Pre-hypertension and Central Aortic Haemodynamics

Hendrik Le Roux Booysen

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ABSTRACT

One quarter of any community may have normal (normal/high-normal) as opposed to optimal or hypertensive blood pressures (BP). These individuals may be at risk for a BP-related cardiovascular event, but do not qualify for BP-lowering therapy as those at risk are difficult to identify. In the present thesis I sought to determine whether aspects of non-invasively determined aortic BP may refine BP-related cardiovascular risk assessment in those with brachial BP values within normotensive ranges.

In 1169 participants from a community sample of African ancestry, 319 (27%) of whom had a normal/high-normal brachial BP, aortic BP was determined from radial tonometry and target organ changes assessed from carotid-femoral pulse wave velocity (PWV)(n=1025), estimated glomerular filtration rate (eGFR) (n=944), and left ventricular mass index (LVMI)(n=690). Normal versus high-normal brachial BP categories failed to differentiate between those participants with a BP above optimal values with versus without multivariate-adjusted target organ changes. However, in those with a normal/high-normal BP with aortic systolic BP (SBP) values that were <95% confidence interval of healthy participants with optimal BP values (45% of those with a normal/high-normal BP), no unadjusted or multivariate adjusted target organ changes were noted. In contrast, those with a normal/high-normal BP with aortic SBP values that exceeded optimal thresholds, demonstrated unadjusted and multivariate adjusted increases in PWV and LVMI and decreases in eGFR ($p<0.05$ to $p<0.005$ after multivariate adjustments). Thus, aortic BP measurements may refine the ability to detect those with a normal/high-normal BP at risk of BP-related cardiovascular damage.

Although indices of aortic wave reflection could enhance risk prediction in normotensives, 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 is uncertain. In participants from a community

sample I assessed the relative contribution 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), and LVMI (n=793). 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 those <50 years of age, while Pb (partial $r=0.28$, $p<0.0001$) contributed more than Pf (partial $r=0.15$, $p<0.001$, $p<0.05$ for comparison of r values), Pa (partial $r=0.13$, $p<0.005$) contributed to a similar extent as Pi (partial $r=0.22$, $p<0.0001$) to variations in LVMI. Further, in those ≥50 years of age, Pb (partial $r=0.21$, $p<0.0001$), but not Pf ($p=0.98$), whilst Pi (partial $r=0.23$, $p<0.0001$), but not Pa ($p=0.80$) were associated with LVMI. Thus, as compared to relations between indices of aortic pressure augmentation and PPc or LVMI, strikingly better relations are noted between aortic wave reflection and PPc or LVMI.

In 1185 participants of a community-based sample, 27% of whom had normal/high-normal BP values, I then determined whether indices of wave reflection enhance the ability to detect cardiovascular damage beyond brachial and aortic BP. In normotensives aortic SBP was associated with LVMI ($g/m^{1.7}$) (n=410, partial $r=0.18$, $p<0.0005$), PWV (n=570, partial $r=0.16$, $p<0.0005$) and eGFR (n=605, partial $r=-0.08$, $p<0.05$) independent of confounders and brachial BP. Similar findings were noted for PPc. In contrast, although Pb was independently associated with LVMI (partial $r=0.22$, $p<0.0001$) and a trend for an effect was noted for eGFR (partial $r=-0.07$, $p=0.08$) independent of confounders and brachial BP, no independent relations were noted with PWV (partial $r=0.06$, $p=0.15$). Similar relations were noted between RI and end-organ changes. The area under the receiver operating curve (AUC) for the detection of left ventricular hypertrophy (LVH)(n=168 of 410 normotensives) showed a greater ability of PPc (AUC=0.68±0.03) and Pb (AUC=0.67±0.03), but not RI (AUC=0.65±0.03) to detect LVH as compared to brachial SBP (AUC=0.60±0.03)

and brachial pulse pressure (PPb) (AUC=0.61±0.03) ($p<0.05$ for comparison of AUC). However, the performance for LVH detection was no greater for Pb than for PPc. Therefore, in normotensives although Pb is better than brachial BP for the detection of end-organ damage, indices of wave reflection do not enhance the ability to detect end-organ changes beyond aortic SBP or pulse pressure (PP).

Although aortic BP may refine the ability to detect normotensives at risk of BP-related cardiovascular damage, the cost of measurement devices precludes the use of this approach in resource-limited settings. I assessed whether aortic BP imputed from simple clinical measures may similarly refine the ability to detect normotensives at risk of BP-related cardiovascular damage. An imputation equation for PPc, incorporating brachial PP, age, mean arterial pressure and pulse rate was identified from multivariate modelling of the factors associated with tonometry-derived PPc in 1179 community participants. Imputed PPc values closely approximated tonometry-derived PPc in all participants of the community-based sample (r^2=0.96, slope=1.00±0.006, mean difference (±2xSD)=1.4±6.2 mm Hg) and in 351 patients from a clinical sample (r^2=0.943, slope=0.96±0.01, mean difference (±2xSD)=-2.17±7.44 mm Hg). In normotensives imputed PPc was associated with LVMI (n=410, partial r=0.17, $p<0.01$) and eGFR (n=605, partial r=-0.15, $p<0.0005$) independent of confounders and brachial BP. Independent relations with end-organ changes were similar for imputed and tonometry-derived aortic BP. The AUC for LVH detection (n=168 of 410 normotensives) showed a greater performance of both imputed (AUC=0.656±0.027) and tonometry-derived (AUC=0.678±0.027) PPc as compared to brachial PP (AUC=0.613±0.028) or brachial systolic BP (AUC=0.595±0.029) ($p<0.05$ for comparisons of AUC). Thus, aortic BP imputed from simple clinical measures closely approximates tonometry-derived aortic BP and refines the ability to detect normotensives at risk of BP-related cardiovascular damage.

In conclusion, in the present thesis I provide a possible solution to the conundrum of how best to identify normotensives who may be at risk of a BP-related cardiovascular event. In this regard I show that tonometry-derived aortic BP may refine the ability to detect cardiovascular damage in normotensives; that although aortic wave reflection largely accounts for the ability of aortic BP to detect end-organ damage better than brachial BP in normotensives, that these effects are no better than aortic BP *per se*; and that aortic BP imputed from simple clinical measures closely approximates tonometry-derived aortic BP and performs as well as tonometry-derived aortic BP in the detection of cardiovascular damage in normotensives.

DECLARATION

I Hendrik Le Roux Booysen declare that the work contained in this thesis 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.

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Hendrik Le Roux Booysen

Signed on……day of ……., 2015

I certify that the studies contained in this thesis have the approval of the Human Ethics Screening Committee of the University of the Witwatersrand, Johannesburg. The ethics clearance number is M02-04-72 renewed as M07-04-69 & M12-04-108.

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Hendrik Le Roux Booysen

Signed on……day of ……., 2015

Prof G. Norton (Supervisor)	Prof A. Woodiwiss (Supervisor)	Prof E. Libhaber (Supervisor)
_____ day of _____ 2015	_____ day of _____ 2015	_____ day of _____ 2015

PUBLICATIONS

The following publications are offered in support of this thesis.

1) Booysen, H. L., Norton, G. R., Maseko, M. J., Libhaber, C. D., Majane, O. H., Sareli, P., & Woodiwiss, A. J. (2013). Aortic, but not brachial blood pressure category enhances the ability to identify target organ changes in normotensives. *Journal of Hypertension* 31(6), 1124-1130. (reprint provided in appendix 2)
2) Booysen, H.L., Woodiwiss, A. J., Moekanyi, J. S., Hodson, B., Raymond, A., Libhaber, E., Sareli, P., Norton, G. R. (2015) Indexes of aortic pressure augmentation markedly underestimates the contribution of reflected waves toward variations in aortic pressure and left ventricular mass. *Hypertension,* 65(3), 540-546 (reprint provided in appendix 3).

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TABLE OF CONTENTS **PAGE**

LIST OF FIGURES **PAGE**

Figure number

Chapter 1

Chapter 2

Chapter 3

Chapter 4

Chapter 5

LIST OF TABLES **PAGE**

Table number

Chapter 1

Chapter 2

Chapter 3

Chapter 4

Chapter 5

LIST OF ABBREVIATIONS

#	=	Female
$	=	Patient Years
+	=	Male
ABI	=	Atherothrombotic Brain Infarction
AIx	=	Augmentation Index
ARIC	=	Artherosclerosis Risk in Communities
AUC	=	Area Under the Receiver Operating Curve
BH	=	Body Height
BMI	=	Body Mass Index
BP	=	Blood pressure
BSA	=	Body Surface Area
BW	=	Body Weight
CA	=	Cardiac Arrest
CAD	=	Coronary Artery Disease
CAFÉ	=	Conduit Artery Function Evaluation
CAS	=	Coronary Artery Stenosis
CCB	=	Calcium Channel Blocker
CD	=	Cardiovascular Death
CHD	=	Coronary Heart Disease
CHF	=	Congestive Heart Failure
Chol	=	Cholesterol
CI	=	Confidence Interval
Circ Sys	=	Circulatory System
cm	=	Centimeter
CO	=	Cardiac Output

con	=	Controlled
CR	=	Cardiac Revascularization
CR	=	Coronary Revascularization
CV	=	Cardiovascular
CVD	=	Cardiovascular Disease
CVE	=	Cardiovascular Event
DASH	=	Dietry Approaches to Stop Hypertension
DBP	=	Diastolic Blood Pressure
Dia or Dp	=	Diastolic
DM	=	Diabetes Mellitus
e.g.	=	For Example
ECG	=	Electrocardiogram
EF	=	Ejection Fraction
eGFR	=	Estimated Glomerular Filtration Rate
ESH	=	European Society of Hypertension
ESRD	=	End Stage Renal Disease
EUROPA	=	European trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease
F(t)	=	Constructed Triangular Flow Wave
g	=	Gram
GFR	=	Glomerular Filtration Rate
GTF	=	Generalized Transfer Function
HA	=	Heart Attack
HAn	=	Hospitalisation for Angina
HbA1c	=	Percentage Glycated Haemoglobin
HCHF	=	Hospitalisation for Congestive Heart Failure
HChol	=	Hypercholesterolemia

HDL	=	High-density Lipoprotein
HF	=	Heart Failure
Hg	=	Mercury
HR	=	Hazards Ratio
Hr	=	Heart Rate
ht	=	Height
HT	=	Hypertension
HYP	=	Hypertensive
IHD	=	Ischemic Heart Disease
IMT	=	Intima Media Thickness
I-P	=	Independent predictor
JNC	=	Joint National Committee
kg	=	Kilogram
LA	=	Left Atrium
LDL	=	Low-density Lipoprotein
LV	=	Left Ventricle
LVEDD	=	Left ventricle internal diameter in end diastole
LVESD	=	Left ventricle internal diameter in end systole
LVH	=	Left Ventricular Hypertrophy
LVM	=	Left Ventricular Mass
LVMI	=	Left Ventricular Mass Index
LVMI-$ht^{1.7}$	=	Left Ventricular Mass Index to the Height of $^{1.7}$
LVMI-$ht^{2.7}$	=	Left Ventricular Mass Index to the Height of $^{2.7}$
m	=	Meter
MAP or Mp	=	Mean Arterial Pressure
MDRD	=	Modification of Diet in Renal Disease
mg	=	Milligram

MI	=	Myocardial Infarction
min	=	Minutes
mls	=	Milliliters
mm	=	Millimeters
mV	=	Millivolts
n	=	Sample size
NHANES	=	National Health and Nutrition Examination Survey
N-P	=	Not an independent predictor
NT	=	Normotensive
NT-proBNP	=	NT-probrain Natriuretic Peptide
Pa	=	Aortic Augmentation Pressure
P(t)	=	Measured Pressured Wave
P2	=	Second Pressure Wave of the Radial Pulse Wave
Pb	=	Backward Wave Pressure
Pf	=	Forward wave pressure
PHARAO	=	Patients with High Normal Blood Pressure
Pi	=	Incident wave pressure
PP	=	Pulse Pressure
PPamp	=	Pulse Pressure amplification
PPb	=	Brachial Pulse Pressure
PPc	=	Central Aortic Pulse Pressure
PR	=	Pulse Rate
PROGRESS	=	Perindropril protection against recurrent stroke study
PVD	=	Peripheral Vascular Disease
PW	=	Pulse Wave
PWA	=	Pulse Wave Analysis
PWED	=	Posterior wall thickness in end diastole

PWES	=	Posterior wall thickness in systole
PWV	=	Pulse Wave Velocity
RAAS	=	Renin-Angiotensin-Aldosterone System
Rand	=	Randomised
RCA	=	Resuscitated Cardiac Arrest
RI	=	Wave Reflection Index
ROC	=	Reciever Operating Characteristics
RR	=	Relative Risk Ratio
SBP	=	Systolic Blood Pressure
SBPb	=	Brachial Systolic Blood Pressure
SBPc	=	Central Aortic Systolic Blood Pressure
SBPc	=	Conventional Systolic Blood Pressure
SD	=	Standard Deviation
sec	=	Second
SEM	=	Standard Error of the Mean
SEPED	=	Septal wall thickness in end diastole
SEPES	=	Septal wall thickness in systole
SOWETO	=	South West Township
SV	=	Stroke Volume
Sys or Sp	=	Systolic
TChol	=	Total Cholesterol
TIA	=	Transient Ischaemic Attack
Trig	=	Triglycerides
TRP	=	Total Peripheral Resistance
VALUE	=	Valsartan antihypertensive long-term use evaluation
VC	=	Vascular Event
vs	=	Versus

WBC	=	White Blood Cell Count
WC	=	Waist Circumference
Zc	=	Characteristic Impedance

PREFACE

At a global level, cardiovascular disease (CVD) accounts for 30% of all deaths worldwide. In the next two decades, the burden of death from CVD across the globe is predicted to occur in low and middle-income countries such as South-Africa. In groups of African ancestry living in Africa, hypertension is the leading cause of CVD. Although most guidelines use a blood pressure (BP) threshold of 140/90 mm Hg for the diagnosis and treatment of hypertension, there is considerable evidence that BP effects on CVD occur at levels well below this threshold. Indeed BP values in the pre-hypertensive range (120-129 systolic BP/80-85 diastolic BP), which occurs in a quarter of any adult population, have repeatedly been demonstrated to predict outcomes. However, as BP lowering to values well below 140/90 mm Hg have failed to consistently improve outcomes, further antihypertensive therapy is not advocated for those with BP values in this range. However, inconsistencies in the ability of antihypertensive therapy to reduce CV outcomes in this BP range may be explained by the marked heterogeneity in CV risk associated with pre-hypertension.

The present thesis was therefore prompted by a need to better identify those of African descent living in Africa with BP values in the pre-hypertensive range at risk of BP-related CV damage. Central aortic BP may be considerably different from brachial BP. Moreover, aortic BP predicts risk independent of brachial BP. Because marked overlap in aortic BP values have been noted across optimal, pre-hypertensive and hypertensive BP ranges, in the present thesis I explored whether various aspects of aortic BP measurement may better detect pre-hypertensives with cardiovascular end-organ changes. In the present thesis I evaluated whether aortic pulse pressure, systolic BP and/or aortic backward wave pressures enhance the ability to detect end-organ changes in a community

sample of black African ancestry living in the South West Township (SOWETO) of Johannesburg, South Africa. I explored with non-invasive measurements of aortic BP derived from applanation tonometry, as well as aortic BP determined using an imputation equation that I identified and applied at no additional cost, may enhance the ability to detect end-organ changes. In support of the value of the findings described in the present thesis, the data presented in chapters 2 and 3 have been published in the *Journal of Hypertension* 31(6), 1124-1130 (Chapter 2)(Booysen et al 2013) and *Hypertension* 65(3), 540-546 (Chapter 3)(Booysen et al 2015) respectively. The data provided in the other chapters are currently in preparation for submission to international journals for review (Chapter 4) or currently under-review (Chapter 5).

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.

Chapter 1

Introduction

Current Understanding and Controversies in Pre-hypertension and Central Aortic Haemodynamics

1.0 Introduction

Cardiovascular disease (CVD) includes a wide variety of clinical conditions such as myocardial infarction (MI) (*ne* coronary heart disease [CHD] or coronary artery disease [CAD]), stroke, heart failure, peripheral vascular disease and renal failure, which often share common risk factors. In 2005, 17.5 million deaths worldwide were attributed to CVD (Mendis et al 2007) and current estimates are that CVD will account for 25 million deaths per year by the year 2020 (Yusuf et al 2001). At a global level, CVD by far exceeds other causes of death, contributing overall to 30% of deaths and this contribution is thought to be increasing every year (Mendis et al 2007). Urbanisation, globalisation and ageing populations are the major causes of the increasing prevalence of CVD. Whilst in the previous century, CVD was mainly a disease of the developed world, presently, of all deaths caused by CVD, 80% occur in low-to-middle income countries (Mendis et al 2007) such as South Africa. What is our current understanding of the contribution of CVD to death rates in South Africa and is there a prevalent risk factor?

In South Africa, CVD is the leading cause of death in the elderly; and the third most common cause of death in younger age groups in rural communities of African ancestry (Tollman et al 2008). Cardiovascular disease probably accounts for substantially more deaths in black African communities in urban areas in South Africa. Current estimates are that hypertensive heart disease is the 2nd, and cerebrovascular disease is the 5th most common cause of death in South Africa (South African Medical Research Council Causes of Death Report, 2014). Hypertension is the most important risk factor for CVD in groups of black African ancestry in South Africa (Rayner 2010). In urban communities of African ancestry in South Africa, hypertension may account for up to a third of heart failure cases (Stewart et al 2008), hypertension is strongly associated with MI (Steyn et al 2005), and hypertension is the major risk factor for strokes (Conner et al 2009, O'Donnell et al 2010).

Hence, a critical target for CVD prevention and consequently prevention of overall death rates in black South African communities is control of blood pressure (BP).

Presently, the diagnosis of hypertension is based on brachial BP thresholds that best predict cardiovascular outcomes and which, when BP is treated to below these targets produce significant decreases in CVD. These thresholds are 140/90 mm Hg, and whilst some recent guidelines advocate higher thresholds for the elderly (Kjeldsen et al 2014), and lower thresholds for many patients with co-morbidities such as diabetes mellitus or renal disease (Kjeldsen et al 2014), these thresholds have been adopted by more recent guidelines and for most patient populations (Kjeldsen et al 2014). However, BP is a continuous trait and several studies have demonstrated that independent of confounders CVD occurs well below these thresholds and that a significant proportion of cardiovascular deaths may occur in the normal (BP=120-129/80-84 mm Hg) or high-normal (BP=130-139/85-89 mm Hg) BP ranges (Hsia et al 2007, Conen et al 2007, Dorjgochoo et al 2009, Qureshi et al 2005, Vasan et al 2001, Blake et al 2003, Liszka et al 2005, Gu et al 2009, Zhang et al 2006, Butler et al 2011, Kshirsagar et al 2006, Lewington et al 2002), that is in the pre-hypertensive BP range. However, intervention studies evaluating the effect of antihypertensive treatment to lower than currently accepted thresholds (140/90 mm Hg) have produced contrasting outcomes (Law et al 2009, Cushman et al 2010, Nissen et al 2004, McMurray et al 2010, Remme et al 2009, Staessen and Jiguang 2001, Yusuf et al 2008, Schrier et al 2002, Trialists Collaboration 2003, Patel 2007, Cooper-DeHoff et al 2010). Hence the current thresholds of 140/90 mm Hg for the diagnosis and treatment of hypertension have remained in recent guidelines (Kjeldsen et al 2014). The consequence is that there may be a considerable number of individuals (one quarter of any community may have BP values in the normal/high-normal range) at risk of a BP-related cardiovascular event whom would not receive antihypertensive therapy. One possible explanation for discrepant results obtained from intervention studies evaluating the effect of antihypertensive treatment to lower than currently accepted thresholds (Law et al 2009, Cushman et al 2010, Nissen et al 2004,

McMurray et al 2010, Remme et al 2009, Staessen and Jiguang 2001, Yusuf et al 2008, Schrier et al 2002, Trialists Collaboration 2003, Patel 2007, Cooper-DeHoff et al 2010), is that not all with a BP below 140/90 and above 120/80 mm Hg (pre-hypertensives) are at risk of a cardiovascular event. The question that obviously arises is whether there is an approach that may be adopted which may identify those who have brachial BP values below 140/90 mm Hg who are at risk of a BP-related cardiovascular event?

Aortic BP is well-recognised as being lower than brachial BP, and because of the proximity of the aorta to cardiovascular target organs it has been hypothesised that aortic BP is more closely associated with cardiovascular damage than brachial BP. Indeed, several studies have shown that aortic BP is associated with end-organ changes (reviewed by Roman and Devereux 2014, Boutouyrie et al 1999, Covic et al 2000, Wang et al 2009, Roman et al 2010, Neisius et al 2012, Norton et al 2012, Wohlfahrt et al 2011) and cardiovascular outcomes (Safar et al 2002, Williams et al 2006, Wang et al 2009, Benetos et al 2010, Benetos et al 2012, Regnault et al 2012, Jankowski et al 2008, Pini et al 2008, Roman et al 2007, Roman et al 2009) better than or independent of brachial BP. In the present thesis I therefore hypothesised that aortic BP may better identify pre-hypertensives at risk of cardiovascular damage (end-organ changes) than brachial BP thresholds (high-normal vs normal). As aortic reflected waves, which contribute to aortic BP, may also be associated with end-organ changes and cardiovascular outcomes independent of brachial BP (Hashimoto et al 2007, Hashimoto et al 2006, Weber et al 2006, Westerbacka et al 2005, Sibiya et al 2014, London et al 2001, Ueda et al 2004, Weber et al 2005, Chirinos et al 2005a & b, Wang et al 2010, Chirinos et al 2012, Weber et al 2012, Zamani et al 2014), I also assessed whether aortic reflected waves may improve on the ability to identify pre-hypertensives at risk of cardiovascular damage (end-organ changes). Prior to conducting the research necessary to evaluate this aim of in the present thesis, I first addressed the question of whether aortic reflected wave function, determined from aortic pressure augmentation or from the magnitude of backward wave pressures is more closely associated with age-related increases in aortic BP and end-

organ damage across the adult lifespan. This question was evaluated as part of the present thesis as there is currently little clarity as to whether aortic augmentation indices do indeed closely approximate aortic reflected wave effects. As the cost of performing aortic BP measurements is presently too high to advocate for routine use in countries such as South Africa, I further evaluated whether aortic BP can be estimated using simple clinical measures and whether imputed aortic BP thresholds also better identify pre-hypertensives at risk of cardiovascular damage (end-organ changes) than brachial BP thresholds (high-normal vs normal).

As the present thesis is designed to answer the question as to whether current approaches to risk prediction can be enhanced in those with a BP in the normotensive range, in the first part of the present chapter I will review the evidence to show that pre-hypertension predicts cardiovascular outcomes, and the evidence from intervention studies evaluating the effect of antihypertensive treatment to lower than currently accepted thresholds (140/90 mm Hg) that have produced discrepant outcomes. I will also discuss the arguments posed to suggest that pre-hypertension may be associated with CVD through mechanisms unrelated to BP or through increases in aortic BP.

As I subsequently addressed the issue of whether aortic BP rather than brachial BP thresholds in pre-hypertension enhance the ability to detect end-organ changes, in the second part of the present chapter I will then review the evidence that aortic BP is associated with end-organ changes and cardiovascular outcomes better than or independent of brachial BP and provide reasons for these possible differences. In this section of the chapter I will highlight the factors that contribute to aortic BP that may not be detected by brachial BP measurements and suggest possible methods of estimating aortic BP that may be cost-effective in low-to-intermediate income countries. In this regard I will highlight the problems with previous studies that have employed these approaches and indicate how in the present thesis I addressed these problems. Importantly the present chapter is designed as a critical review that will lead the reader through a series

of arguments in favour of performing the studies described in the present thesis and will end with a summary of the problem statements and aims of the thesis.

1.2.0 Pre-hypertension and cardiovascular disease

As BP is a continuous trait and BP values as low as 115/75 mm Hg are positively related to cardiovascular outcomes (Lewington et al 2002), the concept of thresholds of BP that define the presence of hypertension and hence an increased risk for cardiovascular events, although necessary for clinical practice, is largely artificial. Indeed, over the past 3-4 decades the definition of hypertension has changed from threshold levels of 160/100 mmHg or even higher to values of 140/90 mm Hg or even lower (Ventura et al 2001). In 2003, the 7th Joint National Committee guidelines on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) acknowledged that those with a BP>120 mm Hg and <140 mm Hg systolic BP (SBP); or >80 mm Hg<90 mm Hg diastolic BP (DBP) were at an increased risk of CVD (Chobanian et al 2003). The JNC 7 called this BP category ‘pre-hypertension’ (Chobanian et al 2003) largely because it is well-recognized that those with pre-hypertension are more likely to develop BP values within hypertensive ranges (Moreira et al 2008) and that the early lowering of BP reduces the chances of progressing to hypertension (Julius et al 2006, Luders et al 2008). However, more recently, the terms normal BP (SBP≥120 mm Hg<130 mm Hg; DBP≥80 mm Hg<85 mm) and high-normal BP (SBP≥130 mm Hg<140 mm Hg; DBP≥85 mm Hg<90 mm) have been employed to replace the term pre-hypertension (Mancia et al 2007).

The classification of normal and high-normal BP categories (pre-hypertension) was specifically designed to increase awareness of those individuals with a BP within this range who should receive advice to adopt a healthier lifestyle, in order to decrease their risk for a cardiovascular event, attenuate the rate of progression to hypertension or prevent hypertension completely and in turn decrease the risk of CVD (Chobanian et al

2003, Mancia et al 2007). However, JNC 7 did not recommend that antihypertensive therapy should be employed in those whose BP lies within the pre-hypertensive range (Chobanian et al 2003). However, the European Society of Hypertension (ESH) recommended antihypertensive therapy even within these BP ranges if overall risk is sufficiently high to warrant even further lowering of BP (Mancia et al 2007). In this respect, the presence of CVD, diabetes mellitus, renal disease, the metabolic syndrome or end-organ changes together with the presence of pre-hypertension was regarded as sufficient reason to initiate antihypertensive therapy (Mancia et al 2007). However, there is still considerable uncertainty as to whether pre-hypertension even in those at a high risk warrants antihypertensive therapy. Indeed, most recent guidelines recognise that drug therapy should only be initiated at or above BP levels of 140/90 mm Hg (Kjeldsen et al 2014). What is the evidence that pre-hypertension is associated with an increased cardiovascular risk and why is there still ongoing debate and uncertainty as to whether pre-hypertension warrants BP lowering with antihypertensive medication?

1.2.1 Pre-hypertension is associated with cardiovascular events

As previously alluded to, evidence derived from large longitudinal studies indicates that a linear relationship exists between BP and cardiovascular (CV) risk (Lewington et al 2002). In this regard, a 2-fold increase in mortality occurs with each 20 mm Hg SBP or 10 mm Hg DBP, or both, increase above BP values of 115/75 mm Hg (Lewington et al 2002). Hence, there is significant evidence that CV risk increases from optimal BP levels (<120/80 mm Hg) to pre-hypertensive ranges. Indeed, several large prospective, observational studies have demonstrated the risk for CVD and death in normal and high-normal BP ranges as compared to optimal BP ranges (Table 1.1) (Vasan et al 2001, Liszka et al 2005, Qureshi et al 2005, Hsia et al 2007, Conen et al 2007, Gu et al 2009, Blake et al 2003, Dorjgochoo et al 2009, Kshirsagar et al 2006, Butler et al 2011,

Table 1.1. Summary of important characteristics of prospective, observational studies evaluating the impact of normal-high normal blood pressures (BP) on cardiovascular outcomes and mortality.

