *Adjustors are stroke volume (as indicated), age, mean arterial pressure, body height, body weight, pulse rate, diabetes mellitus or an HbA1c>6.1%, regular smoking and regular alcohol intake. †p<0.0001 for comparisons of partial r values with Pf, $^{\#}$p<0.01,$^{\#\#}$p<0.005 for comparison of partial r values with Pa, $^{\$}$p<0.0001 for comparison of partial r values with AIx (z-statistics).

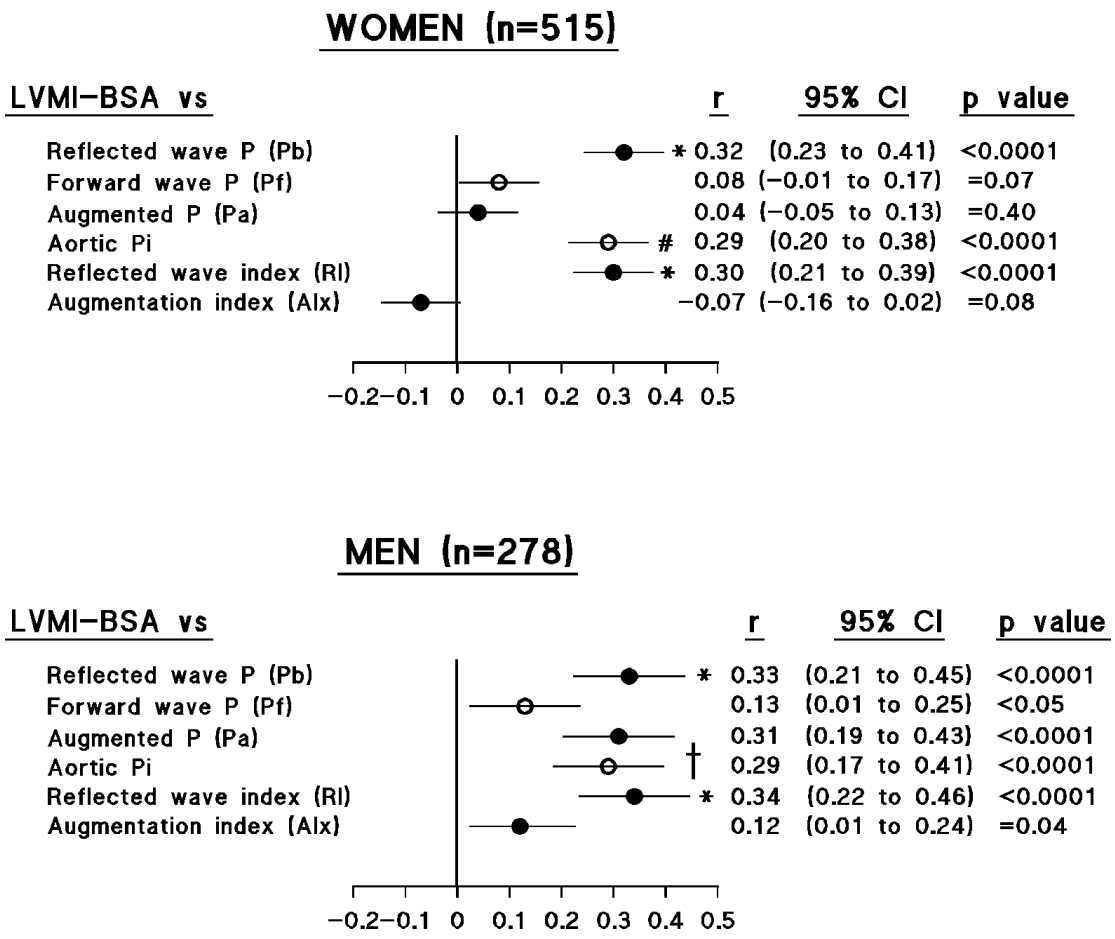


Figure 3.2. Contribution of aortic hemodynamic variables to variations in left ventricular mass indexed to body surface area (LVMI-BSA) in sex-specific categories in a group of African descent. Closed circles indicate indexes of wave reflection; open circles indicate indexes of forward or incident wave pressures. Potential confounders included in the model are age, mean arterial pressure, body height, pulse rate, diabetes mellitus or an HbA1c>6.1%, regular smoking and regular alcohol intake. Those factors not independently associated with LVMI were forced into the model. Pi=Aortic pulse pressure-Pa. *p<0.05 for comparisons of partial r values with Pf and AIx, †p<0.05 for comparison of partial r values with AIx, $^{\#}$p<0.05 for comparison of partial r values with Pa and AIx (z-statistics).

reflected wave effects. Indeed, Pb or RI-LVMI relations were similar in men and women (Figure 3.2). Similar findings were also noted in participants not receiving antihypertensive therapy (Table 3.6). Stroke volume was correlated with LVMI ($r=0.64$, $p<0.0001$). However, with further adjustments for stroke volume, relative differences in relations between reflected versus forward wave indexes and LVMI were retained (Table 3.7).

3.5 **Discussion**

The main findings of the present study are as follows: In a large (n=1185), community-based sample of African ancestry, independent of confounders including MAP (distending pressures), reflected waves (RI or Pb) accounted for more of the variation in PPc and LVMI than did forward wave pressures (Pf) in both women and men. However, incident wave pressure (Pi) accounted for more of the variation in PPc than did aortic systolic pressure augmentation (AIx or Pa) in both women and in men, and Pi accounted for as much of the variation in LVMI as Pa or AIx in men, whilst Pi, but not Pa or AIx accounted for variations in LVMI in women.

Several prior studies have reported on a relatively greater contribution of Pa as compared to Pi to age-related increases in PPc (McEniery et al 2005, Namasivayam et al 2009, Cecelja et al 2009). However, it is now recognised that Pa may be confounded by considerable overlap between forward and backward waves and that there is a poor relationship between the magnitude of the reflected wave and Pa (Davies et al 2010, Cheng et al 2012, Hughes et al 2013). Nevertheless, studies which have employed approaches to separate Pb from Pf, suggest that Pb contributes little to age-related increases in PPc (Mitchell et al 2010b, Segers et al 2007). These studies were nonetheless conducted either in a sample where BP values were largely well-controlled (Mitchell et al 2010b), or in a sample with a narrow age range. In contrast, using wave separation analysis in the present study

Table 3.6. Independent relationships between aortic hemodynamics and left ventricular mass indexed to body surface area (LVMI-BSA) in women and men of African ancestry not receiving antihypertensive therapy.

	Women (n=354)		Men (n=231)	
LVMI-BSA vs	partial r (CI)*	p value	partial r (CI)*	p value
Pb	0.34 (0.24 to 0.49)†	<0.0001	0.39 (0.26 to 0.52)†	<0.0001
Pf	0.15 (0.05 to 0.25)	<0.005	0.17 (0.04 to 0.300	<0.01
Pa	0.05 (-0.05 to 0.15)	=0.36	0.33 (0.20 to 0.46)	<0.0001
Pi	0.30 (0.19 to 0.40)#	<0.0001	0.34 (0.21 to 0.47)	<0.0001
RI	0.30 (0.20 to 0.40)$	<0.0001	0.39 (0.26 to 0.52)$	<0.0001
AIx	-0.06 (-0.16 to 0.05)	=0.27	0.10 (-0.03 to 0.22)	=0.18

CI, confidence intervals. See tables 1 and 2 for further abbreviations. *Adjustors are age, mean arterial pressure, body height, body weight, pulse rate, diabetes mellitus or an HbA1c>6.1%, regular smoking and regular alcohol intake. †p<0.05 for comparisons of partial r values with Pf, #p<0.0001 for comparison of partial r values with Pa, $p<0.005 for comparison of partial r values with AIx (z-statistics).

Table 3.7 Impact of adjustments for stroke volume (SV) on the independent relationships between indexes of aortic wave reflection and left ventricular mass indexed to body surface area (LVMI-BSA) in women and men of African ancestry.

LVMI-BSA vs	Women (n=515)				Men (n=278)			
SV adjusted	Before		After		Before		After	
	partial r (CI)*	p value	partial r (CI)*	p value	partial r (CI)*	p value	partial r (CI)*	p value
Pb	0.31 (0.22 to 0.40)†	<0.0001	0.15 (0.06 to 0.23)†	<0.0001	0.34 (0.22 to 0.45)†	<0.0001	0.22 (0.10 to 0.34)†	<0.0001
Pf	0.08 (0.01 to 0.16)	<0.05	0.03 (-0.05 to 0.11)	=0.33	0.14 (0.02 to 0.25)	<0.05	0.06 (-0.06 to 0.17)	=0.18
Pa	0.03 (-0.05 to 0.11)	=0.40	0.01 (-0.07 to 0.09)	=0.72	0.31 (0.19 to 0.42)	<0.0001	0.21 (0.09 to 0.33)	<0.0001
Pi	0.29 (0.20 to 0.37)$^{\#\#}$	<0.0001	0.15 (0.06 to 0.23)$^{\#}$	<0.0001	0.30 (0.18 to 0.41)	<0.0001	0.18 (0.06 to 0.29)	<0.0001
RI	0.30 (0.21 to 0.38)$^{\$}$	<0.0001	0.14 (0.05 to 0.22)$^{\$}$	<0.0001	0.35 (0.23 to 0.46)$^{\$}$	<0.0001	0.22 (0.10 to 0.33)$^{\$}$	<0.0001
AIx	-0.07 (-0.15 to 0.01)	=0.08	-0.05 (-0.14 to 0.03)	=0.11	0.12 (0.01 to 0.23)	<0.05	0.10 (-0.01 to 0.22)	=0.10

CI, confidence intervals. See tables 1 and 2 for further abbreviations. *Adjustors are stroke volume (as indicated), age, mean arterial pressure, body height, body weight, pulse rate, diabetes mellitus or an HbA1c>6.1%, regular smoking and regular alcohol intake. †p<0.0001 for comparisons of partial r values with Pf, $^{\#}$p<0.01,$^{\#\#}$p<0.0005 for comparison of partial r values with Pa, $^{\$}$p<0.0001 for comparison of partial r values with AIx (z-statistics).

conducted in a community sample with a wide age range and with a high prevalence of uncontrolled hypertension, I show that Pb has a far stronger relationship with PPc than Pf, and that these associations occurred independent of gender. Hence, the present study provides the first direct evidence to show that in both women and in men reflected waves account for more of the variation in PPc than do forward wave pressures and that indexes of aortic pressure augmentation underestimate the contribution of aortic wave reflection to variations in PPc.

A few prior studies have suggested that indexes of reflected waves derived from wave separation analysis (Pb or RI) are more closely associated with end-organ damage than augmented pressure indexes (Pa and AIx) (Wang et al 2010, Weber et al 2012). However, in neither study were these comparisons made with adjustments for confounders. Hence, the differences reported on (Wang et al 2010) may be attributed to confounders including distending pressures and heart rate. Furthermore, in one study (Weber et al 2012) no comparisons were made between correlation coefficients and similar relations were noted between reflected wave indices derived from wave separation analysis and end-organ changes as compared to relations between indices of aortic systolic pressure augmentation and end-organ changes (Weber et al 2012). In the present study I provide clear evidence that relations between indices of wave reflection and LVMI were markedly stronger than forward wave pressure effects, whilst indices of aortic systolic pressure augmentation considerably underestimated the contribution of reflected as compared to forward wave pressures. As previously described (chapter 2, Sibiya et al 2014), the lack of ability of augmentation indices to independently relate to LVMI was particularly striking in women where no significant relations were noted, whilst in men, although the effect was still diminished, a significant relation was still noted. Importantly, the present study advances this previous work by demonstrating that differences in the independent relationships between aortic augmentation indices and LVMI are not attributed to a sex-specific effect of aortic backward wave pressures on LVMI.

Prior studies have demonstrated that impact of aortic pressure augmentation on end-organ changes (Sibiya et al 2014) or cardiovascular outcomes (Wang et al 2010) is attenuated in women as compared to men. In the present study we similarly show that relations between Pa or AIx and LVMI were diminished in women as compared to men. However, these differences were not attributed to disparities in reflected wave effects. Indeed, Pb or RI-LVMI relations were similar in men as compared to women. Hence, the weaker associations between augmentation indexes and cardiovascular damage in women as compared to men (Sibiya et al 2014, Wang et al 2010) are likely to be attributed to a greater degree of inaccuracy of pressure augmentation as an index of wave reflection in women as compared to men.

Increases in indices of augmentation index are not just determined by increases in reflected wave magnitude, but also by an enhanced aortic reservoir function as well as factors that influence the forward traveling wave amplitude (Chirinos et al 2005, Davies et al 2010, Vlachopoulos et al 2010, Cheng et al 2012, Hashimoto et al 2007, Hughes et al 2013, Hashimoto et al 2006, Fok et al 2014a), the magnitude of the forward wave (Weber et al 2006, Torjesen et al 2014), forward wave peak width (Weber et al 2006, Torjesen et al 2014), and the slope of the backward wave upstroke (Weber et al 2006, Torjesen et al 2014). Although a shorter stature, and hence an earlier return of reflected waves has generally been the explanation for an increased AIx in women, more recently an increased forward wave peak width, slope of the backward pressure wave, and forward wave amplitude, but not backward wave amplitude have been suggested to be the main determinants of an increased AIx in women of the Framingham Heart study (Weber et al 2006). In this regard, if one or more of these factors contributes little to increases in LVMI, but influences augmentation indices in women more so than men, then this could explain the lack of relationship between aortic augmentation indices and LVMI in women, whilst a significant relationship was still noted in men. As the manufacturer's software does not allow for the determination of the forward wave peak width or slope of the backward pressure wave, I could not assess whether one or more of

these additional factors modified the relationship between augmentation indices and LVMI to a greater extent in women as compared to men.

As previously demonstrated (Kips et al 2009) the assumptions intrinsic to the use of the 'triangulation method' of aortic wave separation are not ideal. However, this approach produces correlations between reflected wave indexes derived from the 'triangulation method' and actual aortic flow waveforms (r^2=0.55) that are considerably stronger than between AIx and indexes derived from actual aortic flow waveforms (r^2=0.34) (Kips et al 2009). Thus, the triangulation method of wave separation is better than augmentation indices at identifying reflected wave effects. Despite employing a relatively imprecise method of identifying reflected wave magnitude and index, we were still able to show that indices of aortic wave reflection were more closely associated with PPc and LVMI than forward wave pressures, whilst indices of aortic pressure augmentation showed weaker associations than forward wave pressures with PPc and LVMI. Hence, the present study provides evidence that improved measures of wave reflection are indeed better than augmentation indexes at detecting relations between reflected wave effects and both PPc and LVMI.

Dobutamine, which enhances PPc through increases in myocardial contractility and stroke volume, largely increases forward wave pressures (Fok et al 2014b). In contrast, norepinephrine, which augments PPc through marked vasoconstriction, mainly increases backward wave pressures but does not produce as much of an increase in PPc (Fok et al 2014b). Further, increases in forward wave pressures may account for more of the increment in PPc in hypertensives than reflected wave pressures (Fok et al 2014b). It has therefore been suggested that forward wave pressures, mediated by increases in stroke volume may be more important than reflected wave pressures in determining variations in PPc in hypertension (Fok et al 2014b). However, as in the present and previous (Cecelja et al 2009, Segers et al 2007) studies where no increase (Segers et al 2007) or only modest increases (present study) in stroke volume were noted with increasing age, or where stroke volume contributed little to

variations in PPc (Cecelja et al 2009), increases in stroke volume are unlikely to explain a significant proportion of age-related increases in PPc in either women or men. Moreover, norepinephrine-induced effects on aortic reflected waves (Fok et al 2014b) are more likely to represent the hypertensive state where a major effect on BP is through increases in vascular smooth muscle tone. Further, in the present study the greater impact of Pb as compared to Pf on variations in PPc and LVMI were replicated even when stroke volume was included in multivariate adjusted analysis.

Additional limitations of the present study are as follows: The present study was a cross-sectional design. Therefore, I cannot determine whether the age-related changes reported on are attributed to the long-term impact of age or a cumulative effect of alternative risk factors over time or whether relations between aortic hemodynamics and LVMI are indeed cause and effect. Further longitudinal studies are required to determine these effects. Moreover, in the present study calibration of the radial waveform from brachial BP measurements ignores amplification of BP from brachial to radial arteries. Hence, aortic pressures are likely to have been underestimated using the current approach.

In conclusion, in the present study conducted in a community sample with a high prevalence of uncontrolled hypertension, I show that in both women and in men, reflected waves are more closely associated with PPc and LVMI than forward waves, but that indices of aortic systolic pressure augmentation markedly underestimate these effects. These data provide support for a role of reflected wave function in mediating the adverse effects of aortic PP, effects which nonetheless cannot be accurately detected using indices of aortic systolic pressure augmentation. Moreover, given the high prevalence of hypertension and related cardiovascular events in urban communities in Africa, the present study suggests that approaches to decreasing age-related increases in aortic wave reflection may produce a major impact on the burden of disease in these communities.

CHAPTER 4

Reflected Rather than Forward Wave Pressures Account for Brachial Pressure-Independent Relations Between Aortic Pressure and End-Organ Changes in an African Community.

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4.1 **Abstract**

As the relative impact of aortic backward as compared to forward wave pressures on cardiovascular damage independent of brachial blood pressure (BP) is uncertain, I aimed to determine whether brachial BP-independent relations between aortic pressure and cardiovascular damage are better explained by reflected (backward)(Pb) or forward (Pf) wave pressure effects. In 1174 participants from a community sample of African ancestry I assessed central aortic pulse pressure (PPc), Pb and Pf (radial applanation tonometry, SphygmoCor software) as well as left ventricular mass index (LVMI)(n=786), aortic pulse wave velocity (PWV)(n=1019), carotid intima-media thickness (IMT)(n=578), transmitral early-to-late LV diastolic velocity (E/A)(n=779) and estimated glomerular filtration rate (eGFR)(n=1174). Independent of mean arterial pressure and confounders, PPc and both Pb and Pf were associated with end-organ measures or damage ($p<0.05$ to <0.0001). With adjustments for brachial PP and confounders, Pb remained directly associated with LVMI (partial $r=0.10$, $p<0.01$), PWV (partial $r=0.28$, $p<0.0001$), and IMT (partial $r=0.28$, $p<0.0001$), and inversely associated with E/A (partial $r=-0.31$, $p<0.0001$) and eGFR (partial $r=-0.14$, $p<0.0001$). Similar relations were noted with the presence of end-organ damage ($p<0.05$ to <0.0001). In contrast, with adjustments for brachial PP and confounders, Pf no longer retained direct relations with LVMI, PWV, and IMT or inverse relations with E/A and eGFR. Adjustments for Pb, but not Pf diminished brachial PP-independent relationships between PPc and end-organ measures. Independent relations between Pb, but not Pf and end-organ measures were largely attributed to Pb accounting for most of the variation in brachial-to-aortic PP amplification. In conclusion in communities of African ancestry, brachial BP-independent relations between aortic pressure and end-organ changes are largely attributed to an impact of reflected rather than forward wave pressures.

Key words: aortic pressure, reflected waves, forward waves, end organ changes.

4.2 **Introduction**

Although pulse pressure (PP) measured at the brachial artery is closely correlated with central aortic PP (PPc), amplification of PP occurs from the aorta to brachial arteries (Avolio et al 2009, Agabiti-Rosei et al 2007). As there may be marked differences in aortic versus brachial blood pressure (BP) (Avolio et al 2009, Agabiti-Rosei et al 2007) and because of the close proximity of the aorta to end organs, aortic BP has been proposed to be of greater pathophysiological significance than brachial BP. Indeed, several studies have demonstrated that PPc or the ratio of brachial and aortic BP, an index of PP amplification, are associated with cardiovascular outcomes (Safar et al 2002, Roman et al 2007, Jankowski et al 2008, Pini et al 2008, Wang et al 2009, Williams et al 2006, Benetos et al 2010, Regnault et al 2012, Benetos et al 2012, Vlachopoulos et al 2010) and end-organ measures (Roman et al 2014) either independent of or better than brachial BP. However, the exact changes that determine PPc and account for brachial BP-independent relations between PPc and cardiovascular damage are uncertain.

Numerous factors contribute toward PPc and these may influence PPc by modifying either aortic forward (Pf) or backward (reflected) (Pb) wave pressures. Several studies have evaluated the contribution of Pf and Pb to age-related increases in PPc (Segers et al 2007, Mitchell et al 2010a) and the contribution of Pf and Pb to variations in end-organ measures or cardiovascular outcomes (Wang et al 2010, Chirinos et al 2012, Weber et al 2012, Zamani et al 2014, Hughes et al 2014). Importantly, in some of these studies (Wang et al 2010, Chirinos et al 2012, Zamani et al 2014, Hughes et al 2014) indices of reflected waves predicted cardiovascular outcomes independent of brachial BP. However, whether forward wave pressures also associate with cardiovascular damage independent of brachial BP, and the relative contribution of Pf and Pb to the brachial BP-independent relationship between PPc and cardiovascular damage is uncertain. In the present study, I therefore aimed to assess in a

community of African ancestry whether brachial BP-independent associations between Pb, Pf or both and end-organ measures or damage occur and whether brachial BP-independent associations between PPc and cardiovascular end-organ measures or damage are accounted for by an impact of Pb, Pf or both.

4.3 **Methods**

4.3.1 Study group.

The present study was conducted according to the principles outlined in the Helsinki declaration. The Committee for Research on Human Subjects of the University of the Witwatersrand approved the protocol (approval number: M02-04-72 and renewed as M07-04-69 and M12-04-108). Participants gave informed, written consent. The present study design has previously been described (Norton et al 2008, Woodiwiss et al 2009, Redelinghuys et al 2010, Norton et al 2012). Briefly, 1174 participants from families of black African descent (Nguni and Sotho chiefdoms) with siblings older than 16 years with central hemodynamic measurements were randomly recruited from the South West Township (SOWETO) of Johannesburg, South Africa. In a series of sub-studies, 1019 had aortic pulse wave velocity (PWV), 786 had left ventricular mass index (LVMI) (echocardiography), 578 had carotid intima media thickness (IMT), and 779 had LV diastolic function (transmitral velocity) determined.

*4.3.2 Clinical, demographic and anthropometric measurements***.**

See section 2.3.2 for details

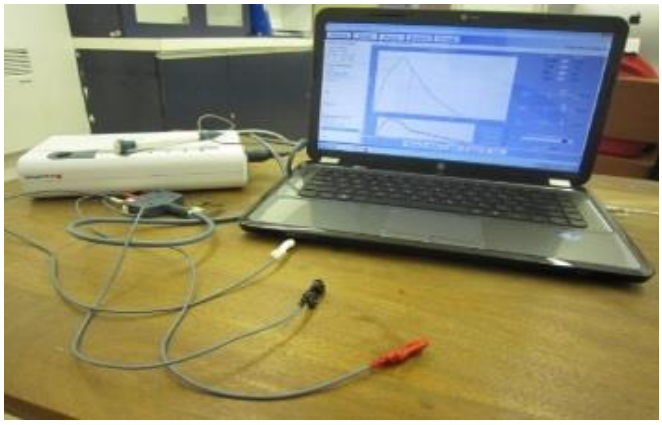
4.3.3 Pulse wave analysis.

See section 2.3.4 for details

4.3.4 End-organ measures.

Echocardiographic measurements were recorded and analysed off-line by experienced investigators who were unaware of the clinical data of the participants and whom had a low degree of inter- and intra-observer variability (Norton et al 2012). Left ventricular mass index (LVMI) was determined as described in section 2.3.5. Left ventricular mass was determined using a standard formula (Devereux et al 1986) and indexed (LVMI) to height$^{2.7}$. Left ventricular hypertrophy (LVH) was identified as LVMI >51 g/m$^{2.7}$ (Woodiwiss et al 2015). Left ventricular diastolic function was assessed from a pulsed wave Doppler examination of the mitral inflow at rest (Libhaber et al 2014). Transmitral flow velocity in early (E) and late (atrial) diastole was assessed and data expressed as E/A. A reduced E/A was identified as <0.75 (Quinones et al 2002).

Aortic PWV was determined from sequential waveform measurements at carotid and femoral sites using applanation tonometry and SphygmoCor software as previously described (Norton et al 2008, Woodiwiss et al 2009) (see figure 4.1). The time delay in the pulse waves between the carotid and femoral sites was determined using an electrocardiograph-derived R wave as a fiducial point. Pulse transit time was taken as the average of 10 consecutive beats. The distance which the pulse wave travels was determined as the difference between the distance from the femoral sampling site to the suprasternal notch, and the distance from the carotid sampling site to the suprasternal notch. Aortic PWV was calculated as the ratio of the distance to the transit time (m/sec). An increased PWV was identified as >10 m/sec (Mancia et al 2013).



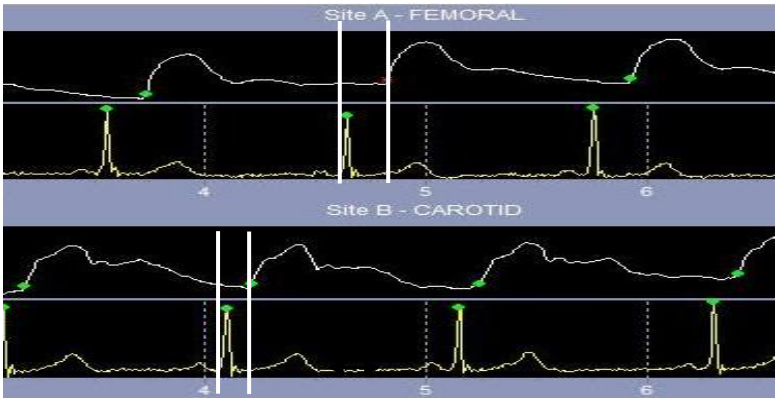


Figure 4.1. Photograph of the SphygmoCor device (upper panel) used to determine aortic pulse wave velocity. Images in the lower panel show carotid and femoral pressure waves together with the electrocardiographic trace showing R waves which were used as fiducial points to calculate transit time. The transit time is the difference between time A and B.

Carotid intima-media thickness (IMT) was determined using high resolution B-mode ultrasound (SonoCalc IMT, Sonosite Inc, Bothell, Washington) employing a linear array 7.5 MHz probe as described previously (Norton et al 2012). Images of at least 1cm length of the far wall of the distal portion of the right common carotid artery from an optimal angle of incidence (defined as the longitudinal angle of approach where both branches of the internal and external carotid artery are visualized simultaneously) at least 1 cm proximal to the flow divider were obtained. Carotid IMT measurements were determined using semi-automated border-detection and quality control software (see figure 4.2). An increased IMT was identified as >0.90 mm (Mancia et al 2013).

Estimated glomerular filtration rate (eGFR) was determined using the abbreviated Modification of Diet in Renal Disease (MDRD) study group equation: 186.3 x (serum creatinine in mg/decilitre$^{-1.154}$) x (age in years$^{-0.203}$) x 1.212 x 0.742 (if female). A reduced eGFR was identified as <60 ml/min/1.73 m^2 (Mancia et al 2013).

4.3.5 Statistical analysis.

For database management and statistical analysis, SAS software, version 9.1 (SAS Institute Inc., Cary, NC) was employed. Multiple linear regression analysis was performed to determine the independent effects of aortic BP on end-organ measures considered as continuous traits. Logistic regression analysis was performed to determine the independent effects of aortic BP on end-organ damage considered as categorical traits. Adjustments included in multivariate models were those correlated with central haemodynamic variables or end-organ measures in bivariate analysis. In order to avoid the effects of co-linearity, in primary analysis age was not included as an adjustor as Pb and Pf are strongly related to age over the

adult age range. However, in secondary analysis, age was included as an adjustor to confirm the impact of Pb or Pf beyond age. To determine probability values, further adjustments for non-

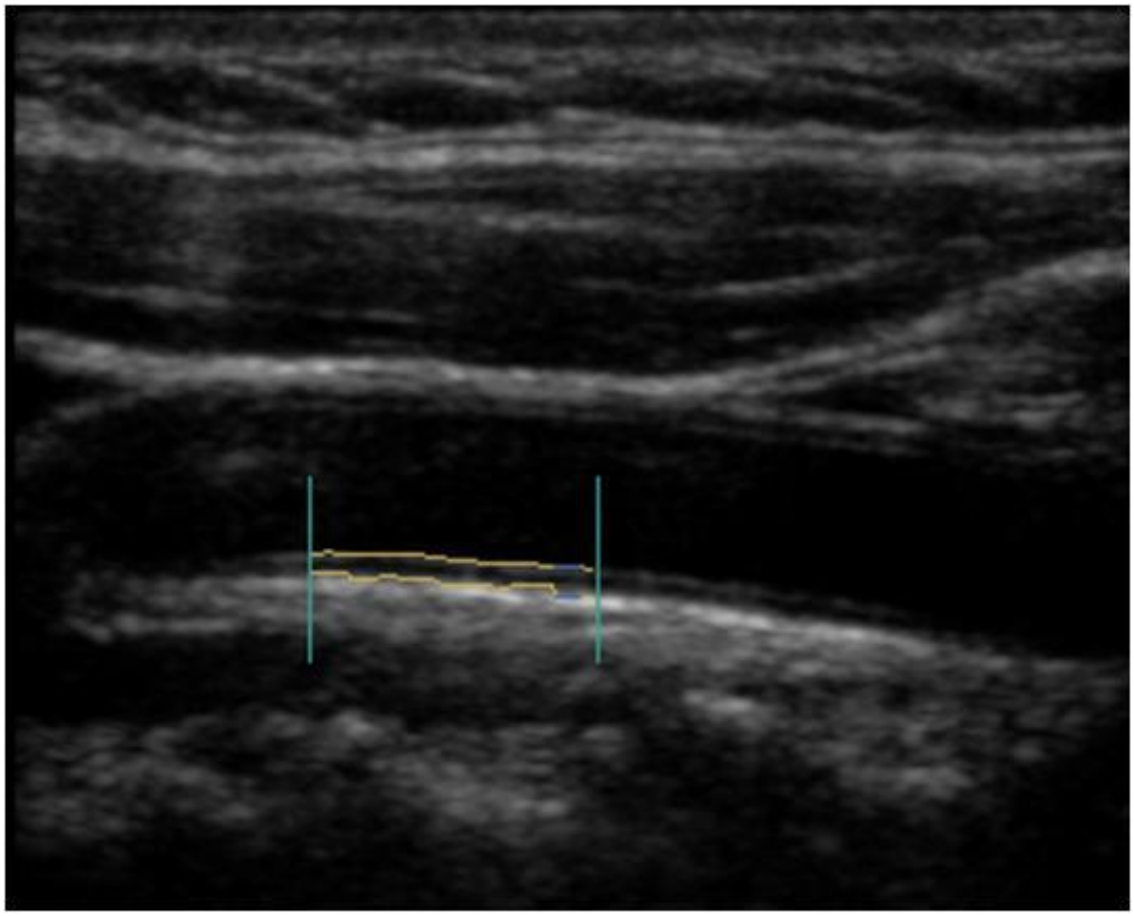


Figure 4.2. Ultrasonic image of the right common carotid artery showing semi-automated border detection (yellow lines) to obtain intima-media thickness measurement (of 1cm length, between blue lines) at least 1cm proximal to the flow divider.

independence of family members was performed using non-linear regression analysis (mixed procedure as defined in the SAS package). To ensure that relationships occurred independent of the use of antihypertensive therapy or as a result of sex-specific effects of aortic function, sensitivity analysis was conducted in participants not receiving antihypertensive therapy and in sex-specific groups. Regression coefficients were compared with z statistics.

4.4 **Results**

4.4.1 Characteristics of the participants.

Table 4.1 gives the demographic and clinical characteristics of the participants. Tables 4.2-4.4 give the demographic and clinical characteristics of the participants recruited in the sub-studies where LVMI, E/A or IMT were measured as compared to participants without these measurements. More women than men participated in the study. As compared to those without IMT measurements, those with IMT measurements were modestly younger with a trend toward higher BP values (Table 4.3). Otherwise, no differences were noted in participants recruited in the sub-studies where LVMI and E/A were measured as compared to participants without these measurements (Tables 4,2 and 4.4). A high proportion of participants had an increased LVMI and decreased E/A (Table 4.1). A low-to-intermediate proportion had an increased IMT, PWV or a reduced eGFR (Table 4.1).

Table 4.1. Characteristics of the study sample.

Sample number (% female)	1174 (65.1%)
Age (years)	44.2±18.2
Body mass index (kg/m^2)	29.5±8.0
% Overweight/obese	23.0/43.1
Regular tobacco (% subjects)	15.3
Regular alcohol (% subjects)	21.1
% Diabetes mellitus or an HbA_{1c}>6.1%	25.7
% Hypertensive	45.6
% Treated for hypertension	24.0
Total cholesterol (mmol/l)	4.62±1.35
HDL cholesterol (mmol/l)	1.40±0.43
Estimated GFR (eGFR) (mls/min/1.73 m^2)	116±32
Brachial SBP/DBP (mm Hg)	128±22/84±13
Brachial pulse pressure (mm Hg)	44±15
Aortic SBP (mm Hg)	120±22
Aortic pulse pressure (mm Hg)	35±14
Forward wave pressure (Pf) (mm Hg)	24±8
Backward (reflected) wave pressure (Pb) (mm Hg)	17±8
Reflected wave index (RI)(Pb/Pf)	71.6±21.5
Left ventricular mass index (LVMI)(g/$m^{2.7}$)	41.7±15.1 (n=786)
Left ventricular E/A	1.28±0.49 (n=779)
Aortic pulse wave velocity (PWV)(m/sec)	6.39±2.65 (n=1019)
Carotid intima-media thickness (mm)	0.64±0.13 (n=578)
LVMI>51 g/$m^{2.7}$ (%)	20.7
PWV>10 m/sec (%)	8.5
IMT>0.90 mm (%)	3.3
E/A<0.75 (%)	13.5
eGFR<60 mls/min/1.73 m^2)(%)	1.4

Data are shown as mean±SD or proportions (%). HDL, high density lipoprotein; GFR, glomerular filtration rate; SBP, systolic blood pressure; DBP, diastolic BP; E/A, transmitral early/atrial diastolic blood flow velocity.

Table 4.2. Characteristics of the study sample with and without left ventricular mass measurements.

	With	Without
Sample number (% female)	786 (65.0)	388 (65.2)
Age (years)	44.7±18.0	43.0±18.5
Body mass index (kg/m^2)	29.6±7.8	29.4±8.6
% Overweight/obese	23.8/44.0	21.4/41.2
Regular tobacco (% subjects)	14.9	16.2
Regular alcohol (% subjects)	19.9	23.7
% Diabetes mellitus or an HbA_{1c}>6.1%	26.1	25.0
% Hypertensive	46.6	43.6
% Treated for hypertension	25.7	20.6
Total cholesterol (mmol/l)	4.64±1.44	4.56±1.15
HDL cholesterol (mmol/l)	1.38±0.39	1.43±0.43
Brachial SBP/DBP (mm Hg)	128±22/84±13	128±21/84±13
Brachial pulse pressure (mm Hg)	44±15	43±13
Aortic SBP (mm Hg)	120±22	119±22
Aortic pulse pressure (mm Hg)	35±14	34±13
Forward wave pressure (Pf) (mm Hg)	24±8	23±7
Backward wave pressure (Pb) (mm Hg)	17±8	17±7
Reflected wave index (RI)(Pb/Pf)	71.8±21.4	71.2±21.7

Data are shown as mean±SD or proportions (%). SBP, systolic blood pressure; DBP, diastolic BP.

Table 4.3. Characteristics of the study sample with and without carotid intima-media thickness measurements.

	With	Without
Sample number (% female)	578 (65.2)	596 (64.9)
Age (years)	45.3±18.1	43.0±18.2*
Body mass index (kg/m^2)	29.9±8.2	29.2±7.9
% Overweight/obese	22.7/44.5	23.3/41.8
Regular tobacco (% subjects)	16.1	14.6
Regular alcohol (% subjects)	21.3	21.0
% Diabetes mellitus or an HbA_{1c}>6.1%	25.6	25.8
% Hypertensive	45.3	45.8
% Treated for hypertension	25.4	22.7
Total cholesterol (mmol/l)	4.66±1.08	4.58±1.57
HDL cholesterol (mmol/l)	1.40±0.43	1.40±0.43
Brachial SBP/DBP (mm Hg)	126±21/83±13	130±23**/85±13*
Brachial pulse pressure (mm Hg)	43±14	45±15*
Aortic SBP (mm Hg)	118±21	121±23*
Aortic pulse pressure (mm Hg)	34±13	36±14*
Forward wave pressure (Pf) (mm Hg)	23±8	24±8
Backward wave pressure (Pb) (mm Hg)	17±7	18±8*
Reflected wave index (RI)(Pb/Pf)	71.1±21.5	72.1±21.5

Data are shown as mean±SD or proportions (%). SBP, systolic blood pressure; DBP, diastolic BP. * $p<0.05$, ** $p<0.005$ vs with.

Table 4.4. Characteristics of the study sample with and without left ventricular diastolic function measurements.

	With	Without
Sample number (% female)	779 (65.0)	395 (65.3)
Age (years)	44.6±17.9	43.3±18.7
Body mass index (kg/m^2)	29.6±7.8	29.4±8.5
% Overweight/obese	23.8/43.9	21.5/41.5
Regular tobacco (% subjects)	15.0	16.0
Regular alcohol (% subjects)	20.0	23.3
% Diabetes mellitus or an HbA_{1c}>6.1%	25.8	25.6
% Hypertensive	46.2	44.3
% Treated for hypertension	25.3	21.5
Total cholesterol (mmol/l)	4.64±1.45	4.57±1.14
HDL cholesterol (mmol/l)	1.38±0.39	1.43±0.43
Brachial SBP/DBP (mm Hg)	128±22/84±13	128±22/84±13
Brachial pulse pressure (mm Hg)	44±15	44±14
Aortic SBP (mm Hg)	120±22	119±22
Aortic pulse pressure (mm Hg)	35±14	34±14
Forward wave pressure (Pf) (mm Hg)	24±8	24±8
Backward wave pressure (Pb) (mm Hg)	17±8	17±8
Reflected wave index (RI)(Pb/Pf)	71.8±21.2	71.2±21.9

Data are shown as mean±SD or proportions (%). SBP, systolic blood pressure; DBP, diastolic BP.

4.4.2 *Both reflected and forward wave pressures are independently associated with end-organ measures and damage*.

With adjustments for confounders including mean arterial pressure, PPc, Pb, Pf, and RI were independently associated with end-organ measures (Table 4.5) and damage (Table 4.6). The magnitude of the effect on end-organ measures (slope or β-coefficient) was greater for Pb as compared to Pf (Table 4.5). Moreover, for several end-organ measures relations with Pb were stronger than with Pf (comparison of partial r values in Table 4.5).