Reference	Blood Pressure Range	N	Median Follow-up	N of events	Outcomes	Result HR / RR (95% CI)	Adjustments
Hsia et al 2007	Normal & High Normal	21 187#	7.7 years	219	CD	HR 1.58(1.12-2.21)	Age, BMI, diabetes
				407	Strokes	HR 1.93(1.49-2.50)	Smoking, High Chol
				351	CHF	HR 1.36(1.05-1.77)	
				442	MI	HR 1.76(1.40-2.22)	
Conen et al 2007	Normal	11 326#	10.2 years	176	CVE	HR 0.61(0.48-0.76)	Age, smoking, drinking,
				85	Stroke	HR 0.74(0.53-1.03)	diabetes, HCL, exercise,
				70	MI	HR 0.50(0.36-0.71)	education, BMI
				37	CD	HR 0.65(0.39-1.06	Treatment regime
				123	CR	HR 0.49(0.38-0.64)	
	High Normal	4 988#		159	CVE	HR 1.0	
				63	Stroke	HR 1.0	
				77	MI	HR 1.0	
				32	CD	HR 1.0	
				140	CR	HR 1.0	
Dorjgochoo et al 2009	Normal & High Normal	26 689	5 years	527	All-Cause Mortality	HR 0.86(0.75-0.99)	Education, waist-to-hip ratio,
				64	Stroke Mortality	HR 1.65(0.98-2.78)	smoking, history of CVD,
				19	CHD Mortality	HR 0.74(0.35-1.57)	history of diabetes

Table 1.1 Continued

Reference	Blood Pressure Range	N	Median Follow-up	N of events	Outcomes	Result HR / RR (95% CI)	Adjustments
Qureshi et al 2005	Normal & High Normal	2 127	9.9 years	24	ABI	RR 2.2(0.5-9.3)	Age, sex, smoking, obesity,
				56	Strokes	RR 2.3(0.8-6.3)	diabetes, HChol, Study
				138	MI	RR 3.5(1.6-7.5)	period
				285	CAD	RR 1.7(1.2-2.4)	
Mainous III et al 2004	Normal	9 087	12.8 years	-	All-cause Mortality	HR 0.82(0.60-1.13)	Age, Race, sex, smoking,
				-	CVD mortality	HR 0.99(0.66-1.50)	BMI, activity, TChol,
	High Normal			-	All-cause Mortality	HR 0.97(0.74-1.27)	diabetes, HF. HA, Stroke
				-	CVD mortality	HR 1.19(0.82-1.71)	
Vasan et al 2001	Normal	3 979	11.1 years	40#	CVE#	HR 1.1(0.6-2.0)	Age, BMI, smoking, TChol,
				96+	CVE+	HR 1.3(1.1-2.3)	Diabetes
	High Normal			72#	CVE#	HR 1.8(1.0-3.1)	
				108+	CVE+	HR 1.6(1.1-2.3)	
Blake et al 2003	Normal	15 215#	8.1 years	-	CVE	HR 1.39(-)	Asprin, Vitamin E, Age,
	High Normal			-	CVE	HR 2.45(-)	BMI, smoking, LDL, HDL,
							diabetes
Liszka et al 2005	Normal	2 708	18 years	-	MI, Stroke, CHF	HR 1.24(0.96-1.59)	Age, race, sex, smoking,
	High Normal			-	MI, Stroke, CHF	HR 1.42(1.09-1.84)	BMI, exercise, TChol,
							diabetes, CHF, MI, stroke

Table 1.1 Continued

Reference	Blood Pressure Range	N	Median Follow-up	N of events	Outcomes	Result HR / RR (95% CI)	Adjustments
Pednekar et al 2009	Normal	56 996	5.5 years	1 921+	Mortality+	HR 0.91(0.84-0.98)	Age, education, religion,
				521+	Circ Sys death+	HR 1.11(0.95-1.29)	Smoking, BMI
				41+	HYP disease death+	HR 0.91(0.55-1.53)	Mother Tongue
				338+	IHD death+	HR 1.19(0.97-1.45)	
				78+	Cerebrovascular death+	HR 1.16(0.78-1.74)	
				392#	Mortality#	HR 0.74(0.65-0.85)	
				80#	Circ Sys death#	HR 0.70(0.52-0.95)	
				12#	HYP disease death#	HR 0.69(0.32-1.47)	
				39#	IHD death#	HR 0.73(0.47-1.14)	
				10#	Cerebrovascular death#	HR 0.51(0.23-1.13)	
	High Normal			1 135+	Mortality+	HR 0.99(0.91-1.07)	
				333+	Circ Sys death+	HR 1.18(0.99-1.39)	
				36+	HYP disease death+	HR 1.26(0.74-2.15)	
				189+	IHD death+	HR 1.11(0.89-1.38)	
				70+	Cerebrovascular death+	HR 1.73(1.15-2.61)	
				337#	Mortality#	HR 0.98(0.85-1.13)	
				87#	Circ Sys death#	HR 1.08(0.80-1.45)	
				14#	HYP disease death#	HR 1.06(0.51-2.21)	
				44#	IHD death#	HR 1.15(0.75-1.78)	
				16#	Cerebrovascular death#	HR 1.19(0.59-2.41)	

Table 1.1 Continued

Reference	Blood Pressure Range	N	Median Follow-up	N of events	Outcomes	Result HR / RR (95% CI)	Adjustments
Gu et al 2009	Normal & High Normal	58 569	10 years	3556	CVD	RR 1.34(1.27-1.42)	Age, sex, education,
				2316	CVD mortality	RR 1.22(1.15-1.30)	smoking, Alcohol, activity,
				634	CHD	RR 1.32(1.16-1.50)	HYP, BMI, history of CVD,
				384	CHD mortality	RR 1.47(1.23-1.75)	diabetes, geographic region,
				2021	Stroke	RR 1.72(1.59-1.86)	Urbanization, anti-
				971	Stroke mortality	RR 1.67(1.50-1.86)	Hypertensive treatment
Zhang et al 2006	Normal & High Normal	2 629	12 years	97	CVD	HR 1.80(1.28-2.54)	Age, Sex, gender, BMI, Waist circumference, LDL Chol, HDL Chol, Trig, activity Smoking, alcohol use
Butler et al 2011	Normal & High Normal	1 765	10 years	-	HF	HR 1.63(1.23-2.16)	Cohort, sex, race, age, BMI History of CAD, smoking Diabetes, LVH, Hr, fasting Glucose, creatinine, albumin, TChol, LDL Chol, HDL Chol, Trig

Table 1.1 Continued

Reference	Blood Pressure Range	N	Median Follow-up	N of events	Outcomes	Result HR / RR (95% CI)	Adjustments
Kshirsagar et al 2006	Normal	2 059	11.6 years	221	CVD	HR 1.69(1.37-2.02)	Center, age, race, sex, BMI,
				192	CHD	HR 1.70(1.35-2.13)	diabetes, smoking, LDL,
				38	Stroke	HR 1.53(0.92-2.54)	education, sport index, Chol
	High Normal	1 279		158	CVD	HR 2.33(1.85-2.92)	medication, fibrinogen, HDL,
				136	CHD	HR 2.44(1.92-3.12)	von Willebrand factor, WBC
				25	Stroke	HR 1.31(0.70-2.45)	

CVE; Cardiovascular event, CR; coronary revascularisation, CD; Cardiovascular death, Chol; Cholesterol, BMI; body mass index, HChol; Hypercholesterolemia, LDL; low-density lipoprotein; HDL; high-density lipoprotein, Trig; Triglycerides, CVD; cardiovascular disease, CHF; congestive heart failure, MI; Myocardial infarction, HYP; hypertensive, ABI; Atherothrombotic brain infarction, CAD; coronary artery disease, HF; Heart failure, HA; Heart attack, TChol; Total cholesterol, CHD; Coronary heart disease, #; Female, +; Male, Circ Sys; Circulatory system, IHD; Ischemic heart disease, HR; Hazard Ratio, RR; Relative risk, Hr; Heart rate, LVH; Left ventricular hypertrophy, WBC; White blood cell count.

Zhang et al 2006). In this regard, in 23 706 women, pre-hypertension predicted CVD including MI, stroke, heart failure and CV death and these relations were noted independent of age, body mass index (BMI), diabetes, high cholesterol concentrations, smoking, drinking and activity level (Hsia et al 2007). Further, in the Framingham Heart Study pre-hypertension predicted an increased incidence of CAD, MI, atherothrombotic brain infarction, cardiovascular death, and congestive heart failure, but not strokes, independent of age, BMI, smoking, diabetes, sex, cholesterol and obesity (Qureshi et al 2005). In the Atherosclerosis Risk in Communities (ARIC) study both normal and high-normal BP predicted an increased risk of CVD, CHD, and strokes independent of many confounding variables (Kshirsagar et al 2006). Moreover, in 38 322 woman free of cardiovascular disease, cancer or other major illness, a high-normal BP was associated with an increased cardiovascular risk (Conen et al 2007). In the 1991 China National Hypertension Survey, after 10 years of follow-up, pre-hypertension was related to an increased risk of CVD (MI, stroke, cardiovascular death) independent from age, sex, education, alcohol, activity, treatment for hypertension, BMI, diabetes, geographic region and urbanization (Gu et al 2009). In the Strong Heart Study, after 12 years of follow-up, pre-hypertensive participants free from CVD at baseline had an 80% increased risk of incident CVD (Zhang et al 2006). Participants with pre-hypertension have also been reported to have a 63% increased risk of incident heart failure as compared to those with an optimal BP (Butler et al 2011). Pre-hypertension in a United States cohort was similarly associated with major cardiovascular events independent of any other cardiovascular risk factor (Liszka et al 2005). Importantly, the risk for CVD appears to be stronger in the high-normal as compared to the normal BP range (Vasan et al 2001). Indeed, in Chinese woman, after a five year follow-up period, a high-normal, but not a normal BP was associated with stroke mortality (Dorjgochoo et al 2010). Moreover, the predictive value of pre-hypertension for cardiovascular events is additive to that of inflammation as assessed from C-reactive protein concentrations (Blake et al 2003).

Have all studies demonstrated that pre-hypertension is associated with the risk of CVD? In the NHANES II (National Health and Nutrition Examination Survey) and NHANES II Mortality Study, pre-hypertension was not associated with an increased risk of all-cause mortality or cardiovascular disease (Mainous III et al 2004). Furthermore, in a study conducted in Mumbai, India in 56 996 participants, although hypertension was, a normal and high normal BP were not associated with all-cause mortality, circulatory system related death, death caused by hypertension, or ischemic heart disease (Pednekar et al 2009). However, in this study a high normal but not normal BP was related to an increased risk of deaths caused by cerebrovascular disease (Pednekar et al 2009).

1.2.2 Does the treatment of pre-hypertension with antihypertensive therapy reduce cardiovascular event rates?

A higher level of evidence to support a role for pre-hypertension as a cause of CVD would come from intervention studies where the impact on CVD is assessed when BP is decreased to values considered to be lower than what would normally be achieved if the target was 140/90 mm Hg. These studies have been summarised in Table 1.2 (Law et al 2009, Cushman et al 2010, Nissen et al 2004, McMurray et al 2010, Remme et al 2009, Staessen and Jiguang 2001, Yusuf et al 2008, Schrier et al 2002, Trialists Collaboration 2003, Patel 2007, Cooper-DeHoff et al 2010).

Several studies have reported on the impact of BP lowering in hypertensives to values considered far lower than current thresholds. In this regard, in a meta-analysis of 29 randomised clinical trials consisting of 162 341 participants, the authors noted that irrespective of baseline BP the greater the reduction of BP to values far below current BP thresholds of 140/90 mm Hg, the greater the decrease in the risk of all major cardiovascular events (Trialists Collaboration 2003). Moreover, in a further randomised, controlled trial, a significant reduction

Table 1.2. Characteristics of intervention studies where the impact of blood pressure BP lowering to values well below current thresholds for the diagnosis of hypertension on cardiovascular outcomes and mortality were assessed.

Authors **(Population Group)**	**Sample size**	**Study design**	**Duration Follow-up**	**Average drop in BP (Sys/Dia mm Hg)**	**BP Achieved (mm Hg)**	**Result**	**Outcome evaluated**	**Adjustors**
Law et al 2009 (No CVD, Normotensive)	464 000	Rand trials	-	6/3	<120 Sys <80 Dia	Reduced risk	CHD, Stroke	BP reduction
Cushman et al 2010 (Type 2 diabetics, normotensive)	4 733	Rand trial	5 years	19.9 Sys	<120 Sys	No effect on risk	MI, Stroke, Death	Unadjusted
Nissen et al 2004 (With CAD, normotensive)	1991	Double blind Rand con trial	2 years	4.85/2.45	<125 Sys <80 Dia	Reduced risk	CD, MI, CR, HAn HCHF, Stroke, PVD	Unadjusted
McMurray et al 2010 (Impaired Glucose Tolerance & one CV risk factor, normotensive)	9 306	Double blind Rand trial	5 years	6.3 Sys	<130 Sys <80 Dia	No effect on risk	CD, MI, Stroke, HCHF CR, Han	Unadjusted
Remme et al 2009 (With CAD, normotensive)	12 218	Double blind Rand trial	4.2 years	5/2	<120 Sys <80 Dia	Reduced risk	CD, MI, RCA	Start SBP, age, sex, diabetes Treatment Regime
Staessen and Jiguang 2001 (History of Stroke or TIA, normotensive)	1 587	Double blind Rand trial	4 years	9/4	<130 Sys <80 Dia	Reduced risk	Stroke, VE, Mortality	Unadjusted

Table 1.2. Continued

Authors **(Population Group)**	**Sample size**	**Study design**	**Duration Follow-up (Average)**	**Average drop in BP (Sys/Dia mm Hg)**	**BP Achieved (mm Hg)**	**Result**	**Outcome evaluated**	**Adjustors**
Yusuf et al 2008 (Ischemic Stroke, normotensive)	3 413	Two-by-two Factorial	2.5 years	8.3 Sys	<130 Sys	No effect on risk	Stroke, CVE	Age, diabetes Treatment Rankin scale
Schrier et al 2002 (Normotensive diabetics)	480	Rand con trial	5.3 years	10 Dia	<130 Sys <80 Dia	Reduced risk	Stroke	Unadjusted
Trialists Collaboration 2003 (Hypertensive)	162 341	Rand con Trial	700 000 $	various	various	Reduced risk	Stroke, CHD, HF, CVE CD, Total mortality	Unadjusted
Patel 2007 (Type II Diabetics, hypertensive & Normotensive)	4 567 NT	Rand con Trial	4.3 years 24 005 $	5.6/2.2	various	Reduced risk	CVE, Deaths	Unadjusted
Cooper-DeHoff et al 2010 (With diabetes & CAD, Hypertensive)	6400	Prospective, Rand trial	16 893 $	22.5 Sys	<130 Sys	Reduced risk below 110 mm Hg	All-cause mortality MI & Stroke	Age, race, sex, history of MI, HF

Rand; Randomised, $; Patient years, con; Controlled, Sys; Systolic, Dia; Diastolic, MI; Myocardial Infarct, CD; Cardiovascular death, HAn; Hospitalisation for Angina, HCHF; Hospitalisation for congestive heart failure, PVD; Peripheral vascular disease, CHD; Coronary heart disease, RCA; Resuscitated cardiac arrest, SBP; Systolic blood pressure, VC; Vascular event, LVH; Left ventricular hypertrophy, HF; Heart failure, CVE; Cardiovascular events, TIA; Transient ischaemic attack. NT; Normotensive

in mortality was only evident among patients with a SBP below 110 mm Hg (Cooper-DeHoff et al 2010).

With respect to studies specifically reporting on the impact of antihypertensive therapy in normotensive participants, in the largest meta-analysis conducted to-date, a 10 mm Hg drop in SBP and a 5 mm Hg drop in DBP reduced the risk of CHD and stroke across all BP ranges including NT ranges (Law et al 2009). In the “Perindopril Protection Against Recurrent Stroke Study” (PROGRESS), antihypertensive treatment reduced the risk of stroke in hypertensive and non-hypertensive participants (Staessen and Jiguang 2001). In a small study conducted in 480 diabetic pre-hypertensive participants, where DBP was decreased by more than 10 mm Hg, therapy reduced the incidence of stroke, but not MI, congestive heart failure (CHF), CHD, or all-cause mortality (Schrier et al 2002). Furthermore, in normotensives, perindopril in the “European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease’’ (EUROPA) study reduced the risk of cardiovascular death, non-fatal MI and cardiac arrest in patients with a history of CHD (Remme et al 2009). In the EUROPA study, the greatest risk reduction in cardiovascular events from anti-hypertensive treatment was noted in patients with BP values in the optimal range (<120/80 mm Hg) (Nissen et al 2004). In addition, in pre-hypertensive participants, a BP reduction of ±5/2.5 mm Hg was reported to reduce all cardiovascular events (angina, strokes, CHF, MI) (Nissen et al 2004). Moreover, in normotensive and hypertensive type 2 diabetic participants, treatment with anti-hypertensive agents for an average of 4.3 years resulted in a reduction in major vascular events (coronary events, cerebrovascular events, renal events, eye events) and cardiovascular deaths irrespective of baseline BP (Patel 2007).

In contrast to the evidence to suggest that lowering BP well below 140/90 mm Hg produces benefits, several studies nevertheless show a lack of risk reduction with antihypertensive therapy in the pre-hypertensive range (McMurray et al 2010, Yusuf et al 2008, Cushman et al 2010). In this regard, in pre-hypertensives, BP lowering for 5 years showed no risk reduction for MI, cardiovascular death, strokes, angina, heart failure and

arterial revascularization (McMurray et al 2010). Further, in a relatively short follow-up study of 2.5 years, antihypertensive treatment failed to reduce recurrent strokes or major cardiovascular events in the normotensive BP range (Yusuf et al 2008). Moreover, in those in whom BP was reduced to below 120/80 mm Hg, the same risk for major cardiovascular events was noted as compared to participants in whom BP was lowered to below 140/90 mm Hg (Cushman et al 2010).

Thus, meta-analyses of several clinical studies provide evidence that there may be significant benefits derived from decreasing BP no matter what the initial BP category and that the benefit may occur in those where the initial BP values are well within the pre-hypertensive range. However, although some randomised, controlled, clinical trials support the notion that decreasing BP to values that would be considered well below current BP thresholds provide benefits (Nissen et al 2004, Remme et al 2009, Staessen and Jiguang 2001, Schrier et al 2002, Patel 2007, Trialists Collaboration 2003, Law et al 2009, Cooper-DeHoff et al 2010), not all intervention studies show the same benefit. Indeed, several trials do not support a role for BP as a cause of CVD in pre-hypertension (Yusuf et al 2008, Cushman et al 2010, McMurray et al 2010). Thus, several intervention studies suggest that brachial BP in the pre-hypertensive range may not be a factor involved in contributing significantly to overall CV risk in these individuals. However, one must consider that intervention studies in pre-hypertension have been conducted over relatively short periods and hence there still remains the possibility that longer periods of BP reduction may have uncovered beneficial effects on CVD in those studies that failed to show benefit.

1.2.3 Impact of lifestyle modification on pre-hypertension and cardiovascular disease in pre-hypertension.

Several studies show that modifying lifestyle with exercise, weight loss and dietary changes lowers BP in pre-hypertension. In this regard, the Dietary Approaches to Stop

Hypertension (DASH) trial showed that a healthy diet of fruits, vegetables and dairy products lowered BP by 5.5/3.0 (SBP/DBP) mm Hg overall and 3.5/2.1 mm Hg in pre-hypertensives (Appel et al 1997). Further, in 2082 ethnically diverse pre-hypertensives, therapeutic lifestyle changes including exercise, nutritional changes, weight management, stress management and smoking cessation decreased SBP by 7 mm Hg and DBP by 6 mm Hg (Bavikati et al 2008). Importantly however, do lifestyle-related BP changes translate into a decreased CVD in pre-hypertension? In this regard, in a 10-15 year follow-up study, decreasing sodium intake reduced the risk of CVD including MI, stroke and CV related death in middle-aged pre-hypertensives (Cook et al 2007). Whether these benefits of salt reduction could be attributed to a decrease in BP is nevertheless uncertain (Cook et al 2007). Considering that the benefits of salt reduction on CVD are thought to be largely attributed to BP effects, we assume that BP did indeed explain the benefits of salt reduction on BP. However, why BP lowering with a reduced salt intake reduces CV risk in pre-hypertensives (Cook et al 2007), whereas BP lowering with antihypertensive therapy is unable to achieve risk reduction in some studies (Yusuf et al 2008, Cushman et al 2010, McMurray et al 2010) remains unexplained.

1.2.4 Other non-blood pressure-related factors could account for an increased cardiovascular risk in pre-hypertension?

If brachial BP indeed does not account for CV risk in pre-hypertension, what then may contribute toward the well-described increased CV risk in the normal-high normal BP range? Several studies provide consistent evidence that pre-hypertension is associated with CV risk factors other than BP levels above optimal values. These risk factors include obesity, dyslipidaemia and diabetes mellitus. In this regard, the National Health and Nutrition Examination Survey (NHANES) 1999-2000 study demonstrated that 64% of individuals with pre-hypertension had at least one other concomitant CV risk factor (Greenlund et al 2004). In the same study in those older than 60 years of age with pre-

hypertension, 94% of participants had at least one other concomitant CV risk factor (Greenlund et al 2004). In the NHANES II mortality study, 90% of pre-hypertensives had at least one other CV risk factor (Mainous III et al 2004). In 36 424 participants, in whom 51% males and 36% females had pre-hypertension the pre-hypertensives had higher blood concentrations of glucose, low-density lipoprotein (LDL) cholesterol, total cholesterol, and triglycerides, lower high-density lipoprotein (HDL) cholesterol concentrations, and a higher BMI (Grotto et al 2006). Moreover, after 12 years of follow-up, participants with pre-hypertension developed more diabetes mellitus as compared to participants with optimal BP levels (Zhang et al 2006).

Inflammatory markers associated with an enhanced risk of CVD also increase in pre-hypertension (King et al 2004, Chrysohoou et al 2004). Indeed, in the NHANES III and ATTICA epidemiological studies, (in the ATTICA study participants were enrolled from the Attica area of Greece), higher blood concentrations of C-reactive protein (King et al 2004, Chrysohoou et al 2004), tumour necrosis factor-α, amyloid-α, and homocysteine and higher white blood cell counts (Chrysohoou et al 2004) were noted in pre-hypertensives as compared to those with optimal BP levels. Thus, there is considerable evidence to suggest that the association between pre-hypertension and CVD may be through other risk factors. Is there evidence to show that pre-hypertension is indeed associated with cardiovascular damage or CVD through associations with risk factors other than BP?

1.2.5 Associations between pre-hypertension and cardiovascular damage may be accounted for by risk factors other than blood pressure.

Work from our group was the first to show that although marked cardiovascular end-organ changes are noted in pre-hypertension, that these changes do not persist when adjustments for risk factors other than BP are made in multivariate regression models (Norton et al 2008). Although subsequent studies suggest that risk factors other than BP do not fully account for end-organ changes in pre-hypertension, the quality of office BP

measurements was not reported in that study (Kim et al 2011). In contrast, we have reported high quality office BP measurements employed to define pre-hypertension (Norton et al 2008, Woodiwiss et al 2009). Our laboratories data (Norton et al 2008) therefore provided a possible explanation as to relationships between pre-hypertension and cardiovascular damage that may not be modified by BP lowering therapy. However, evidence to suggest that relationships between pre-hypertension and CVD can be explained by associated risk factors is missing. Previously described relationships between pre-hypertension and CVD have largely been adjusted for confounding variables including associated risk factors (Table 1.1), but only one study adjusted for the increases in inflammatory markers that may be noted in pre-hypertension. Further, as discussed in section 2.3 why BP lowering with a reduced salt intake reduces CV risk in pre-hypertensives (Cook et al 2007), whereas BP lowering with antihypertensive therapy is unable to achieve risk reduction in some studies (Yusuf et al 2008, Cushman et al 2010, McMurray et al 2010) remains unexplained.

1.2.6 Pre-hypertensives have aortic blood pressures that lie within hypertensive or optimal BP ranges.

An alternative explanation for the relationship between pre-hypertension and CVD which cannot consistently be modified through BP lowering therapy is that considerable overlap occurs in aortic BP across categories of optimal, pre-hypertensive (normal or high-normal) and hypertensive BP ranges (McEniery et al 2008). In this regard, as shall be discussed in the following sections of the present chapter, aortic SBP may be considerably lower than brachial SBP and possibly because of the closer proximity of the aorta as opposed to the brachial artery to cardiovascular target organs, aortic BP has been demonstrated in several populations to predict outcomes better than brachial BP (Safar et al 2002, Roman et al 2007, Roman et al 2009, Jankowski et al 2008, Pini et al 2008, Wang et al 2010, Benetos et al 2010, Regnault et al 2012, Benetos et al 2012). As a

significant proportion of pre-hypertensives may have aortic SBP values within the range normally found in hypertensives (McEniery et al 2008), these individuals may be at a high risk of CVD. In contrast, as a significant proportion of pre-hypertensives may have aortic SBP values within the range normally found in individuals with optimal BP levels (McEniery et al 2008), these individuals may be at a low risk of CVD. Hence, the use of brachial BP to risk stratify in pre-hypertensives may be inaccurate. Further, the impact of antihypertensive therapy on aortic as compared to brachial BP may differ (Agabiti-Rosei et al 2007). Thus when lowering brachial BP in pre-hypertensives with antihypertensive therapy, the effect on those BP values that may be responsible for cardiovascular end-organ changes (aortic BP) may not be accurately predicted from brachial BP changes.

As considerable overlap occurs in aortic BP across categories of optimal, pre-hypertensive (normal or high-normal) and hypertensive BP ranges (McEniery et al 2008) and because aortic rather than brachial BP may be more representative of BP values responsible for cardiovascular damage (Safar et al 2002, Roman et al 2007, Roman et al 2009, Jankowski et al 2008, Pini et al 2008, Benetos et al 2010, Wang et al 2009, Regnault et al 2012, Benetos et al 2012), **in the present thesis** I first hypothesised that *aortic BP values may better identify pre-hypertensives with cardiovascular damage*. In this regard, in chapter 2 I describe these data which have been published in the *Journal of Hypertension* (Booysen et al 2013). As I was able to show that aortic BP best identified pre-hypertensives with end-organ changes, I subsequently evaluated whether these effects are attributed to aortic reflected waves (Chapter 4). This question was addressed in order to try and identify whether aortic reflective wave indices may further refine the ability to identify end-organ changes and hence possibly cardiovascular risk in pre-hypertension.