4.4.3 Brachial BP-independent associations between reflected or forward wave pressures and end-organ measures or damage.

With adjustments for brachial PP (Figure 4.3) or SBP (Figure 4.4) in addition to confounders, PPc, Pb and RI were directly associated with LVMI, PWV, and IMT or increases in these variables and inversely associated with E/A and eGFR or decreases in these variables. However, with adjustments for brachial PP (Figure 4.3) or SBP (Figure 4.4) in addition to confounders, Pf was inversely associated with LVMI, PWV, and IMT or increases in these variables and directly associated with E/A and eGFR or decreases in these variables. With further adjustments for age, the independent relations between Pb and

Table 4.5. Multivariate adjusted (including adjustments for mean arterial pressure) relationships (partial correlation coefficients [r] and 95% confidence intervals [CI]) between central aortic haemodynamics and end-organ measures.

	n=	β-coefficient (±SEM)*	Partial r* (95% CI)	p value
Left ventricular mass index (LVMI) vs				
PPc	786	0.29±0.05	0.22 (0.15 to 0.29)	<0.0001
Pf	786	0.31±0.07	0.16 (0.09 to 0.23)	<0.0001
Pb	786	0.53±0.09†	0.21 (0.15 to 0.28)	<0.0001
RI	786	0.08±0.03	0.10 (0.03 to 0.17)	<0.01
Aortic pulse wave velocity (PWV) vs				
PPc	1019	0.08±0.01	0.38 (0.33 to 0.43)	<0.0001
Pf	1019	0.08±0.01	0.25 (0.19 to 0.31)	<0.0001
Pb	1019	0.16±0.01†††	0.40 (0.34 to 0.44)†††	<0.0001
RI	1019	0.03±0.04	0.22 (0.16 to 0.28)	<0.0001
Carotid intima-media thickness (IMT) vs				
PPc	578	0.004±0.0004	0.33 (0.25 to 0.40)	<0.0001
Pf	578	0.003±0.0007	0.20 (0.12 to 0.28)	<0.0001
Pb	578	0.007±0.0008†††	0.35 (0.27 to 0.41)††	<0.0001
RI	578	0.001±0.0003	0.21 (0.13 to 0.29)	<0.0001
Left ventricular E/A vs				
PPc	779	-0.008±0.001	-0.21 (-0.27 to -0.14)	<0.0001
Pf	779	-0.004±0.002	-0.06 (-0.13 to 0.01)	=0.08
Pb	779	-0.016±0.003†††	-0.23 (-0.30 to -0.16)††	<0.0001
RI	779	-0.006±0.0008	-0.25 (-0.31 to -0.18)	<0.0001
Estimated glomerular filtration rate (eGFR) vs				
PPc	1174	-0.43±0.008	-0.15 (-0.21 to -0.09)	<0.0001
Pf	1174	-0.35±0.13	-0.08 (-0.14 to -0.02)	<0.01
Pb	1174	-0.84±0.16†	-0.16 (-0.21 to -0.10)†	<0.0001
RI	1174	-0.23±0.05	-0.13 (-0.19 to -0.08)	<0.0001

PPc, central aortic pulse pressure; Pb, aortic backward (reflected) wave pressure; Pf, aortic forward wave pressure; RI, reflected wave index (Pb/Pf); E/A, transmitral early/atrial diastolic

blood flow velocity.*Adjusted for mean arterial pressure, sex, body mass index (except for LVMI which was adjusted for body weight), total cholesterol, HDL cholesterol, regular tobacco use, regular alcohol intake, diabetes mellitus or an HbA_{1c}>6.1%, and pulse rate. $^{\dagger}p=0.05$, $^{\dagger\dagger}p<0.005$, $^{\dagger\dagger\dagger}p<0.0005$ versus β-coefficient or partial r with the forward wave (z-statistics for comparison of partial r values).

Table 4.6. Multivariate adjusted (including adjustments for mean arterial pressure) relationships (partial correlation coefficients [r] and 95% confidence intervals [CI]) between central aortic haemodynamics and end-organ damage.

	n=	n with damage	Odds ratio (95% CI)	p value
Left ventricular mass index (LVMI) >51 g/m$^{2.7}$ vs				
PPc	786	163	1.03 (1.01 to 1.05)	<0.005
Pf	786	163	1.02 (1.00 to 1.05)	<0.05
Pb	786	163	1.06 (1.03 to 1.09)	<0.0005
RI	786	163	1.01 (1.00 to 1.02)	<0.05
Aortic pulse wave velocity (PWV)>10 m/sec vs				
PPc	1019	87	1.09 (1.07 to 1.12)	<0.0001
Pf	1019	87	1.10 (1.07 to 1.14)	<0.0001
Pb	1019	87	1.19 (1.14 to 1.24)	<0.0001
RI	1019	87	1.03 (1.02 to 1.05)	<0.0001
Carotid intima-media thickness (IMT) >0.90 mm vs				
PPc	578	19	1.08 (1.03 to 1.12)	<0.005
Pf	578	19	1.07 (1.01 to 1.14)	<0.05
Pb	578	19	1.14 (1.05 to 1.23)	<0.005
RI	578	19	1.03 (1.01 to 1.06)	<0.02
Left ventricular E/A <0.75 vs				
PPc	779	105	1.05 (1.03 to 1.07)	<0.0001
Pf	779	105	1.05 (1.02 to 1.08)	<0.005
Pb	779	105	1.08 (1.04 to 1.12)	<0.0001
RI	779	105	1.01 (1.00 to 1.03)	=0.05
Estimated glomerular filtration rate (eGFR) <60 mls/min/1.73 m^2 vs				
PPc	1174	16	1.06 (1.01 to 1.11)	<0.05
Pf	1174	16	1.05 (0.99 to 1.12)	=0.09
Pb	1174	16	1.12 (1.03 to 1.21)	<0.01
RI	1174	16	1.02 (0.996 to 1.05)	=0.09

PPc, central aortic pulse pressure; Pb, aortic backward (reflected) wave pressure; Pf, aortic forward wave pressure; RI, reflected wave index (Pb/Pf); E/A, transmitral early/atrial diastolic

blood flow velocity. Adjusted for mean arterial pressure, sex, body mass index (except for LVMI which was adjusted for body weight), total cholesterol, HDL cholesterol, regular tobacco use, regular alcohol intake, diabetes mellitus or an HbA_{1c}>6.1%, and pulse rate.

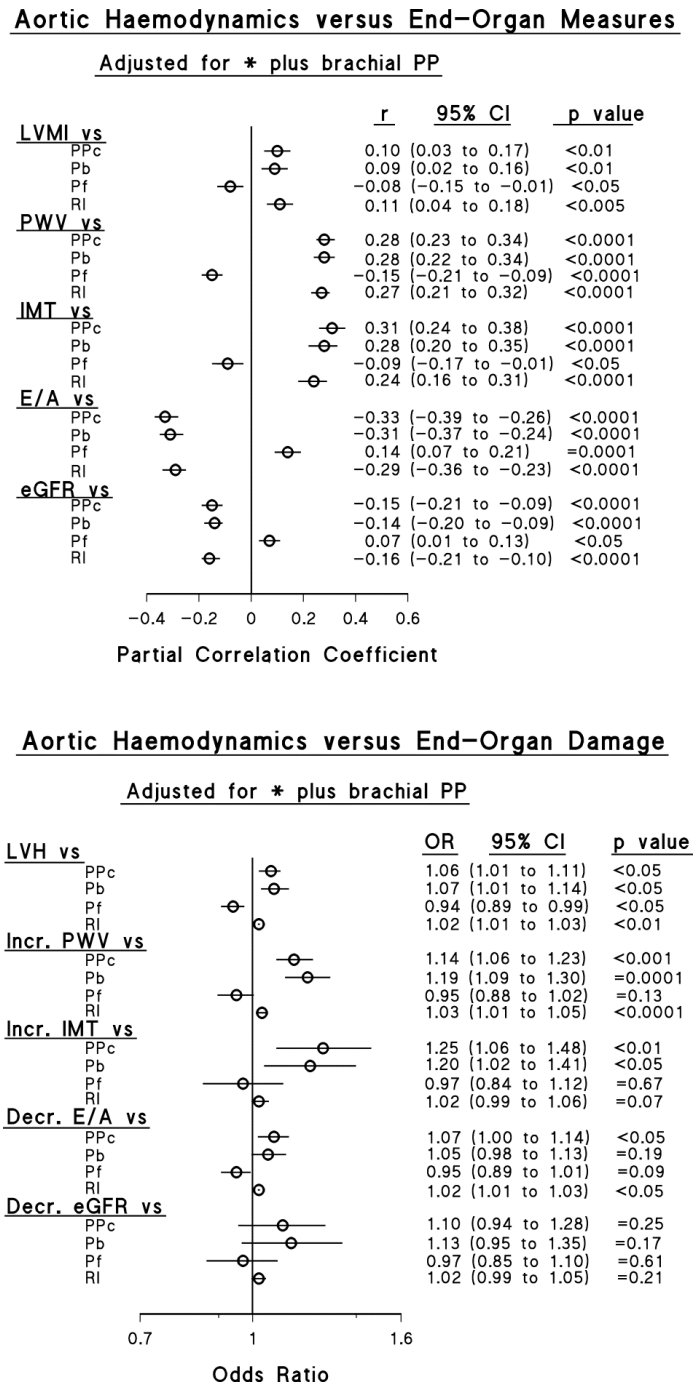


Figure 4.3. Brachial pulse pressure (PP)-independent relations between central aortic haemodynamics and end-organ measures (upper panel) or damage (lower panel). Pb, aortic backward (reflected) wave pressure; Pf, aortic forward wave pressure; LVMI, left ventricular mass index; PWV, aortic pulse wave velocity; IMT, carotid intima-media thickness; E/A, transmitral early/atrial diastolic blood flow velocity; eGFR, estimated glomerular filtration rate; LVH, LV hypertrophy; Incr., increased; Decr., decreased. *Adjustments are for brachial PP as well as sex, body mass index (except for LVMI which was adjusted for body weight), total

cholesterol, HDL cholesterol, regular tobacco use, regular alcohol intake, diabetes mellitus or an HbA_{1c}>6.1%, and pulse rate.

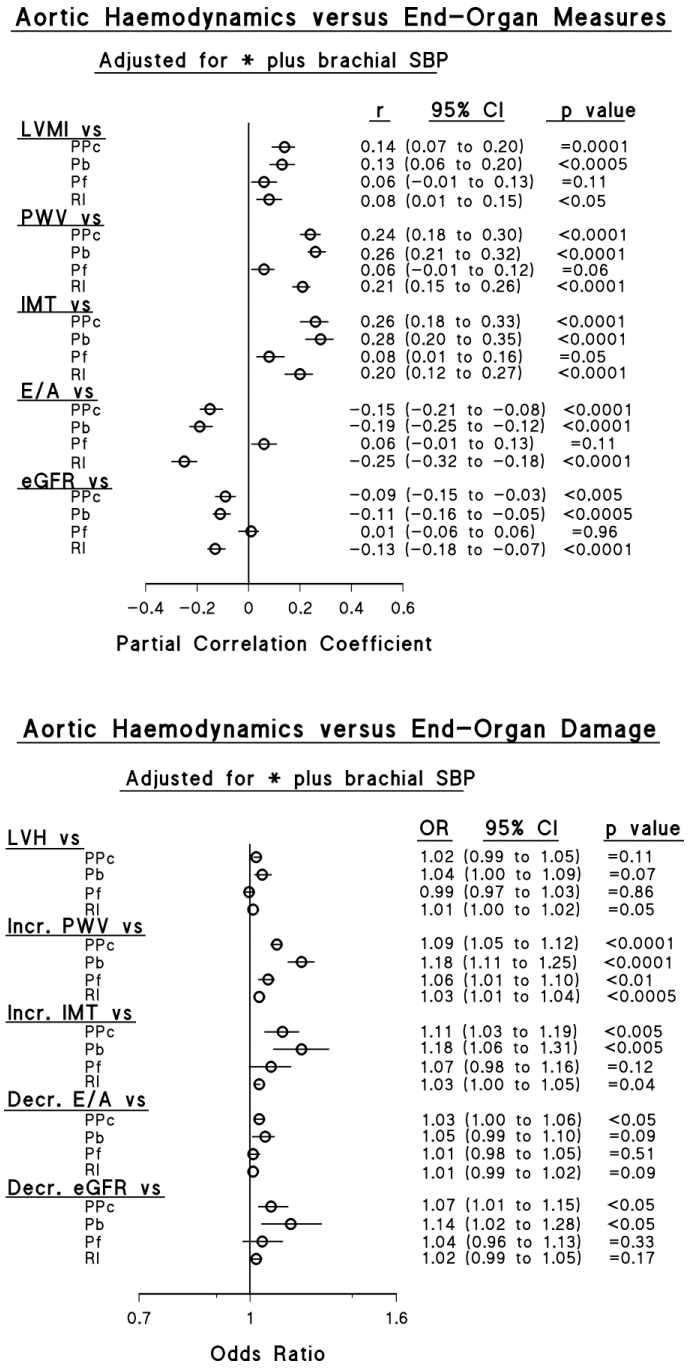


Figure 4.4. Brachial systolic pressure (SBP)-independent relations between central aortic haemodynamics and end-organ measures (upper panel) or damage (lower panel). Pb, aortic backward (reflected) wave pressure; Pf, aortic forward wave pressure; RI, reflected wave index (Pb/Pf); LVMI, left ventricular mass index; PWV, aortic pulse wave velocity; IMT, carotid intima-media thickness; E/A, transmitral early/atrial diastolic blood flow velocity; eGFR, estimated glomerular filtration rate; LVH, LV hypertrophy; Incr., increased; Decr., decreased. *Adjustments

are for SBP as well as sex, body mass index (except for LVMI which was adjusted for body weight), total cholesterol, HDL cholesterol, regular tobacco use, regular alcohol intake, diabetes mellitus or an HbA_{1c}>6.1%, and pulse rate.

PWV (Tables 4.7 and 4.8), IMT (Tables 4.7 and 4.8), E/A (Table 4.7) and LVMI (Table 4.8) were retained. The non-age and age-adjusted relations noted in all participants were similarly also noted in participants not receiving antihypertensive therapy (Tables 4.9 and 4.10). Moreover, brachial BP-independent relations between either PPc or Pb and end-organ measures were largely reproduced in both women (Table 4.11) and men (Table 4.12).

4.4.4 Reflected, but not forward wave pressures account for brachial BP-independent relations between aortic PP and end-organ measures or damage.

Adjustments for Pb, but not for Pf eliminated or significantly attenuated brachial PP (Figure 4.5) or brachial SBP (Figure 4.6)-independent relations between aortic PP and end-organ measures.

4.4.5 Relative contribution of forward and backward wave pressures to pulse pressure amplification.

Aortic Pb was more strongly correlated with aortic-to-brachial PP amplification than Pf (Figure 4.7) and these effects were noted in both women (Pb vs PP amplification, $r=-0.57$, $p<0.0001$; Pf vs PP amplification, $r=-0.08$, $p<0.05$) and in men (Pb vs PP amplification, $r=-0.64$, $p<0.0001$; Pf vs PP amplification, $r=-0.27$, $p<0.001$) ($p<0.0001$ for comparison of r values with z statistics in both women and in men).

Table 4.7 Brachial pulse pressure (PP) and age-independent relations between central aortic haemodynamics and end-organ measures.

	n=	Partial r* (95% CI)	p value
Left ventricular mass index (LVMI) vs			
PPc	786	0.04 (-0.03 to 0.11)	=0.21
Pf	786	-0.06 (-0.13 to 0.01)	=0.11
Pb	786	0.05 (-0.03 to 0.12)	=0.21
RI	786	0.07 (-0.01 to 0.14)	=0.06
Aortic pulse wave velocity (PWV) vs			
PPc	1019	0.08 (0.02 to 0.14)	<0.01
Pf	1019	-0.07 (-0.14 to -0.01)	<0.05
Pb	1019	0.10 (0.04 to 0.16)	<0.005
RI	1019	0.09 (0.03 to 0.16)	<0.005
Carotid intima-media thickness (IMT) vs			
PPc	578	0.10 (0.01 to 0.18)	<0.05
Pf	578	0.01 (-0.07 to 0.09)	=0.78
Pb	578	0.09 (0.01 to 0.17)	<0.05
RI	578	0.04 (-0.05 to 0.12)	=0.39
Left ventricular E/A vs			
PPc	779	-0.11 (-0.18 to -0.04)	<0.005
Pf	779	0.06 (-0.01 to 0.13)	=0.11
Pb	779	-0.12 (-0.19 to -0.05)	<0.005
RI	779	-0.11 (-0.18 to -0.04)	<0.005
Estimated glomerular filtration rate (eGFR) vs			
PPc	1174	0.04 (-0.02 to -0.10)	=0.18
Pf	1174	0.003 (-0.05 to 0.06)	=0.91
Pb	1174	0.02 (-0.03 to -0.08)	=0.41
RI	1174	0.001 (-0.06 to 0.06)	=0.98

PPc, central aortic pulse pressure; Pb, aortic backward (reflected) wave pressure; Pf, aortic forward wave pressure; RI, reflected wave index (Pb/Pf); E/A, transmitral early/atrial diastolic blood flow velocity.*Adjusted for brachial pulse pressure, age, sex, body mass index (except for

LVMI which was adjusted for body weight), total cholesterol, HDL cholesterol, regular tobacco use, regular alcohol intake, diabetes mellitus or an HbA_{1c}>6.1%, and pulse rate.

Table 4.8. Brachial systolic blood pressure (SBP) and age-independent relations between central aortic haemodynamics and end-organ measures.

	n=	Partial r* (95% CI)	p value
Left ventricular mass index (LVMI) vs			
PPc	786	0.10 (0.03 to 0.17)	<0.01
Pf	786	0.05 (-0.02 to 0.12)	=0.14
Pb	786	0.09 (0.02 to 0.16)	<0.02
RI	786	0.04 (-0.03 to 0.11)	=0.28
Aortic pulse wave velocity (PWV) vs			
PPc	1019	0.09 (0.03 to 0.15)	<0.005
Pf	1019	0.04 (-0.02 to 0.10)	=0.18
Pb	1019	0.10 (0.04 to 0.16)	<0.002
RI	1019	0.09 (-0.02 to 0.10)	=0.18
Carotid intima-media thickness (IMT) vs			
PPc	578	0.08 (0.00 to 0.16)	<0.05
Pf	578	0.05 (-0.03 to 0.13)	=0.21
Pb	578	0.09 (0.01 to 0.17)	<0.05
RI	578	0.01 (-0.07 to 0.09)	=0.79
Left ventricular E/A vs			
PPc	779	0.03 (-0.04 to 0.10)	=0.37
Pf	779	0.09 (0.02 to 0.16)	<0.05
Pb	779	0.002 (-0.07 to 0.07)	=0.97
RI	779	-0.09 (-0.16 to 0.02)	<0.02
Estimated glomerular filtration rate (eGFR) vs			
PPc	1174	0.05 (-0.01 to 0.10)	=0.12
Pf	1174	0.01 (-0.04 to 0.07)	=0.62
Pb	1174	0.05 (-0.01 to 0.10)	=0.12
RI	1174	0.01 (-0.04 to 0.07)	=0.65

PPc, central aortic pulse pressure; Pb, aortic backward (reflected) wave pressure; Pf, aortic forward wave pressure; RI, reflected wave index (Pb/Pf); E/A, transmitral early/atrial diastolic blood flow velocity.*Adjusted for brachial SBP, age, sex, body mass index (except for LVMI

which was adjusted for body weight), total cholesterol, HDL cholesterol, regular tobacco use, regular alcohol intake, diabetes mellitus or an HbA_{1c}>6.1%, and pulse rate.

Table 4.9. Brachial blood pressure (BP) independent relations between central aortic haemodynamics and end-organ measures in participants not receiving antihypertensive therapy.