As a consequence of the aforementioned questions that have been addressed in the present thesis, in the following section of this chapter I will subsequently review the evidence to show that aortic BP may be more closely associated with, or a better predictor of cardiovascular damage than brachial BP, or may be associated with or predict

cardiovascular damage independent of brachial BP. Furthermore, I will then review the evidence to suggest that aortic reflected wave indices may further risk stratify and the evidence to indicate whether antihypertensive therapy reduces forward or reflected wave pressures. In the process of reviewing this evidence I will highlight current controversies as to the role of forward and reflected waves in contributing to aortic BP and cardiovascular damage and describe how, in the present thesis, I addressed these issues prior to assessing whether the use of reflected wave indices further refine the ability to identify end-organ changes in pre-hypertension (Chapter 3). In this regard, this work has resulted in the acceptance of a paper in the journal *Hypertension* (Booysen et al 2015), to be published in March 2015 (see reprint in appendix 3). Finally, as the devices for non-invasive aortic BP measurement are presently far too expensive for routine use at a primary healthcare level in most African countries including South Africa, I also evaluated whether an equation that employs simple clinical measurements can be derived that may closely approximate aortic BP (Chapter 5) and whether this imputation equation may be applied to pre-hypertensives to better identify end-organ damage (Chapter 5). In this regard, data on the derivation of the imputation equation for aortic BP are presently under review for consideration of publication in the journal *PLoS One*. Hence, in the following section of this chapter I will also review the evidence to suggest that an equation that employs simple clinical measurements can be derived that may closely approximate aortic BP, and the evidence to show that such equations may be useful in cardiovascular risk prediction.

1.3.0 Aortic versus brachial blood pressure.

Several large population-based studies have demonstrated that the most important risk factor for hypertension, that is advancing age, is associated with linear increases in SBP across the adult lifespan (Franklin et al 1997, US National Health Survey 1977, Burt et al 1995). In contrast, DBP increases until 50 years of age and then begins to decline

thereafter (Franklin et al 1997, US National Health Survey 1977, Burt et al 1995). These data (Franklin et al 1997, US National Health Survey 1977, Burt et al 1995) raise the question of whether SBP or DBP are more important in risk prediction. In comparison to DBP, the Framingham Heart Study showed in 5127 participants with a follow-up duration of 14 years, that SBP is a stronger predictor of cardiovascular risk than DBP (Kannel et al 1971). In this regard, consistent with age-related changes in SBP and DBP most evidence points toward SBP being more important than DBP in cardiovascular risk prediction in the middle-aged to elderly, whilst DBP tends to be more important than SBP in young adults (Chobanian et al 2003, Mancia et al 2007). However, the only reason why in young adults DBP may be more important than SBP when risk predicting is because brachial SBP in young adults considerably overestimates aortic SBP (McEniery et al 2008), the BP which is thought to be responsible for cardiovascular damage. Indeed there is substantial evidence that aortic SBP may be markedly lower than brachial SBP, but that with ageing, aortic SBP may begin to approximate brachial SBP (McEniery et al 2008). Therefore, there is generally a consensus that SBP rather than DBP is the BP that is responsible for cardiovascular damage and that aortic SBP may be more important than brachial SBP when risk predicting.

In contrast to SBP which increases from the aorta to the brachial artery, neither DBP nor mean arterial pressure (MAP) differ to any substantial degree across this large artery bed (Nichols et al 2011). As SBP, but not DBP increases from the aorta to the brachial artery, the main change in BP from the aorta to the brachial artery is an increase in pulse pressure (PP)(PP=SBP-DBP). Hence BP or PP is amplified from the aorta to the brachial artery (PP amplification)(Nichols et al 2011). The question that arises is what evidence supports a closer or independent relationship between aortic as compared to brachial BP with cardiovascular damage? Furthermore, why is aortic SBP lower than brachial SBP and what determines increases in aortic, but not brachial BP and hence a decrease in PP amplification with ageing?

1.3.1 What evidence supports a closer or independent relationship between aortic as compared to brachial blood pressure and cardiovascular damage?

Several studies provide the evidence to support the view that aortic BP is associated with cardiovascular end-organ changes better than or independent of brachial BP (Boutouyrie et al 1999, Covic et al 2000, Wang et al 2009, Roman et al 2010, Neisius et al 2012, Norton et al 2012, Wohlfahrt et al 2011) and this topic has been extensively reviewed by Roman and Devereux (2014). Furthermore, 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, Wang et al 2009, Benetos et al 2010, Benetos et al 2012, Regnault et al 2012, Jankowski et al 2008, Pini et al 2008, Roman et al 2007, Roman et al 2009)(Table 1.3).

Most of the earlier studies provided the evidence that beyond brachial BP, central aortic PP or SBP or PP amplification were predictors of CV events. 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 & 2009)(Table 1.3). In contrast however, in female hypertensives, brachial, but not central aortic BP predicted CV outcomes (Dart et al 2006)(Table 1.3). This study (Dart et al 2006) has nevertheless been criticised for the use of inaccurate mean arterial pressures as applied to central pressures. In a meta-analysis of these studies published at that time (Table 1.3)(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 (p=0.057). This meta-analysis however, included the study by Dart et al (2006) which, as mentioned, employed inaccurate mean arterial pressures, and 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

Table 1.3. Characteristics of studies comparing the impact of central aortic to brachial blood pressures on cardiovascular outcomes or mortality.

Authors	Sample size	Study design	Duration (median follow-up)	Outcomes evaluated	Result	Adjustors
Safar et al 2002	180	Prospective	52 months	All-cause mortality	PPamp is an I-P	Age, Time on dialysis, previous CVE
Williams et al 2006	2 073	Prospective	3 years	CVE and CV procedures	PPc is an I-P	Age, baseline risk factors
Wang et al 2009	1 272	Longitudinal	10 years	All-cause mortality & CD	PPc is an I-P	Age, sex, Hr, BMI, smoking, Glucose, Chol:HDL ratio, PWV, LVM, IMT, eGFR
Mitchell et al 2010a	2 232	Prospective	7.8 years	MI, Angina, HF, Stroke	Aortic BP is N-P PPamp is N-P	Age, sex, SBPb, treatment, TChol, HDL, smoking, diabetes
Benetos et al 2010	125 151	Epidemilogical	12 years	All-cause mortality and CD	PPamp is an I-P	Age, sex, smoking, activity, Cholesterol, diabetes, pulse rate
Benetos et al 2012	1 126	Prospective	2 years	Mortality, CVE	PPamp is an I-P	Age, activity, BMI, sex, Charlson comorbidity index, previous CVD, treatment, MAP, Hr
Regnault et al 2012	125 121	Prospective	12 years	All-cause mortality & CD	PPamp is an I-P	Age, Height, weight, smoking, Activity, cholesterol, diabetes, Heart rate, sex
Chirinos et al 2012	5 960	Prospective	7.61 years	CVE, CHF	PPamp is N-P	Race, treatment, TChol, HDL, Smoking, heart rate, eGFR, sex, SBP, DBP, diabetes, BH, BW, treatment
Jankowski et al 2008	1 109	Prospective	4.5 years	CR, MI, HF, CD, Stroke, CA, Heart Transplant	PPc is an I-P	Age, sex, EF, CAS, HF, Hr, risk factors, CV history, GFR Drug Treatment
Pini et al 2008	864	Prospective	8 years	Fatal & Non -fatal CVE	PPc is an I-P	Age, sex

Table 1.3. Continued.

Authors	Sample size	Study design	Duration (median follow-up)	Outcomes evaluated	Result	Adjustors
Roman et al 2007	3 520	Longitudinal	4.8 years	MI, Stroke, CHF, CHD, CD	PPc is an I-P	Age, sex, smoking, BMI, TChol:HDL, serum creatinine Fibrinogen, diabetes, HR
Roman et al 2009	2 405	Longitudinal	5.6 years	MI, Stroke, CHF, CHD	PPc is an I-P	Age, sex, smoking, BMI, TChol:HDL, serum creatinine Fibrinogen, diabetes, Hr
Dart et al 2006	484	Prospective	4.1 years	MI, CR, HF, cerebral or coronary Occlusion, stroke, TIA	PPc is N-P	Age, Chol, smoking
Vlachopoulos et al 2010	5 648	Longitudinal	3.75 years	MI, Stroke, CR, CD, All-cause mortality	PPc is N-P	Meta-Analysis

PPc; Central aortic pulse pressure, CVE; Cardiovascular events, I-P; Independent predictor, N-P; Not an independent predictor, CV; Cardiovascular, BP; Blood pressure, PPamp; Pulse Pressure Amplification, Pb; reflected wave magnitude, SBPb; Brachial Systolic Blood Pressure, MI; Myocardial infarction, HF; Heart failure, CR; Cardiac revascularization, TChol; Total cholesterol, HDL; High-density lipoprotein, CD; Cardiovascular death, BMI; Body mass index, CVD; Cardiovascular disease, MAP; Mean arterial pressure, CHF; Congestive heart failire, eGFR; Estimated Glomerular Filtration Rate, BH; Body height, BW; Body weight, CA; Cardiac arrest, EF; Ejection fraction, CAS; Coronary artery stenosis, Hr; Heart rate, GFR; Glomerular Filtration Rate, TIA; Transient ischemic event, Chol; Cholesterol, PWV; Pulse wave velocity, LVM; Left ventricular mass, IMT; Intima-media thickness

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. When excluding the study by Dart et al (2006), the meta-analysis did indeed show that central aortic BP predicted CV events beyond brachial BP. Nevertheless, the Framingham Heart Study, which was similarly not published at the time of the meta-analysis, demonstrated that neither aortic BP, nor PP amplification offered an ability to risk predict beyond brachial BP (Mitchell et al 2010a)(Table 1.3). However, in the Framingham Heart Study, in contrast to the expected 5-15 mm Hg difference between aortic and brachial BP (PP amplification), little difference was noted across the adult lifespan (Mitchell et al 2010b). This has been explained on the basis of the application of tonometry at a site where the principles of tonometry cannot be achieved (brachial artery to calibrate the carotid artery pulse) and the use of an inaccurate mean pressure for calibrating carotid artery pressures (O'Rourke et al 2010). In this regard, the brachial artery, with tendon aponeurosis superficial to it, and with no bone to support it, cannot be reliably applanated, so that the theory of Drzewiecki et al (1983), cannot be relied upon. This error resulted in an assumption that little carotid to brachial amplification occurs, but that marked brachial-to-radial amplification occurs. In contrast, several additional studies have demonstrated that a decreased PP amplification provides strong prognostic information beyond brachial BP (Benetos et al 2010, Regnault et al 2012, Benetos et al 2012)(Table 1.3). However, in these studies aortic BP itself failed to show an ability to risk predict beyond brachial BP (Benetos et al 2010, Regnault et al 2012, Benetos et al 2012)(Table 1.3). Nevertheless, a further recent study (Chirinos et al 2012), although demonstrating a strong relationship between aortic reflected waves and cardiovascular outcomes, failed to show a stronger relationship between PP amplification and cardiovascular outcomes (Table 1.3).

In order to understand how increases in aortic SBP or PP, or decreases in PP amplification could enhance cardiovascular risk prediction beyond brachial SBP, and why some but not other studies may show an ability to enhance risk prediction, It is essential

that an understanding of the factors that result in variations in aortic, but not brachial SBP and hence the determinants of decreases in PP amplification is gained. The critical question is what are the factors which determine variations in these differences?

1.3.2 What explains the variability in the difference between aortic and brachial systolic blood pressures?

The evolution of arterial pulse wave analysis has largely driven our understanding of differences between aortic and brachial BP. In this regard an excellent historical context has been provided by Nichols et al (2011) in McDonald's textbook. Briefly, the first paper to establish many of the properties of propagated and reflected waves was published in a monograph entitled 'Wellenlehre' in 1825 by the Weber brothers (WE and EH Weber, physicist and physician respectively) (Nichols et al 2011). The first recording of the human pulse occurred in 1855 and involved a lever placed over the radial artery, which was attached to a pencil dipped in Indian ink (Nichols et al 2011). Changes in the contour of the arterial pressure pulse wave with age and in hypertension were first described by the physicians Marcy (1863) and Mahomed (1872) (Nichols et al 2011). This was followed by the publication of experimental work on wave propagation by Moens in a monograph in 1878 (Nichols et al 2011). Unfortunately, with the introduction of the cuff sphygmomanometer in 1896, the changes observed in the characteristics of arterial pressure waves with age and elevated blood pressure, were largely forgotten. Nevertheless, in the early 1900's manometers measuring pulsatile pressure were developed and principles that underpin these technique are still used today as standard clinical measurement tools (Nichols et al 2011). Luminaries such as Carl Wiggers and William Hamilton together with Otto Frank developed improved manometers with an increased sensitivity and these early manometers again sparked interest in wave reflection throughout the arterial tree (Nichols et al 2011). Indeed, in 1899, Frank held the view that the arterial pressure pulse has a basic pattern on which was superimposed a

damped oscillation which was created by wave travel and reflection hence generating a type of resonance (Nichols et al 2011). Despite the focus on systolic and diastolic blood pressure values, as a consequence of the introduction of the cuff sphygmomanometer, and hence the failure to take into account the characteristics of pressure waves, during the 1950's, McDonald took interest in the pulsatile pressure-flow relations, which at the time were largely based on the Windkessel theory (Nichols et al 2011). In this regard the Windkessel theory states that pressure rises as blood is pumped into the vessels (Nichols et al 2011). The Windkessel theory has caused much controversy as this theory, although useful for calculating stroke volume, is inadequate to predict instantaneous flow rate (Nichols et al 2011). In comparison, arterial input impedance better describes the relationship between aortic pressures and flow (Nichols et al 2011). By the 1960's the arterial pulse was accurately measured and by the mid-1960's the principles were incorporated in physiology textbooks (Nichols et al 2011). Based on the principles of arterial pulse wave analysis, the mechanisms explaining differences in aortic and brachial blood pressure soon began to emerge. What is the current state of knowledge with respect to the understanding variations in these differences?

As the aorta stiffens through structural alterations, a change largely explained by ageing effects, but which may also be produced by the chronic effects of hypertension, smoking, diabetes mellitus, dyslipidaemia and chronic inflammation, 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 is a complex process that is thought to involve 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) (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), which is determined by stroke volume and hence left ventricular contractility as well as aortic impedance, increases as the aorta stiffens. Whilst aortic stiffness may increase, especially with the

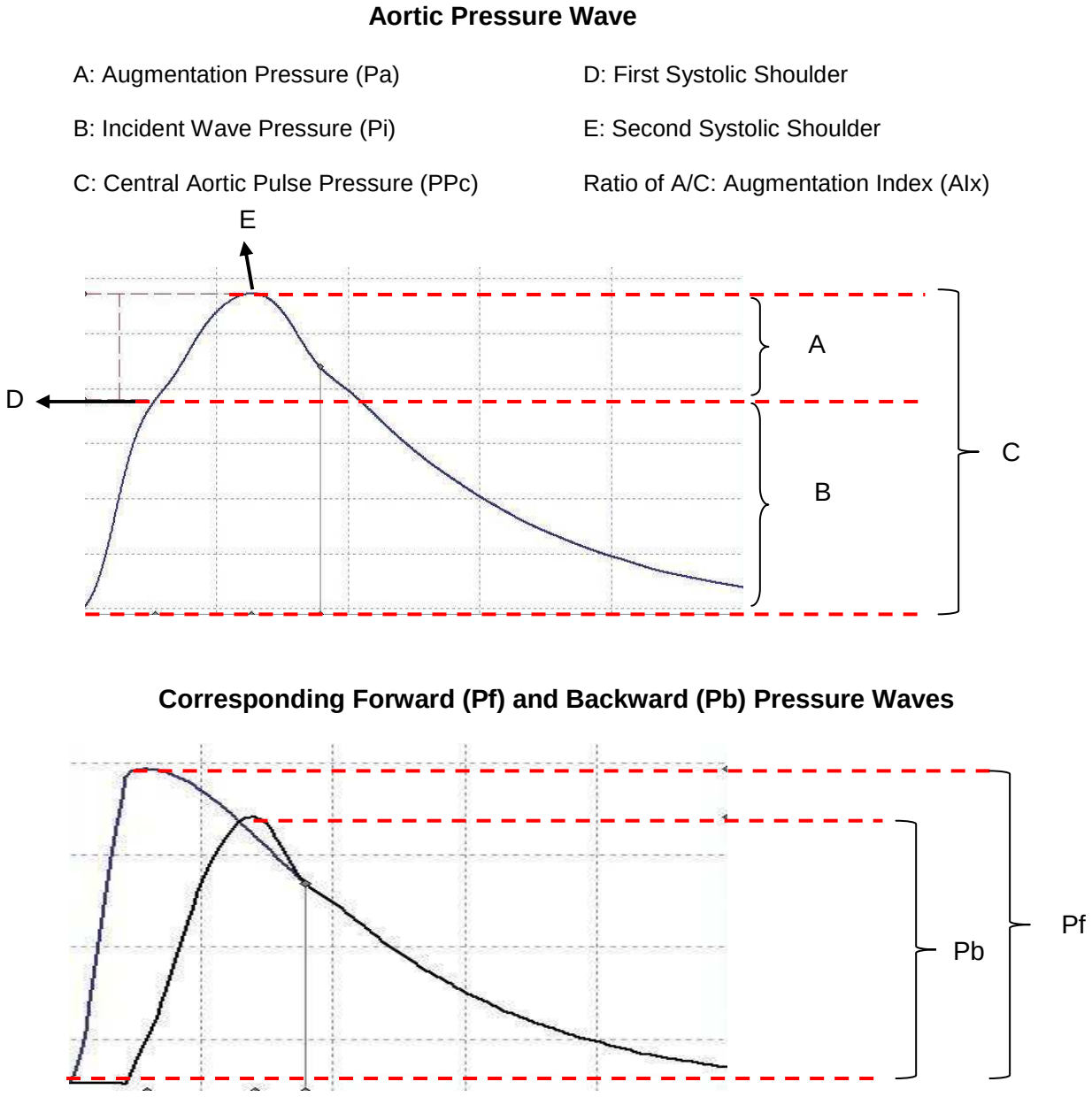


Figure 1.1 Aortic pressure wave (upper panel) as determined by the combined effect of the aortic forward (Pf) and aortic backward (Pb) pressure waves (lower panel). Definitions of various measures of arterial pulse wave analysis are also shown. The figure shows actual data obtained from SphygmoCor recordings.

ageing process, the stiffness of peripheral arteries in the upper limb increases to a lesser degree across the adult lifespan (Nichols et al 2011). The stiffer aorta causes a shift of peripheral/central pressure amplification curves to higher frequencies (decreased distensibility increases characteristic impedance in the ascending aorta and through its effects on wave velocity causes a shift of the impedance curves to a higher velocity) (O'Rourke 1970). 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 between the ages of 20–80 years (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, either aortic BP or PP amplification may be better indices than brachial BP, or indices that add to the ability of brachial BP to predict CVD.

Variability in the difference between aortic and brachial BP is attributed to variations in aortic backward wave pressure (Figure 1.1). 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)(discontinuities in the arterial tree produced by branch points, changes in wall structure and tapering). At these sites pressure waves are reflected back and return to the ascending aorta. Summation of the numerous reflected waves derived from multiple arterial reflection points is thought to occur on wave return and this results in largely a single backward wave reaching the aorta. The backward wave in most adults returns sufficiently early that the pressure generated by this wave (Pb) may add to the pressure generated by the forward wave (Pf) and this augments aortic SBP (see Figure 1.1). However, differences in the timing of the generation of Pf

and Pb in the aorta translate into differences in the brachial as compared to the aortic pulse waveform. How do these differences in the timing of Pf and Pb in the aorta translate into the generation of a brachial artery waveform that may differ markedly from the aortic waveform?

Because aortic Pb usually occurs later than aortic Pf, subsequent transmission of Pb outward to the brachial artery occurs after the transmission of Pf. Hence, in the brachial artery two pressure waves are generated, 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 the effect of late transmission of aortic Pb (Figure 1.2). As the forward wave is larger than the backward wave, the percussion wave is similarly larger than the tidal wave. 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 (Figure1.2). Hence, although aortic pressures are lower than brachial pressures because of differences in stiffness between these vascular beds, peak brachial BP in most adults, especially the young and in middle-aged adults, largely ignores the impact of Pb on aortic BP (tidal wave) and only assesses the impact of Pf (percussion wave)(Figure 1.2). With age and in the presence of cardiovascular risk factors, as Pb increases, brachial BP increases less than aortic BP. This is because brachial BP only detects the peak of the percussion wave which is driven by Pf (Figure 1.3). In contrast, aortic BP increases more than brachial BP as aortic BP is determined by both Pf and Pb (Figure 1.3). With advanced age and with the effects of cardiovascular risk factors, Pb may be generated sufficiently early that its transmission outward to the brachial artery coincides with Pf and hence peak brachial BP is a summation of Pf and Pb effects (Figure 1.3)(Nichols et al 2011). Under these circumstances brachial BP closely approximates the combined effects of Pf and Pb and PP amplification is close to 0. Hence, variations in differences between aortic and brachial BP and in PP amplification may be attributed to variations in aortic stiffness and hence in the impact of stiffness on wave reflection (O'Rourke 1970).

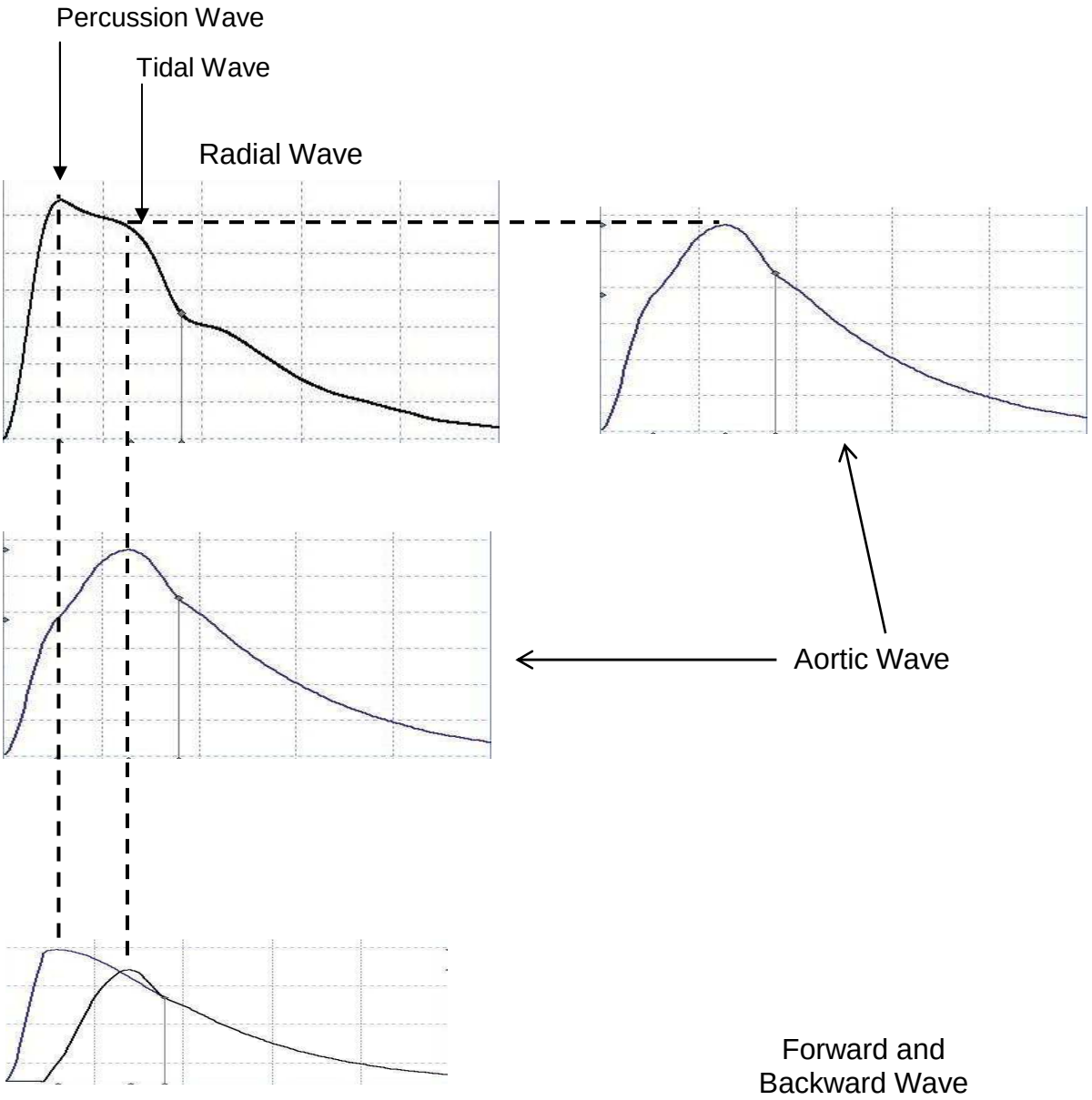


Figure 1.2. The contribution of aortic forward and aortic backward waves to aortic and radial (approximate of brachial) pulse waves. The dashed lines show temporal alignment (left panels) and alignment of the magnitude (left versus right panels) of pressure waves. The figure shows actual data obtained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

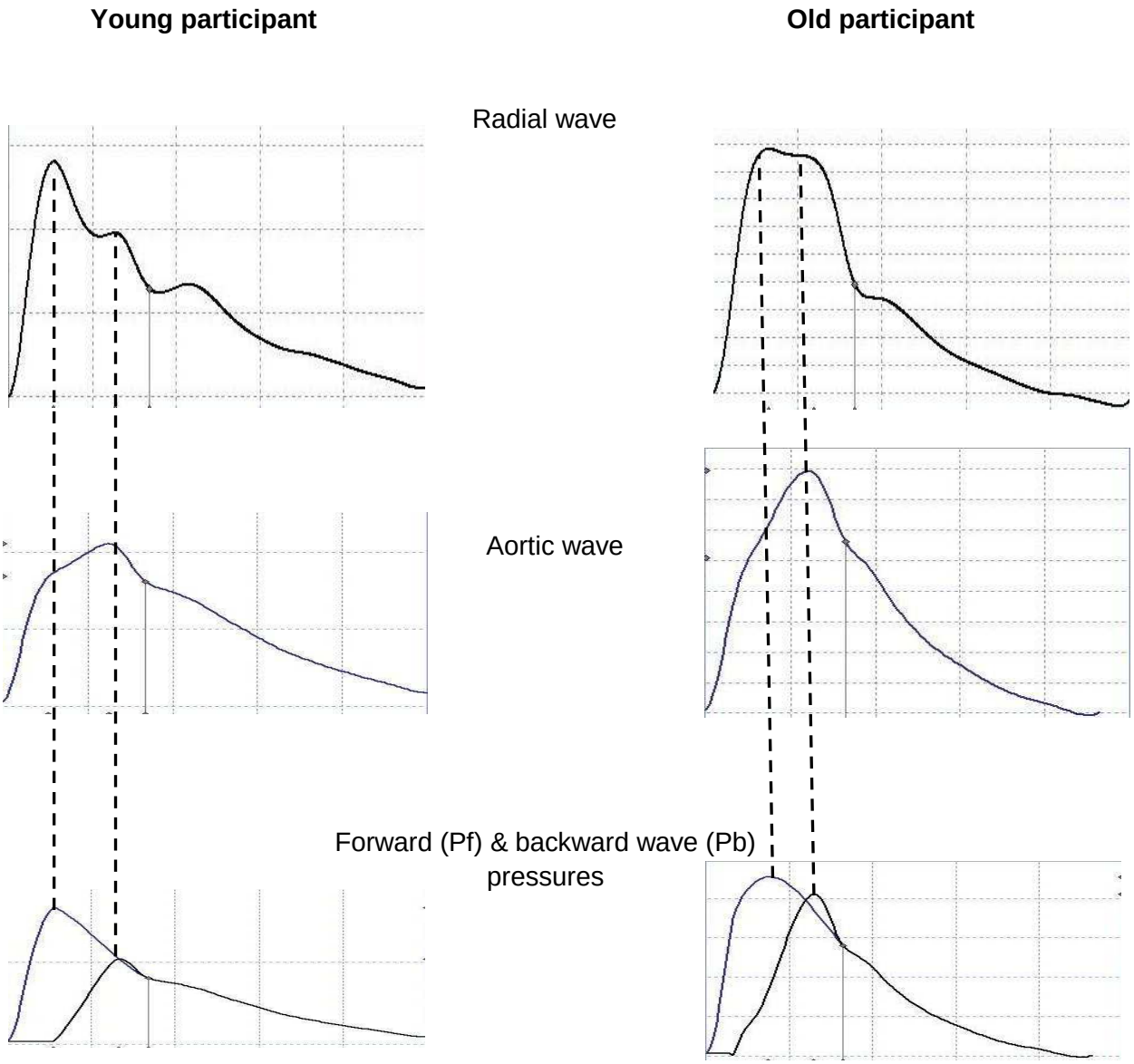


Figure 1.3. Age effects on aortic and radial artery pressure waves (which approximate brachial pressure waves). The figure shows changes in the combined effect of the aortic forward and aortic backward waves on pressure waveforms with age. The dashed line show how the forward and backward pressure waves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

The question that arises is whether it is variations in forward or reflected (backward) wave pressures or both that determine age- and cardiovascular risk factor-related increases in aortic BP, end-organ damage and cardiovascular outcomes? As alluded to in the aforementioned discussion, prior to assessing whether the use of forward or backward wave pressure measurements further refine the ability to identify end-organ changes in pre-hypertension, I first addressed some of the controversies as to the role of forward and backward wave pressures in contributing to aortic BP and cardiovascular damage (Chapter 3). Hence, in the following section I will highlight these disputes and indicate how, in the present thesis I addressed some of these issues. Many of these controversies are related to how best to identify forward and backward wave effects. In the next section I will therefore review the role of forward and backward wave pressures in contributing to aortic BP and cardiovascular damage in the light of the of these controversies are related to how best to identify forward and backward wave effects.

1.3.3 What is the role of forward and backward waves in contributing to variations in aortic BP and cardiovascular damage?

A number of earlier studies indicate that across the adult age range, reflected waves, assessed from indices of pressure augmentation, dominate age-related increases in aortic pressure (McEniery et al 2008, Namasivayam et al 2009, Cecelja et al 2009) and that reflected waves account for increases in aortic pressure in hypertension (Mitchell et al 2003). Aortic pressure augmentation is the extent to which aortic pressure is enhanced by wave reflection and is identified as the difference between peak systolic pressure and the pressure at the first systolic shoulder of the aortic pressure wave (Figure 1.1). Several earlier studies also demonstrate that reflected waves, determined from indices of pressure augmentation, predict cardiovascular damage (Hashimoto et al 2007, Hashimoto et al 2006, Weber et al 2006, Westerbacka et al 2005, Sibiya et al 2014), and cardiovascular outcomes (Chirinos et al 2005b, London et al 2001, Ueda et al 2004, Weber et al 2005) beyond brachial BP. In this regard, a meta-analysis of these and other

outcome studies provided 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, several lines of evidence subsequently cast doubt on the use of pressure augmentation as a useful surrogate index for the impact of wave reflection on CVD. What is this evidence?

The Framingham Heart Study failed to show that indices of aortic pressure augmentation predict outcomes independent of brachial BP (Mitchell et al 2010a). However, as previously pointed out, in the Framingham Heart Study, in contrast to the expected 5-15 mm Hg difference between aortic and brachial BP (PP amplification), little difference was noted across the adult lifespan (Mitchell et al 2010b). This has been explained on the basis of the application of tonometry at a site where the principles of tonometry cannot be achieved (brachial artery to calibrate the carotid artery pulse) and the use of an inaccurate mean pressure for calibrating carotid artery pressures (O'Rourke et al 2010). In this regard, the brachial artery, with tendon aponeurosis superficial to it, and with no bone to support it, cannot be reliably applanated, so that the theory of Drzewiecki et al (1983), cannot be relied upon. This error resulted in an assumption that little carotid to brachial amplification occurs, but that marked brachial-to-radial amplification occurs. Nevertheless, as shown in Figure 1.1, Pa is calculated as the difference between peak systolic aortic pressure and the first systolic shoulder of the aortic pressure wave. Aortic augmentation index is calculated as either Pa/aortic PP x 100 or, to avoid negative values in younger persons, aortic SBP/pressure at the first systolic shoulder of the aortic pressure wave x 100 (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 ends and the reflected wave begins is obscure (Figure 1.1). What is the evidence that indices of aortic pressure augmentation are inaccurate assessments of wave reflection?

The use of Pa or AIx as measures of aortic wave reflection have recently been criticised (Davies et al 2010, Cheng et al 2012, Hughes et al 2013, Fok et al 2014, Torjesen et al 2014, Schultz et al 2013). Although in several of these studies (Davies et al 2010, Hughes et al 2013, Fok et al 2014), the method of wave intensity analysis has been seriously questioned on methodological and theoretical grounds (Segers et al 2015), and Fok et al (2014) report an impossible flow-frequency response, apparently hand-drawn representative waves are shown, and control impedance values are given that differ markedly from Yaginuma et al (1985), these and several other studies nevertheless suggest that marked overlap between aortic forward and reflected waves may confound Pa and AIx (Cheng et al 2012, Fok et al 2014, Torjesen et al 2014, Schultz et al 2013). Hence these measures may be poor indices of wave reflection. Indeed, there is a weak relationship between the magnitude of the reflected wave and Pa or AIx with 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 (Cheng et al 2012, Hughes et al 2013, Fok et al 2014, Torjesen et al 2014, Schultz et al 2013). In this regard, to avoid the confounding influence of these factors on wave reflection, aortic pressure waveforms may be separated using simultaneous aortic flow measurements or with an assumed aortic flow waveform (Westerhof et al 2006). How are aortic pressure waves separated using aortic flow waveforms? In essence to assess the magnitude of Pf and Pb, one requires pressure and flow waveforms. The following formula is used to calculate Pf and Pb:

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

$$Pb(t)=[P(t) – Zc \bullet F(t)]/2$$

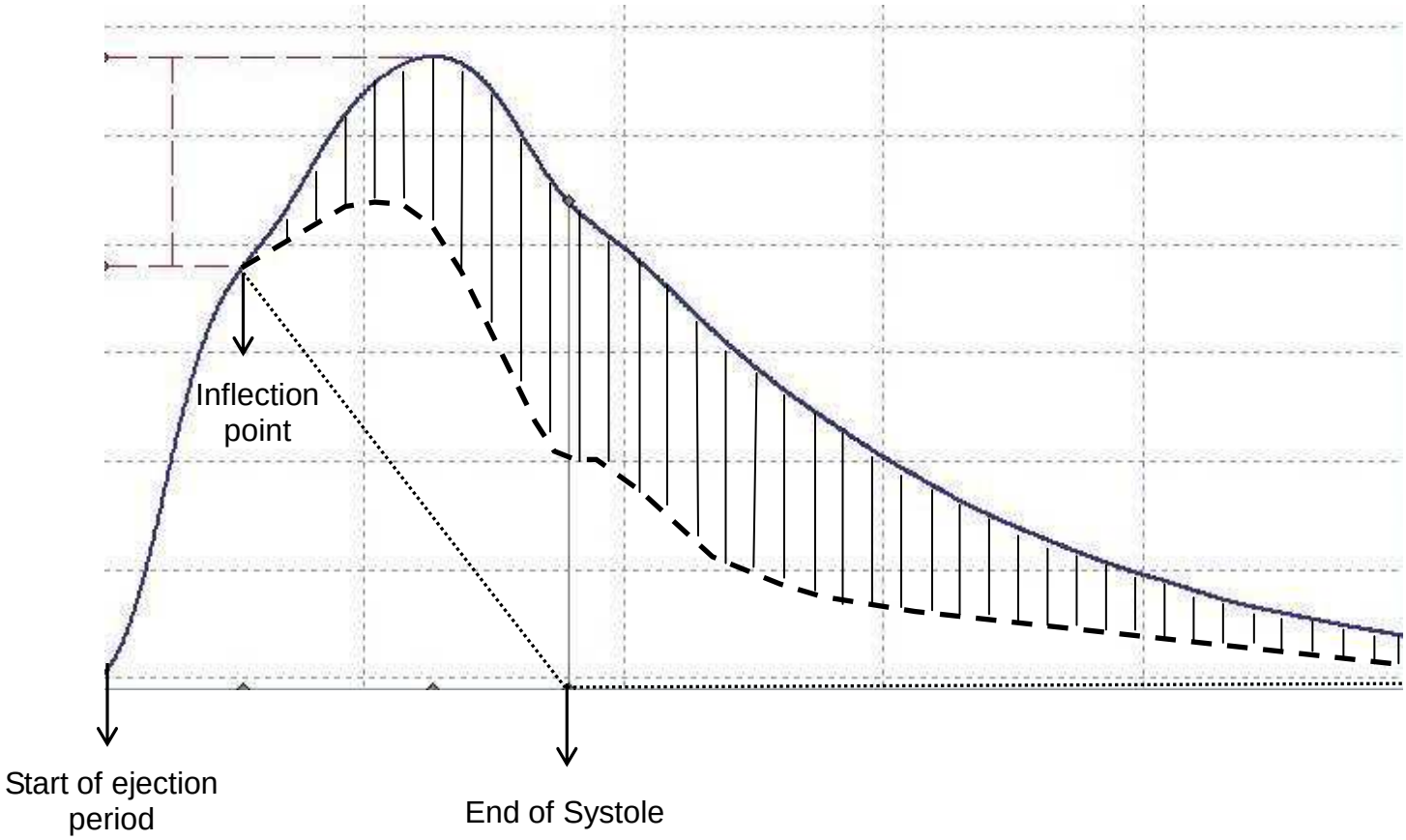
where P(t) is the measured pressured wave, F(t) is the flow wave, and Zc is characteristic impedance of the proximal aorta (Westerhof et al 2006). Characteristic impedance (Zc) is derived from the 4^{th} to 7^{th} harmonic (Westerhof et al 2006). In the calculation of Pb and

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).

The assumed aortic flow waves that have been employed for wave separation analysis include a triangular aortic waveform or a “physiological” waveform (Kips et al 2009, Westerhof et al 2006). From actual flow and pressure 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 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 simply placed at these points (Figure 1.4) and the forward and backward waves are calculated as shown in Figure 1.4. As the aortic flow wave is not exactly a triangular waveform, 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).

What is the evidence derived from wave separation analysis to indicate whether aortic reflected waves play an important role in contributing to CVD? Importantly, to address this point, the first question to consider is whether current evidence supports an important role for reflected waves, derived from wave separation analysis, in determining age-related increases in aortic pressures?

In the only study conducted at the time, which employed wave separation analysis to identify Pb (Segers et al 2007), in contrast to studies demonstrating that Pa dominates age-related increases in aortic pressure (McEniery et al 2005, Namasivayam et al 2009, Cecelja et al 2009) and variations in aortic BP (Cecelja et al 2009), Pb was noted to



Thick Solid line= **Measured pressure wave**

Fine dashed line = **Triangular flow wave**

Thick dashed line = **Forward wave = Measured pressure wave – pressure at same time point in triangular waveform**

Shaded area = **Reflected wave**

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

make a small contribution to variations in aortic pressure (Segers et al 2007). However, this study (Segers et al 2007) was conducted in participants evaluated over a very narrow age- range (average 15 year age range) and hence is unlikely to reflect what occurs overthe full adult age-range. Nevertheless, subsequent studies employing wave separation analysis provided discrepant data. In this regard, notwithstanding the finding that little difference in aortic and brachial BP was noted across the adult lifespan (Mitchell et al 2010b), data explained on the basis of the application of tonometry at a site where the principles of tonometry cannot be achieved (brachial artery to calibrate the carotid artery pulse) and the use of an inaccurate mean pressure for calibrating carotid artery pressures (O'Rourke et al 2010), the Framingham Heart Study nevertheless demonstrated only modest contributions of wave reflection (backward wave pressures or Pb), derived from wave separation analysis to variations in aortic pressure across the adult age range (Mitchell et al 2010b). In contrast, in an alternative large community-based study where the community had a high prevalence of uncontrolled hypertension, Pb derived from aortic wave separation analysis was strongly and linearly related to age (Wang et al 2010). However, whether in that study (Wang et al 2010) Pb contributed more, less or the same amount as forward wave pressures (Pf) to variations in aortic pressure across the adult lifespan was not described. Hence, **in the present thesis**, before I evaluated whether the ability of aortic reflected waves better identify pre-hypertensives with end-organ changes (Chapter 4), I first *assessed whether indices of pressure augmentation are sufficient to determine the impact of wave reflection on age-related increases in aortic pressure across the adult lifespan or whether Pb should be assessed from wave separation analysis (Chapter 3)*. As previously alluded to, these data have been accepted for publication in the journal *Hypertension* (Booysen et al 2015). More importantly however, what is the evidence derived from wave separation analysis to indicate whether aortic reflected waves play an important role in contributing to cardiovascular damage or CVD?

As previously indicated, earlier studies evaluating the impact of reflected waves on cardiovascular end-organ changes (Hashimoto et al 2007, Hashimoto et al 2006,

Weber et al 2006, Westerbacka et al 2005, Sibiya et al 2014), and cardiovascular outcomes (Chirinos et al 2005b, London et al 2001, Ueda et al 2004, Weber et al 2005) beyond brachial BP did not employ wave separation analysis to identify reflected or backward wave pressure effects. In the last few years however, 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) to risk predict beyond brachial BP (Wang et al 2010, Weber et al 2012, Chirinos et al 2012, Zamani et al 2014). These studies are summarised in Table 1.4. However, neither Pb nor RI were independently associated with outcomes in the Framingham study (Cooper et al 2014) (Table 1.4), a finding that may be explained by the fact that application of tonometry was at a site where the principles of tonometry cannot be achieved (brachial artery to calibrate the carotid artery pulse) and the use of an inaccurate mean pressure for calibrating carotid artery pressures (O'Rourke et al 2010). What are the outstanding issues in these studies which prompted me, as part of the present thesis, to further pursue the role of wave reflection as a possible determinant of cardiovascular damage beyond brachial BP?

Importantly, in these studies, relations with end-organ damage were not adjusted for confounders (Wang et al 2010, 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, Weber et al 2012); and whether the increase in forward wave pressures at 50 years of age (McEniery et al 2008, Mitchell et al 2010b) impacts on these relations was not considered (Wang et al 2010, Weber et al 2012, Chirinos et al 2012, Zamani et al 2014) (Table 1.4). Hence, **in the present thesis**, before I evaluated whether the ability of aortic pressure to better identify pre-hypertensives with end-organ changes are attributed to aortic reflected waves (Chapter 4), I first *evaluated whether indices of pressure augmentation are sufficient to assess the impact of wave reflection on end-organ changes (as indexed by left ventricular mass index) across the adult lifespan, or whether Pb should be assessed from wave separation analysis*

Table 1.4. Characteristics of studies assessing the impact of aortic reflected (backward) wave effects on cardiovascular damage and outcomes.

Authors	Sample Size	Study design	Duration	Outcomes Evaluated	Result	Adjustors
Wang et al 2010	1 272	Community based Survey	15 years	LVMI, IMT, eGFR, PWV	Correlated	None
Wang et al 2010	1 272	Community based Survey	15 years	All-cause mortality & CVE	I-P	None
Weber et al 2012	725	Prospective	1 399 days	GFR, LA Diameter, LVM E/É, Aortic PWV	Correlated	None
Weber et al 2012	725	Prospective	1 399 days	Mortality, MI, Stroke, CR Peripheral & Cerebrovascular Revascularization	I-P	Sex, age, systolic function, Statin use MAP, LA Diameter, GFR, CAD, Aortic PWV angioscore, diabetes, smoking, NT-proBNP hypertension, E/É, Hr, previous MI, treatment, LV end-diastolic pressure
Chirinos et al 2012	5 960	Prospective	7.61 years	Heart Failure	I-P	Race, Treatment, TChol, HDL-Chol, Smoking, HR, eGFR

Table 1.4. Continued

Authors	Sample Size	Study design	Duration	Outcomes Evaluated	Result	Adjustors
Zamani et al 2014	5 984	Prospective	9.8 years	All-cause mortality, CD	I-P	Hr, age, sex, race, SBP, Urinary Albumin/creatinine ratio, Tchol, LDL-Chol, HDL-Chol, treatment, smoking, BMI, previous MI, diabetes, C-reactive protein, education, family income, alcohol, calorie intake, calories from fat, physical activity, ankle-brachial index, maximum IMT, NT-proBNP, eGFR, score, Aortic Agatson calcium score, Agaston coronary calcium
Cooper et al 2014	2 492	Longitudinal	6.8 years	MI, Angina, HF, Ischemic & hemorrhagic stroke, CVD	N-P	Age, sex, antihypertensive therapy BMI, Hr, TChol, HDL, smoking Diabetes

LVMI; Left Ventricular Mass Index, IMT; Intima Media Thickness, eGFR; Estimated Glomerular Filtration Rate, PWV; Pulse Wave Velocity, CVE; Cardiovascular Events, I-P; Independent predictor; GFR; Glomerular Filtration Rate, LA; Left Atrium, LVM; Left Ventricular Mass, MI; Myocardial Infarction, CR; Coronary Revascularization, Hr; Heart Rate, CAD; Coronary Artery Disease, TChol; Total Cholesterol, HDL; High-density Lipoprotein, CD; Cardiovascular Death, SBP; Systolic Blood Pressure, NT-proBNP; NT-probrain Natriuretic peptide, Chol; Cholesterol, LDL; Low-density lipoprotein, BMI; Body Mass Index, N-P; Not an independent predictor

(Chapter 3). In doing so I describe the relative contribution of wave reflection (assessed with or without wave separation analysis) versus forward wave pressures to end-organ changes independent of confounders, and in those less than or more than 50 years of age. As indicated in aforementioned discussion, these data have been accepted for publication in the journal *Hypertension* (Booysen et al 2015) and provided the evidence that prompted me to further pursue whether aortic reflected waves may further refine the ability to identify pre-hypertensives with end-organ changes.

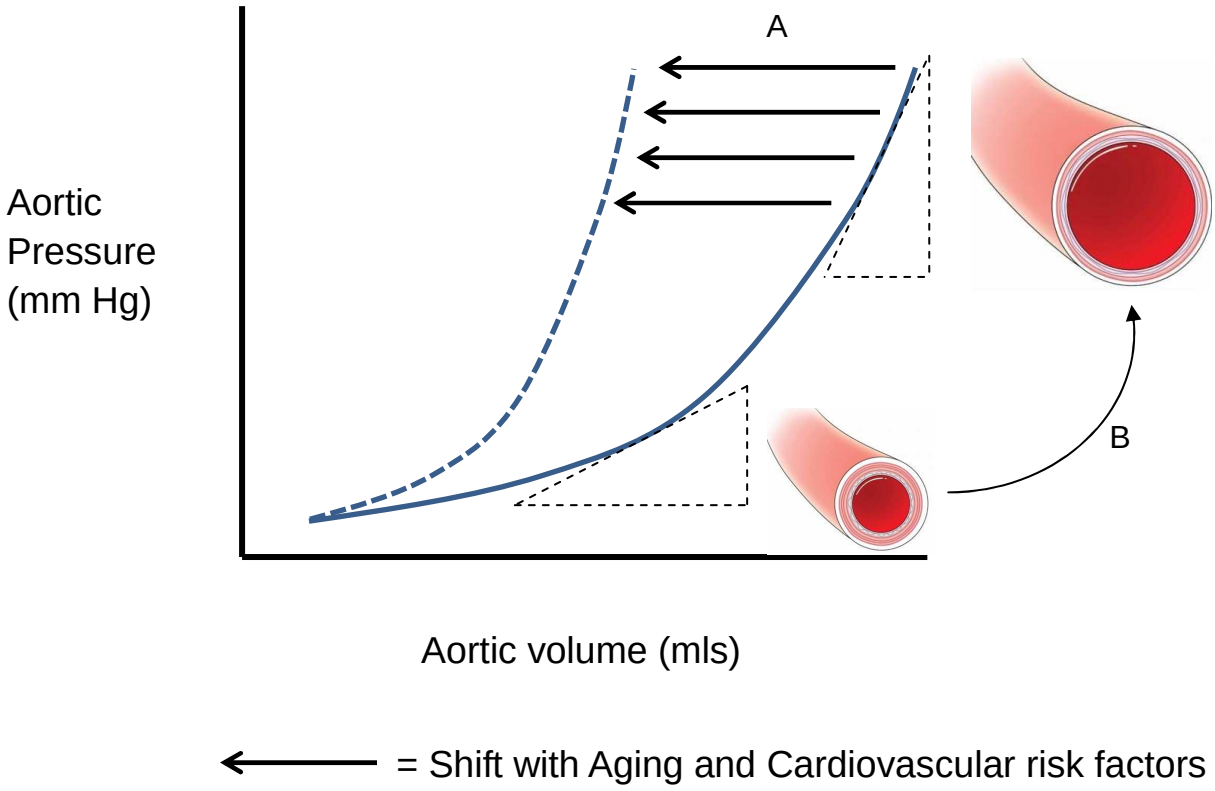
1.3.4 Additional determinants of aortic forward and backward wave pressures.

Although to a large extent the determinants of aortic forward (Pf) and backward (Pb) wave pressures have already been discussed in section 1.3.2, there are several additional factors which require consideration to place the present thesis in context. To summarise previous discussion, the aortic forward wave pressure (Pf) is determined by stroke volume and aortic impedance or stiffness and the aortic backward wave pressure (Pb) is determined by wave reflection. What are the factors that determine stroke volume, aortic stiffness and wave reflection?

Stroke volume is determined by cardiac contractility and ventricular filling volumes (Frank-Starling effect). However, stroke volume does not increase with age or account for age-related increases in aortic pressure (Segers et al 2007). Although there is some recent evidence that increases in left ventricular contractility may determine increases in Pf and hence aortic pressure in hypertension (Fok et al 2014), this study was conducted in a small sample of patients (n=20) and controls (n=20)(Fok et al 2014) and as previously indicated, Fok et al (2014) report an impossible flow-frequency response, apparently hand-drawn representative waves are shown, and control impedance values are given that differ markedly from Yaginuma et al (1985). Hence, stroke volume may not be a major determinant of increases in aortic Pf.

As previously described in section 1.3.2, aortic impedance or stiffness is determined by the structural characteristics of the aorta which change with age and the presence of cardiovascular risk factors. When structural aortic changes occur, the relationship between aortic pressure and volume shifts to a steeper curve (Figure 1.5) and these changes are thought to make a major contribution to variations in Pf with age and in hypertension. However, importantly, because of the exponential relationship between aortic volume and pressure, distension of the aorta (increased volume) may also change aortic stiffness through passive mechanisms, where wall tension is transferred from distensible elastin fibres to stiff collagen fibres as the volume in the aorta increases (Figure 1.5). In this regard, the main determinant of aortic distension is mean arterial pressure (MAP) and hence any factor that augments MAP will produce marked increases in Pf through passive mechanisms (Nichols et al 2011).

As previously discussed, aortic Pb is determined by wave reflection. However, the mechanisms responsible for increases in wave reflection are less well understood. In this regard, although not a strong relationship, Pb is associated with aortic stiffness as determined by aortic pulse wave velocity (PWV)(Nichols et al 2011), the current 'gold-standard' non-invasive assessment of aortic stiffness. This may be explained by impedance mismatching at arterial reflection points, and hence in alterations in the magnitude of wave reflection (Nichols et al 2011). As MAP is an important determinant of aortic stiffness, any factor that influences MAP (through effects on either total peripheral resistance [TPR] or cardiac output [CO]) will obviously also increase wave reflection and Pb. Importantly however, there is also the possibility that alterations in vascular smooth muscle tone at various reflection sites may produce an increased magnitude of wave reflection. In this regard, the ability of nitrates to decrease Pa and AIx, as well as aortic pressure, without producing much change in brachial pressure and at doses which do not influence TPR (Simkus and Fitchett 1990, Takazawa et al 1995), was previously thought to be through an impact on medium sized-artery smooth muscle tone and consequently reflected waves. However, more recent evidence suggests that the impact of nitrates on



A: Produced by structural aortic changes

B: Produced by aortic distension

Figure 1.5. Aortic pressure-volume relations and the impact of structural aortic changes (destruction of elastin fibres, increased collagen or changes in collagen phenotypes) in the aorta or aortic distension (e.g. as may occur with increases in mean arterial pressure) on these relations.

aortic pressure is through changes in cardiac function and hence Pf, rather than Pb (Fok et al 2014). The previously described benefits of nitrates on Pa and AIx (Simkus and Fitchett 1990, Takazawa et al 1995) may therefore be attributed to an impact on forward rather than reflected waves. However, as previously indicated, Fok et al (2014) report an impossible flow-frequency response, apparently hand-drawn representative waves are shown, and control impedance values are given that differ markedly from Yaginuma et al (1985). As indicated in the aforementioned discussion, as aortic SBP is likely to be the principal BP responsible for cardiovascular damage and adverse outcomes, it is important to consider how antihypertensive therapy may produce the well-described benefits of these agents in risk prevention. In this regard, the crucial question is how does antihypertensive therapy influence Pf, Pb and hence aortic pressure?

1.3.5 Effects of antihypertensive therapy on aortic pressures and the component waves.

Although in the present thesis I did not assess the impact of antihypertensive therapy on aortic pressures or the component waveforms, if aortic BP or specific component waveforms better identify pre-hypertensives with cardiovascular end-organ changes, it is important to understand whether current approaches to BP lowering are effective in reducing these pressures in pre-hypertension.

It is well-recognised that current antihypertensive agents were designed to target CO and TPR (MAP=CO x TPR). Indeed, current therapy largely influences resistance arteries (arterioles and pre-capillary sphincters) and/or stroke volume, heart rate or cardiac contractility. In this regard, thiazide and thiazide-like diuretics, renin-angiotensin-aldosterone system (RAAS) blockers, calcium channel blockers (CCB), non-specific vasodilators, α_1-adrenergic receptor blockers, centrally acting α_2-adrenergic receptor agonists, and neutral endopeptidase inhibitors, all decrease TPR. Moreover, thiazide and thiazide-like diuretics, RAAS blockers, and β_1-adrenoreceptor blockers will decrease CO through effects on heart rate, blood volume and hence cardiac filling volumes, or cardiac

contractility. If one is to understand how antihypertensives produce benefits to cardiovascular risk, the essential question however is whether these agents are able to decrease Pf and Pb and hence aortic BP?