Adjustments→		*+Brachial pulse pressure		*+Brachial systolic BP	
	n=	Partial r (95% CI)	p value	Partial r (95% CI)	p value
Left ventricular mass index (LVMI) vs					
PPc	584	0.16 (0.08 to 0.24)	<0.0001	0.15 (0.07 to 0.23)	<0.0005
Pf	584	-0.004 (-0.09 to 0.08)	=0.92	0.09 (0.01 to 0.17)	<0.05
Pb	584	0.14 (0.06 to 0.22)	<0.001	0.14 (0.06 to 0.22)	<0.001
RI	584	0.11 (0.03 to 0.19)	<0.01	0.07 (-0.01 to 0.15)	=0.08
Aortic pulse wave velocity (PWV) vs					
PPc	780	0.37 (0.31 to 0.43)	<0.0001	0.25 (0.19 to 0.32)	<0.0001
Pf	780	-0.15 (-0.22 to -0.08)	<0.0001	0.04 (-0.03 to 0.11)	=0.31
Pb	780	0.37 (0.31 to 0.43)	<0.0001	0.30 (0.24 to 0.36)	<0.0001
RI	780	0.32 (0.26 to 0.39)	<0.0001	0.25 (0.19 to 0.32)	<0.0001
Carotid intima-media thickness (IMT) vs					
PPc	431	0.30 (0.21 to 0.38)	<0.0001	0.25 (0.16 to 0.33)	<0.0001
Pf	431	-0.05 (-0.14 to 0.05)	=0.33	0.09 (-0.01 to 0.19)	=0.06
Pb	431	0.26 (0.16 to 0.34)	<0.0001	0.25 (0.16 to 0.34)	<0.0001
RI	431	0.22 (0.13 to 0.31)	<0.0001	0.18 (0.09 to 0.27)	<0.0002
Left ventricular E/A vs					
PPc	582	-0.37 (-0.40 to -0.26)	<0.0001	-0.16 (-0.24 to -0.08)	=0.0001
Pf	582	0.15 (0.07 to 0.23)	=0.0004	0.06 (-0.02 to 0.14)	=0.15
Pb	582	-0.32 (-0.39 to -0.24)	<0.0001	-0.20 (-0.28 to -0.12)	<0.0001
RI	582	-0.30 (-0.38 to -0.23)	<0.0001	-0.26 (-0.34 to -0.18)	<0.0001
Estimated glomerular filtration rate (eGFR) vs					
PPc	892	-0.19 (-0.25 to -0.12)	<0.0001	-0.10 (-0.16 to -0.03)	<0.01
Pf	892	0.03 (-0.03 to 0.10)	=0.32	-0.004 (-0.07 to 0.06)	=0.91
Pb	892	-0.17 (-0.23 to -0.11)	<0.0001	-0.11 (-0.18 to -0.05)	<0.001
RI	892	-0.16 (-0.22 to -0.09)	<0.0001	-0.13 (-0.19 to -0.06)	<0.0005

PPc, central aortic pulse pressure; Pb, aortic backward (reflected) wave pressure; Pf, aortic forward wave pressure; RI, reflected wave index (Pb/Pf); E/A, transmitral early/atrial diastolic

blood flow velocity.*Adjusted for brachial blood pressure as indicated, sex, body mass index (except for LVMI which was adjusted for body weight), total cholesterol, HDL cholesterol, regular tobacco use, regular alcohol intake, diabetes mellitus or an HbA_{1c}>6.1%, and pulse rate.

Table 4.10. Brachial blood pressure (BP) and age-independent relations between central aortic haemodynamics and end-organ measures in participants not receiving antihypertensive therapy.

Adjustments→		*+Brachial pulse pressure		*+Brachial systolic BP	
	n=	Partial r (95% CI)	p value	Partial r (95% CI)	p value
Left ventricular mass index (LVMI) vs					
PPc	584	0.11 (0.03 to 0.19)	<0.01	0.11 (0.03 to 0.19)	<0.01
Pf	584	0.02 (-0.06 to 0.10)	=0.59	0.09 (0.01 to 0.17)	<0.05
Pb	584	0.09 (0.01 to 0.17)	<0.05	0.10 (0.02 to 0.18)	<0.05
RI	584	0.06 (-0.02 to 0.14)	=0.13	0.03 (-0.06 to 0.11)	=0.53
Aortic pulse wave velocity (PWV) vs					
PPc	780	0.14 (0.07 to 0.21)	<0.0001	0.07 (0.01 to 0.14)	<0.05
Pf	780	-0.05 (-0.13 to 0.02)	=0.13	0.02 (-0.05 to 0.09)	=0.63
Pb	780	0.17 (0.10 to 0.24)	<0.0001	0.11 (0.03 to 0.17)	<0.005
RI	780	0.12 (0.05 to 0.19)	<0.002	0.06 (0.01 to 0.13)	=0.12
Carotid intima-media thickness (IMT) vs					
PPc	431	0.03 (-0.07 to 0.12)	=0.57	0.04 (-0.06 to 0.13)	=0.42
Pf	431	0.07 (-0.03 to 0.16)	=0.17	0.07 (-0.03 to 0.16)	=0.15
Pb	431	0.01 (-0.09 to 0.10)	=0.86	0.02 (-0.08 to 0.12)	=0.68
RI	431	-0.01 (0.11 to 0.08)	=0.80	-0.03 (-0.13 to 0.06)	=0.49
Left ventricular E/A vs					
PPc	582	-0.09 (-0.17 to -0.01)	<0.05	0.03 (-0.05 to 0.11)	=0.44
Pf	582	0.05 (-0.03 to 0.13)	=0.20	0.08 (-0.003 to 0.16)	=0.06
Pb	582	-0.11 (-0.19 to -0.02)	<0.02	-0.003 (-0.08 to 0.08)	=0.95
RI	582	-0.10 (-0.18 to -0.02)	<0.02	-0.08 (-0.17 to -0.003)	<0.05
Estimated glomerular filtration rate (eGFR) vs					
PPc	892	0.02 (-0.05 to 0.08)	=0.59	0.05 (-0.01 to 0.12)	=0.12
Pf	892	-0.04 (-0.11 to 0.02)	=0.20	0.003 (-0.06 to 0.07)	=0.93
Pb	892	0.01 (-0.05 to 0.08)	=0.72	0.05 (-0.01 to 0.12)	=0.12
RI	892	0.02 (-0.05 to 0.08)	=0.59	0.03 (-0.04 to 0.10)	=0.36

PPc, central aortic pulse pressure; Pb, aortic backward (reflected) wave pressure; Pf, aortic forward wave pressure; RI, reflected wave index (Pb/Pf); E/A, transmitral early/atrial diastolic

blood flow velocity.*Adjusted for brachial blood pressure as indicated, sex, body mass index (except for LVMI which was adjusted for body weight), total cholesterol, HDL cholesterol, regular tobacco use, regular alcohol intake, diabetes mellitus or an HbA_{1c}>6.1%, and pulse rate.

Table 4.11. Brachial blood pressure (BP) independent relations between central aortic haemodynamics and end-organ measures in women.

Adjustments→		*+Brachial pulse pressure		*+Brachial systolic BP	
	n=	Partial r (95% CI)	p value	Partial r (95% CI)	p value
Left ventricular mass index (LVMI) vs					
PPc	511	0.08 (-0.01 to 0.16)	=0.09	0.10 (0.02 to 0.19)	<0.01
Pf	511	-0.10 (-0.18 to -0.01)	<0.05	0.03 (-0.06 to 0.12)	=0.52
Pb	511	0.09 (0.00 to 0.17)	=0.05	0.11 (0.02 to 0.19)	<0.02
RI	511	0.11 (0.02 to 0.19)	<0.02	0.07 (-0.02 to 0.15)	=0.14
Aortic pulse wave velocity (PWV) vs					
PPc	645	0.25 (0.18 to 0.32)	<0.0001	0.11 (0.04 to 0.19)	<0.005
Pf	645	-0.10 (-0.17 to -0.02)	<0.02	0.003 (-0.07 to 0.08)	=0.93
Pb	645	0.22 (0.15 to 0.29)	<0.0001	0.12 (0.04 to 0.20)	<0.005
RI	645	0.23 (0.15 to 0.30)	<0.0001	0.14 (0.06 to 0.22)	<0.0005
Carotid intima-media thickness (IMT) vs					
PPc	377	0.25 (0.15 to 0.30)	<0.0001	0.04 (-0.06 to 0.13)	=0.42
Pf	377	-0.13 (-0.22 to -0.02)	<0.02	0.009 (-0.09 to 0.11)	=0.86
Pb	377	0.23 (0.13 to 0.32)	<0.0001	0.19 (0.09 to 0.29)	<0.0005
RI	377	0.22 (0.12 to 0.32)	<0.0001	0.17 (0.07 to 0.27)	<0.002
Left ventricular E/A vs					
PPc	506	-0.31 (-0.38 to -0.23)	<0.0001	-0.10 (-0.18 to 0.01)	<0.05
Pf	506	0.13 (0.04 to 0.22)	<0.005	0.08 (-0.01 to 0.17)	=0.07
Pb	506	-0.28 (-0.36 to -0.20)	<0.0001	-0.14 (-0.22 to -0.05)	<0.005
RI	506	-0.26 (-0.34 to -0.18)	<0.0001	-0.22 (-0.30 to -0.13)	<0.0001
Estimated glomerular filtration rate (eGFR) vs					
PPc	764	-0.11 (-0.18 to -0.04)	<0.005	-0.03 (-0.10 to 0.04)	=0.38
Pf	764	0.06 (-0.01 to 0.13)	=0.12	0.02 (-0.05 to 0.09)	=0.60
Pb	764	-0.11 (-0.18 to -0.04)	<0.002	-0.05 (-0.12 to 0.02)	=0.17
RI	764	-0.12 (-0.19 to -0.05)	<0.001	-0.08 (-0.15 to -0.01)	<0.05

PPc, central aortic pulse pressure; Pb, aortic backward (reflected) wave pressure; Pf, aortic forward wave pressure; RI, reflected wave index (Pb/Pf); E/A, transmitral early/atrial diastolic blood flow velocity.*Adjusted for brachial blood pressure as indicated, body mass index (except

for LVMI which was adjusted for body weight), total cholesterol, HDL cholesterol, regular tobacco use, regular alcohol intake, diabetes mellitus or an HbA_{1c}>6.1%, and pulse rate.

Table 4.12. Brachial blood pressure (BP) independent relations between central aortic haemodynamics and end-organ measures in men.

Adjustments→		*+Brachial pulse pressure		*+Brachial systolic BP	
	n=	Partial r (95% CI)	p value	Partial r (95% CI)	p value
Left ventricular mass index (LVMI) vs					
PPc	275	0.14 (0.02 to 0.26)	<0.05	0.20 (0.08 to 0.31)	<0.001
Pf	275	-0.02 (-0.14 to 0.10)	=0.80	0.13 (0.01 to 0.24)	<0.05
Pb	275	0.11 (-0.006 to 0.23)	=0.06	0.19 (0.07 to 0.30)	<0.005
RI	275	0.13 (0.01 to 0.24)	<0.05	0.14 (0.02 to 0.25)	<0.05
Aortic pulse wave velocity (PWV) vs					
PPc	374	0.28 (0.18 to 0.37)	<0.0001	0.37 (0.27 to 0.45)	<0.0001
Pf	374	-0.22 (-0.31 to -0.12)	<0.0001	0.14 (0.04 to 0.24)	<0.01
Pb	374	0.32 (0.22 to 0.41)	<0.0001	0.40 (0.31 to 0.48)	<0.0001
RI	374	0.31 (0.22 to 0.40)	<0.0001	0.30 (0.20 to 0.39)	<0.0001
Carotid intima-media thickness (IMT) vs					
PPc	201	0.34 (0.21 to 0.46)	<0.0001	0.36 (0.22 to 0.47)	<0.0001
Pf	201	0.03 (-0.11 to 0.17)	=0.64	0.22 (0.08 to 0.35)	<0.005
Pb	201	0.29 (0.15 to 0.41)	<0.0001	0.35 (0.22 to 0.47)	<0.0001
RI	201	0.20 (0.05 to 0.33)	<0.01	0.20 (0.06 to 0.33)	<0.01
Left ventricular E/A vs					
PPc	273	-0.36 (-0.46 to -0.25)	<0.0001	-0.19 (-0.30 to -0.07)	<0.005
Pf	273	0.16 (0.04 to 0.28)	<0.01	0.06 (-0.06 to 0.18)	=0.34
Pb	273	-0.35 (-0.45 to -0.24)	<0.0001	-0.23 (-0.34 to -0.11)	<0.0005
RI	273	-0.36 (-0.46 to -0.25)	<0.0001	-0.34 (-0.44 to -0.23)	<0.0001
Estimated glomerular filtration rate (eGFR) vs					
PPc	410	-0.17 (-0.27 to -0.08)	<0.001	-0.16 (-0.25 to -0.06)	<0.005
Pf	410	0.08 (-0.01 to 0.18)	=0.09	-0.04 (-0.13 to 0.06)	=0.48
Pb	410	-0.16 (-0.25 to -0.06)	<0.002	-0.16 (-0.26 to -0.07)	<0.001
RI	410	-0.19 (-0.28 to -0.09)	<0.0005	-0.19 (-0.28 to -0.09)	<0.0005

PPc, central aortic pulse pressure; Pb, aortic backward (reflected) wave pressure; Pf, aortic forward wave pressure; RI, reflected wave index (Pb/Pf); E/A, transmitral early/atrial diastolic

blood flow velocity.*Adjusted for brachial blood pressure as indicated, body mass index (except for LVMI which was adjusted for body weight), total cholesterol, HDL cholesterol, regular tobacco use, regular alcohol intake, diabetes mellitus or an HbA_{1c}>6.1%, and pulse rate.

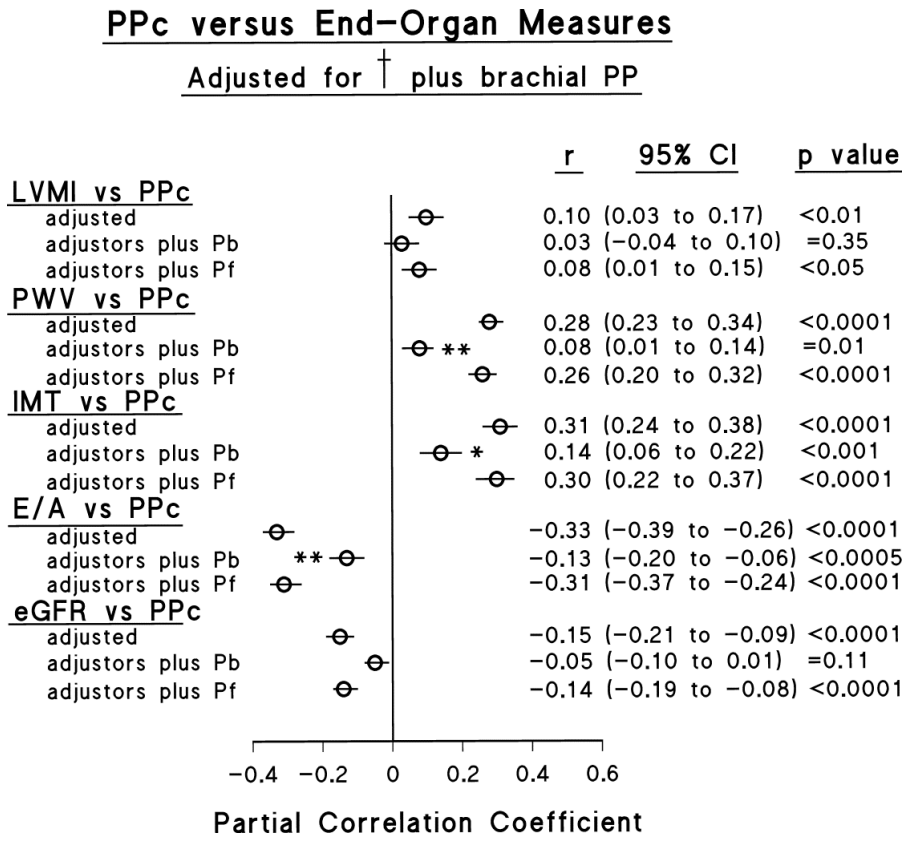


Figure 4.5. Impact of adjustments for forward (Pf) or backward (reflected) (Pb) wave pressures on the brachial pulse pressure (PP)-independent relations between central aortic pulse pressure (PPc) and end-organ measures. LVMI, left ventricular mass index; PWV, aortic pulse wave velocity; IMT, carotid intima-media thickness; E/A, transmitral early/atrial diastolic blood flow velocity; eGFR, estimated glomerular filtration rate. †Adjustments are for brachial PP as well as sex, body mass index (except for LVMI which was adjusted for body weight), total cholesterol, HDL cholesterol, regular tobacco use, regular alcohol intake, diabetes mellitus or an HbA_{1c}>6.1%, and pulse rate. *p<0.005, **p<0.0001 versus without adjustments for Pb.

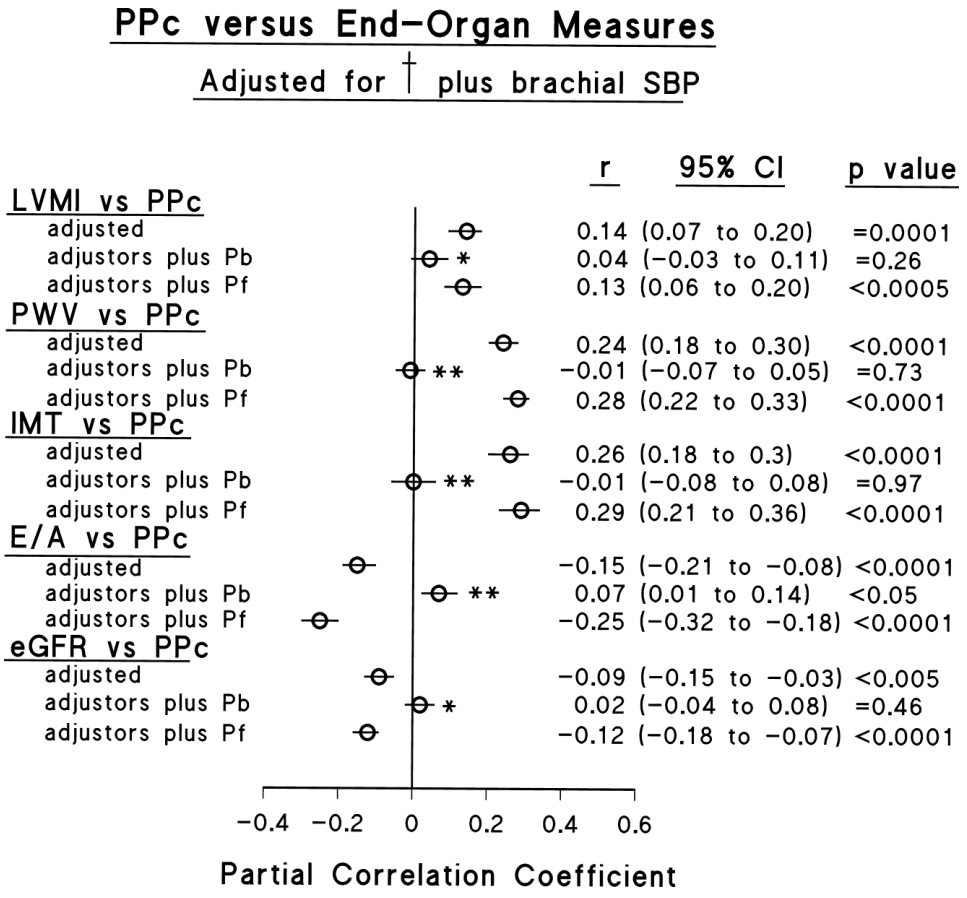


Figure 4.6. Impact of adjustments for forward (Pf) or backward (reflected) (Pb) wave pressures on the brachial systolic blood pressure (SBP)-independent relations between central aortic pulse pressure (PPc) and end-organ measures. LVMI, left ventricular mass index; PWV, aortic pulse wave velocity; IMT, carotid intima-media thickness; E/A, transmitral early/atrial diastolic blood flow velocity; eGFR, estimated glomerular filtration rate. †Adjustments are for SBP as well as sex, body mass index (except for LVMI which was adjusted for body weight), total cholesterol, HDL cholesterol, regular tobacco use, regular alcohol intake, diabetes mellitus or an HbA_{1c}>6.1%, and pulse rate. *p<0.005, ** p<0.0001 versus without adjustments for Pb.