As Pf and Pb are both influenced by MAP, there is no question that all antihypertensive agents, because they decrease MAP through effects on either TPR and/or CO will decrease both Pf and Pb. However, what has attracted considerable attention over the years is whether antihypertensive agents are able to target aortic forward and reflected waves independent of effects on MAP. In this regard, to the best of my knowledge most studies that have evaluated the impact of antihypertensive therapy on aortic BP and the component waves of aortic PP, have assessed the effects on forward and reflected wave effects without separating the waveforms. In this regard, a number of studies have reported that antihypertensive therapy decreases Pa, AIx and aortic pressure and hence the authors of these studies have concluded that most classes of agents reduce wave reflection and hence aortic pressure (Agabiti-Rosei et al 2007). The exception to this rule is that it appears that diuretics and β-adrenoreceptor blockers may not produce the same benefits, with less of a reduction in Pa and AIx and hence aortic pressures with these agents than with more modern classes of agents including RAAS blockers and CCBs (Williams et al 2006, Agabiti-Rosei et al 2007). These findings have been employed to explain differential benefits of older agents (diuretics or β-adrenoreceptor blockers) as compared to newer agents (RAAS blockers and CCBs) on cardiovascular outcomes independent of brachial BP, with newer agents showing superiority over older agents (Dahlof et al 2002, Williams et al 2006). However, whether these differential benefits are attributed to the magnitude of reflected wave effects on aortic pressure or through other effects on aortic pressures (impact on Pf or the timing of wave reflection) is uncertain as to the best of my knowledge no study has evaluated whether RAAS blockers and CCBs are better at decreasing Pb derived from wave separation analysis than older agents. What is nevertheless generally accepted is that the MAP-independent benefits of antihypertensive therapy on the structural aortic changes

that determine aortic stiffness and hence stiffness-induced increases in Pf over short-term periods is minimal (Agabiti-Rosei et al 2007). However, diuretics and β-adrenoreceptor blockers may produce MAP-independent effects on stroke volume and hence Pf and therefore may have benefits on Pf and thus aortic pressure that go beyond MAP.

1.4.0 Deriving aortic pressures: Cost implications and possible alternative approaches

Assuming that central aortic pressure measurement does indeed improve on cardiovascular risk prediction, the question arises as to how it should be measured? In this regard, central aortic BP should ideally be measured invasively with a non-fluid-filled (transducer-tipped) catheter placed in the proximal aorta. However, for obvious reasons invasive measurements are impractical for general clinical use. Are there reasonable alternatives? More than 100 years ago, premature arteriosclerotic changes were measured from the pulse waveform in the radial artery by sphygmography (Osler 1898, Mackenzie 1902). The first graphic recordings of the arterial pulse revealed differences in waveform shape between young and old (Marey 1863). These early studies set the scene for the development of devices to derive central aortic pressures from non-invasive measurements, measurements from which most current knowledge of the role of aortic haemodynamics in CVD has been derived.

One method is based on applanation tonometry of the radial artery to derive an accurate arterial pulse waveform (pulse wave analysis or PWA), which, coupled with the use of a validated population-based generalized transfer function (GTF), converts the radial pulse wave into an aortic pulse wave. This technique has previously been criticised for the use of a population-based transfer function which may not apply to all clinical populations (Hope et al 2008, Khoshdel et al 2007, Hope et al 2004, Hope et al 2002). However, this approach produces aortic pressures which closely approximate aortic pressures derived from the second systolic shoulder of the radial waveform (which does

not require a population-based transfer function to derive aortic pressures) and is as closely associated with end-organ damage as aortic pressures derived from the second systolic shoulder (Norton et al 2012). More recently however, this approach has been criticised for using brachial pressures to calibrate the waveform as BP amplification has been suggested to be significant from the brachial to the radial artery (Mahieu et al 2010, Verbecke et al 2005). However, high radial amplification (Mahieu et al 2010, Verbecke et al 2005) has never been shown in invasive studies of the brachial and radial pulse wave and non-invasively determined brachial-to-radial amplification has been attributed to inappropriate use of applanation tonometry at the brachial artery. In this regard, the brachial artery, with tendon aponeurosis superficial to it, and with no bone to support it, cannot be reliably applanated, so that the theory of Drzewiecki et al (1983), cannot be relied upon.

An alternative method of deriving aortic pressures non-invasively employs carotid applanation tonometry calibrated against the brachial artery. Although this approach has the benefit of not requiring a population-based transfer function to derive an aortic waveform, it suffers from inaccuracies in deriving the waveform in obese individuals (there is no bony structure to compress the carotid artery against to perform the measurement) and the concern of a potential risk of emboli if complicated plaque exists in advanced atheroma. This is in contrast to radial PWA where the artery can be flattened against a bony structure and hence where obesity does not limit the ability to obtain an accurate pulse wave, and where the risk of emboli to essential organs does not exist in patients with complicated plaque. Criticism of carotid tonometry derived central haemodynamic values obtained in some studies includes the use of inaccurate brachial tonometry to calibrate carotid pressure traces (O'Rourke et al 2010). In this regard, as previously indicated, in contrast to the expected 5-15 mm Hg difference between aortic and brachial BP (PP amplification), in one study little difference was noted across the adult lifespan (Mitchell et al 2010b). This has been explained on the basis of the application of tonometry at a site where the principles of tonometry cannot be achieved (brachial artery

to calibrate the carotid artery pulse) and the use of an inaccurate mean pressure for calibrating carotid artery pressures (O'Rourke et al 2010). In this regard, the brachial artery, with tendon aponeurosis superficial to it, and with no bone to support it, cannot be reliably applanated, so that the theory of Drzewiecki et al (1983), cannot be relied upon. This error resulted in an assumption that little carotid to brachial amplification occurs, but that marked brachial-to-radial amplification occurs (Mitchell et al 2010b).

An essential criticism of the use of any form of PWA is that the instruments that have been developed are costly in comparison to current oscillometric devices validated for BP measurement. In relative terms, in South Africa, validated oscillometric devices are available for a few thousand rands (South African currency), whilst devices for PWA are a few hundred thousand rands (100 times the price). Furthermore, in resource-limited settings in Africa, even oscillometric devices are out of the price range and BP measurements may require much simpler approaches which do not rely on electronic devices. Although finger photoplethysmography may also allow for PWA, and these devices may be considerably cheaper than present devices available for PWA, these devices have not as yet been made commercially available. Moreover, although discarded manometers used for cardiac catheterisation may also be used for PWA, the recording devices available that these manometers are coupled to, are considerably more expensive than devices employed for the simple measurement of brachial BP. Hence, the question which arises is whether simple clinical tools, which do not rely on electronic devices for their measurement, may allow for an approximation of aortic pressure that can improve on risk prediction?

1.4.1 Imputing aortic blood pressure from simple clinical measures.

The major determinants of central aortic BP (Wilkinson et al 2000 & 2001, McEniery et al 2008) are normally acquired as part of routine cardiovascular risk prediction. It has therefore been suggested that aortic BP may be imputed (or calculated)

from simple clinical measures derived from multivariate regression modelling (Camacho et al 2004). In this regard, although brachial pressure may considerably underestimate aortic pressures, a close correlation exists between brachial PP and aortic PP (Benetos et al 2010). Hence, brachial PP may account for more than 80% of the variability of aortic PP (Benetos et al 2010) and is an essential component of an equation employed to derive aortic PP and SBP. To adequately account for differences in aortic and brachial BP, the impact of backward wave pressures may in-part be accounted for by age, as age is linearly associated with Pb (Wang et al 2010). Furthermore, the impact of forward wave pressures may also in-part be accounted for by age, as age is the strongest recognized determinant of aortic stiffness. Hence, age may be an essential component of an equation derived from multivariate regression modelling that is employed to impute aortic BP. As indicated in previous discussion, MAP, through passive effects on aortic stiffness increases both Pf and Pb and hence aortic pressures. Therefore, MAP may also be an essential component of an equation derived from multivariate regression modelling that is employed to impute aortic BP. Heart rate is a well-recognized determinant of aortic pressure augmentation, not because it changes the magnitude of the backward pressure wave, but because it influences the extent to which the forward and backward pressure waves overlap (Wilkinson et al 2000, Wilkinson et al 2001). In this regard, a slower heart rate is thought to prolong the forward pressure wave and hence increase the chances that the backward wave arrives at a similar time as the forward wave (Wilkinson et al 2000, Wilkinson et al 2001). Therefore, heart rate may also be an essential component of an equation derived from multivariate regression modelling that is employed to impute aortic BP. A shorter stature, as occurs in women, may result in a reduced distance required by the backward wave to travel, the consequence being that the backward wave arrives earlier and coincides with the forward wave thus augmenting aortic SBP (Hughes et al 2013, Wilkinson et al 2000, Wilkinson et al 2001). Therefore, height and sex may also be essential components of an equation derived from multivariate regression modelling that is employed to impute aortic BP. As indicated in previous discussion, recognized

cardiovascular risk factors, including smoking, diabetes mellitus, hypertension, and dyslipidaemia are all causes of structural changes in the aorta and hence aortic stiffness. Thus, these risk factors may also be associated with Pf and Pb and hence aortic pressure. Therefore, a number of cardiovascular risk factors may also be essential components of an equation derived from multivariate regression modelling that is employed to impute aortic BP. Is there evidence that aortic BP determined from an imputation equation derived from simple clinical assessments predicts cardiovascular damage beyond brachial BP?

1.4.2 Relationships between imputed aortic blood pressure and cardiovascular damage.

Recent studies have demonstrated an ability of PP amplification, determined from aortic PP imputed from an equation derived from multivariate regression modelling of simple clinical parameters, to predict cardiovascular outcomes, independent from brachial BP (Benetos et al 2010, Regnault et al 2012). However, in these studies imputed aortic PP *per se* failed to predict outcomes beyond brachial BP (Benetos et al 2010, Regnault et al 2012). Nevertheless, in these studies (Benetos et al 2010, Regnault et al 2012), only brachial PP, age and diabetes mellitus were employed in the imputation equation and the relationship between imputed aortic PP and measured aortic PP (r^2=0.888) was only marginally improved on the relationship between brachial PP and aortic PP (r^2=0.835). In neither of these studies was MAP or heart rate, two strong determinants of aortic PP included in the multivariate model (Benetos et al 2010, Regnault et al 2012). Further, although the imputation equation produced mean differences (Bland Altman analysis) between imputed aortic PP and measured aortic PP (-0.50 mm Hg for men and -6.45 mm Hg for woman) that improved on the mean difference (Bland Altman analysis) between brachial PP and measured aortic PP, whether any intrinsic bias in the slope of the brachial PP versus aortic PP relationship occurred and whether the imputation model improved on

this intrinsic bias was not reported on (Benetos et al 2010, Regnault et al 2012). In addition, the imputation equation derived by Benetos et al (2010), failed to predict outcomes in alternative populations (unpublished data). Thus further work is required to evaluate whether an imputation equation employing simple clinical measures closely approximates aortic BP and whether this imputation equation produces aortic BP values which may enhance the ability to identify cardiovascular damage in pre-hypertensives beyond brachial BP. In **the present thesis** in Chapter 5 I therefore *identified an imputation equation employing simple clinical measures that closely approximates aortic BP*. In chapter 5 I further assessed whether *imputed aortic BP values may better identify pre-hypertensives with cardiovascular damage and whether this effect is similar to the ability of aortic BP derived from PWA to identify pre-hypertensives with cardiovascular damage*.

1.5 Problem statement

In summary therefore, individuals with normal/high-normal BP values are at risk of cardiovascular events, but the risk attributed to BP within this BP category may be highly heterogeneous. As aortic BP may enhance risk prediction beyond brachial BP and considerable overlap in aortic BP occurs across optimal, normal, high-normal and hypertensive BP categories, I hypothesized that aortic BP may refine the ability to identify those with a normal-high normal BP whom are at risk for BP-related sub-clinical cardiovascular disease (end-organ changes). As variations in the difference between aortic and brachial BP are attributed largely to aortic reflected waves, I also hypothesized that aortic reflected waves may enhance the ability to identify sub-clinical cardiovascular disease in normotensives. However, before addressing this question, whether the use of aortic augmentation indices adequately evaluates the impact of aortic reflected waves on aortic pressure and cardiovascular damage required clarification. Although the assessment of aortic BP may enhance the ability to identify cardiovascular damage in

those with BP values within normal-high normal BP ranges, the devices designed to measure aortic BP non-invasively are cost-prohibitive for routine use at a primary healthcare level in low-to-middle income countries, such as South Africa. As aortic BP is closely associated with a number of routinely determined clinical measures, I also hypothesized that an imputation equation derived from these routine clinical measures may closely approximate aortic BP and that imputed aortic BP would improve on the ability of brachial BP to detect sub-clinical cardiovascular disease as well as actual aortic BP.

1.6 Aims

Hence, as part of the present thesis I aimed:

1) To determine whether aortic BP enhances the ability of brachial BP to identify end-organ changes in a community sample of participants with normal/high-normal BP values. These data are described in chapter 2 and have been published in the *Journal of Hypertension* (Booysen et al 2013).
2) To determine whether aortic augmentation indices closely reflect the impact of backward waves on aortic BP and end-organ changes. These data are described in chapter 3 and have been accepted for publication in the journal *Hypertension* (Booysen et al 2015)(scheduled for publication in March 2015).
3) To determine whether aortic reflected (backward) waves explain the capacity of aortic BP to enhance the identification of end-organ changes in normotensives and to assess whether reflected (backward) waves improve on the ability of aortic BP to identify end-organ changes. These data are described in chapter 4.
4) To determine whether an imputation equation derived from routine clinical measures closely approximates aortic BP and whether imputed aortic BP improves on the ability of brachial BP to detect end-organ changes as well as actual aortic BP. These data are described in chapter 5.

Chapter 2

Aortic, but Not Brachial Blood Pressure Category Enhances the Ability to Identify Target Organ Changes in Normotensive.

The data in this chapter have been published in the *Journal of Hypertension*:

Booysen, H. L., Norton, G. R., Maseko, M. J., Libhaber, C. D., Majane, O. H., Sareli, P., & Woodiwiss, A. J. (2013). Aortic, but not brachial blood pressure category enhances the ability to identify target organ changes in normotensives. *Journal of Hypertension* 31(6), 1124-1130. (reprint provided in appendix 2)

2.1 Abstract

As those at risk of blood pressure (BP)-related cardiovascular damage in pre-hypertension are difficult to identify, I sought to determine whether within normal/high-normal BP ranges (120-139/80-89 mm Hg), aortic BP may further refine BP-related cardiovascular risk assessment, as determined from target organ changes. In 1169 participants from a community sample of African ancestry, 319 (27%) of whom had a normal/high-normal BP, aortic BP was determined using radial applanation tonometry and SphygmoCor software, and target organ changes assessed from carotid-femoral pulse wave velocity (PWV)(n=1025), estimated glomerular filtration rate (eGFR) (n=944), and left ventricular mass indexed to height$^{2.7}$ (LVMI)(n=690). Normal versus high-normal BP categories failed to differentiate between those participants with a BP above optimal values with versus without multivariate-adjusted target organ changes. However, in those with a normal/high-normal BP with aortic systolic BP values that were <95% confidence interval of healthy participants with optimal BP values (45% of those with a normal/high-normal BP), no unadjusted or multivariate adjusted target organ changes were noted. In contrast, those with a normal/high-normal BP with aortic systolic BP values that exceeded optimal thresholds, demonstrated unadjusted and multivariate adjusted increases in PWV and LVMI and decreases in eGFR ($p<0.05$ to $p<0.005$ after multivariate adjustments). In conclusion, in contrast to normal versus high-normal BP categories which do not clearly distinguish normotensives with from those without end-organ changes, non-invasively determined aortic BP measurements may refine the ability to detect those with a normal/high-normal BP at risk of BP-related end-organ changes.

2.2 Introduction

Although guidelines recommend threshold blood pressure (BP) values of 140/90 mm Hg for the diagnosis of hypertension, BP is continuously associated with cardiovascular outcomes from values as low as 115/75 mm Hg (Lewington et al 2002). Prospective, observational studies indicate that those with BP values in the normal/high-normal range (120-139/80-89 mm Hg) are at an increased risk for cardiovascular events (Hsia et al 2007, Conen et al 2007, Dorjgochoo et al 2009, Qureshi et al 2005, Vasan et al 2001, Blake et al 2003, Liszka et al 2005, Gu et al 2009, Zhang et al 2006, Butler et al 2011, Kshirsagar et al 2006). In addition, some randomised, controlled trials (Nissen et al 2004, Remme et al 2009, Staessen and Jiguang 2001, Schrier et al 2002, Patel 2007) and meta-analyses of BP lowering trials (Trialists Collaboration 2003, Law et al 2009) in high risk patients support a view that treatment of those with a normal/high-normal BP has benefits for outcomes. In contrast, several more recent intervention studies suggest that antihypertensive treatment to thresholds lower than 140/90 mm Hg has no added benefit (Yusuf et al 2008, Cushman et al 2010, McMurray et al 2010). Contrasting results of intervention studies in normal/high-normal BP ranges (Law et al 2009, Cushman et al 2010, Nissen et al 2004, McMurray et al 2010, Remme et al 2009, Staessen and Jiguang 2001, Yusuf et al 2008, Schrier et al 2002, Trialists Collaboration 2003, Patel 2007, Cooper-DeHoff et al 2010) highlight the markedly variable BP-related risk conferred by a normal/high-normal BP. Strategies are therefore required to better identify those with a normal/high-normal BP at risk for BP-related cardiovascular outcomes.

One possible reason for the variable BP-related cardiovascular risk in those with a normal/high-normal BP is that brachial BP measurements may be insufficiently accurate for risk determination. In this regard, prior studies indicate that a number of those with a normal/high-normal BP may have aortic BP values that are more consistent with either an optimal or hypertensive BP range (McEniery et al 2008). As aortic BP as assessed using easy and reproducible non-invasive measurements is more closely associated with

cardiovascular outcomes than brachial BP (Safar et al 2002, Wang et al 2009, Benetos et al 2010, Benetos et al 2012, Regnault et al 2012, Jankowski et al 2008, Pini et al 2008, Roman et al 2007, Roman et al 2009), non-invasive aortic BP measurement may further refine cardiovascular risk in those with a normal/high-normal BP. To test this hypothesis, in the present study I therefore assessed whether aortic BP enhances the ability to identify independent relationships between BP and target organ changes in the normotensive range and whether "optimal" aortic BP thresholds may refine the ability to identify end-organ changes in the normal/high-normal BP range.

2.3 Methods

The study protocol was approved by the University of the Witwatersrand Committee for Research in Human Subjects (approval numbers: M02-04-72 renewed as M07-04-69 and M12-04-108). Participants gave informed, written consent. The study design has previously been described (Norton et al 2008, Redelinghuys et al 2010, Norton et al 2012). Briefly, nuclear families of black African ancestry consisting of siblings with a minimum age of 16 years were randomly recruited from the South West Township (SOWETO) of Johannesburg, South Africa. Of the 1191 participants enrolled, 1169 had central aortic BP measurements and in these participants, carotid-femoral pulse wave velocity (PWV) was available in 1025 participants, estimated glomerular filtration rate (eGFR) in 944 participants, and in a substudy, echocardiographic data in 690 participants. 782 participants had ambulatory BP recordings that met with pre-specified quality control criteria (longer than 20 hours and more than 10 and 5 readings for the computation of daytime and night-time means, respectively).

2.3.1 Clinical, demographic and anthropometric measurements.

A standardized questionnaire was administered to obtain demographic data and information on each participant's medical history, smoking habits, intake of alcohol, use of medication, and menopausal status (Norton et al 2008, Redelinghuys et al 2010, Norton et al 2012). Height and weight were measured with participants standing, wearing indoor clothing and no shoes. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. 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. Waist circumference was measured using standard approaches. Laboratory blood tests of renal function, liver function, blood glucose, haematological parameters, lipid profiles and percentage glycated haemoglobin (HbA_{1C})(Roche Diagnostics, Mannheim, Germany) were performed. Diabetes mellitus was defined as the use of insulin or oral hypoglycaemic agents and an impaired blood glucose control was identified from an HbA_{1C}>6.1% (Bennett et al 2007).

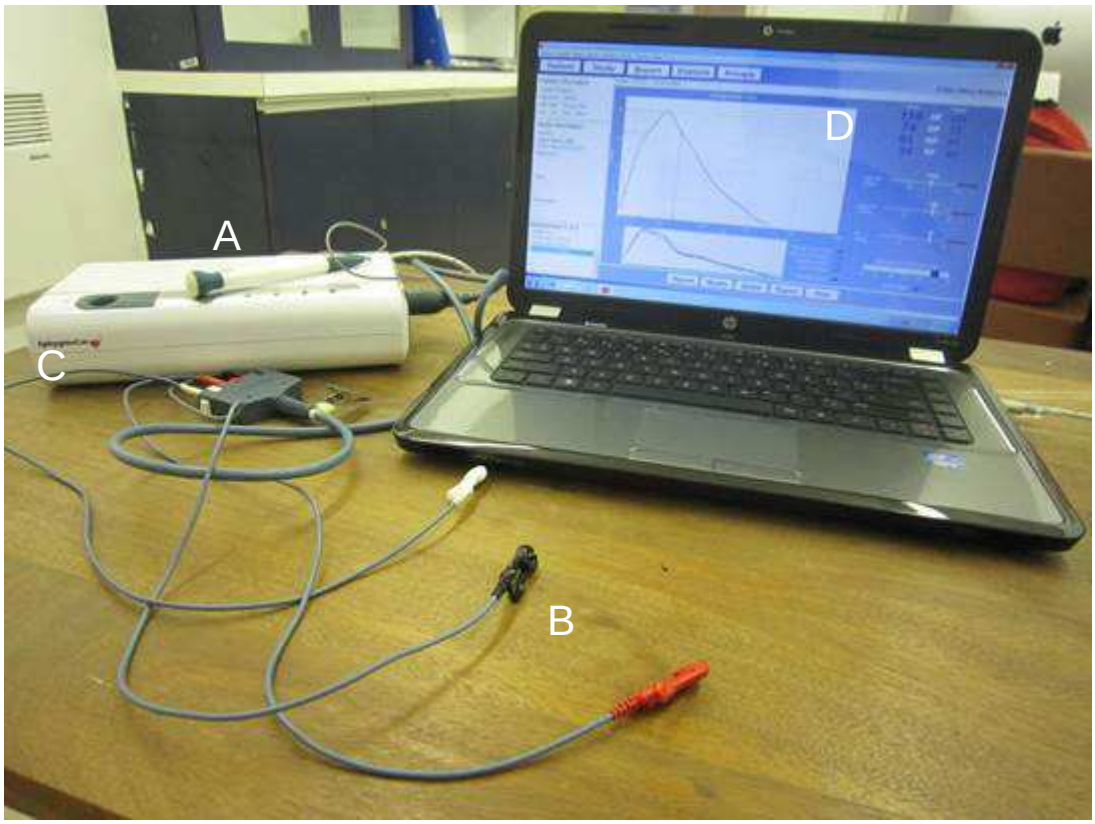
2.3.2 Conventional and 24-hour BP.

Nurse-derived conventional BP and 24-hour BP measurements were obtained as previously described (Norton et al 2008, Redelinghuys et al 2010). A trained nurse-technician measured conventional (brachial) blood pressure (BP) using a standard mercury sphygmomanometer. After participants had rested in a seated position for five minutes brachial BP was measured five consecutive times, 30 to 60 seconds apart. The cuff was deflated at approximately 2 mm Hg per second and Korotkov phases I and V were employed to identify systolic and diastolic BP respectively. Care was taken to avoid auscultatory gaps. Standard cuffs were used with an inflatable bladder with a length of 22 cm and a width of 12 cm except when arm circumference exceeded 31 cm, when larger cuffs with a 31 x 15 cm bladder were employed. The five readings were averaged to

obtain a single systolic and diastolic BP reading. Hypertension was defined as the presence of antihypertensive treatment or a mean conventional BP≥140/90 mm Hg; a high-normal BP as a conventional BP ≥130/85 and <140/90 mm Hg; a normal BP as a conventional BP ≥120/80 and <130/85 mm Hg; and an optimal BP as <120/80 mm Hg.

2.3.3 Aortic BP and target organ changes.

Aortic BP and carotid-femoral PWV were determined using applanation tonometry and SphygmoCor software as previously described (Norton et al 2008, Redelinghuys et al 2010, Norton et al 2012, Shiburi et al 2006). After participants had rested for 15 minutes in the supine position, arterial waveforms were determined at the radial (dominant arm) pulse 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) (Figure 2.1). 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. The pulse wave was calibrated by manual measurement (auscultation) of BP taken immediately before the recordings. From a validated inbuilt transfer function an aortic waveform was generated from which central systolic, diastolic and mean arterial BP were derived (Figure 2.2). Central PP (PPc) was determined from SphygmoCor software and mean arterial pressure (MAP) was calculated as [central diastolic BP + 1/3(central PP)]. Although applanation tonometry at the carotid artery is the most accurate non-invasive assessment of the forward and augmented pressures, carotid tonometry cannot be reliably applied in obesity (Laurent et al 2006). Considering the high prevalence of obesity in the study participants (≈43%) I therefore assessed the pressure components of PPc using radial tonometry.



A Applanation tonometer.

B Electrocardiograph electrodes.

C SphygmoCor device.

D Image of radial artery and aortic pressure waves recorded from a participant (see Figure 2.2 for further details).

Figure 2.1 SphygmoCor device coupled to an applanation tonometer used to determine central (aortic) haemodynamics and aortic pulse wave velocity.

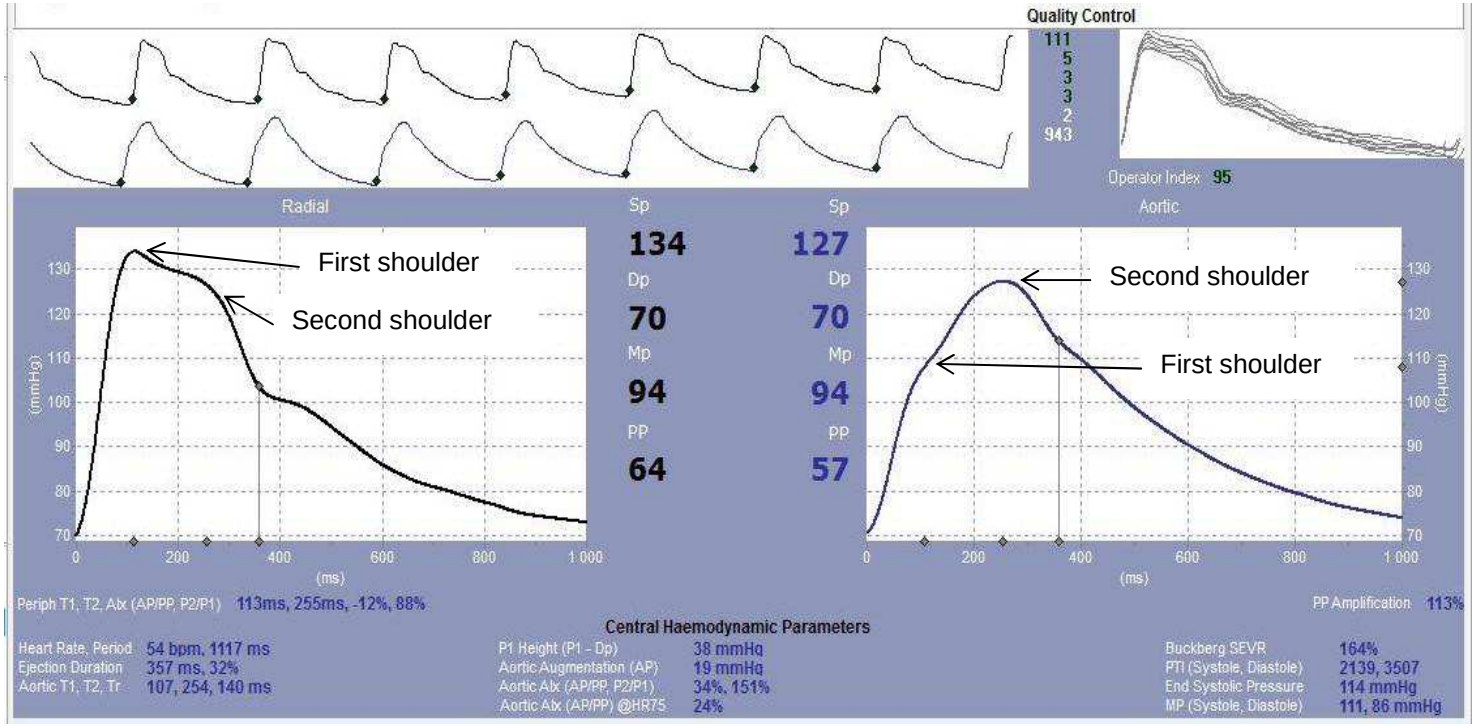


Figure 2.2. Example of a pulse wave recording obtained to determine central haemodynamics. The figure shows the radial artery pulse wave obtained from applanation tonometry (lower left panel) and the aortic pulse wave derived from a population-based transfer function built into the software (lower right panel). The first and second systolic shoulders are identified. See text for a further description. Quality control assessments are shown in the top panel. Sp, systolic blood pressure (BP); Dp, diastolic BP; MP, mean arterial pressure; PP, pulse pressure.

Aortic PWV was measured from sequential waveform measurements at carotid and femoral sites as previously described (Shiburi et al 2006) (Figure 2.3). 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.

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) (Levey et al 1999).

Echocardiographic measurements of left ventricular (LV) diastolic dimensions were performed using previously described methods (Norton et al 2008, Woodiwiss et al 2009, Norton et al 2012) (Figure 2.4). 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. 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 (Carlos D Libhaber and Angela J Woodiwiss) 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. 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 was derived according to an anatomically validated formula (Devereux et al 1986) and indexed to height$^{2.7}$ (LVMI).

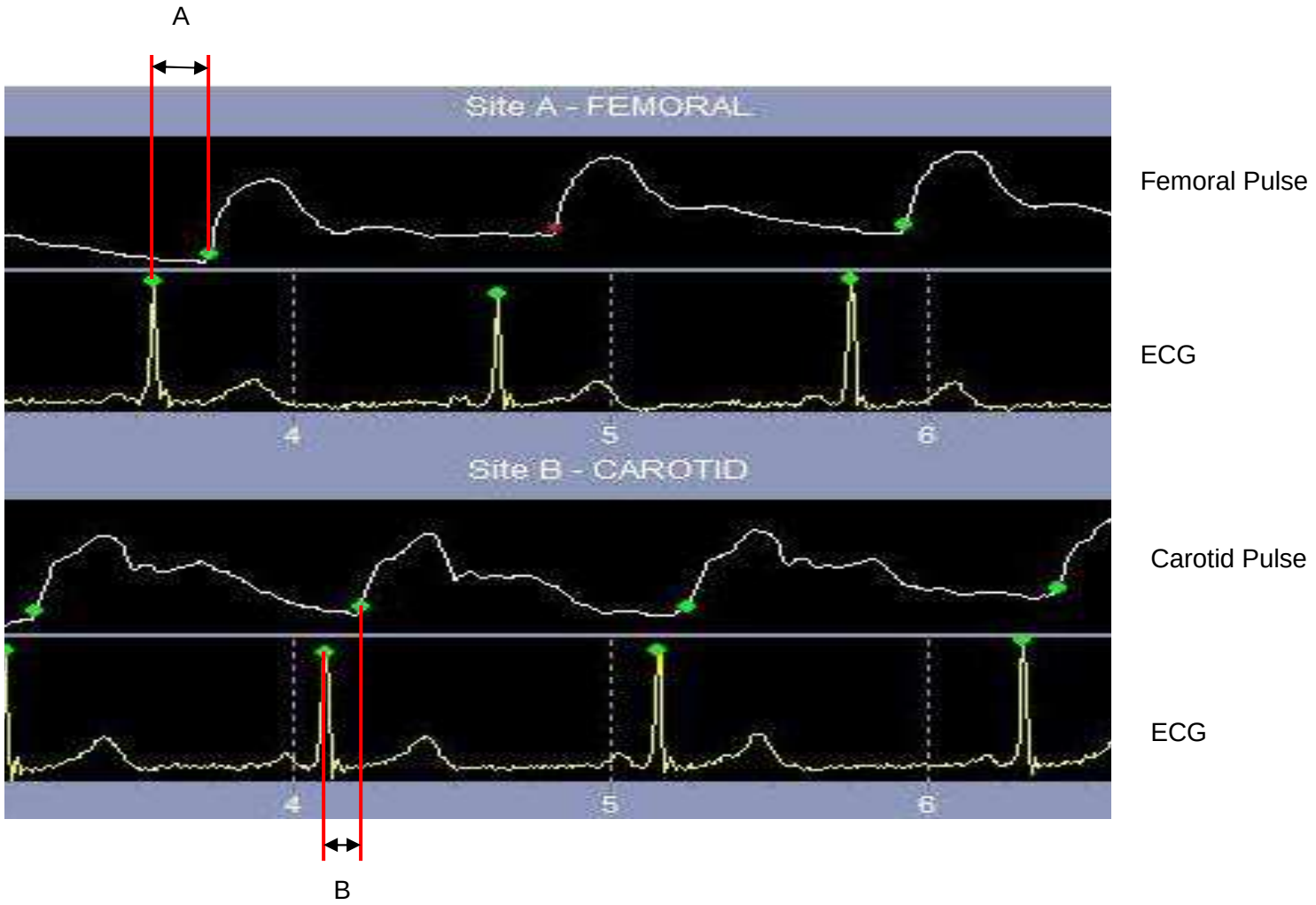


Figure 2.3 Representative example of simultaneous carotid pulse wave and electrocardiogram (ECG) recording and simultaneous femoral pulse wave and electrocardiogram recording. The speed of aortic wave travel is determined from difference between time A and time B.

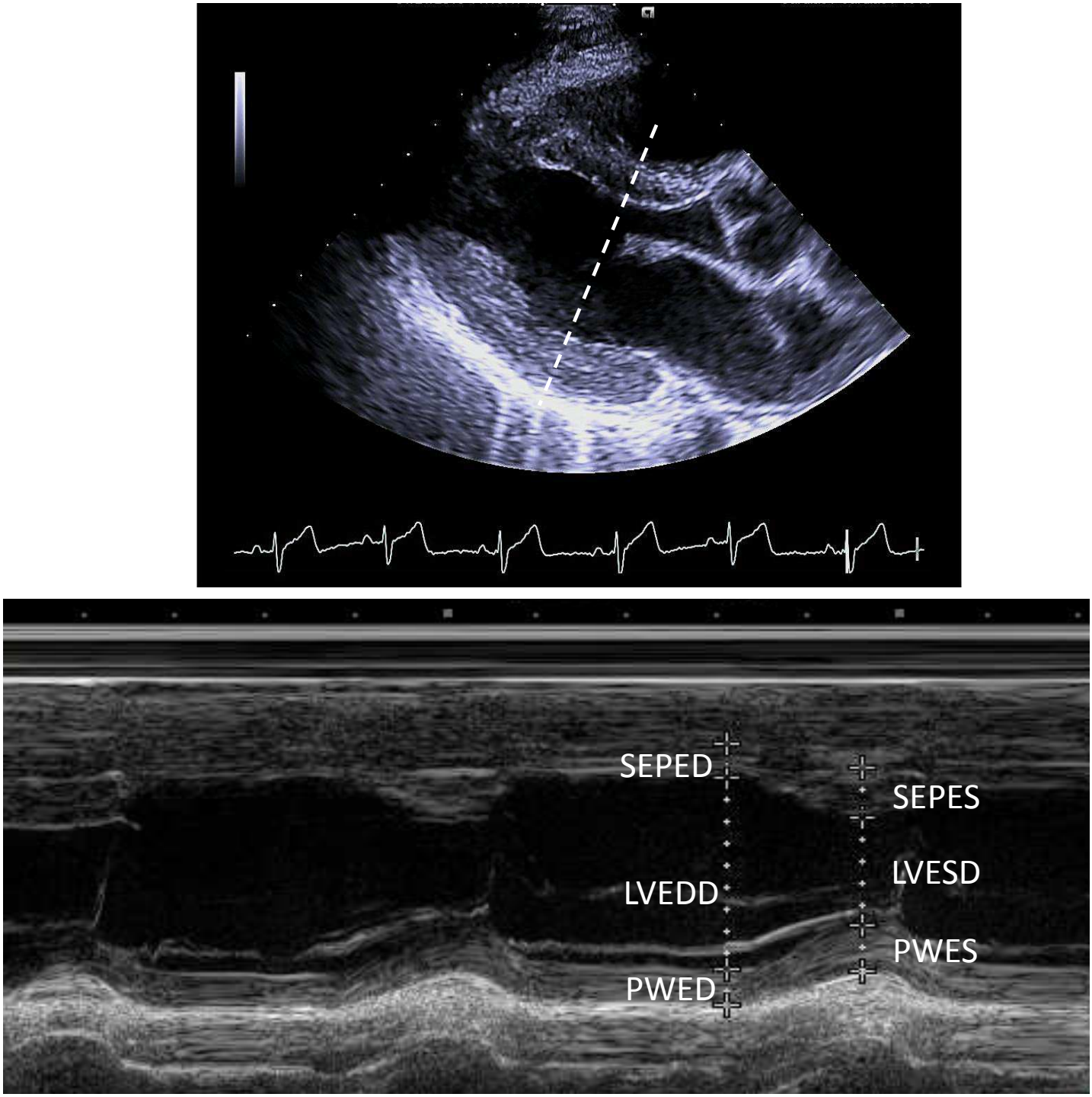


Figure 2.4. Representative example of a two-dimensional directed M-mode echocardiogram recording showing the dimension measurements employed to calculate left ventricular mass index. Note the position of the cursor in the long axis view of the left ventricle. SEPED = Septal wall thickness in end diastole. PWED = Posterior wall thickness in end diastole. SEPES = Septal wall thickness in systole. PWES = Posterior wall thickness in systole. LVEDD = Left ventricle internal diameter in end diastole. LVESD = Left ventricle internal diameter in end systole.

2.3.4 Data analysis.

For database management and statistical analysis, SAS software, version 9.1 (SAS Institute Inc., Cary, NC) was employed. Unadjusted means and proportions were compared by the large-sample z-test and the χ^2-statistic, respectively. Optimal thresholds for aortic and 24-hour BP were identified from upper 95% confidence intervals obtained in 311 participants with optimal conventional BP values and without diabetes mellitus, 212 of whom had 24-hour BP measurements that met with pre-specified quality control criteria. The aortic systolic BP threshold was identified as 112 mm Hg and the 24-hour systolic and diastolic BP thresholds as 123 and 78 mm Hg respectively. Differences in indices of organ changes between participants in categories of BP and independent relations between BP and target organ changes were determined using multivariate regression analysis with adjustments for age, sex, BMI, diabetes mellitus and/or an HbA1c>6.1%, regular tobacco use, regular alcohol intake and pulse rate in the models. 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).

2.4 Results

2.4.1 Characteristics of participants in categories of BP.

Of the total sample 27.3% of participants had either normal or high-normal BP. 16.5% had a normal BP and 10.8% had high-normal BP values. Age, BMI, waist circumference, and the frequency of participants who were overweight or obese were intermediate in those with a normal or high-normal BP between values noted in persons with an optimal BP and in hypertensives (Table 2.1). Hypertensives, but not those with a

Table 2.1 Characteristics of study participants.

BP categories	Optimal	Normal	High-normal	Hypertensives
BP range (mm Hg)	<120/80	≥120/80 and <130/85	≥130/85 and <140/90	≥140/90 or Treatment
Sample size (% female)	311 (69.1)	193 (62.7)	126 (61.1)	539 (64.9)
Age (years)	30.7±12.4	34.0±13.6	40.2±16.8***††	55.1±15.0***$^{\dagger\dagger\dagger\#\#}$
Body mass index (kg/m^2)	25.3±6.3	28.0±8.1**	29.6±8.0***†	32.4±7.9***$^{\dagger\dagger\dagger\#\#}$
Waist circumference (cm)	80.6±13.9	86.2±15.5**	89.2±15.1***	97.6±15.4***$^{\dagger\dagger\dagger\#\#}$
% Overweight/obese	21.2/22.5	22.8/32.6*	22.2/43.7**	23.9/57.9***$^{\dagger\dagger\dagger\#}$
Regular tobacco intake (%)	13.8	18.7	16.7	14.3
Regular alcohol intake (%)	18.7	21.8	25.4	21.9
% with DM or HbA_{1C}>6.1%	10.0	15.0	10.3	41.4***$^{\dagger\dagger\dagger\#\#}$
Pulse rate (beats/min)	69.5±11.3	69.5±10.9	69.0±11.0	69.4±10.3
total/HDL cholesterol	3.13±1.17	3.22±1.06	3.60±1.53	3.84±1.26***††

BP, blood pressure; DM, diabetes mellitus; HbA_{1C}, glycosylated haemoglobin; HDL:, high density lipoprotein. *p<0.05, **p<0.005, ***p<0.0001 vs optimal; †p<0.05, ††p<0.005, †††p<0.0005 vs normal; $^{\#}$p<0.005, $^{\#\#}$p<0.0001 vs high-normal.

normal or high-normal BP, had more diabetes mellitus and/or an impaired blood glucose control, and an increased total/HDL cholesterol (Table 2.1). No differences were noted between BP categories in regular alcohol and tobacco intake or pulse rate (Table 2.1).

2.4.2 Blood pressures and proportions with elevated aortic or ambulatory BP within BP categories.

Conventional, 24-hour and central aortic BP values were intermediate in those with a normal or high-normal BP between values noted in persons with an optimal BP and in hypertensives (Table 2.2). A greater proportion of hypertensives as well as those with a normal or high-normal BP had aortic systolic BP values that exceeded that of the upper 95% confidence intervals of healthy participants with an optimal BP (Table 2.2). Of those with a normal/high-normal BP, 45% had an aortic systolic BP that did not exceed the upper 95% confidence intervals of healthy participants with an optimal BP. A greater proportion of hypertensives and those with high-normal BP values, but not those with normal BP values had 24-hour systolic and diastolic BP values that exceeded that of the upper 95% confidence intervals of healthy participants with an optimal BP (Table 2.2).

2.4.3 Continuous relationships between various measures of BP and target organ changes in normotensive participants.

In normotensive participants (BP<140/90 mm Hg and no antihypertensive treatment), with adjustments for confounders, conventional and central aortic BP were correlated with target organ changes (Table 2.3). After further adjustments for aortic BP, the relationship between conventional BP and target organ changes in normotensives was abolished. In contrast, with further adjustments for conventional BP, aortic BP retained independent relationships with target organ changes in normotensives (Table 2.3). In addition, with further adjustments for 24-hour systolic BP, aortic BP also retained

Table 2.2. Blood pressures (BP) of study participants.

BP categories	Optimal	Normal	High-normal	Hypertensives
BP range (mm Hg)	<120/80	≥120/80 and <130/85	≥130/85 and <140/90	≥140/90 or Treatment
Sample size	311	193	126	539
Conventional SBP/DBP (mm Hg)	108±7/72±6	119±7/80±4***	128±8/86±4***†††	146±22/92±13***†††$^{\#\#\#}$
Aortic SBP (mm Hg)	100±13	110±7***	119±8***†††	136±22***†††$^{\#\#\#}$
Aortic pulse pressure (mm Hg)	26.6±11.0	29.1±7.5	33.6±8.8*	43.5±16.7***†††$^{\#\#\#}$
24-hour SBP (mm Hg)(n)	109±9(212)	113±9*(134)	117±11***†††(84)	127±16***†††$^{\#\#\#}$(352)
24-hour DBP (mm Hg)(n)	67±7(212)	69±7(134)	72±7*(84)	78±11***†††$^{\#\#\#}$(352)
n (%) with aortic SBP>threshold‡	16 (5)	75 (39)***	99 (80)***†††	471 (88)***†††$^{\#}$
n (%) with 24-hour SBP>threshold‡‡	12 (6)	16 (12)	21 (25)*†	201 (57)***†††$^{\#\#\#}$
n (%) with 24-hour DBP>threshold‡‡	11 (5)	10 (8)	18 (21)**††	147 (42) ***†††$^{\#\#}$

SBP, systolic BP; DBP, diastolic BP. ‡Upper threshold for aortic SBP in those with an optimal conventional BP=112 mm Hg; ‡‡Upper threshold for 24-hour SBP/DBP in those with an optimal conventional BP=123/78 mm Hg. *p<0.05, **p<0.005, ***p<0.0001 vs optimal; †p<0.05, ††p<0.005, †††p<0.0005 vs normal; $^{\#}$p<0.05, $^{\#\#}$p<0.005, $^{\#\#\#}$p<0.0001 vs high-normal.

Table 2.3. Multivariate adjusted relationships between systolic blood pressure (SBP) and target organ changes in normotensive participants (conventional BP<140/90 mm Hg).

BP vs	n	partial r	CI	p-value	partial r	CI	p-value
		SBPc adjusted for*			SBPc adjusted for aortic SBP+*		
Pulse wave velocity	568	0.24	0.16 to 0.32	<0.0001	0.05	-0.03 to 0.13	=0.24
Estimated GFR	501	-0.10	-0.19 to -0.01	<0.05	0.06	-0.03 to 0.14	=0.22
LV mass index	372	0.20	0.10 to 0.30	<0.0001	-0.05	-0.15 to 0.06	=0.36
		Aortic SBP adjusted for*			Aortic SBP adjusted for SBPc+*		
Pulse wave velocity	568	0.26	0.18 to 0.34	<0.0001	0.12	0.04 to 0.20	<0.005
Estimated GFR	501	-0.17	-0.25 to -0.08	<0.0005	-0.15	-0.23 to -0.06	=0.001
LV mass index	372	0.28	0.18 to 0.37	<0.0001	0.20	0.10 to 0.30	=0.0001

CI, confidence intervals; SBPc, conventional systolic BP; GFR, glomerular filtration rate; LV, left ventricle. *Adjustments are for age, sex, BMI, diabetes mellitus and/or an HbA1c>6.1%, regular tobacco intake, regular alcohol intake and pulse rate.

independent relationships with target organ changes in normotensives (PWV; partial r=0.18, confidence intervals=0.08 to 0.28, p<0.0005, n=389; eGFR; partial r= -0.15, confidence intervals= -0.25 to -0.04, p<0.01, n=342; LVMI; partial r=0.22, confidence intervals=0.10 to 0.33, p<0.0005, n=265).

2.4.4 Target organ changes in those with a normal or high-normal BP irrespective of aortic BP.

Before adjustments for confounders, as compared to participants with optimal BP values, hypertensives and those with either normal or high-normal BP values had a markedly increased PWV and LVMI and decreased eGFR (Table 2.4). However, after adjustments for confounders, only modest target organ changes were noted in those with a normal or high-normal BP (Table 2.4). Moreover, normal versus high-normal BP categories failed to distinguish between those with and without target organ changes (Table 2.4).

2.4.5 Aortic BP distinguishes target organ changes in those with a normal/high-normal BP.

As compared to those with an optimal BP, both unadjusted and multivariate adjusted target organ changes were consistently noted in those with a normal/high-normal BP with, but not in those without aortic systolic BP values≥upper 95% confidence interval for healthy participants with optimal BP values (Table 2.5). Importantly, even those with a normal as opposed to high-normal conventional BP values, but whom had an aortic BP that exceeded “optimal” values had multivariate adjusted decreases in eGFR

Table 2.4. Unadjusted and multivariate adjusted indices of target organ changes of study participants.

BP categories	Optimal	Normal	High-normal	Hypertensives
BP range (mm Hg)	<120/80	≥120/80 and <130/85	≥130/85 and <140/90	≥140/90 or Treatment
Unadjusted values				
PWV (m/sec)(n)	4.83±1.24(289)	5.36±1.55*(172)	6.09±1.97**(107)	7.90±2.99***$^{\dagger\dagger\dagger\#\#\#}$(457)
eGFR (mls/min/1.73 m^2)(n)	128±32(244)	122±29*(153)	111±28**(104)	103±28***$^{\dagger\dagger\dagger\#}$(443)
LV mass index (g/$m^{2.7}$)(n)	35.5±10.2(181)	41.1±11.2**(117)	42.2±13.3**(74)	47.5±15.8***$^{\dagger\dagger\dagger\#\#}$(318)
Multivariate adjusted values				
PWV (m/sec)(n)	5.89±2.21(289)	6.15±1.97(172)	6.34±1.97(107)	6.87±2.35***$^{\dagger\dagger\dagger\#}$(457)
eGFR (mls/min/1.73 m^2)(n)	117±31(244)	113±28(153)	108±27*(104)	113±31(443)
LV mass index (g/$m^{2.7}$)(n)	40.3±14.4(181)	43.6±13.0*(117)	42.4±12.6(74)	43.8±14.6*(318)

BP, blood pressure; PWV, aortic pulse wave velocity; eGFR, estimated glomerular filtration rate; LV, left ventricle. Adjustments are for age, sex, BMI, diabetes mellitus and/or an HbA1c>6.1%, regular tobacco use, regular alcohol intake and pulse rate. *p<0.05, **p<0.005, ***p<0.0001 vs optimal; †p<0.05, ††p<0.005, †††p<0.0005 vs normal; $^{\#}$p<0.05, $^{\#\#}$p<0.005, $^{\#\#\#}$p<0.0001 vs high-normal.

Table 2.5. Unadjusted and multivariate adjusted indices of target organ changes of prehypertensives with (Yes) or without (No) aortic systolic blood pressures (SBP) greater than thresholds (112 mm Hg) defined in those with optimal conventional BP values.

Blood pressure categories	Optimal	Normal/high-normal		Hypertensives
Blood pressure range (mm Hg)	<120/80	≥120/80 and <140/90		≥140/90 or
		with aortic SBP≥112 mm Hg		Treatment
		No	Yes	
Unadjusted values				
Pulse wave velocity (m/sec)(n)	4.83±1.24(289)	5.07±1.30 (128)	6.12±1.94***†††(151)	7.90±2.99$^{***\dagger\dagger\dagger\#\#\#}$(457)
Estimated GFR (mls/min/1.73 m^2)(n)	128±32(244)	126±32(108)	111±26***†††(149)	103±28$^{***\dagger\dagger\dagger\#\#}$(443)
LV mass index (g/$m^{2.7}$)(n)	35.5±10.2(181)	38.2±11.0(82)	44.0±12.1***†††(109)	47.5±15.8$^{***\dagger\dagger\dagger\#}$(318)
Multivariate adjusted values				
Pulse wave velocity (m/sec)(n)	5.89±2.21(289)	6.09±2.05(128)	6.30±1.95*(151)	6.87±2.29$^{***\dagger\dagger\dagger\#\#}$(457)
Estimated GFR (mls/min/1.73 m^2)(n)	118±29(244)	115±27(108)	108±26**†(104)	112±30*(443)
LV mass index (g/$m^{2.7}$)(n)	40.0±14.3(181)	40.7±13.2(82)	44.5±12.6**†(109)	44.0±14.6*(318)

eGFR, estimated glomerular filtration rate LV, left ventricle. Adjustments are for age, sex, BMI, diabetes mellitus and/or an HbA1c>6.1%, regular tobacco use, regular alcohol intake and pulse rate. *p<0.05, **p<0.005, ***p<0.0001 vs optimal; †p<0.05, ††p<0.005, †††p<0.0005 vs aortic BP<112 mm Hg; $^{\#}$p<0.05, $^{\#\#}$p<0.005, $^{\#\#\#}$p<0.0001 vs aortic BP≥112 mm Hg.

(mls/min/1.73 m^2)(108±4 vs 116±2, $p<0.05$) and increases in LVMI ($g/m^{2.7}$)(46.7±1.8 vs 40.8±1.2, $p<0.005$).

2.5 Discussion

The main findings of the present study are as follows: First, in a randomly selected community sample, although a normal/high-normal BP was noted in 27% of the sample, 45% of these participants had central aortic BP values that did not exceed the upper 95% confidence interval of aortic BP values in healthy participants with optimal BP values. Second, normal and high-normal BP categories failed to identify those with target organ changes. In contrast, in those with either a normal or high-normal BP, aortic BP values above “optimal” thresholds clearly identified those with target organ changes.

Persons with a BP in the normal/high-normal range are considered at sufficient risk to warrant antihypertensive therapy if in-part they have diabetes mellitus, or established cardiovascular or renal disease (Mancia et al 2007). However, intervention studies targeting high risk patients with pre-existing cardiovascular disease or diabetes mellitus have produced discrepant outcomes (Law et al 2009, Cushman et al 2010, Nissen et al 2004, McMurray et al 2010, Remme et al 2009, Staessen and Jiguang 2001, Yusuf et al 2008, Schrier et al 2002, Trialists Collaboration 2003, Patel 2007, Cooper-DeHoff et al 2010). This approach nevertheless assumes that most high risk patients with normal/high-normal conventional BP values would benefit from BP lowering therapy. In contrast, as indicated in the present study, in those participants with normal/high-normal BP values whom also had “optimal” aortic BP values (45% of participants), no evidence of target organ changes were noted. Thus, a high proportion of persons with a normal/high-normal BP are not at risk for BP-related sub-clinical cardiovascular disease.

As suggested by guidelines (Mancia et al 2007), the presence of organ damage may identify persons with a BP in the high-normal range at sufficient risk to warrant antihypertensive therapy. Indeed, two recent studies indicate that by adding markers of

sub-clinical cardiovascular disease to traditional risk assessment, risk prediction may be considerably improved (Sehestedt et al 2009, Sehestedt et al 2010). However, the mean BP values in those experiencing a cardiovascular event in the one study (Sehestedt et al 2010) suggest that almost half of these participants were hypertensive. Moreover, in the other study (Sehestedt et al 2009), 42% were hypertensives. Thus, in neither of these studies (Sehestedt et al 2009, Sehestedt et al 2010) can conclusions be drawn from data obtained only in the normotensive range. Moreover, in these studies (Sehestedt et al 2009, Sehestedt et al 2010), the presence of sub-clinical cardiovascular disease identified using one measure of target organ change, did not necessarily imply the presence of sub-clinical cardiovascular disease using another measure. Thus, the benefit of target organ assessment would require the evaluation of sub-clinical cardiovascular disease in multiple organs (Sehestedt et al 2009, Sehestedt et al 2010). This combined approach would incur considerable costs, necessitate the use of trained technicians, and not necessarily identify organ damage attributed to BP effects as opposed to alternative risk factors. In contrast, aortic BP measurements are simple, reliable and reproducible, are likely to incur considerably lower costs, and reflect the impact of BP rather than alternative risk factors.