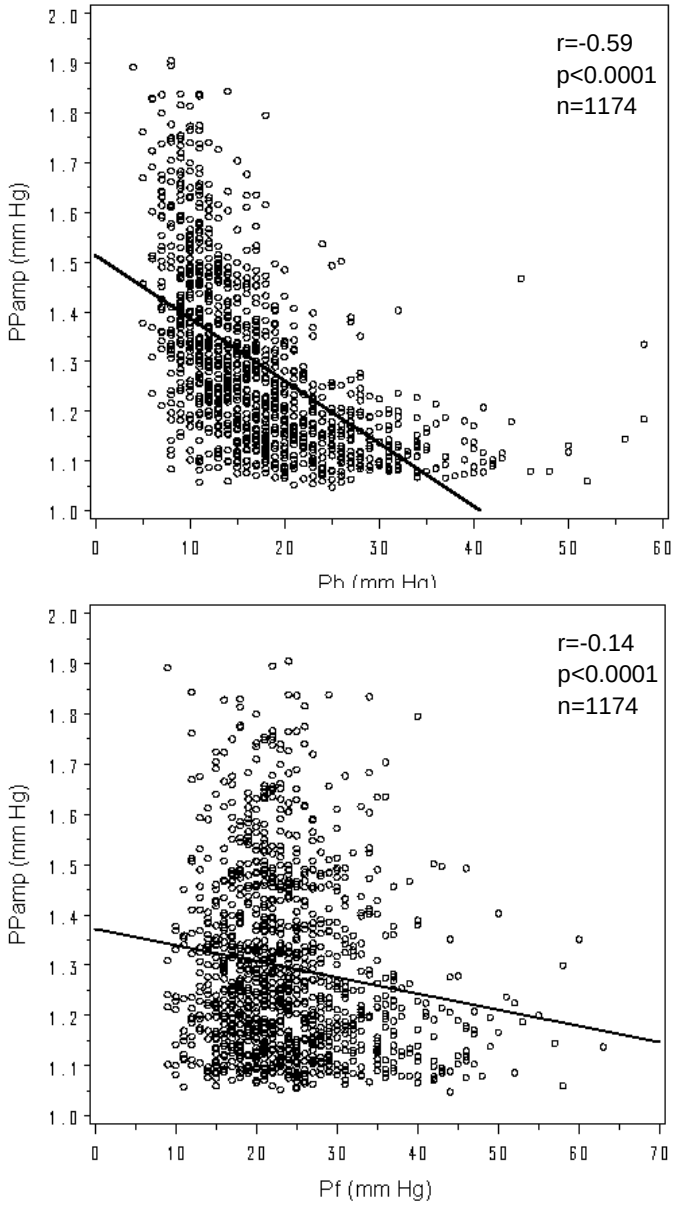


Figure 4.7. Bivariate relationships between either aortic forward (Pf) or backward (reflected) wave (Pb) pressures and aortic-to-brachial pulse pressure (PP) amplification. Comparison of r values using z-statistics, p<0.0001.

4.5 **Discussion**

The main findings of the present study are as follows: In a large community-based sample of African ancestry after multivariate adjustments including adjustments for distending pressures (mean arterial pressure), independent relationships were noted between PPc, Pf, Pb or RI and several end-organ changes. However, with adjustments for brachial PP, aortic PPc, Pb and RI, but not Pf remained independently and directly associated with LVMI, PWV, and IMT or increases thereof and inversely associated with E/A and eGFR or decreases thereof. Furthermore, Pb, but not Pf accounted for the brachial BP-independent relations between aortic PP and end-organ measures.

Several studies have suggested that indices of aortic wave reflection provide unique prognostic information beyond brachial BP (Wang et al 2010, Chirinos et al 2012, Zamani et al 2014, Hughes et al 2014). However, whether forward wave pressures, which have previously been demonstrated to account for most of the age-related (Mitchell et al 2010b) or hypertension-related (Mancia et al 2013) increases in aortic pulse pressure, also account for cardiovascular damage independent of brachial BP, is uncertain. Moreover, whether forward, or backward (reflected) wave pressures or both account for the brachial BP-independent relationship between aortic PP and cardiovascular damage (Safar et al 2002, Roman et al 2007, Jankowski et al 2008, Pini et al 2008, Wang et al 2009, Williams et al 2006, Benetos et al 2010, Regnault et al 2012, Benetos et al 2012, Vlachopoulos et al 2010, Roman et al 2014), is similarly unknown. In the present study I show that Pb and RI, but not Pf is associated with end-organ measures and damage independent of brachial BP. Further, I show that the brachial BP-independent relationships between aortic PP and end-organ measures are largely accounted for by Pb, but not by Pf. Hence, the present study suggests that brachial BP-independent relations between aortic pressure and cardiovascular end-organ changes are largely attributed to backward (reflected) rather than forward wave pressure effects.

An important caveat of the present study is that brachial BP-independent relationships between reflected, but not forward wave pressures does not imply that forward wave pressures do not contribute to end-organ measures. Indeed, with adjustments for mean arterial pressure (distending pressures), both forward and backward wave pressures contributed to variations in end-organ measures and damage. The results of the present study could be explained in two possible ways. First, as demonstrated in the present study, reflected wave pressures may be more closely associated with amplification of PP from the aorta to the brachial artery. Hence, relations between brachial BP and end-organs are likely to closely reflect associations between forward rather than backward wave pressures and end-organ measures. In contrast, backward wave pressure effects are more likely to be detected using aortic BP measurements. Second, as compared to relations between Pf and end-organ measures, the relations between Pb and end-organ measures had a greater slope (magnitude) and for several end-organs the relationship was also stronger. Hence, Pb may contribute more than Pf to variations in end-organ measures. In this regard, prior studies have reported on closer relations between reflected as compared to forward wave indices and end-organ measures (Wang et al 2010, Weber et al 2012) or cardiovascular outcomes (Zamani et al 2014). However, in neither of the studies reporting on relations between Pf or Pb and end-organ measures (Wang et al 2010, Weber et al 2012) were these relations assessed with adjustments for brachial BP. Nevertheless, even without adjustments for brachial BP, Pb but not Pf has been demonstrated to predict cardiovascular outcomes (Zamani et al 2014).

The clinical implications of the brachial BP-independent relations between Pb, but not Pf and end-organ measures require consideration. The present results suggest that brachial BP-independent relations between aortic pressure and cardiovascular damage (Safar et al 2002, Roman et al 2007, Jankowski et al 2008, Pini et al 2008, Wang et al 2009, Williams et al 2006, Benetos et al 2010, Regnault et al 2012, Benetos et al 2012, Vlachopoulos et al 2010, Roman et al 2014) are attributed largely to reflected wave pressure effects, with little contribution from

forward wave pressure effects. Hence, whilst the adverse effects of forward wave pressures are likely to be revealed using brachial BP measurements, backward wave pressure effects are unlikely to be readily detected using brachial BP measurements. These results may in-part explain why in community samples where the backward wave contributes little to age-related increases in aortic BP (Mitchell et al 2010b), aortic pressure does not predict cardiovascular outcomes beyond brachial BP (Mitchell et al 2010a), whilst in community samples where a strong age-related increase in the backward wave pressures occurs (Wang et al 2010), aortic BP predicts outcomes beyond brachial BP (Wang et al 2009).

Although I provide clear evidence that aortic PWV is more strongly associated with reflected as compared to forward wave pressures, it is possible that the association between PWV and Pb may be interpreted as an increased aortic stiffness enhancing the magnitude of wave reflection. However, more recent studies suggest that increases in aortic stiffness reduce the degree of wave reflection and hence cause microvascular damage by augmenting flow pulsatility (Mitchell et al 2011, Hashimoto et al 2011). Thus, it is possible that the association between Pb and PWV reflects an effect of Pb on aortic stiffness, rather than aortic stiffness on Pb.

The limitations of the present study are as follows: First, the present study was a cross-sectional design and end-organ measures rather than hard outcomes were assessed. Therefore, I cannot determine whether relations between aortic haemodynamics and cardiovascular damage are indeed cause and effect. Further longitudinal studies with cardiovascular outcomes are required to determine these effects. Second, in the present study calibration of the radial waveform from brachial BP measurements ignores amplification of BP from brachial to radial arteries. Hence, aortic pressures may have been underestimated using the current approach. Third, as previously described (Westerhof et al 2006), a triangular aortic flow waveform was assumed for wave separation analysis, rather than separating forward and backward waves with measured aortic flows. In this regard, the assumptions intrinsic to the use

of the ‘triangulation method’ of wave separation may not be ideal (Kips et al 2009). Hence, it is possible that I may have over- or underestimated the contribution of forward or reflected waves to variations in end-organ measures. Fourth, the present study was conducted in a group of African ancestry and hence the results require confirmation in other ethnic groups.

In conclusion, in a group of African ancestry, I show that although both forward and reflected wave effects contribute to end-organ measures and damage, independent of brachial BP, the impact of aortic BP is accounted for largely by backward (reflected) wave effects. This finding is attributed in-part to reflected, rather than forward wave pressures contributing to aortic-to-brachial BP amplification and in-part to stronger relations between reflected rather than forward wave pressures and end-organ changes. These findings may explain why in community samples which show strong age-related increases in reflected wave pressures (Wang et al 2010), aortic BP predicts outcomes beyond brachial BP (Wang et al 2009), whilst in community samples where backward waves contribute little to age-related increases in aortic BP (Mitchell et al 2010b), aortic pressure does not predict cardiovascular outcomes beyond brachial BP (Fok et al 2014b).

CHAPTER 5

Aortic Backward Waves Rather Than Stiffness Account for Independent Associations Between Pulse Pressure Amplification and Left Ventricular Mass in a Young-to-Middle Aged Sample.

This chapter has been accepted for publication as the following paper:

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5.1 **Abstract**

A decreased aortic-to-brachial pulse pressure amplification (PP amplification), which is independently associated with cardiovascular outcomes, may index several aortic functional changes. However, that aortic functional change most likely to account for this effect is uncertain. In 706 randomly selected community participants of African ancestry with a mean age of 44.4±18.2 years I assessed aortic function using radial applanation tonometry and SphygmoCor software (including forward [Pf] and backward [Pb] wave separation analysis assuming a triangular flow waveform) and left ventricular mass index (LVMI)(echocardiography). In multivariate models with the inclusion of brachial PP, 1/PP amplification (partial r=0.12, p<0.005), reflected wave pressures (partial r=0,09, p<0.05), and aortic pulse wave velocity (PWV) (partial r=0.09, p<0.05) were independently associated with LVMI. Similarly, in multivariate models with the inclusion of brachial PP, 1/PP amplification (p<0.005), the reflected wave pressure (p<0.01), and aortic PWV (p<0.01) were independently associated with LV hypertrophy (LVH). With adjustments for reflected wave pressures, the brachial PP-independent relationships between 1/PP amplification and LVMI or LVH were abolished (p>0.08 for both). However, adjustments for PWV failed to modify brachial PP-independent relations between 1/PP amplification and LVMI or LVH. Similar results were noted when brachial SBP rather than PP was included in regression models and in sensitivity analysis conducted in participants not receiving antihypertensive therapy. In conclusion, the independent relations between the reciprocal of aortic-to-brachial PP amplification and LVMI or LVH in a largely young-to-middle-aged sample are accounted for by variations in backward wave pressures rather than aortic stiffness.

Key words: Central blood pressure, aortic pulse pressure, reflected waves, pulse pressure amplification, left ventricular mass.

5.2 **Introduction**

Pulse pressure (PP) is a strong determinant of cardiovascular damage beyond steady-state pressures and as such is incorporated in guidelines for risk prediction (Mancia et 2013). Brachial PP may not however accurately reflect aortic PP measurements. Indeed, PP is amplified from the aorta to the brachial artery (PP amplification) and this effect is due to differences in stiffness between the aorta and peripheral arteries (Avolio et al 2009, Nichols et al 2011). With age, PP amplification is reduced due to increases in aortic stiffness and a consequent attenuation in the difference between the stiffness of the aorta and peripheral arteries, as well as because of an earlier timing and an increased amplitude of aortic backward waves (Avolio et al 2009, Nichols et al 2011). In this regard, reductions in PP amplification predict risk beyond brachial blood pressure (BP) (Benetos et al 2010, Regnault et al 2012, Benetos et al 2012, Bursztyn et al 2016). However, the mechanisms that explain the ability of PP amplification to risk predict beyond brachial PP are uncertain.

Increases in aortic pulse wave velocity (PWV), an index of aortic stiffness, and a determinant of variations in PP amplification, is now an accepted measure of risk prediction beyond brachial BP (Vlachopoulos et al 2010[a], Ben-Shlomo et al 2014). Moreover, several studies suggest that increases in aortic backward waves, which are also a determinant of variations in PP amplification, predict the risk of cardiovascular events (Vlachopoulos et al 2010[b], Wang et al 2010, Chirinos et al 2012, Weber et al 2012, Zamani et al 2014), or associate with end-organ changes (Booysen et al 2015, Sibiya et al 2015) beyond brachial PP. However, no study has assessed whether increases in aortic stiffness or backward waves account for the brachial BP-independent association between PP amplification and cardiovascular end-organ changes. As one of the key end-organ changes that occur in response to aortic hemodynamic loads is left ventricular hypertrophy (LVH), in the present study I evaluated first whether PP amplification adds to brachial BP in associations with LV mass index (LVMI) and LVH in a large

randomly selected community-based sample of largely young-to-middle aged participants. I subsequently assessed whether this relationship can be accounted for either by aortic PWV, and/or by aortic backward wave function.

5.3 **Methods**

5.3.1 Study group.

The present study was conducted according to the principles outlined in the Helsinki declaration. The Committee for Research on Human Subjects of the University of the Witwatersrand approved the protocol (approval number: M02-04-72 and renewed as M07-04-69 and M12-04-108). Participants gave informed, written consent. The present study design has previously been described (Booysen et al 2015, Sibiya et al 2015, Norton et al 2008, Woodiwiss et al 2009, Redelinghuys et al 2010, Norton et al 2012). Briefly, 1197 participants from randomly recruited (from the population census figures of 2001) families of black African descent (Nguni and Sotho chiefdoms) from the South West Township (SOWETO) of Johannesburg, South Africa, with siblings older than 16 years with all central aortic haemodynamic measurements were evaluated. In a sub-study, 706 had left ventricular mass index (LVMI) determined by echocardiography and PWV assessments.

5.3.2 Clinical, demographic and anthropometric measurements.

See section 2.3.2 for details.

5.3.3 Pulse wave analysis.

See section 2.3.4 for details. In addition, PP amplification was determined as the ratio of brachial-to-aortic PP. As PP amplification is inversely associated with cardiovascular damage, for comparisons of PP amplification-LVMI or LVH relations with relations between alternative indexes of aortic function and LVMI or LVH (which are directly proportional to LVMI and LVH), PP amplification was expressed as a reciprocal (1/PPamp).

5.3.4 Echocardiography.

See sections 2.3.5 for details (Chirinos et al 2010). In the present study sample, in bivariate analysis height is correlated with LVM ($r=0.19$, $p<0.0001$), height becomes inversely correlated with LVM when indexed to height$^{2.7}$ ($r=-0.24$ $p<0.0001$), but no significant relationship between height and LVM is noted when LVM is indexed to height$^{1.7}$ ($r=-0.07$, $p=0.08$). In addition, left ventricular hypertrophy (LVH) was identified as an LVMI-ht$^{1.7}$>80 g/m$^{1.7}$ for men and >60 g/m$^{1.7}$ for women (Chirinos et al 2010). Left ventricular end diastolic and systolic volumes were determined from M-mode images using the Teichholz method. Left ventricular ejection fraction (EF) was calculated as [(LV end diastolic volume-LV end systolic volume)/ LV end diastolic volume] x 100.

5.3.5 Data analysis.

For database management and statistical analysis, SAS software, version 9.3 (SAS Institute Inc., Cary, NC) was employed. Multiple linear regression analysis was performed to determine the independent relations between aortic hemodynamic parameters and LVMI (continuous data). Multivariate adjusted logistic regression analysis was performed to determine the independent relations between aortic haemodynamic parameters and LVH (discrete data). Adjustments included in multivariate models were those correlated with central haemodynamic

variables and LVMI in bivariate analysis. To determine probability values, further adjustments for non-independence of family members was performed using non-linear regression analysis (mixed procedure as defined in the SAS package). Regression coefficients were compared with z statistics. In order to ensure that the results were not influenced by the presence of antihypertensive therapy, sensitivity analysis was also conducted in participants not receiving antihypertensive therapy. Moreover, to ensure that wave separation analysis using the triangular flow wave did not influence our results, we evaluated whether the essential findings of the study could be replicated in the 336 participants in whom wave separation analysis was conducted using aortic flow measurements and who had aortic pulse wave velocity measurements.

5.4 **Results**

5.4.1 Characteristics of the participants.

The clinical and demographic characteristics of the participants are shown in Table 1. Body mass index and aortic PWV were modestly greater in those in whom echocardiography was not available (Table 5.1). Otherwise, no marked differences in the clinical and demographic characteristics of the participants included in the echocardiographic sub-study were noted as compared to those not included in the sub-study (Table 5.1). The study sample was largely young-to-middle aged. 2% of participants had a history of cardiovascular disease. Importantly, a high proportion of participants had hypertension, and a significant proportion were not receiving therapy (Table 5.1). Moreover, 35% of all participants and 58% of participants receiving antihypertensive therapy had uncontrolled hypertension. Of the participants, 45% had LVH.

5.4.2 Relations between aortic hemodynamic measures and PP amplification.

PP amplification was correlated with several aortic hemodynamic measures including PPc, Pb, PWV and AIx, but not with Pf (Table 5.2). Importantly, the correlation between Pb and PP amplification was markedly stronger than that between PWV and PP amplification (Table 5.2). The relations between aortic Pb, as determined using the aortic flow wave, and PPc (r^2=0.95), PP amplification (r^2=0.36), Pf (r^2=0.59), PWV (r^2=0.21), and AIx (r^2=0.31), were similar

Table 5.1. Characteristics of the study sample.

	Echocardiographic Sub-study	No echocardiography
Sample size (% Female)	706 (64.7)	491 (66.3)
Age (years)	44.4±18.2	44.1±18.5
Body mass index (kg/m^2)	29.0±7.4	30.3±8.8*
% Obese	42.1	45.6
Regular tobacco (% subjects)	16.5	13.8
Regular alcohol (% subjects)	19.7	21.7
% with DM or HbA_{1c}>6.1%	24.5	26.9
% Hypertensive	45.8	45.9
% Treated for hypertension	25.8	21.9
Pulse rate (beats/min)	69±10	69±11
Brachial SBP/DBP (mm Hg)	128±23/84±12	129±23/84±13
Brachial pulse pressure (PP)(mm Hg)	45±17	45±16
Central aortic SBP (mm Hg)	120±23	120±23
Central aortic PP (PPc) (mm Hg)	35±15	35±15
PP amplification (PPamp) (mm Hg)	1.29±0.18	1.30±0.18
Augmentation index (AIx) (%)	141±25	142±25
Aortic forward wave pressure (Pf) (mm Hg)	24±10	24±8
Aortic reflected wave pressure (Pb)(mm Hg)	17±8	17±8
Aortic pulse wave velocity (PWV) (m/sec)	6.14±2.71	6.71±2.48**
Left ventricular mass index (g/m$^{1.7}$)	66.2±21.7	-

Data expressed as mean ± SD or proportions. DM, diabetes mellitus; HbA_{1c}, glycosylated haemoglobin; BP, blood pressure; SBP, systolic BP; DBP, diastolic BP; PP amplification, aortic-to-brachial PP amplification. *p<0.05, **p<0.005 vs echocardiographic sub-study group.

Table 5.2. Correlations (r^2 values) between aortic hemodynamic variables in a community sample (n=706).

	PPamp	PPc	Pb	Pf	AIx	PWV
PPamp	-					
PPc	0.27*	-				
Pb	0.37*	0.95*	-			
Pf	0.02	0.73*	0.57*	-		
AIx	0.63*	0.19*	0.30*	0.002*	-	
PWV	0.10*†	0.32*	0.28*	0.22*	0.09*	-

See table 1 for abbreviations. *p<0.0001 for significant correlations. †p<0.0001 versus correlation between PP amplification and Pb.

to those relations obtained between aortic Pb, as determined using the triangular wave form and these aortic hemodynamic variables (Table 5.2).

5.4.3 Associations between aortic function and LVMI or LVH.

Aortic PP, 1/PP amplification, Pb and PWV, but not AIx or Pf were associated with LVMI (Table 5.3) and LVH (Table 5.4) independent of brachial PP or SBP and additional confounders. The relations between Pb or Pf and LVMI obtained with a triangular flow wave were similar to these relations determined using Pb and Pf obtained using an actual aortic flow wave (Table 5.3). Importantly, 1/PP amplification added to the ability of brachial BP to associate with LVMI or LVH (Tables 5.3 and 5.4). Indeed, with the inclusion of 1/PP amplification together with brachial BP in multivariate models, brachial BP retained similar independent relations with LVMI or LVH and 1/PP amplification further added to these effects (Tables 5.3 and 5.4). Of importance, the brachial PP-independent relationship between Pb and LVMI was similar after (partial r=0.09, p=0.02) as compared to before (partial r=0.09, p=0.02) adjustments for LV ejection fraction.

5.4.4 Aortic function variables that accounts for relations between 1/PP amplification and LVMI or LVH.

Adjustments for Pb attenuated the relations between 1/PP amplification and LVMI, or LVH (Tables 5.5 and 5.6). However, adjustments for PWV, Pf or AIx failed to modify the relations between 1/PP amplification and LVMI, or LVH (Tables 5.5 and 5.6). Importantly, the impact of adjustments for Pb and Pf on relations between 1/PP amplification and LVMI were similar irrespective of whether Pb or Pf were derived from wave separation analysis performed using a triangular wave form or an actual aortic flow wave (Table 5.5).

Table 5.3. Relations between brachial or aortic hemodynamic parameters and left ventricular mass index in all participants and participants having never received antihypertensive therapy (untreated).

Models with→		Pulse pressure (PP)		Systolic BP (SBP)	
	Adjustors	Partial r (95% CI)	p-value	Partial r (95% CI)	p-value
Models: LVMI-ht$^{1.7}$ vs					
		All participants (n=706)			
1. Brachial PP/SBP	*	0.185 (0.112 to 0.256)	<0.0001	0.204 (0.131 to 0.274)	<0.0001
2. Brachial PP/SBP	*	-0.009 (-0.083 to 0.065)	=0.81	0.025 (-0.049 to 0.099)	=0.50
PPc/SBPc		0.080 (0.005 to 0.153)	<0.05	0.021 (-0.053 to 0.095)	=0.58
3. Brachial PP/SBP	*	0.183 (110 to 0.254)	<0.0001	0.187 (0.114 to 0.257)	<0.0001
1/PP amplification		0.120 (0.046 to 0.193)	<0.005	0.091 (0.017 to 0.165)	<0.02
4. Brachial PP/SBP	*	0.047 (-0.028 to 0.121)	=0.22	0.082 (0.007 to 0.156)	<0.05
Pb		0. 092 (0.018 to 0.166)	<0.02	0.082 (0.007 to 0.156)	<0.05
5. Brachial PP/SBP	*	0.157 (0.083 to 0.229)	<0.0001	0.173 (0.099 to 0.244)	<0.0001
Pf		-0.055 (-0.129 to 0.0.020)	=0.15	-0.023 (-0.098 to 0.051)	=0.54
6. Brachial PP/SBP	*	0.154 (0.080 to 0.226)	<0.0001	0.170 (0.097 to 0.241)	<0.0001
PWV		0.093 (0.019 to 0.166)	<0.05	0.080 (0.006 to 0.154)	<0.05
7. Brachial PP/SBP	*	0.186 (0.113 to 0.257)	<0.0001	0.199 (0.126 to 0.269)	<0.0001
AIx		0.051 (-0.023 to 0.125)	=0.18	0.018 (-0.056 to 0.092)	=0.63
8. Brachial PP/SBP	*				
Pb† (n=336)	*	0. 130 (0.022 to 0.236)	<0.02	0.130 (0.019 to 0.236)	<0.05
9. Brachial PP/SBP	*				
Pf† (n=336)	*	-0. 107 (-0.213 to 0.007)	=0.54	-0.066 (-0.174 to 0.043)	=0.
		Untreated participants (n=524)			
1. Brachial PP/SBP	*	0.224 (0.140 to 0.304)	<0.0001	0.227 (0.143 to 0.307)	<0.0001
2. Brachial PP/SBP	*	-0.039 (-0.125 to 0.047)	=0.37	0.008 (-0.079 to 0.094)	=0.86
PPc/SBPc		0.126 (0.039 to 0.210)	<0.005	0.048 (-0.038 to 0.134)	=0.27
3. Brachial PP/SBP	*	0.226 (142 to 0.306)	<0.0001	0.204 (0.119 to 0.285)	<0.0001
1/PP amplification		0.194 (0.109 to 0.275)	<0.0001	0.164 (0.078 to 0.247)	<0.0005
4. Brachial PP/SBP	*	0.048 (-0.039 to 0.135)	=0.28	0.062 (-0.026 to 0.148)	=0.17
Pb		0. 148 (0.062 to 0.232)	<0.001	0.155 (0.068 to 0.239)	=0.0005

5. Brachial PP/SBP	*	0.153 (0.067 to 0.237) =0.0005	0.161 (0.074 to 0.244) <0.0005
Pf		-0.007 (-0.094 to 0.0.080) =0.88	0.029 (-0.058 to 0.116) =0.51
6. Brachial PP/SBP	*	0.185 (0.100 to 0.267) <0.0001	0.181 (0.096 to 0.263) <0.0001
PWV		0.095 (0.008 to 0.180) <0.05	0.094 (0.008 to 0.179) <0.05
7. Brachial PP/SBP	*	0.225 (0.141 to 0.305) <0.0001	0.220 (0.136 to 0.300) <0.0001
AIx		0.068 (-0.018 to 0.154) =0.12	0.033 (-0.054 to 0.119) =0.46

LVMI-ht$^{1.7}$, left ventricular mass indexed to height$^{1.7}$. See table 1 for additional abbreviations. Untreated refers to never having received antihypertensive therapy *Adjustments are for age, sex, body weight, pulse rate, regular smoking, regular alcohol intake, diabetes mellitus or an HbA_{1c}>6.1% and treatment for hypertension (in all). †Refers to data obtained in 392 participants in whom wave separation analysis was performed using aortic flow assessments. Variance inflation factors (VIF) for all aortic function variables except PPc/SBPc ranged from only 1.43 to 4.39. VIFs for aortic PPc or SBPc were however 12.31-30.56. VIFs for 1/PP amplification were only 1.55 to 1.60.

Table 5.4. Relations between brachial and aortic hemodynamic parameters and left ventricular hypertrophy (LVH) (317 of all 706 participants and 202 of 524 participants never having received antihypertensive therapy [untreated]).

Models with→		Pulse pressure (PP)		Systolic BP (SBP)	
	Adjustors	OR (95% CI)	p-value	OR (95% CI)	p-value
Models: LVH versus					
		All participants			
1. Brachial PP/SBP	*	1.020 (1.008 to 1.032)	<0.001	1.016 (1.007 to 1.025)	<0.001
2. Brachial PP/SBP	*	0.988 (0.956 to 1.022)	=0.49	0.995 (0.956 to 1.035)	=0.81
PPc/SBPc		1.040 (1.000 to 1.081)	<0.05	1.022 (0.981 to 1.065)	=0.30
3. Brachial PP/SBP	*	1.020 (1.008 to 1.032)	<0.005	1.013 (1.004 to 1.023)	<0.005
1/PP amplification		36.2 (4.2 to 309.6)	<0.005	21.99 (2.51 to 192.71)	=0.005
4. Brachial PP/SBP	*	0.997 (0.976 to 1.019)	=0.78	1.003 (0.990 to 1.016)	=0.67
Pb		1.066 (1.016 to 1.118)	<0.01	1.053 (1.011 to 1.097)	<0.02
5. Brachial PP/SBP	*	1.025 (1.004 to 1.047)	<0.02	1.015 (1.004 to 1.027)	<0.01
Pf		0.997 (0.953 to 1.023)	=0.47	1.000 (0.974 to 1.026)	=0.97
6. Brachial PP/SBP	*	1.015 (1.003 to 1.028)	<0.05	1.012 (1.002 to 1.021)	<0.02
PWV		1.132 (1.037 to 1.236)	<0.01	1.125 (1.030 to 1.229)	<0.01
7. Brachial PP/SBP	*	1.020 (1.008 to 1.032)	<0.001	1.016 (1.006 to 1.025)	<0.001
AIx		1.003 (0.995 to 1.011)	=0.42	1.001 (0.993 to 1.009)	=0.81
		Untreated participants			
1. Brachial PP/SBP	*	1.021 (1.006 to 1.036)	<0.01	1.016 (1.005 to 1.027)	<0.005
2. Brachial PP/SBP	*	0.971 (0.930 to 1.013)	=0.18	0.984 (0.938 to 1.032)	=0.50
PPc/SBPc		1.063 (1.012 to 1.117)	<0.02	1.035 (0.985 to 1.087)	=0.17
3. Brachial PP/SBP	*	1.021 (1.005 to 1.036)	<0.01	1.013 (1.002 to 1.025)	<0.02
1/PP amplification		93.6 (7.7 to 999.1)	<0.0005	59.62 (4.82 to 737.82)	<0.005
4. Brachial PP/SBP	*	0.995 (0.968 to 1.022)	=0.70	1.002 (0.985 to 1.018)	=0.85
Pb		1.079 (1.016 to 1.146)	<0.02	1.066 (1.012 to 1.122)	<0.02
5. Brachial PP/SBP	*	1.015 (0.994 to 1.037)	=0.17	1.013 (0.999 to 1.027)	=0.07
Pf		1.009 (0.970 to 1.049)	=0.66	1.011 (0.979 to 1.045)	=0.50
6. Brachial PP/SBP	*	1.015 (1.000 to 1.031)	<0.05	1.013 (1.000 to 1.026)	<0.05
PWV		1.133 (1.006 to 1.275)	<0.05	1.139 (1.004 to 1.293)	<0.05
7. Brachial PP/SBP	*	1.021 (1.006 to 1.036)	<0.01	1.016 (1.005 to 1.027)	=0.005

AIx	1.004 (0.995 to 1.013) =0.43	1.002 (0.993 to 1.011) =0.74

OR, odds ratios. See table 1 for additional abbreviations. * Adjustments are for age, sex, body weight, pulse rate, regular smoking, regular alcohol intake, diabetes mellitus or an HbA_{1c}>6.1% and treatment for hypertension (in all).

Table 5.5. Impact of adjustments for aortic function measurements on relations between the reciprocal of pulse pressure amplification (1/PP amplification) and left ventricular mass index (LVMI) or LV hypertrophy (LVH) (317 of 706 participants) in all participants.

	Adjustors	β-coeff±SEM†	Partial r (95% CI)	p-value
LVMI-ht$^{1.7}$ vs				
		With adjustments for brachial pulse pressure		
1/PP amplification	*	29.0±9.1	0.120 (0.046 to 0.193)	<0.005
1/PP amplification	* + PWV	29.5±9.1	0.123 (0.049 to 0.195)	=0.001
1/PP amplification	* + AIx	40.6±12.8	0.119 (0.045 to 0.192)	<0.005
1/PP amplification	* + Pf	25.6±9.6	0.102 (0.027 to 0.176)	<0.01
1/PP amplification	* + Pb	20.0±11.7	0.065 (-0.010 to 0.139)	=0.09
1/PP amplification†	*			
1/PP amplification†	* + PWV			
1/PP amplification†	* + AIx			
1/PP amplification†	* + Pf			
1/PP amplification†	* + Pb			
		With adjustments for brachial systolic blood pressure		
1/PP amplification	*	22.3±9.2	0.091 (0.017 to 0.164)	<0.02
1/PP amplification	* + PWV	23.8±9,2	0.098 (0.023 to 0.171)	<0.01
1/PP amplification	* + AIx	37.4±12.9	0.110 (0.036 to 0.183)	<0.005
1/PP amplification	* + Pf	20.6±9.9	0.079 (0.004 to 0.153)	<0.05
1/PP amplification	* + Pb	13.1±10.3	0.049 (-0.026 to 0.123)	=0.20
1/PP amplification†	*	31.1±13.0	0.131 (0.023 to 0.237)	<0.02
1/PP amplification†	* + PWV			
1/PP amplification†	* + AIx			
1/PP amplification†	* + Pf	32.0±13.8	0.129 (0.020 to 0.234)	=0.02
1/PP amplification†	* + Pb	21.4±14.7	0.081 (-0.029 to 0.189)	=0.15
	Adjustors	Odds ratio (95% CI)	Wald X^2	p-value
LVH versus				
		With adjustments for brachial pulse pressure		

1/PP amplification	*	36.2 (4.2 to 309.6)	10.73	<0.005
1/PP amplification	* + PWV	37.9 (4.3 to 330.7)	10.80	=0.001
1/PP amplification	* + AIx	324.4 (15.8 to 999.0)	14.1	<0.0005
1/PP amplification	* + Pf	32.4 (3.4 to 309.9)	9.12	<0.005
1/PP amplification	* + Pb	10.0 (0.6 to 157.9)	2.66	=0.10
		With adjustments for brachial systolic blood pressure		
1/PP amplification	*	22.0 (2.5 to 192.7)	7.79	=0.005
1/PP amplification	* + PWV	27.9 (3.0 to 242.3)	8.66	<0.005
1/PP amplification	* + AIx	264.4 (12.5 to 989.9)	12.85	<0.0005
1/PP amplification	* + Pf	25.4 (2.4 to 264.9)	7.30	<0.01
1/PP amplification	* + Pb	7.3 (0.6 to 82.4)	2.58	=0.11

See table 1 for abbreviations. * Adjustments are for brachial pulse pressure or systolic blood pressure as indicated, age, sex, body weight, pulse rate, regular smoking, regular alcohol intake, diabetes mellitus or an HbA_{1c}>6.1% and treatment for hypertension. †Refers to data obtained in 336 participants where Pb and Pf were derived from wave separation analysis using actual aortic flow waves Variance inflation factors for 1/PP amplification for all models ranged from only 1.55 to 3.12.

Table 5.6. Impact of adjustments for aortic function measurements on relations between the reciprocal of pulse pressure amplification (1/PP amplification) and left ventricular mass index (LVMI) in participants not receiving antihypertensive therapy (n=524).

	Adjustors	β-coeff±SEM†	Partial r (95% CI)	p-value
LVMI-ht$^{1.7}$ vs				
		With adjustments for brachial pulse pressure		
1/PP amplification	*	44.8±9.2	0.211 (0.126 to 0.292)	<0.0001
1/PP amplification	* + PWV	44.7±9.2	0.206 (0.121 to 0.287)	<0.0001
1/PP amplification	* + AIx	64.0±12.9	0.215 (0.131 to 0.296)	<0.0001
1/PP amplification	* + Pf	45.8±9.7	0.207 (0.121 to 0.289)	<0.0001
1/PP amplification	* + Pb	30.0±11.6	0.114 (0.027 to 0.200)†	<0.05
		With adjustments for brachial systolic blood pressure		
1/PP amplification	*	39.5±9.4	0.184 (0.098 to 0.266)	<0.0001
1/PP amplification	* + PWV	39.2±9.4	0.183 (0.097 to 0.265)	<0.0001
1/PP amplification	* + AIx	61.7±13.0	0.207 (0.122 to 0.288)	<0.0001
1/PP amplification	* + Pf	44.4±10.1	0.194 (0.108 to 0.276)	<0.0001
1/PP amplification	* + Pb	24.0±10.5	0.101 (0.014 to 0.187)	<0.05

See table 1 for abbreviations. *Adjustments are for brachial pulse pressure or systolic blood pressure as indicated, age, sex, body weight, pulse rate, regular smoking, regular alcohol intake, and diabetes mellitus or an HbA_{1c}>6.1%. †p=0.05 versus adjustors alone. Variance inflation factors for 1/PP amplification for all models ranged from only 1.55 to 3.08.

5.5 **Discussion**

The main findings of the present study are as follows: In a community-based sample of largely young-to-middle-aged participants of African ancestry I show that the reciprocal of PP amplification was independently associated with and added to the ability of brachial BP to associate with LVMI and LVH. This was noted even when aortic PP, although showing independent relations with LVMI and LVH replaced rather than added to brachial BP in associations with LVMI and LVH. The brachial BP-independent relations between the reciprocal of PP amplification and LVMI or LVH were abolished with adjustments for the reflected (backward) wave pressure (Pb), but not aortic PWV, suggesting that variations in wave reflection largely account for the ability of PP amplification to associate with LVMI and LVH beyond brachial BP in this community sample.

Several studies have demonstrated a brachial BP-independent relationship between aortic-to-brachial PP amplification and outcomes (Benetos et al 2010, Regnault et al 2012, Benetos et al 2012, Bursztyn et al 2016). However, the mechanisms of this effect are uncertain. To the best of our knowledge, the present study represents the first study to show an ability of the reciprocal of PP amplification to add to the ability of brachial BP to associate with LVMI or LVH, suggesting that adverse effects on cardiovascular outcomes may be mediated in-part through an independent effect on LVM.

Prior studies reporting on the adverse effects of PP amplification on outcomes (Benetos et al 2010, Regnault et al 2012, Benetos et al 2012, Bursztyn et al 2016) have assumed that all of those physiological factors that determine variations in PP amplification contribute to the ability of this aortic function variable to risk predict. In this regard, amplification of PP from the aorta to the brachial artery is largely determined by increments in stiffness from the aorta to the brachial artery (Avolio et al 2009, Nichols et al 2011). With an increasing aortic stiffness whilst brachial stiffness remains relatively stable, PP amplification decreases and hence associations

between a reduced PP amplification and LVMI are thought to be through an enhanced aortic stiffness. However, the inclusion of aortic PWV in multivariate models, an accepted referent method of assessing aortic stiffness, failed to modify relations between PP amplification and LVMI or LVH. Thus, the ability of PP amplification to independently associate with LVMI and LVH in the young-to-middle-aged is unlikely to be accounted for by variations in aortic stiffness.

Decreases in PP amplification are also determined by increases in aortic backward waves, produced either by increments in the magnitude of the pressure or the speed of backward wave travel (Avolio et al 2009, Nichols et al 2011). An increased magnitude of the backward wave or an earlier time of backward wave arrival will enhance aortic PP with a lesser effect on brachial PP, the consequence being a reduced PP amplification. In the present study, as with PP amplification, reflected wave pressure was also independently related to LVMI and LVH. Moreover, adjusting for reflected wave pressure markedly attenuated or abolished the independent relations between the reciprocal of PP amplification and LVMI and LVH and the ability of the reciprocal of PP amplification to add to brachial PP-LVMI or LVH associations. These data suggest that reflected wave pressure may in-part account for the independent relations between the reciprocal of PP amplification and LVMI and LVH in the young-to-middle-aged.

Pulse pressure amplification is often attributed to increases in aortic PWV causing a greater speed of wave reflection, an enhanced overlap between the forward and reflected waves and an increase in aortic augmentation index and hence aortic PP. However, PP amplification was more strongly correlated with reflected wave pressure (r^2=0.37) than with PWV (r^2=0.10). Moreover, whilst reflected wave pressure was independently associated with LVMI and LVH and made a significant contribution to relations between PP amplification and LVMI or LVH, augmentation index was not independently associated with LVMI and LVH and made no significant contribution to relations between PP amplification and LVMI or LVH. Hence, the contribution of reflected wave pressure to variations in PP amplification or to the relationship

between PP amplification and LVMI or LVH cannot be attributed to an enhanced overlap between the forward and reflected waves with a consequent increase in augmentation index.

The present study design (cross-sectional) does not allow me to draw conclusions as to cause and effect. It may therefore be argued that LVH enhances systolic function and hence aortic backward wave pressures (reverse causality) rather than increases in aortic backward wave pressures increase LVMI. However, the relationship between aortic backward wave pressure and LVMI or LVH was unchanged with adjustments for LV ejection fraction. Hence, I assume that this relationship is explained by increases in backward wave pressures resulting in increases in LVMI and LVH rather than LVH promoting an enhanced systolic function and hence an increased backward wave pressure.