In the present study 39% of those with a BP in the normal conventional BP range as compared to 80% in the high-normal BP range had aortic BP values that exceeded “optimal” values. Rather than measure aortic BP, a more cost-effective approach could therefore be to treat those with a high-normal, but not a normal BP. However, 75 of the total sample of 319 participants with a normal or high-normal conventional BP had a normal conventional, but an increased aortic BP. Importantly, these individuals had multivariate adjusted decreases in eGFR and increases in LVMI. Hence, approximately one quarter of all those with a normal/high-normal BP at risk of sub-clinical cardiovascular disease would be excluded from potentially necessary antihypertensive therapy if treatment were withheld from those with a normal BP. Clearly, this dilemma would be avoided if aortic BP rather than normal versus high-normal conventional BP categories were employed to identify at-risk persons.

In the present study, in those with normal/high-normal BP values, aortic BP was associated with an increased PWV, an index of aortic stiffness. This relationship may be explained, not only by an effect of BP on aortic stiffness, but also by an impact of aortic stiffness on central BP. If increases in aortic stiffness mediate aortic BP changes in those with normal/high normal BP values, therapeutically targeting aortic stiffness may prevent the progression to hypertension. In this regard, a normal/high-normal BP is a risk factor for the development of hypertension and progression to hypertension may occur within 10 years in 80% of those with a normal/high-normal BP (Moreira et al 2008).

The present results suggest that assessing the impact of BP lowering therapy on cardiovascular outcomes in those with normal/high-normal BP values may warrant the selection of only those participants with central aortic BP values that exceed optimal values. If this approach were adopted, a decrease in the heterogeneity of the impact of BP lowering therapy on outcomes may occur in those with a normal/high-normal BP, which as outcome studies have demonstrated (Law et al 2009, Cushman et al 2010, Nissen et al 2004, McMurray et al 2010, Remme et al 2009, Staessen and Jiguang 2001, Yusuf et al 2008, Schrier et al 2002, Trialists Collaboration 2003, Patel 2007, Cooper-DeHoff et al 2010), is large.

In normotensives from the present randomly selected community sample, only 14% had day BP values that exceeded 135/85 mm Hg (masked hypertension). In contrast, in employees of a university hospital or private company (Shimbo et al 2012) or in referrals to a hypertension clinic (Manios et al 2011) 34% and 24.7% respectively of those with a normal/high-normal BP had masked hypertension and only those with masked hypertension had target organ changes. As masked hypertension is independently associated with cardiovascular outcomes, it is possible that ambulatory BP monitoring also has an important role to play in further refining risk in those with a normal/high-normal BP, at least in groups with a high prevalence of masked hypertension.

The limitations of the present study include the cross-sectional design which prevents conclusions being drawn regarding cause and effect, and the use of target organ

changes as surrogates for risk. Prospective studies are therefore required to assess whether aortic BP measurements identify earlier separation of curves describing cardiovascular outcomes in those with a normal/high-normal BP as compared to those with an optimal BP. In this regard, those persons with a normal/high-normal BP may experience significantly more cardiovascular events only 10-15 years after detection (Fukuhara et al 2012). Moreover, the present study was conducted only in a group of black African ancestry. Corroboration of the present findings is required in other ethnic groups. Last, as thresholds for central aortic BP values have not been identified from outcome-based studies, thresholds were identified from participants with optimal brachial BP values.

In conclusion, in contrast to the lack of ability of normal or high-normal BP categories to identify normotensives with target organ changes, in the present study I show that in normotensives, “optimal” central aortic BP values clearly identify the presence of target organ changes. Thus, the use of aortic BP measurements may enhance the ability to risk stratify those with a normal/high-normal brachial BP. Whether further refinement of risk stratification in pre-hypertensives may be achieved by assessing the impact of reflected waves, which have been demonstrated in several studies to predict outcomes beyond brachial BP (Wang et al 2010, Weber et al 2012, Chirinos et al 2012, Torjesen et al 2014), requires further study. This question was addressed in Chapter 4. However, before this question could be answered I first evaluated whether whether indices of pressure augmentation are sufficient to assess the impact of wave reflection on age-related increases in aortic pressure or end-organ changes across the adult lifespan or whether reflected wave effects should be assessed from wave separation analysis? This question was addressed in the next chapter (Chapter 3).

Chapter 3

Indexes of Aortic Pressure Augmentation Markedly Underestimate the Contribution of Reflected Waves Toward Variations in Aortic Pressure and Left Ventricular Mass.

The data in this chapter has been accepted for publication in the journal *Hypertension:*

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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 is uncertain. In participants from a community sample (age>16 years) the relative contribution 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), and left ventricular mass index (LVMI [n=793]) were compared. Aortic haemodynamics and LVMI were determined using radial applanation tonometry (SphygmoCor) and echocardiography. 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 those <50 years of age, while Pb (partial $r=0.28$, $p<0.0001$) contributed more than Pf (partial $r=0.15$, $p<0.001$, $p<0.05$ for comparison of r values), Pa (partial $r=0.13$, $p<0.005$) contributed to a similar extent as Pi (partial $r=0.22$, $p<0.0001$) to variations in LVMI. Further, in those ≥50 years of age, Pb (partial $r=0.21$, $p<0.0001$), but not Pf ($p=0.98$), whilst Pi (partial $r=0.23$, $p<0.0001$), but not Pa ($p=0.80$) were associated with LVMI. Thus, as compared to relations between indices of aortic pressure augmentation and PPc or LVMI, strikingly better relations are noted between aortic wave reflection and PPc or LVMI.

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 (Avolio 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 (Avolio 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), indices of wave reflection, are associated with cardiovascular outcomes (London et al 2001, Ueda et al 2004, Weber et al 2005, Chirinos et al 2005b, Vlachopoulos et al 2005) and sub-clinical cardiovascular disease (Hashimoto et al 2007, Hashimoto et al 2006, Weber et al 2006, Westerbacka et al 2005, Sibiya et al 2014) independent of brachial BP. Although in several of these studies (Davies et al 2010, Hughes et al 2013, Fok et al 2014), the method of wave intensity analysis has been seriously questioned on methodological and theoretical grounds (Segers et al 2015), and Fok et al (2014) report an impossible flow-frequency response, apparently hand-drawn representative waves are shown, and control impedance values are given that differ markedly from Yaginuma et al (1985), more recently the use of Pa or AIx as indices of wave reflection in risk prediction has been challenged (Davies et al 2010, Cheng et al 2012, Hughes et al 2013, Fok et al 2014, Torjesen et al 2014, Schultz et al 2013).

Although in several of these studies (Davies et al 2010, Hughes et al 2013, Fok et al 2014), the method of wave intensity analysis has been seriously questioned on methodological and theoretical grounds (Segers et al 2015), and Fok et al (2014) report an impossible flow-frequency response, apparently hand-drawn representative waves are shown, and control impedance values are given that differ markedly from Yaginuma et al (1985), marked overlap between aortic forward and reflected waves may confound Pa and

AIx (Cheng et al 2012, Fok et al 2014, Torjesen et al 2014, Schultz et al 2013) and hence these measures may be poor indices of wave reflection. Indeed, there is a weak relationship between the magnitude of the reflected wave and Pa or AIx with increases in the timing or magnitude of the forward (Pf) or incident (Pi) wave pressures, and left ventricular systolic function playing a more important role than wave reflection in contributing to variations in Pa and AIx (Cheng et al 2012, Hughes et al 2013, Fok et al 2014, Torjesen et al 2014, Schultz et al 2013). More recent studies have therefore focussed 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 sub-clinical cardiovascular disease (Wang et al 2010, Chirinos et al 2012, Weber et al 2012, Zamani et al 2014, Cooper et al 2014). However, in these studies (Wang et al 2010, Chirinos et al 2012, Weber et al 2012, Zamani et al 2014, Cooper et al 2014) the extent to which Pb or RI are more closely associated with PPc or sub-clinical cardiovascular disease than Pa or AIx is uncertain. In this regard in these studies, relations with sub-clinical cardiovascular disease were not adjusted for confounders (Wang et al 2010, Weber et al 2012) discrepancies in the index of wave reflection that was better associated with sub-clinical cardiovascular disease beyond forward wave pressures were noted (Wang et al 2010, Weber et al 2012); and whether the increase in forward wave pressures at 50 years of age impacts on these relations was not considered (Wang et al 2010, Chirinos et al 2012, Weber et al 2012). In addition, although in the Framingham Heart Study little difference in aortic and brachial BP was noted across the adult lifespan (Mitchell et al 2010b), an effect that has been explained on the basis of the application of tonometry at a site where the principles of tonometry cannot be achieved (brachial artery to calibrate the carotid artery pulse) (O'Rourke et al 2010), aortic forward wave pressure rather than Pb was reported to be the main determinant of PPc and outcomes (Mitchell et al 2010b, Cooper et al 2014). To clarify the extent to which indices of aortic systolic pressure augmentation underestimate the impact of wave reflection on cardiovascular disease, in the present study I therefore aimed to evaluate, in a large

community-based sample with a high prevalence of uncontrolled BP, the degree to which Pb or RI are more closely related to multivariate adjusted increases in PPc and left ventricular mass index (LVMI) beyond forward wave pressures than Pa or AIx, and whether these effects are age-specific.

3.3 Methods

3.3.1 Study group.

The present study has been described in chapter 2, page 60. In the present analysis 1185 participants were evaluated and in a sub-study, 793 participants had LVMI determined using echocardiography.

3.3.2 *Clinical, demographic and anthropometric measurements.*

The clinical, demographic and anthropometric measurements have been described in chapter 2, page 61.

3.3.3 Pulse wave analysis.

Central aortic blood pressures were estimated using radial applanation tonometry and SphygmoCor software as described in chapter 2, page 62 (Sibiya et al 2014). 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. Pb and Pf were determined using SphygmoCor software

which separates the aortic waveform using a triangular flow wave (Westerhof et al 2006). Reflected wave index (RI) was calculated as Pb/(Pf+DBP) as previously described (Hughes et al 2013). In the present study I 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 (Kips et al 2009) 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.

3.3.4 Echocardiography.

Left ventricular mass (LVM) and stroke volume were determined from transthoracic two-dimensional targeted M-mode echocardiographic images obtained in the parasternal long-axis view as largely described in chapter 2, page 65 (Sibiya et al 2014). Left ventricular mass was 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 Data 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 haemodynamic 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). As a sharp age-related increase in Pf and Pi occurred between 40 and 50 years of age, relationships between aortic haemodynamic variables and PPc or LVMI were evaluated in participants < or ≥50 years of age. To ensure that relationships occured 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.

3.4.2 Age-related increases in aortic haemodynamics.

Pb, Pa and RI increased linearly across the adult lifespan, whilst Pf and Pi increased from between 40 and 50 years of age (Figure 3.1). In contrast, age-related

increases in AIx showed an increase in early life, which peaked at 50 years and then failed to further increase with age (Figure 3.1). In multivariate-adjusted models, including

Table 3.1. Characteristics of the study sample.

Characteristics	All (n=1185)	<50 years (n=703)	≥50 years (n=482)
% Female	65.0	64.6	65.8
Age (years)	44.3±18.3	31.4±10.0	63.0±9.2
Body mass index (kg/m^2)	29.6±8.1	27.4±7.4	32.7±8.0
% Obese	43.3	32.9	58.5
Regular tobacco (% subjects)	15.2	17.1	12.5
Regular alcohol (% subjects)	20.9	23.6	17.0
% with DM or HbA1c>6.1%	25.8	12.4	45.4
% Hypertensive	45.9	24.0	77.8
% Treated for hypertension	24.2	6.3	50.4
% Hypertensives controlled to target BP	20.8	13.0	24.3
% of all with uncontrolled BP	36.4	20.9	58.9
Pulse rate (beats/min)	66±12	65±11	67±13
Brachial SBP/DBP (mm Hg)	130±22/84±13	121±17/81±12	143±23/88±12
Brachial pulse pressure (mm Hg)	46±16	39±13	53±18
Brachial mean arterial pressure (mm Hg)	100±16	95±14	108±16
Central aortic SBP (mm Hg)	120±23	111±18	133±23
Central aortic pulse pressure (PPc) (mm Hg)	35±15	29±11	44±16
Aortic forward wave pressure (Pf) (mm Hg)	24±9	21±7	28±10
Aortic reflected wave pressure (Pb)(mm Hg)	17±8	14±6	22±9
Aortic reflected wave index	0.16±0.06	0.13±0.04	0.19±0.06
Aortic augmented pressure (Pa)	11±8	7±6	15±8
Aortic Pi	25±9	22±7	29±10
Aortic augmentation index (AIx) (%)	142±25	135±24	153±23
Stroke volume (mls)(n)	63±17 (793)	61±16 (468)	65±18 (325)
Left ventricular mass index (g/m^2)(n)	76±31 (793)	70±27 (468)	84±34 (325)
Left ventricular mass index (g/m$^{1.7}$)(n)	67±24 (793)	61±20 (468)	76±27 (325)

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.

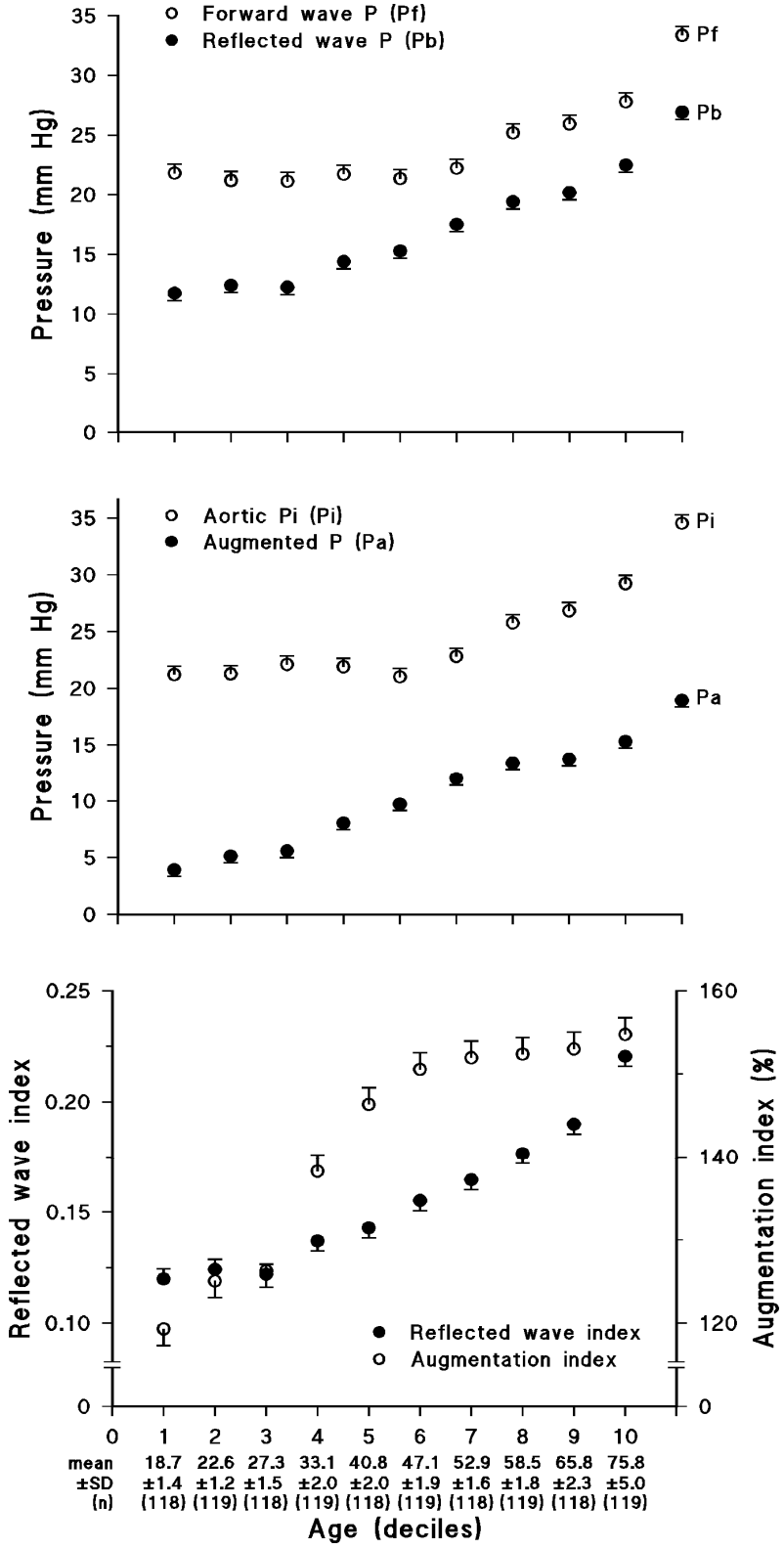


Figure 3.1. Central (aortic) haemodynamic variables across deciles of age of the adult lifespan in a group of African descent (n=1185). See table 2 for multivariate adjusted relationships between age and aortic haemodynamic value in participants < or ≥ 50 years of age. Pi=Aortic pulse pressure-Pa. Mean±SD age in years and sample size at each decile of age are given in the figure.

adjustments for mean arterial pressure (MAP), Pb, Pa and RI were independently and positively associated with age above and below 50 years of age, while Pf and Pi were only positively associated with age above 50 years of age and AIx was associated with age below 50 years of age (Table 3.2). Similar findings were noted in participants not receiving antihypertensive therapy (Table 3.3). A modest relationship between age and stroke volume was noted in participants over 50 years of age only (Table 3.2).

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

When included in separate models (Table 3.4) or in the same multivariatte stepwise models (Figure 3.2) in participants either < or ≥50 years of age, a stronger relationship was noted between RI and PPc or Pb and PPc than between Pf and PPc or AIx and PPc. Similar data were obtained irrespective of whether MAP derived from the equation MAP=DBP + [(SBP-DBP)/3] or from SphygmoCor software (brachial form factor) was included as an adjustor (Appendices 4 and 5). In contrast, a stronger relationship was noted between Pi and PPc, than between Pa and PPc (Table 3.4 and appendix 4) or between AIx and PPc (Table 3.4, Figure 3.2 and appendices 4 and 5). 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 3.2 and appendix 5). Similar findings were noted in participants not receiving antihypertensive therapy (Tables 3.5 and 3.6). 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 3.7).

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

Age versus	Estimate (mm Hg)* (±SEM)	partial r (95% CI)	p-value
	<50 years (n=703)		
Forward wave pressure (Pf)	-0.17±0.05	-0.14 (-0.22 to -0.07)	<0.0005
Reflected wave pressure (Pb)	0.31±0.07	0.17 (0.09 to 0.24)	<0.0001
Reflected wave index (RI=Pb/Pf)	42±8	0.20 (0.13 to 0.28)	<0.0001
Aortic Pi	-0.15±0.05	-0.12 (-0.02 to -0.05)	<0.005
Aortic augmented pressure (Pa)	0.65±0.07	0.34 (0.23 to 0.04)	<0.0001
Aortic augmentation index (AIx)	0.17±0.01	0.43 (0.36 to 0.49)	<0.0001
Stroke volume (n=468)	-0.02±0.03	-0.03 (-0.12 to 0.06)	=0.47
	≥50 years (n=482)		
Forward wave pressure (Pf)	0.30±0.04	0.31 (0.23 to 0.39)	<0.0001
Reflected wave pressure (Pb)	0.42±0.05	0.36 (0.28 to 0.44)	<0.0001
Reflected wave index (Pb/Pf)	69±7	0.33 (0.25 to 0.41)	<0.0001
Aortic Pi	0.40±0.05	0.36 (0.28 to 0.44)	<0.0001
Aortic augmented pressure (Pa)	0.56±0.06	0.30 (0.21 to 0.38)	<0.0001
Aortic augmentation index (AIx)	0.03±0.02	0.07 (-0.02 to 0.16)	=0.10
Stroke volume (n=325)	0.07±0.03	0.14 (0.03 to 0.25)	<0.05

SEM, Standard error of the mean; CI, confidence intervals; Pi=Aortic pulse pressure-Pa. *β-coefficient (slope) of the relations. Pi=aortic pulse pressure-Pa. Adjustors are sex, mean arterial pressure, body height, body weight, pulse rate, diabetes mellitus or an HbA1c>6.1%, regular smoking and regular alcohol intake.

Table 3.3. Multivariate adjusted relations between age and central aortic haemodynamics in age-specific categories in participants from a group of African ancestry not receiving antihypertensive therapy (n=898).

Age versus	Estimate (mm Hg)* (±SEM)	partial r (95% CI)	p-value
	<50 years (n=659)		
Forward wave pressure (Pf)	-0.19±0.05	-0.15 (-0.22 to -0.07)	=0.0001
Reflected wave pressure (Pb)	0.34±0.08	0.18 (0.10 to 0.25)	<0.0001
Reflected wave index (Pb/Pf)	47±9	0.21 (0.14 to 0.28)	<0.0001
Aortic Pi	-0.16±0.05	-0.13 (-0.21 to -0.06)	=0.0005
Aortic augmented pressure (Pa)	0.72±0.07	0.37 (0.31 to 0.44)	<0.0001
Aortic augmentation index (AIx)	0.19±0.01	0.46 (0.40 to 0.52)	<0.0001
	≥50 years (n=239)		
Forward wave pressure (Pf)	0.47±0.06	0.44 (0.32 to 0.53)	<0.0001
Reflected wave pressure (Pb)	0.66±0.07	0.51 (0.41 to 0.60)	<0.0001
Reflected wave index (Pb/Pf)	80±10	0.48 (0.37 to 0.57)	<0.0001
Aortic Pi	0.52±0.06	0.47 (0.36 to 0.56)	<0.0001
Aortic augmented pressure (Pa)	0.61±0.08	0.44 (0.33 to 0.54)	<0.0001
Aortic augmentation index (AIx)	0.05±0.03	0.11 (-0.02 to 0.24)	=0.09

SEM, Standard error of the mean; CI, confidence intervals; Pi=Aortic pulse pressure-Pa. *β-coefficient (slope) of the relations. Adjustors are sex, mean arterial pressure, body height, body weight, pulse rate, diabetes mellitus or an HbA1c>6.1%, regular smoking and regular alcohol intake.

Table 3.4. Independent relationships between aortic hemodynamics and central aortic pulse pressure (PPc) in age-specific categories in a group of African ancestry.

PPc vs	<50 years (n=703)		≥50 years (n=482)	
	partial r (CI)*	p value	partial r (CI)*	p value
Pb	0.87 (0.80 to 0.95)[†]	<0.0001	0.97 (0.88 to 1.10)[†]	<0.0001
Pf	0.65 (0.58 to 0.72)	<0.0001	0.80 (0.71 to 0.89)	<0.0001
Pa	0.80 (0.72 to 0.87)	<0.0001	0.88 (0.79 to 0.97)	<0.0001
Pi	0.88 (0.81 to 0.96)[‡‡]	<0.0001	0.92 (0.83 to 1.01)[‡]	<0.0001
RI	0.79 (0.71 to 0.86)[§]	<0.0001	0.86 (0.77 to 0.95)[§]	<0.0001
AIx	0.17 (0.09 to 0.24)	<0.0001	0.08 (0.00 to 0.16)	<0.05

CI, confidence intervals. See tables 3.1 and 3.2 for further abbreviations. *Adjustors are age, sex, 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<0.0001 for comparisons of partial r values with Pa, [§]p<0.0001 for comparison of partial r values with AIx (z-statistics).

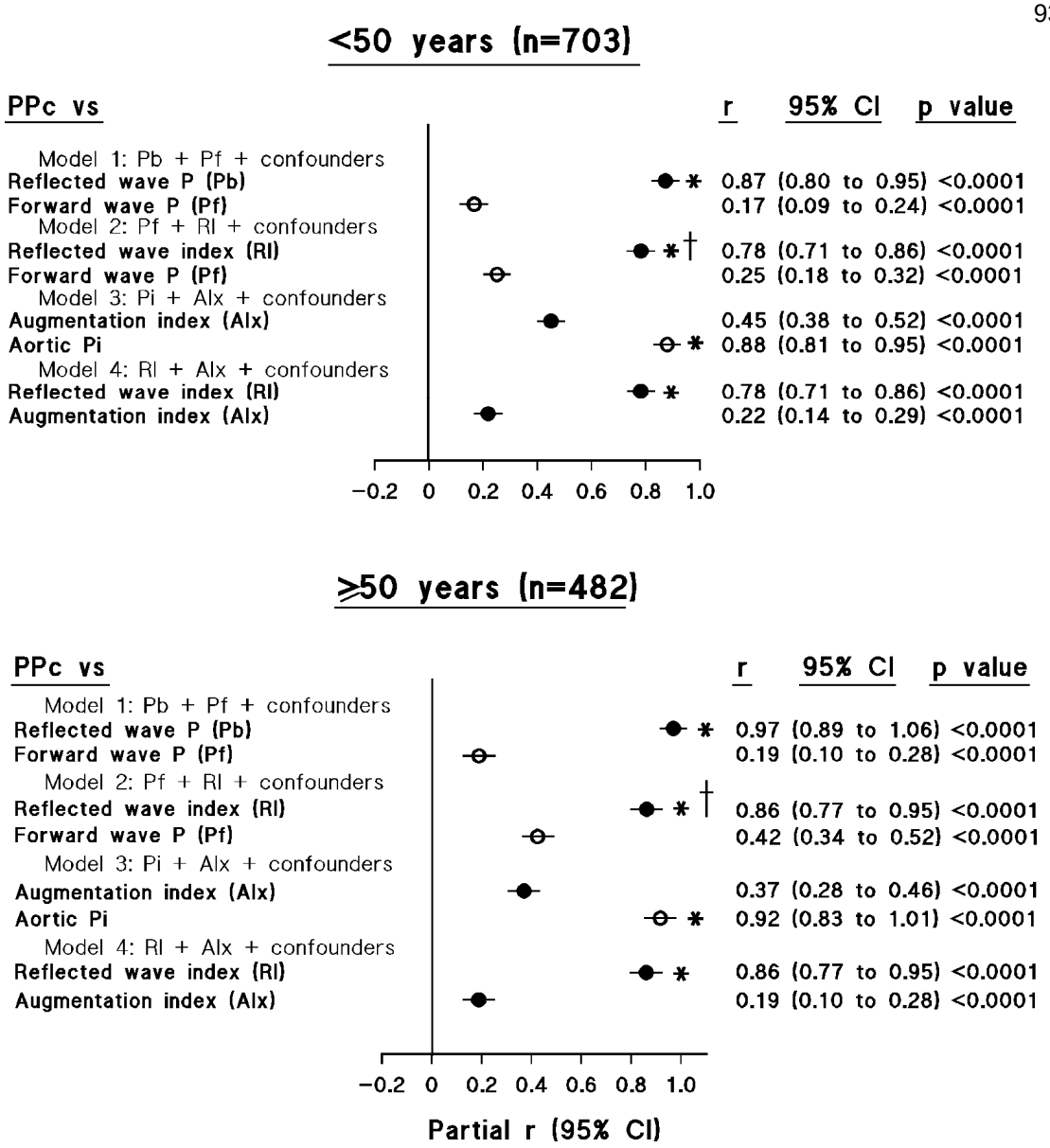


Figure 3.2. Relative contribution of aortic haemodynamic variables to variations in central (aortic) pulse pressure (PPc) in age-specific categories in a group of African descent. Closed circles indicate indexes of wave reflection; open circles indicate indexes of forward or incident wave pressures. 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, sex, 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. Independent relationships between aortic haemodynamics and central aortic pulse pressure (PPc) in age-specific categories in a group of African ancestry not receiving antihypertensive therapy (n=898).