A caveat of the present study is that the present results do not discount the possible role of aortic PWV in mediating brachial PP-independent relations between PP amplification and LVMI or LVH at an older age. In this regard, aortic PWV only begins to increase to a marked extent between 50 to 60 years of age (Mitchell et al 2010b), which is at least a decade older than the average age of the present study group. Hence, in the present sample PWV may not contribute to any marked extent to PP amplification, but may in samples represented by an older age group. Indeed, the correlation (r^2) between PWV and PP amplification in the present study sample was only 0.10 ($p<0.0001$). The present study nevertheless highlights the importance of aortic backward wave function in mediating cardiovascular end-organ changes and explains at least a significant portion of the independent relation between the reciprocal of PP amplification and LVMI and therefore possibly some of the independent relations between PP amplification and outcomes (Benetos et al 2010, Regnault et al 2012, Benetos et al 2012, Bursztyn et al 2016).

A further caveat of the present study is that I studied only one ethnic group (black African) in which aortic backward waves are markedly higher than in alternative groups (Chirinos et al 2011). In this regard some populations, such as the Framingham sample, where

a high proportion of participants were receiving antihypertensive therapy which decreases backward wave pressures, show only small age-related increases in aortic backward waves and hence only modest age-related increments in PP amplification (Mitchell et al 2010b). In the Framingham sample therefore, PP amplification was not an independent predictor of outcomes (Mitchell et al 2010a).

There are several limitations to the present study that warrant consideration. First, the present study was a cross-sectional design and cardiovascular end-organ measures were employed as surrogates of outcomes. Hence, the present study provides no conclusive evidence that aortic backward waves mediate the relationship between PP amplification and LVMI and whether similar relations with hard end-points is unknown. Further longitudinal and intervention (targeting backward waves) studies are therefore required with hard end-points included as outcomes. Second, the assumptions intrinsic to the use of the 'triangulation method' of aortic wave separation may not be ideal (Kips et al 2009). However, in 392 participants of the present sample with aortic velocity measurements, we were able to show a correlation (r^2) between Pb derived from the 'triangulation method' versus 'actual aortic flow' methods of wave separation of 0.82 and a correlation (r^2) between Pf derived from the 'triangulation method' versus 'actual aortic flow' methods of wave separation of 0.88. Moreover, in sensitivity analysis conducted in those participants in whom wave separation analysis was performed using aortic flow waveforms and in whom aortic PWV measurements were available, relations between Pb and other aortic hemodynamic variables were similar to those between Pb determined using a triangular flow wave, and these aortic variables. Furthermore, irrespective of whether wave separation analysis was performed using a triangular wave form or an actual aortic flow wave, relations between Pb or Pf and LVMI were similar and the impact of adjustments for Pb and Pf on relations between PP amplification and LVMI were the same. Hence, at least in the present study, the use of the 'triangulation method' is unlikely to have significantly affected our results. Third, in the present study, calibration of the radial waveform from brachial BP measurements

ignores amplification of BP from brachial to radial arteries (Picone et al 2015). Hence, aortic pressures are likely to have been underestimated using the current approach. However, Pb and Pf are equally susceptible to errors in calibration and Pb and not Pf accounted for the ability of PP amplification to associate with LVMI and LVH beyond brachial BP.

In conclusion, in the present study I show in a largely young-to-middle aged community sample, that the reciprocal of PP amplification adds to the ability of brachial PP and conventional risk factors to associate with LVMI and LVH and that this is in-part accounted for by an increased backward wave pressures, but not by aortic pulse wave velocity. These findings may add to our understanding of the ability of aortic functional variables to detect end-organ changes beyond brachial BP.

CHAPTER 6

Contextual Narrative, Summary and Conclusions

6.1 Introduction

In the present thesis I have performed a series of studies in a group of African ancestry living in SOWETO, South Africa (previously disadvantaged community) that have advanced our knowledge on the role of various indices of aortic function as possible factors that are associated with cardiovascular end-organ measures beyond brachial blood pressure (BP). In the present chapter I will summarize these findings and place them in context with the field of aortic function in general and with the possibility of how aortic function may be employed to enhance risk prediction beyond conventional risk factors in a resource limited country such as South Africa. In this regard, it is important to first emphasize several points highlighted in chapter 1 regarding cardiovascular disease in South Africa.

There is no question that the world's burden of cardiovascular disease is now in developing rather than in developed nations, and South Africa, as an economically developing nation, is no exception to this finding (Roth et al 2015). Whilst in developed countries age-adjusted mortality rates attributed to cardiovascular disease in 2013 were estimated to be 160 per 100 000 persons, in South Africa they were estimated to be 250-to-325 per 100 000 people (Roth et al 2015). In this regard, there are several factors which may account for these higher mortality rates attributed to cardiovascular disease in South Africa as compared to developed nations. As with other developing nations around the world, South African populations are undergoing an epidemiological transition, where diseases of lifestyle are beginning to replace diseases of poverty (infectious diseases and malnutrition). Lifestyle changes in developing nations that are likely to account for a higher prevalence of cardiovascular diseases include more tobacco use, a more sedentary work and social environment, less time to walk to work or other destinations and an easier access to motor vehicles (and hence lower levels of activity), higher stress occupations, and easier access to fast foods with an emphasis on dietary habits that provide instant gratification (high sodium, saturated fat, and high glycaemic index-sugar

diets). All of these changes promote the development of cardiovascular risk factors (an increased BP, cholesterol concentrations and a greater risk of type II diabetes mellitus) and through limited overall education levels in developing nations (few gain tertiary level education), a lack of awareness of the importance of early identification of risk factors and the variety of safe means to treat these risk factors.

The aforementioned factors that contribute toward increasing prevalence rates of cardiovascular risk factors and a lack of awareness and treatment of these risk factors, are all confounded by limited resources at a primary healthcare level. For example primary healthcare clinics in South Africa often do not carry appropriate medication (lipid lowering therapy is not available); do not have the means to assess blood and other markers useful for risk prediction (e.g the assessment of lipid profiles, markers of renal function, glycated haemoglobin levels for patients with diabetes mellitus and electrocardiography); and do not have access to reliable BP monitors (they are often not serviced or for cost purposes are purchased having never been validated). A limited number of primary healthcare clinics and understaffing results in long patient waiting times (often entire days of work are lost) and a lack of faith in healthcare services. Limited budgets necessitates the dispensation of chronic medication on a monthly rather than 6 monthly basis and hence the need for frequent visits to clinics with further loss of work and greater costs to patients. In addition, because of low doctor-patient ratios, primary health care is often only provided by nurses with a limited ability to detect pathology or refer on to secondary or tertiary hospitals. Moreover, limited resources in developing countries prevents appropriate tertiary healthcare so that patients who have an event do not receive the same level of care as in developed countries (e.g. patients with stroke seldom receive thrombolysis; patients with myocardial infarction requiring catheterization and stenting often do not receive this care; and patients requiring valve replacements or bypass grafts do not receive these procedures). It is only with economic development, better education, and more resources for

healthcare that many of the aforementioned factors responsible for the burden of cardiovascular deaths in developing nations can be addressed.

Despite all of the problems listed above, there is overwhelming consensus that prevention of an event is more cost-effective than managing the event once it has occurred. Hence, the focus in developing nations should always be on early cardiovascular risk identification and management of risk factors. As indicated in chapter 1 of the present thesis, of all the risk factors for cardiovascular disease most population attributable risk for cardiovascular events is determined by hypertension (Steyn et al 2005, Rayner et al 2010, Huang et al 2013, Park et al 2015) and presently Africa has the highest prevalence of hypertension (NCD-RisC 2017). For the past century BP has been determined at the brachial artery and there is no question that brachial BP is a strong cardiovascular risk predictor. However, in South Africa and elsewhere in the world there are several reasons to believe that the ability to predict cardiovascular risk may, in the future, be better determined using a combined approach which employs both brachial and aspects of aortic BP measurements. Given the ease (non-invasive and requires little expertise to perform the measurement with accuracy) and reproducibility with which these aortic BP measurements can be made, together with the declining costs of measurement devices (often no more expensive than a reliable and validated oscillometric BP device), due consideration has to be given to the ability to add to risk prediction in South Africa using these approaches. What is the evidence to indicate that the measurement of certain aspects of aortic BP may enhance risk prediction beyond brachial BP; are there compelling reasons why these measurements should be made in Africa; and how has the present thesis added to our understanding of what aspects of aortic BP measurement may add to risk prediction in South Africa?

6.2 Aortic BP measurements and risk prediction beyond brachial BP. A need for clarity

As highlighted in chapter 1 of the present thesis there is considerable controversy as to whether aortic systolic BP (SBP) or pulse pressure (PP) add to brachial SBP or PP in risk prediction. There are several studies that suggest that aortic SBP or PP are more strongly associated with end-organ measures than brachial BP or associated with end-organ measures independent of brachial BP (Safar et al 2002, Williams et al 2006, Roman et al 2007, Jankowski et al 2008, Pini et al 2008, Wang et al 2009, Benetos et al 2010, Regnault et al 2012, Dart et al 2006, Norton et al 2012, Booysen et al 2013). The results of many of these studies has recently been included in a meta-analysis and this meta-analysis clearly shows a stronger association of aortic SBP or PP with end-organ measures than does brachial SBP or PP (Kollias et al 2016). In South Africa, there is also evidence, produced by our group, to show that aortic PP is associated with end-organ measures independent of brachial SBP or PP (Norton et al 2012). In that study (Norton et al 2012) the authors provided the evidence to show that the second systolic shoulder of the peripheral pulse, which closely approximates aortic SBP or PP derived from conversion of the radial into an aortic pulse wave using a generalized transfer function (GTF), is as closely associated with end-organ measures beyond brachial SBP or PP as is aortic SBP or PP derived from a GTF. These data suggested that the GTF, which because it has not been disclosed by the manufacturer has thus been a subject of much criticism, is unnecessary to identify end-organ changes beyond brachial BP (first systolic shoulder). This finding (Norton et al 2012) therefore raised the question of whether simpler approaches (peripheral pulse wave analysis without the need to convert the data to aortic pressures) was sufficient to risk predict beyond brachial pressures. These findings (Norton et al 2012) therefore also raised the question of whether the cost of risk predicting beyond brachial BP using pulse wave analysis may not be considerably cheaper (some of the cost is in the GTF which has a patent on it) than even present costs (which are no more expensive than some validated oscillometric brachial BP devices). However, in contrast to the relatively consistent findings of a brachial SBP and PP- independent relationship between aortic PP and SBP (derived either from

the GTF or estimated only from the second systolic shoulder of the peripheral pulse wave) and end-organ measures, the role of aortic SBP or PP in actual risk prediction beyond brachial BP has been far more controversial. What are the important features of this controversy?

As reviewed in section 1.2.4 of chapter 1 of the present thesis, although several initial studies demonstrated that aortic SBP or PP predicted risk beyond brachial BP, there were additional studies that failed to do so and a meta-analysis of these studies (Vlachopoulos et al 2010), showed only a trend for a stronger relationship with cardiovascular outcomes than brachial SBP or PP. Subsequent larger studies have similarly failed to show consistency, with some (Williams et al, 2006, Wang et al 2010), but not others (Mitchell et al 2010a, Benetos et al 2010, Regnault et al 2012, Benetos et al 2012, Chirinos et al 2012, Bursztyn et al 2016) demonstrating a stronger relationship between aortic PP or SBP and outcomes than brachial SBP or PP. These inconsistent findings are likely to be attributed to the strong correlations between aortic and brachial SBP or PP (r^2=0.96 0r 0.91, p<0.0001 in our large [n=1185] community-based sample) despite often considerable differences in aortic and brachial BP, and question the value of using aortic SBP or PP to replace brachial SBP or PP. These inconsistent findings have led many investigators to seek alternative indices of aortic function when adding to risk prediction beyond aortic BP. What are some of these indices; is there sufficient evidence to support the use of these approaches in Africa and around the world; and how has the current thesis added to our overall understanding of these issues?

6.3 Aortic reflected waves as determined using augmentation indices: Should these be used to risk predict in Africa and elsewhere?

There are two essential explanations for variations in the difference between aortic and peripheral arterial BP and these have been described in chapter 1 of the present thesis (see sections 1.2.2, 1.2.3 and 1.2.4). To recapitulate, these are differences in stiffness between the

aorta and peripheral arteries, where an increased aortic stiffness reduces the difference between aortic and brachial pulse pressure (PP), and the effect of increases in aortic backward (reflected) wave pressures which similarly reduce the difference between aortic and brachial PP. At present aortic stiffness, as determined using aortic pulse wave velocity (PWV) is recommended for risk prediction (Vlachopoulus et al 2010, Ben-Shlomo et al 2014). However, the role of aortic reflected wave function is more controversial. As highlighted throughout this thesis, there are two fundamental approaches to assessing aortic backward (reflected) wave effects. The more commonly employed and easier to use approach is to determine indices of aortic systolic pressure augmentation and these include augmented pressure (Pa) and augmentation index (AIx). In this regard, as described by a collaborative study involving various populations around the world, including the SOWETO community sample reported on in the present thesis, marked ethnic differences in AIx occur with the highest values reported in people living in SOWETO (black African ancestry) (Chirinos et al 2011). These data suggest that if aortic backward wave function is important as a determinant of cardiovascular damage, that brachial BP in groups of African ancestry may be insufficient to detect the adverse effects of increased pressures on the cardiovascular system and that AIx may be an important additional measurement. In work performed by our group at a similar time on the community sample reported on in the present thesis, we demonstrated that salt intake as indexed by urinary Na^+/K^+, was independently associated with AIx (Redelinghuys et al 2010). These data (Redelinghuys et al 2010) suggested a possible mechanism for the increased AIx in the study sample reported on (Chirinos et al 2011) as it is well recognized that groups of African descent have a higher prevalence of salt sensitive hypertension than other ethnic groups. The question therefore is whether AIx should be employed to add to brachial BP to enhance risk prediction in groups of African ancestry in South Africa?

As described in chapter 1 (section 1.3.3) of the present thesis, earlier studies demonstrated that aortic backward (reflected) waves, as determined from indices of pressure

augmentation (Pa or AIx) are associated with cardiovascular damage (Hashimoto et al 2007, Hashimoto et al 2006, Weber et al 2006, Westerbacka et al 2005, Sibiya et al 2014), and predict cardiovascular outcomes (Chirinos et al 2005, London et al 2001, Ueda et al 2004, Weber et al 2005) independent of brachial BP. A meta-analysis of these and other outcome driven studies provides clear evidence that indices of aortic pressure augmentation predict outcomes beyond brachial BP (Vlachopoulos et al 2010). However, several additional studies (Dart et al 2006, Pini et al 2008, Roman et al 2007, Safar et al 2002,), including the Framingham Heart Study (Mitchell et al 2010a) failed to show that indices of aortic pressure augmentation predict outcomes independent of brachial BP. Nevertheless, it has become apparent that Pa and AIx are determined by several factors other than aortic reflected wave magnitude, including changes in aortic reservoir function, the timing or magnitude of the aortic forward wave, the timing rather than the magnitude of the aortic reflected wave, and left ventricular systolic function (Aviolo et al 2009, Agabiti-Rosei et al 2007, London 2001 et al 2001, Ueda et al 2004, Weber et al 2005). It is therefore conceivable that indices of aortic pressure augmentation may be useful for risk prediction in some, but not others, depending on the extent to which the magnitude of wave reflection or other factors play a role in determining Pa or AIx and whether these factors contribute significantly to end-organ changes. What are the possible factors that may modify whether Pa or AIx add to risk prediction?

The impact of gender on aortic augmentation index (AIx) (augmentation pressure/aortic pulse pressure), is well-recognized. In this regard, women may have a higher AIx than men (Weber et al 2005, Mtchell et al 2010b) , but these differences may be attributed to factors unrelated to aortic wave reflection, including a greater forward wave magnitude (Weber et al 2005). Hence, depending on the contribution of these alternative factors to cardiovascular disease, the impact of AIx on cardiovascular damage in women may not be as strong as that in men. Indeed, while AIx predicts outcomes in men, similar relationships may be diminished in women (Wang et al 2010. Nevertheless, in that study (Wang et al 2010) unadjusted

relationships between AIx and end-organ changes were no different in women as compared to men. However, multivariate adjusted relationships between AIx and end-organ changes were not reported on (Wang et al 2010). To clarify whether gender influences relationships between AIx and cardiovascular end-organ changes, as part of the present thesis (chapter 2, Sibiya et al 2014) I therefore compared the association between AIx and left ventricular mass index (LVMI) in men and women in a large, community-based sample in SOWETO. In this regard, LVMI and the regression thereof with antihypertensive therapy are well-recognised independent predictors of cardiovascular outcomes (Hughes et al 2014, Norton et al 2008, Woodiwiss et al 2009, Redelinghuys et al 2010, Norton et al 2012, Westerhof et al 2006, Sahn et al 1978, Devereux et al 1986). What were the findings and clinical implications of that study?

In that study described in chapter 2, and published in the journal *Hypertension Research* (Sibiya et al 2014) I demonstrated that AIx was independently associated with LVMI in men, but not in women. As indicated in the discussion to this chapter (chapter 2), there are several possible explanations for the gender-specific impact on relations between AIx and LVMI noted in that study, or between AIx and cardiovascular outcomes in a previous study (Wang et al 2010). Whether the lack of independent association between AIx and LVMI in women in that study was attributed to the confounding effect of several factors other than reflected wave magnitude contributing to AIx but not LVMI was uncertain at the time of the original publication. Indeed, in women AIx may not depend on reflected wave magnitude as much as on forward wave magnitude, and the timing of aortic forward and backward waves (Weber et al 2005). Some of these factors may have little impact on cardiovascular risk and hence create a low signal-to-noise ratio. Alternatively, reflective wave function may contribute little toward the impact of aortic PPc on cardiovascular damage in women, whereas the effect is prominent in men. Indeed, in a large, community-based study, both AIx and the reflection index derived from wave separation analysis predicted cardiovascular outcomes in men, but not in women (Wang et al 2010). As I did not have access to software to separate the forward and the backward

waves at the time of publishing the data in chapter 2 (Sibiya et al 2014), I could not determine whether the sex-specific relationship reported on was attributed to AIx being a poor index of reflected wave magnitude, or because reflected waves contribute little toward LVMI in women of African ancestry. Hence, further studies were required employing wave separation analysis to address these questions. With the acquisition of the software to separate forward and backward waves, I subsequently performed these analyses and these findings are reported in chapter 3. What are the implications of the findings in chapter 3?

6.4 Aortic reflected waves as determined using wave separation analysis: Should these be used to risk predict in Africa and elsewhere?

As indicated in chapter 1 (sections 1.3.3, 1.3.4 and 1.3.5), there are several studies that have described an association of reflected waves (Pb or the reflected wave index) derived from wave separation analysis with end-organ changes (Wang et al 2010, Weber et al 2012) or an ability of Pb or the reflection index (RI)(or reflected wave magnitude) to risk predict beyond brachial BP (Wang et al 2010, Weber et al 2012, Chirinos et al 2012, Zamani et al 2014). Although there is now considerable evidence to support a role of aortic backward waves in risk prediction, neither Pb nor the reflected wave index were independently associated with cardiovascular outcomes in the Framingham Heart study (Cooper et al 2014). Nevertheless as I have repeatedly pointed out, a high proportion of the participants of the Framingham Study were receiving antihypertensive therapy, and as discussed in section1.3.6, antihypertensive agents reduce aortic backward wave pressures. Consequently, aortic backward waves in the Framingham Heart Study failed to contribute as much as aortic forward waves to age-related increases in aortic PP as did aortic forward wave pressures (Mitchell et al 2010b). Hence, it is likely that the use of antihypertensive therapy confounded the cardiovascular outcomes data in the Framingham Heart study (Cooper et al 2014). As pointed out by the data reported on in

chapter 2 (Sibiya et al 2013), an additional possibility is that aortic reflected waves do not contribute to risk prediction in women. To draw this conclusion nevertheless, it was necessary for me to evaluate relations between aortic backward waves, determined from, wave separation analysis, and aortic PP and LVMI in the SOWETO cohort. This approach is clearly not confounded by the many determinants of Pa and AIx, including forward wave pressures and the timing of forward and backwards waves. In this regard, the manufacturer of the device employed to assess aortic function had recently introduced software to perform wave separation analysis using an assumed 'triangular' flow wave, and hence this afforded me the ability to address this question. What are the results and the implications of this study (chapter 3, Booysen et al 2015)?

As reported in chapter 3, and published in the journal *Hypertension* (Booysen et al 2015) where I am a co-author and responsible for the sex-specific analyses, I have shown that the contribution of aortic backward waves, determined from wave separation analysis, to variations in aortic PP and hence LVMI is similar in men as it is in women (Booysen et al 2015). In contrast, as described in chapter 2 and again shown in chapter 3, Pa and AIx were correlated with LVMI in men, but not in women. These results (Booysen et al 2015) therefore provided the evidence to suggest that the use of Pa or AIx was a particularly poor index of the adverse effects of backward wave function on aortic PP or end organ measures in women (Booysen et al 2015). Moreover, in that study (Booysen et al 2015), although AIx and Pa were independently associated with aortic PP and LVMI in men, even in men the relatively greater contribution of aortic backward as compared to forward wave function was markedly underestimated when AIx or Pa were employed as measures of aortic backward wave pressures. Hence, at least in the African context these data suggest that AIx and Pa should not be employed as approximates of aortic backward wave effects in either women or men (Booysen et al 2015). Rather, these data (Booysen et al 2015) suggest that adverse effects of aortic backward waves can only be accurately assessed using wave separation analysis. Hence, these findings support the view

that further outcome-based studies assessing the ability of aortic backward wave function, as determined using wave separation analysis, to risk predict in groups of African descent, are required.

6.5 Aortic reflected waves as determined using wave separation analysis: Are they better associated with end organ measures than forward wave pressures?

As indicated throughout the present thesis, aortic PP is determined by both forward and backward waves. As also demonstrated in chapter 3, aortic backward wave pressures contribute more toward variations in aortic PP and LVMI than aortic forward wave pressures and this is not sex-specific (Booysen et al 2015) as previous data had suggested (Sibiya et al 2014). In this regard, several studies have similarly evaluated the relative contribution of forward and backward wave pressures to variations in end-organ measures or cardiovascular outcomes (Wang et al 2010, Chirinos et al 2012, Weber et al 2012, Zamani et al 2014, Hughes et al 2014). Importantly, in some of these studies (Wang et al 2010, Chirinos et al 2012, Zamani et al 2014, Hughes et al 2014) indices of reflected waves predicted cardiovascular outcomes independent of brachial BP. However, whether forward wave pressures also associate with cardiovascular damage independent of brachial BP, and the relative contribution of forward and backward wave pressures to the brachial BP-independent relationship between aortic PP and cardiovascular damage was uncertain. In these prior studies, closer relations between reflected as compared to forward wave indices and end-organ measures (Wang et al 2010, Weber et al 2012) or cardiovascular outcomes (Zamani et al 2014) were reported on. However, neither of the studies reporting on relations between forward or backward wave pressures and end-organ measures (Wang et al 2010, Weber et al 2012) were these relations assessed with adjustments for brachial BP. Nevertheless, even without adjustments for brachial BP, backward but not forward wave pressures had been demonstrated to predict cardiovascular outcomes (Zamani et

al 2014). The question of whether aortic forward wave pressures also contribute to cardiovascular damage beyond brachial BP is essential to an understanding of whether aortic PP (which reflects the composite of forward and backward wave pressures) or aortic backward wave pressures (or the reflected wave magnitude) *per se* should be determined when risk predicting. In this regard, because forward wave pressures are amplified from the aorta to the brachial artery, and because aortic backward wave pressures appear as a lower second systolic shoulder on the peripheral pulse, either forward or backward wave pressure effects on end-organ measures could be underestimated with brachial BP measurements. What has the present thesis added to our understanding of the relative role of aortic forward and backward wave pressures, independent of brachial BP, to end-organ measures?

In chapter 4 and published in *J Hypertension* (Sibiya et al 2015) I have provided strong evidence to show that backward wave pressures and the reflected wave magnitude or index, but not forward wave pressures are associated with end-organ measures and damage independent of brachial BP. Further, I show that the brachial BP-independent relationships between aortic PP and end-organ measures are largely accounted for by backward wave pressures, but not by forward wave pressures. Nevertheless, without adjustments for brachial BP, but with adjustments for steady-state pressures (mean arterial pressure) both forward wave and backward wave pressures were associated with end-organ measures. Importantly, unlike in chapters 2 and 3 where my focus was on LVMI as the main end-organ change, in chapter 4 my findings were largely reproduced across several end-organ measures involving LV structure and diastolic function, carotid intima-media thickness, an index of atherosclerosis, aortic PWV, an index of arteriosclerosis, and estimated glomerular filtration rate, an index of renal function. Hence, the present study suggests that although both forward and backward wave pressures contribute to end-organ changes, brachial BP-independent relations between aortic pressure and cardiovascular end-organ changes are largely attributed to backward (reflected) rather than

forward wave pressure effects. As pointed out in chapter 4, these findings have several important clinical implications. What are these implications?

The findings reported in chapter 4 suggest that whilst the adverse effects of forward wave pressures are likely to be revealed using brachial BP measurements, backward wave pressure effects are unlikely to be readily detected using brachial BP measurements. The fact that forward wave pressures are associated with end organ measures, but not independent of brachial BP, suggests that brachial and aortic PP share similar features (both signal forward wave pressure effects) and hence that the better aortic function index to add to risk prediction beyond brachial BP is backward wave pressure effects. The results described in chapter 4 may also in-part explain why in community samples where the backward wave contributes little to age-related increases in aortic BP (Mitchell et al 2010b) aortic pressure does not predict cardiovascular outcomes beyond brachial BP (Mitchell et al 2010a), whilst in community samples where a strong age-related increase in the backward wave pressures occurs (Wang et al 2010), aortic BP predicts outcomes beyond brachial BP (Wang et al 2009).

6.6 Are there alternative approaches to assessing aortic reflected wave effects?

To recapitulate, the work that I have conducted as part of the present thesis and described in chapters 2-4, has demonstrated that although both aortic forward and backward waves associate with end-organ measures independent of steady-state pressures (mean arterial pressure), aortic backward, but not forward waves account for the brachial PP or SBP-independent relations between aortic PP and end organ measures (chapter 4 and published as Sibiya et al 2015). The independent relations between aortic backward wave pressures and end-organ measures are nevertheless poorly indexed by aortic augmented pressure or augmentation index (chapters 2 and 3 and published as Sibiya et al 2013 and Booysen et al 2015) as surrogates of backward wave function. Moreover, the use of aortic augmented

pressure or augmentation index as indexes of the adverse effects of aortic backward wave function on end-organ measures is particularly inappropriate in women (chapter 2 and published as Sibiya et al, 2014). These findings together therefore suggest that in groups of African ancestry in South Africa, aortic backward wave function may enhance risk prediction beyond brachial BP, but that simple approaches to detecting backward wave effects, such as the use of augmented pressure or augmentation index, are inappropriate for routine use. Assuming that these findings translate into cardiovascular outcomes, how does this information better inform as to how best to risk predict in Africa?

Until devices or approaches that assess aortic backward wave effects become no more expensive than validated oscillometric devices employed to assess brachial BP, and where brachial BP and aortic backward wave pressures can be measured together (only one device is required), it is unlikely that developing countries will ever adopt aortic backward wave measurements as part of routine risk prediction. However, more recently, several studies, including data from our own group (Bursztyn et al 2016) have demonstrated that aortic PP can be relatively accurately imputed from simple clinical measures that can be obtained at no additional cost (Benetos et al 2010, Bursztyn et al 2016). Although as highlighted in previous discussion aortic PP may add little to risk prediction beyond brachial BP, findings supported by these studies (Benetos et al 2010, Bursztyn et al 2016), both of these studies provided the evidence to show that aortic-to-brachial PP amplification, calculated from imputed aortic PP, considerably added to (rather than replacing) the ability of brachial PP to risk predict (Benetos et al 2010, Bursztyn et al 2016). As highlighted in chapter 1 (section 1.3.5), there are essentially two factors that determine variations in PP amplification and these are aortic stiffness and aortic backward wave pressures. This then raised the question as to what extent relationships between PP amplification and either end organ measures or cardiovascular outcomes are attributed to backward wave effects? If relations between PP amplification and cardiovascular damage are largely accounted for by backward wave effects, rather than increases in aortic

stiffness, then a simple and costless approach to assessing backward wave effects (imputing aortic PP and calculating PP amplification) would be available.

6.7 To what extent are relations between PP amplification and end-organ measures accounted for by aortic reflected wave effects?

As part of the present thesis I addressed the question as to what extent relationships between PP amplification and end organ measures are attributed to backward wave effects. These data are described in chapter 5 and have been accepted for publication in the *J Am Soc Hypertens* (Sibiya et al 2017 in-press). In this study I showed in a community-based sample of largely young-to-middle-aged participants of African ancestry that the reciprocal of PP amplification was independently associated with and added to the ability of brachial BP to associate with LVMI and LV hypertrophy (LVH). This was noted even when aortic PP, although showing independent relations with LVMI and LVH replaced rather than added to brachial BP in associations with LVMI and LVH. The brachial BP-independent relations between the reciprocal of PP amplification and LVMI or LVH were abolished with adjustments for the reflected (backward) wave pressure, but not aortic PWV, suggesting that variations in wave reflection largely account for the ability of PP amplification to associate with LVMI and LVH beyond brachial BP in this community sample.

There are several aspects of the design of this study that warrant further comment. In this regard, the only end-organ assessment that I studied in this chapter was LVMI, whilst several other end-organ measures were at this time, available. However, in the present community sample aortic PWV was noted to independently associate with LVMI (in women) and estimated glomerular filtration rate (eGFR) (in men and women), but not carotid intima-media thickness or LV diastolic function (Peterson et al 2016). Hence, there was no value in assessing whether relations between PP amplification and carotid intima-media thickness or LV diastolic

function are attributed to PWV. Moreover, as demonstrated in chapter 4, relations between aortic backward wave pressures and eGFR were not independent of age, and hence there was no value in assessing the contribution of aortic backward waves to independent relations between PP amplification and eGFR. Nevertheless, it is important to note that in-keeping with results with LVMI, without adjustments for age (which is the main determinant of PP amplification and backward wave pressures), PP amplification was associated with carotid intima-media thickness, LV diastolic function, and eGFR, and that adjustments for backward, but not forward wave pressures or PWV markedly attenuated these relations (data not shown).

The obvious clinical implication of the findings of chapter 5 are that PP amplification may be a surrogate of aortic backward wave effects on cardiovascular end-organ measures. If these results are confirmed in outcome-based studies, these data provide a cost-effective approach (calculating PP amplification from brachial PP and imputed aortic PP derived from simple clinical measures) to estimating the adverse effects of aortic backward waves and hence risk predicting using this approach.

6.8 Limitations

The limitations of the present thesis have largely been addressed in the discussion to each data chapter or stated in preceding discussion in the present chapter and hence will not be reiterated.

6.9 Conclusions

In conclusion, the present thesis has demonstrated that although both aortic forward and backward waves associate with end-organ measures independent of steady-state pressures (mean arterial pressure), aortic backward, but not forward waves account for the brachial PP or

SBP-independent relations between aortic PP and end organ measures (chapter 4 and published as Sibiya et al 2015). Moreover, the present thesis indicates that the independent relations between aortic backward wave pressures and end-organ measures are poorly indexed by aortic augmented pressure or augmentation index (chapters 2 and 3 and published as Sibiya et al 2014 and Booysen et al 2015). Furthermore, the present thesis suggests that the use of aortic augmented pressure or augmentation index as indexes of the adverse effects of aortic backward wave function on end-organ measures is particularly inappropriate in women (chapter 2 and published as Sibiya et al, 2014). In addition, the present thesis shows that the reciprocal of PP amplification is independently associated with and added to the ability of brachial BP to associate with end-organ measures and that this was noted even when aortic PP, although showing independent relations with end-organ measures replaced rather than added to brachial BP in associations with end organ measures (chapter 5 and in-press as Sibiya et al 2017). Importantly, the brachial BP-independent relation between the reciprocal of PP amplification and end-organs was abolished with adjustments for the reflected (backward) wave pressure, but not aortic PWV, suggesting that variations in wave reflection largely account for the ability of PP amplification to associate with end-organs beyond brachial BP (chapter 5 and in-press as Sibiya et al 2017). These findings taken together and if reproduced in longitudinal or intervention studies with hard outcomes as the end point, suggest that in groups of African ancestry in South Africa, aortic backward wave function may enhance risk prediction beyond brachial BP; that simple approaches to detecting backward wave effects, such as the use of augmented pressure or augmentation index, are inappropriate for routine use; but that the use of the reciprocal of PP amplification, which can be imputed from simple and costless clinical measurements, may be employed as a surrogate of aortic backward wave effects to add to brachial BP when risk predicting.

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Appendix 1

Ethics and clearance certificates

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Prof A/G Woodiwiss/Norton

CLEARANCE CERTIFICATE	**M1204108**
PROJECT	Gene Candidates as Determinants of Blood Pressure and Intermediary Phenotypes in Pathogenesis of Hypertension in Black South Africans (Previously M020472 and M070469)
INVESTIGATORS	Prof A/G Woodiwiss/Norton.
DEPARTMENT	School of Physiology
DATE CONSIDERED	Ad hoc
DECISION OF THE COMMITTEE*	Renewal Approved

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 2012/05/18 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Prof A Woodiwiss

DECLARATION OF INVESTIGATOR(S)
To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Woodiwiss/Norton

CLEARANCE CERTIFICATE	**PROTOCOL NUMBER MO70469**
PROJECT	Gene Candidates As Determinants of Blood Pressure and Intermediary Phenotypes in Pathogenesis of Hypertension in Black S Africans
INVESTIGATORS	Profs A/G Woodiwiss/Norton
DEPARTMENT	School of Physiology
DATE CONSIDERED	07.05.09
DECISION OF THE COMMITTEE*	Approved unconditionally (refer M020472)

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 07.05.09 **CHAIRPERSON** .....
(Professors PE Cleaton-Jones, A Dhai, M Vorster, C Feldman, A Woodiwiss)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Woodiwiss A Prof

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and ONE COPY returned to the Secretary at Room 10005, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

COMMITTEE FOR RESEARCH ON HUMAN SUBJECTS (MEDICAL)
Ref: R14/49 Woodiwiss/Norton et al

CLEARANCE CERTIFICATE **PROTOCOL NUMBER** M02-04-72

PROJECT Gene Candidates As Determinants of Blood Pressure And Intermediary Phenotypes In Pathogenesis of Hypertension In Black South Africans

INVESTIGATORS Prof's AJ/G et al Woodiwiss/Norton et al

DEPARTMENT School of Physiology, Wits Medical School

DATE CONSIDERED 02-04-26

DECISION OF THE COMMITTEE *

Approved unconditionally

UNIVERSITY OF THE WITWATERSRAND
2007-05-09
JOHANNESBURG

This clearance is valid and within the Wits 5-year validity

DATE 02-05-14 **CHAIRMAN** ..... (Professor P E Cleaton-Jones)

* Guidelines for written "informed consent" attached where applicable.

c c Supervisor: Prof AJ Woodiwiss
Dept of School of Physiology, Wits Medical School

Work/Research/Applications/07 web/M 02-04-72

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DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10001, 10th Floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

R14/46 Prof Elena Libhaber

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M1604106

NAME: (Principal Investigator)	Prof Elena Libhaber
DEPARTMENT:	School of Clinical Medicine
PROJECT TITLE:	Comparison of the Effect of Diuretic and Calcium Channel Blocker Based Therapy on Central Blood Pressure and Cardiac Abnormalities in Pre-to-Moderate Hypertensives of African Ancestry
DATE CONSIDERED:	28/11/2010 (Initial Approval) 06/05/2016
DECISION:	Approved unconditionally
CONDITIONS:	Renewal Approved Previously M101146 For the Period 01May 2016 -31 May 2021
SUPERVISOR:	
APPROVED BY:	Professor P Cleaton Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	

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

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004, 10th Floor, Senate House/2nd Floor, Phillip Tobias Building, Parktown/University of the Witwatersrand. We fully understand the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.** The date for annual re-certification will be one year after the date of convenor's meeting where the study was initially reviewed. In this case, the study was initially reviewed in April and will therefore be due in the month of April each year.

Principal Investigator Signature _____ Date _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

M10M10

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Elena Libhaber

CLEARANCE CERTIFICATE	**M10M101146**
PROJECT	Comparison of the Effect of Diuretic and Calcium Channel Blocker-Based Therapy on Central Blood Pressure and Cardiac Abnormalities in Pre-to-Moderate Hypertensives of African Ancestry
INVESTIGATORS	Dr Elena Libhaber.
DEPARTMENT	School of Clinical Medicine
DATE CONSIDERED	26/11/2010
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 25/02/2011 CHAIRPERSON .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. I agree to a completion of a yearly progress report.

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M130951

NAME: (Principal Investigator) Mr Moekanyi Jeffrey Sibiya

DEPARTMENT: Physiology
Cardiocascular Pathophysiology and Genomics

PROJECT TITLE: Measured and Imputed (Calculated) Aortic Pulse Pressure (PP) over a 24-Hour Period in a Small African Cohort

DATE CONSIDERED: 27/09/2013

DECISION: Approved unconditionally

CONDITIONS:

SUPERVISOR: Prof Angela Woodiwiss

APPROVED BY:
Professor PE Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 14/10/2013

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

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University
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 resubmit the application to the Committee. **I agree to submit a yearly progress report**

Principal Investigator Signature M130951 Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix 2

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Turnitin Originality Report

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CHAPTER 1 INTRODUCTION: Current Understanding of the Role of Aortic Pulse Pressure and the Determinants Thereof in Cardiovascular Disease 1.1 Introduction Cardiovascular disease constitutes a group of disorders of the heart and blood vessels which often share similar risk factors. These disorders mainly include cerebrovascular disorders or stroke (ischaemic and haemorrhagic), ischaemic heart disease including myocardial infarction, heart failure, peripheral arterial disease and renal failure. As identified in the Global Burden of Disease (GBD 2015) study, cardiovascular disease is a major cause of global mortality and morbidity (Roth et al 2015, GBD 2015), where in 2013 cardiovascular disease contributed to 32% (17 million) of the more than 54 million deaths recorded world-wide. The GBD study was a comprehensive study that accounted for outcomes based on both death registrations, as well as verbal autopsies, and determined mortality for 240 diseases from 188 countries globally from the year 1990 to 2013. Of the four major categories of non-communicable diseases (diabetes mellitus, cardiovascular disease, cancer and chronic obstructive lung disease) cardiovascular disease was noted to be the most common cause of death compared to the other three categories (Roth et al 2015). The GBD study (2015) was limited by the fact that data from low income or developing countries was not readily available. Economic challenges leading to a lack of education and malnutrition play a major role in the epidemiology of non-communicable disease. Therefore, understanding the burden of non-communicable diseases in developing countries is of critical importance. It is essential to note that approximately 80% of cardiovascular deaths in the year 2005 occured in low-to-middle income countries (Mendis et al 2007). When comparing mortality rates between high and low income countries using age standardized methods, the mortality rate attributable to cardiovascular disease in low income countries decreased from 381 per 100 000 people in 1990 to 332 per 100 000 in the year ending 2013 (13% decline) whilst in high income countries, the mortality rate decreased from 283 per 100 000 people in 1990 to 160 per 100 000 in the year ending 2013 (43% decline) (Roth et al 2015). Thus, the decline in mortality rate from cardiovascular

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