PPc vs	<50 years (n=659)		≥50 years (n=239)	
	partial r (CI)*	p value	partial r (CI)*	p value
	Model with Pb and Pf included together			
Pb	0.86 (0.78-0.94)†	<0.0001	0.98 (0.85-1.11)†	<0.0001
Pf	0.16 (0.08-0.24)	<0.0001	0.19 (0.06-0.32)	<0.0001
	Model with RI and Pf included together			
RI	0.78 (0.70-0.86)†	<0.0001	0.87 (0.74-0.99)†	<0.0001
Pf	0.25 (0.17-0.33)	<0.0001	0.45 (0.32-0.58)	<0.0001
	Model with AIx and Pi included together			
AIx	0.46 (0.38-0.54)	<0.0001	0.35 (0.22-0.48)	<0.0001
Pi	0.88 (0.80-0.96) ‡	<0.0001	0.93 (0.80-1.06) ‡	<0.0001
	Model with RI and AIx included together			
RI	0.78 (0.70-0.86) ‡	<0.0001	0.87 (0.74-1.00) ‡	<0.0001
AIx	0.22 (0.14-0.30)	<0.0001	0.18 (0.05-0.31)	<0.0001

CI, confidence intervals. See tables 3.1 and 3.2 for further abbreviations. *Adjustors are age, sex, 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<0.0001 for comparison of partial r values with AIx (z-statistics).

Table 3.6. Independent relationships between aortic haemodynamics and central aortic pulse pressure (PPc) in age-specific categories in a group of African ancestry not receiving antihypertensive therapy.

PPc vs	<50 years (n=659)		≥50 years (n=239)	
	partial r (CI)*	p value	partial r (CI)*	p value
Pb	0.86 (0.79 to 0.94)[†]	<0.0001	0.98 (0.85 to 1.10)[†]	<0.0001
Pf	0.63 (0.55 to 0.70)	<0.0001	0.87 (0.74 to 0.99)	<0.0001
Pa	0.79 (0.72 to 0.87)	<0.0001	0.90 (0.77 to 1.03)	<0.0001
Pi	0.88 (0.80 to 0.96)[‡]	<0.0001	0.92 (0.80 to 1.05)	<0.0001
RI	0.78 (0.70 to 0.85)[§]	<0.0001	0.87 (0.74 to 0.99)[§]	<0.0001
AIx	0.19 (0.11 to 0.26)	<0.0001	0.05 (-0.08 to 0.18)	=0.24

CI, confidence intervals. See tables 3.1 and 3.2 for further abbreviations. *Adjustors are age, sex, 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<0.0001 for comparisons of partial r values with Pa, [§]p<0.0001 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 indices of aortic wave reflection and central aortic pulse pressure (PPc) in age-specific categories in a group of African ancestry.

PPc vs	<50 years (n=468)				≥50 years (n=325)			
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	0.83 (0.74 to 0.92)†	<0.0001	0.83 (0.74 to 0.92)†	<0.0001	0.97 (0.86 to 1.08)†	<0.0001	0.97 (0.86 to 1.08)†	<0.0001
Pf	0.56 (0.47 to 0.65)	<0.0001	0.56 (0.47 to 0.65)	<0.0001	0.79 (0.68 to 0.90)	<0.0001	0.79 (0.68 to 0.90)	<0.0001
Pa	0.81 (0.72 to 0.90)	<0.0001	0.81 (0.72 to 0.90)	<0.0001	0.88 (0.77 to 0.99)	<0.0001	0.88 (0.77 to 0.99)	<0.0001
Pi	0.88 (0.79 to 0.97)‡‡	<0.0001	0.88 (0.79 to 0.97)‡‡	<0.0001	0.92 (0.81 to 1.03)‡	<0.0001	0.92 (0.81 to 1.03)‡	<0.0001
RI	0.75 (0.66 to 0.84)§	<0.0001	0.75 (0.66 to 0.84)$^{\$}$	<0.0001	0.86 (0.75 to 0.97)§	<0.0001	0.86 (0.75 to 0.97)§	<0.0001
AIx	0.16 (0.07 to 0.25)	<0.0001	0.16 (0.07 to 0.25)	<0.0001	0.05 (-0.06 to 0.16)	=0.18	0.05 (-0.06 to 0.16)	<0.0001

CI, confidence intervals. See tables 3.1 and 3.2 for further abbreviations. *Adjustors are stroke volume (as indicated), age, sex, 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).

3.4.4 Comparison of independent relations between aortic haemodynamics and LVMI.

In participants <50 years of age, Pb was more closely associated with LVMI (Figure 3.3, upper panel, Table 3.8) than Pf and in a multivariate model with Pb and Pf in the same model, Pb (partial r=0.31, CI=0.24 to 0.38, p<0.0001), but not Pf (partial r=0.01, CI=-0.06 to 0.08, p=0.72) was independently associated with LVMI. In contrast however, Pa showed similar associations with LVMI as did Pi (Figure 3.3, upper panel, Table 3.8). In addition, RI was more closely associated with LVMI than AIx (Figure 3.3, upper panel, Table 3.8). In participants ≥50 years of age, Pb, but not Pf was independently associated with LVMI (Figure 3.3, lower panel, Table 3.8). In contrast however Pi, but not Pa was independently associated with LVMI (Figure 3.3, lower panel, Table 3.8). In participants ≥50 years of age RI, but not AIx was independently associated with LVMI-height$^{1.7}$ (Table 3.8), but neither RI nor AIx were independently associated with LVMI-BSA (Figure 3.3, lower panel). Similar data were obtained irrespective of whether MAP derived from the equation MAP=DBP + [(SBP-DBP)/3] or from SphygmoCor software (brachial form factor) was included as an adjustor (Appendices 6 and 7). Similar findings were also noted in participants <50 years of age not receiving antihypertensive therapy (Table 3.9). There were too few participants (n=151) ≥50 years of age not receiving antihypertensive therapy to compare relationships between aortic hemodynamics and LVMI. 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 indices and LVMI were retained (Table 3.10).

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

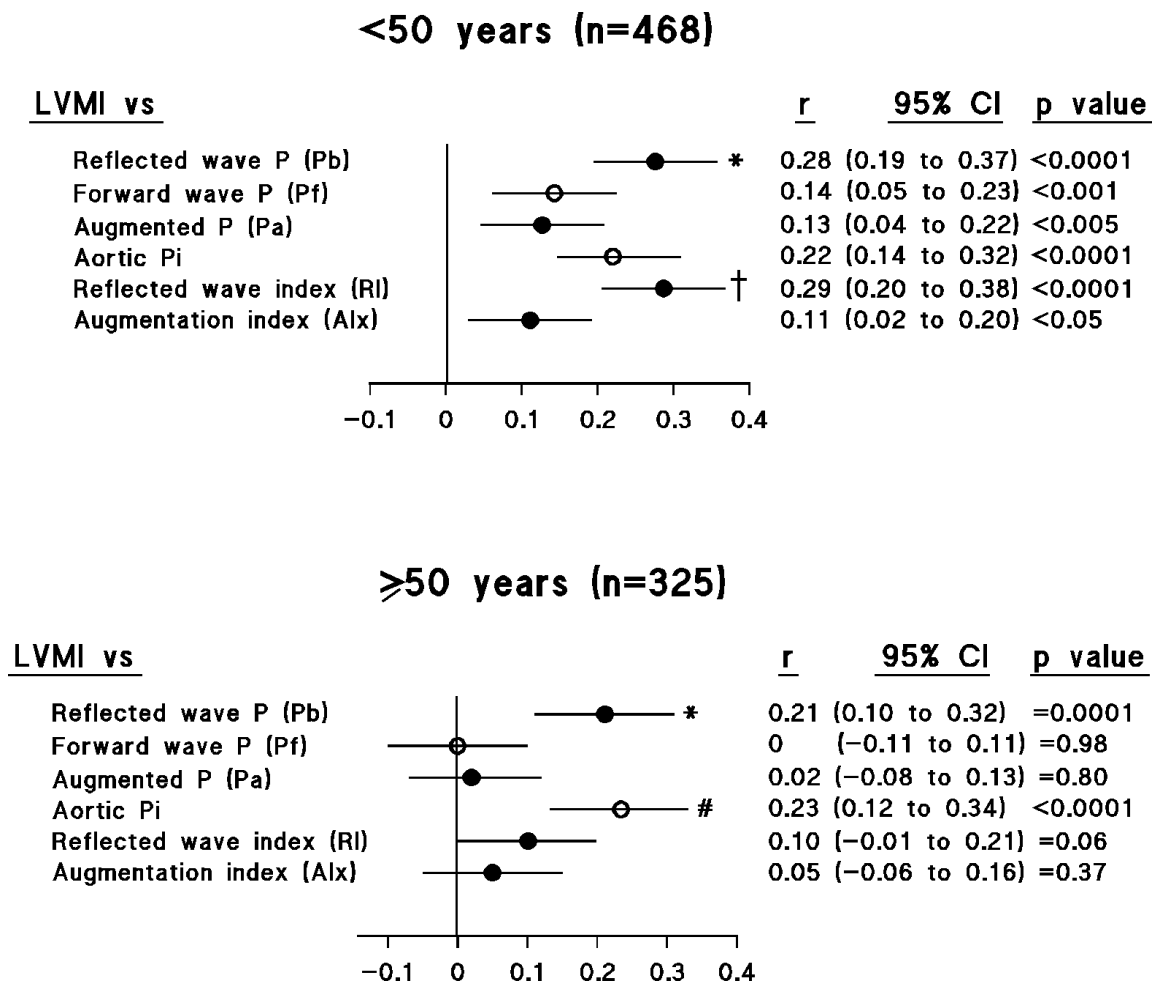


Figure 3.3. Contribution of aortic hemodynamic variables to variations in left ventricular mass indexed to body surface area (LVMI) in age-specific categories in a group of African descent. Closed circles indicate indexes of wave reflection; open circles indicate indexes of forward or incident wave pressures. Potential confounders included in the model are age, sex, mean arterial pressure, pulse rate, 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).

Table 3.8. Independent relationships between aortic hemodynamics and left ventricular mass indexed to height$^{1.7}$ (LVMI-ht$^{1.7}$) in participants of African ancestry.

	<50 years (n=468)		≥50 years (n=325)	
LVMI-ht$^{1.7}$ vs	partial r (CI)*	p value	partial r (CI)*	p value
Pb	0.20 (0.11 to 0.29)†	<0.0001	0.20 (0.09 to 0.31)†	<0.0005
Pf	0.08 (-0.01 to 0.17)	=0.07	0.05 (-0.06 to 0.16)	=0.37
Pa	0.17 (0.08 to 0.26)	=0.0001	0.06 (-0.05 to 0.16)	=0.29
Pi	0.15 (0.06 to 0.24)	=0.0005	0.25 (0.14 to 0.36)‡	<0.0001
RI	0.19 (0.10 to 0.29)§	<0.0001	0.13 (0.02 to 0.24)	<0.02
AIx	0.05 (-0.05 to 0.14)	=0.29	0.03 (-0.08 to 0.14)	=0.52

CI, confidence intervals. See tables 1 and 2 for further abbreviations. *Adjustors are age, sex, mean arterial pressure, 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<0.05 for comparison of partial r values with Pa, §p<0.05 for comparison of partial r values with AIx (z-statistics).

Table 3.9. Independent relationships between aortic hemodynamics and left ventricular mass indexed to body surface area (LVMI-BSA) in participants of African ancestry <50 years of age not receiving antihypertensive therapy (n=436).

LVMI-BSA vs	partial r (CI)*	p value
Pb	0.29 (0.19 to 0.38) †	<0.0001
Pf	0.16 (0.07 to 0.25)	<0.0005
Pa	0.13 (0.04 to 0.22)	<0.005
Pi	0.23 (0.13 to 0.32)	<0.0001
RI	0.25 (0.16 to 0.35)‡	<0.0001
AIx	0.12 (0.03 to 0.22)	=0.01

CI, confidence intervals. See tables 3.1 and 3.2 for further abbreviations. *Adjustors are age, sex, 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, ‡$p<0.05$ for comparison of partial r values with AIx (z-statistics).

Table 3.10. Impact of adjustments for stroke volume (SV) on the independent relationships between indexes of aortic wave reflection and and left ventricular mass indexed to body surface area (LVMI-BSA) in participants of African ancestry (n=793).

LVMI-BSA vs

SV adjusted	Before		After	
	partial r (CI)*	p value	partial r (CI)*	p value
Pb	0.31 (0.24 to 0.38)†	<0.0001	0.19 (0.12 to 0.26)†	<0.0001
Pf	0.13 (0.06 to 0.20)	<0.0005	0.04 (-0.03 to 0.11)	=0.17
Pa	0.26 (0.19 to 0.33)	<0.0001	0.17 (0.10 to 0.24)	<0.0001
Pi	0.30 (0.23 to 0.37)	<0.0001	0.17 (0.10 to 0.24)	<0.0001
RI	0.31 (0.24 to 0.38)‡‡	<0.0001	0.18 (0.11 to 0.25)‡	<0.0001
AIx	0.09 (0.02 to 0.16)	<0.01	0.02 (-0.05 to 0.09)	=0.43

CI, confidence intervals. See tables 3.1 and 3.2 for further abbreviations. *Adjustors are stroke volume, age, sex, mean arterial pressure, body height, body weight, pulse rate, diabetes mellitus or an HbA1c>6.1%, regular smoking and regular alcohol intake and either without (before) or with (after) SV. †p<0.005 for comparisons of partial r values with Pf, ‡p<0.005, ‡‡p<0.0001 for comparisons of partial r values with AIx (z-statistics).

PPc and LVMI than did forward wave pressures (Pf), whilst incident wave pressure (Pi) accounted for more of the variation in PPc and LVMI than did aortic systolic pressure augmentation (AIx or Pa). The marked contrasting contributions of indices of reflected waves, RI or Pb and AIx or Pa, as compared to Pf and Pi toward variations in PPc and LVMI were noted below as well as above the age threshold (50 years) when forward or incident wave pressures (Pf and Pi) began to increase as well as in women and men considered separately.

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 2008, 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 although in several of these studies (Davies et al 2010, Hughes et al 2013, Fok et al 2014), the method of wave intensity analysis has been seriously questioned on methodological and theoretical grounds (Segers et al 2015), and Fok et al (2014) report an impossible flow-frequency response, apparently hand-drawn representative waves are shown, and control impedance values are given that differ markedly from Yaginuma et al (1985), 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, Fok et al 2014, Torjesen et al 2014, Schultz et al 2013). Indeed, Pa may be determined in large part by forward wave pressures (Fok et al 2014). 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 little difference in aortic and brachial BP was noted across the adult lifespan (Mitchell et al 2010b), an effect that has been explained on the basis of the application of tonometry at a site where the principles of tonometry cannot be achieved (brachial artery to calibrate the carotid artery pulse) (O'Rourke et al 2010), or in a sample with a narrow age range (Segers et al 2007). In contrast, using wave separation analysis using techniques that do not rely on brachial tonometry and in a community sample with a wide age range, I show

that Pb has a far stronger relationship with PPc than Pf, and that these associations occurred irrespective of age. Hence, the present study provides the first direct evidence to show that across the adult lifespan of a community sample with poorly controlled hypertension, reflected waves account for more of the variation in PPc than do forward wave pressures and that indices of aortic pressure augmentation underestimate the contribution of aortic wave reflection to variations in PPc.

A few prior studies have suggested that indices 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. Moreover, in neither study (Wang et al 2010, Weber et al 2012) were comparisons of relations made in age-specific categories despite increases in forward wave pressures occurring only later in life. 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 in the present study, age-related increases in AIx occurred in those less than, but not greater than 50 years of age, a lack of relationship between AIx and LVMI in those older than 50 years of age is not unexpected. However, augmented pressures increased across the full adult age range, and yet, in those older than 50 years, reflected, but not augmented wave pressures accounted for variations in LVMI. Thus, without the use of wave separation analysis, even when indices of pressure augmentation that increase with

age across the full adult lifespan are employed, the impact of reflected wave function on end-organ changes may be markedly underestimated.

Although the confounding effects of overlap between aortic forward and backward waves may explain the inferior ability of AIx and AP to associate with aortic PP or LVMI as compared to Pb and RI, other possibilities should be considered. These include the impact of similar increases in augmentation pressure and pulse pressure with age, or a decrease in left ventricular ejection. Irrespective of the explanation however, the present study suggests that Pb and RI may be more useful indices of the adverse effects of aortic reflected waves than indices of aortic augmentation.

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, I was 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 indices 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 2014). 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 2014). Further, increases in forward wave pressures may account for more of the

increment in PPc in hypertensives than reflected wave pressures (Fok et al 2014). 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 2014). 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. Moreover, norepinephrine-induced effects on aortic reflected waves (Fok et al 2014) 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 haemodynamics and LVMI are indeed cause and effect. Further longitudinal studies are required to determine these effects.

In conclusion, in the present study conducted in a community sample with a high prevalence of uncontrolled hypertension, I show that 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. These data therefore provide the evidence to indicate that in a study conducted to assess whether aortic reflected waves may refine the ability to detect end-organ changes in pre-hypertensives, indices of aortic pressure augmentation are likely to underestimate the impact of wave reflection. In this regard, this question was addressed in the subsequent chapter of the present thesis (Chapter 4).

Chapter 4

Reflected Wave Indices Do Not Enhance the Ability of Aortic Blood Pressure to Identify Target Organ Changes in Normotensives.

4.1 Abstract

Whether indices of aortic wave reflection enhance the ability to detect cardiovascular damage beyond brachial and aortic BP in normotensives is uncertain. In 1185 participants of a community-based sample, 27% of whom had normal-high normal BP values, aortic BP, backward wave pressure (Pb) and the reflected wave index (RI) were determined using radial applanation tonometry and SphygmoCor software, and target organ changes assessed from carotid-femoral pulse wave velocity (PWV), estimated glomerular filtration rate (eGFR), and left ventricular mass index (LVMI). In normotensives aortic systolic blood pressure (SBP) was associated with LVMI ($g/m^{1.7}$) (n=410, partial r=0.18, p<0.0005), PWV (n=570, partial r=0.19, p<0.0001) and eGFR (n=605, partial r=-0.08, p<0.05) independent of confounders and brachial BP. Similar findings were noted for aortic pulse pressure (PP). In contrast, although Pb was independently associated with LVMI (partial r=0.19, p<0.0005) and a trend for an effect was noted for eGFR (partial r=-0.07, p=0.09) independent of confounders and brachial BP, no independent relations were noted with PWV (partial r=0.06, p=0.15). Similar relations were noted between RI and end-organ changes. The area under the receiver operating curve (AUC) for the detection of left ventricular hypertrophy (LVH)(n=168 of 410 normotensives) showed a greater ability of aortic PP (AUC=0.68±0.03) and aortic Pb (AUC=0.67±0.03), but not RI (AUC=0.65±0.03) to detect LVH as compared to brachial SBP (AUC=0.60±0.03) and brachial PP (AUC=0.61±0.03) (p<0.05 for comparison of AUC). However, the performance for LVH detection was no greater for Pb than for aortic PP. In conclusion, in normotensives although Pb is better than brachial BP for the detection of sub-clinical cardiovascular disease, indices of wave reflection do not enhance the ability to detect end-organ changes beyond aortic SBP or PP.

4.2 Introduction

Although prospective, observational studies (Hsia et al 2007, Conen et al 2007, Dorjgochoo et al 2009, Qureshi et al 2005, Vasan et al 2001, Blake et al 2003, Liszka et al 2005, Gu et al 2009, Zhang et al 2006, Butler et al 2011, Kshirsagar et al 2006), some randomised, controlled trials (Nissen et al 2004, Remme et al 2009, Staessen and Jiguang 2001, Schrier et al 2002, Patel 2007) and meta-analyses of BP lowering trials (Trialists Collaboration 2003, Law et al 2009) indicate that those with BP values in the normal/high-normal range (120-139/80-89 mm Hg) are at an increased risk for cardiovascular events, several more recent intervention studies suggest that antihypertensive treatment to thresholds lower than 140/90 mm Hg has no added benefit to risk reduction (Yusuf et al 2008, Cushman et al 2010, McMurray et al 2010). These data highlight the markedly variable BP-related risk conferred by a normal/high-normal BP. As recently demonstrated aortic blood pressure (BP) may refine the ability to detect those with a normal/high-normal BP at risk of BP-related cardiovascular damage (Booysen et al 2013, Chapter 2). However, the role of aortic reflected wave indices in risk predicting in those with brachial BP in the normotensive range is uncertain.

Both aortic forward (Pf) and backward (Pb) wave pressures contribute toward aortic BP. Whilst Pf is determined by stroke volume and aortic stiffness and impedance, Pb is determined by wave reflection. Several studies suggest that indices of aortic wave reflection are more closely associated with cardiovascular end-organ damage than brachial BP (Wang et al 2010, Weber et al 2012, Booysen et al 2015) or are better predictors of cardiovascular outcomes than brachial BP (Wang et al 2010, Chirinos et al 2012, Weber et al 2012, Zamani et al 2014). As wave reflection increases across the adult lifespan (Wang et al 2010, Booysen et al 2015), whilst Pf increases only after 50 years of age (Booysen et al 2015), and those with normal-high normal BP values are mostly younger than 50 years of age (Booysen et al 2013), the question arises as to whether indices of aortic wave reflection may further enhance risk prediction beyond even aortic

BP, particularly in those with normal-high normal BP values. Hence, in the present study I compared brachial BP-independent relations between end-organ changes and indices of aortic wave reflection versus aortic BP in normotensive participants of a community-based study. I also compared the ability of brachial BP, aortic BP and indices of wave reflection to detect sub-clinical cardiovascular disease in normotensive individuals.

4.3 Methods

4.3.1 Study samples.

The present study has been described in chapter 2, page 60 In the present analysis 793 participants had echocardiography, 1030 aortic pulse wave velocity (PWV), and 1125 estimated glomerular filtration rate (eGFR).

4.3.2 Clinical, demographic and anthropometric measurements.

The clinical (including office and ambulatory BP), demographic and anthropometric measurements have been described in chapter 2, page 61.

4.3.3 Pulse wave analysis.

Central aortic blood pressures, Pf, Pb and the reflected wave index (RI) were estimated using radial applanation tonometry and SphygmoCor software as described in chapter 2, page 62 and chapter 3, page 84.

4.3.4 End organ changes.

Left ventricular mass (LVM), aortic pulse wave velocity (PWV) and estimated glomerular filtration rate (eGFR) were determined as described in chapter 2, page 65. Left ventricular mass was indexed (LVMI) to body surface area (LVMI-BSA), height$^{2.7}$ (LVMI-ht$^{2.7}$) and height$^{1.7}$ (LVMI-ht$^{1.7}$). Left ventricular hypertrophy (LVH) was identified as an LVMI-BSA ≥83 g/m^2 for women and 111 g/m$^{2.}$ for men (Chirinos et al 2010), LVMI-ht$^{2.7}$ ≥46 g/m$^{2.7}$ for women and 50 g/m$^{2.7}$ for men (de Simone et al 2013), and LVMI-ht$^{1.7}$ ≥60 g/m$^{1.7}$ for women and 80 g/m$^{1.7}$ for men (Chirinos et al 2010). An increased PWV was identified as ≥10 m/sec (van Bortel et al 2012). Estimated GFR was considered to be reduced when <60 mls/min/1.73 m^2 (Levey et al 2003).

4.3.5 Data analysis

Data analysis was performed using SAS version 9.1 (SAS Institute, North Carolina, USA). Unadjusted means and proportions were compared by the large-sample z-test and the χ^2-statistic, respectively. Independent relationships with target organ changes were determined using multivariate regression analysis with adjustments for age, sex, BMI, diabetes mellitus and/or an HbA1c>6.1%, regular tobacco use, regular alcohol intake and pulse rate in the models. 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). Correlation coefficients were compared with z-statistics. The performance of brachial BP, aortic BP and indices of wave reflection for LVH detection was determined from the area under the receiver operating characteristic (ROC) curves (area under the curve [AUC]). The performance of brachial BP, aortic BP and indices of wave reflection for the detection of an increased PWV or

decreased eGFR was not determined as too few participants had these end-organ changes.

4.4 Results

4.4.1 Characteristics of participants

27.7% of participants had either normal or high-normal BP. 17% had a normal BP and 10.6% had high-normal BP values. Age, BMI, waist circumference, and the frequency of participants who were overweight or obese were similar to that described in chapter 2, Table 2.1. Also, hypertensives, but not those with a normal or high-normal BP, had more diabetes mellitus and/or an impaired blood glucose control, and an increased total/HDL cholesterol (see Table 2.2 for representative data). No differences were noted between BP categories in regular alcohol and tobacco intake or pulse rate (see Table 2.2 for representative data).

4.4.2 Blood pressures within BP categories.

Conventional and central aortic BP values as well as aortic Pf, Pb and RI increased across BP categories (Table 4.1).

4.4.3 Continuous relationships between various measures of BP or aortic haemodynamics and target organ changes in normotensive participants.

With adjustments for confounders, with the exception of RI which was not correlated with PWV (Table 4.5), all other BP measurements and aortic haemodynamic values were correlated with target organ changes (Tables 4.2 to 4.5). Relationships between aortic pulse pressure (PP), or Pb, but not Pf and LVMI-BSA were greater than

Table 4.1. Aortic haemodynamic variables across categories of brachial blood pressures (BP).

BP categories	Optimal	Normal	High-normal	Hypertensives
BP range (mm Hg)	<120/80	≥120/80 and <130/85	≥130/85 and <140/90	≥140/90 or Treatment
Sample size	312	202	126	545
Conventional SBP/DBP (mm Hg)	108±7/72±6	119±7/80±4**	129±7/85±4**††	146±22/92±13**$^{\dagger\dagger\#\#}$
Aortic SBP (mm Hg)	100±14	110±9**	119±10**††	136±22**$^{\dagger\dagger\#\#}$
Aortic pulse pressure (mm Hg)	26±11	29±8*	34±9**†	43±17**$^{\dagger\dagger\#\#}$
Aortic Pf (mm Hg)	20±6	21±5	22±5	28±11**$^{\dagger\dagger\#\#}$
Aortic Pb (mm Hg)	12±5	14±4*	17±5**††	22±9**$^{\dagger\dagger\#\#}$
Aortic RI	0.13±0.04	0.14±0.04	0.15±0.05*	0.18±0.07**$^{\dagger\dagger\#\#}$

SBP, systolic BP; DBP, diastolic BP, forward wave pressure; Pf, forward wave pressures; Pb, backward wave pressures; RI, reflected wave index. *p<0.05, **p<0.005, ***p<0.0001 vs optimal; †p<0.05, ††p<0.005, †††p<0.0005 vs normal; $^{\#}$p<0.05, $^{\#\#}$p<0.005, $^{\#\#\#}$p<0.0001 vs high-normal.

Table 4.2. Multivariate adjusted relationships between brachial blood pressures (BP) and target organ changes in normotensive participants (conventional BP<140/90 mm Hg) of the community sample.

	n	partial r (CI)*	p-value
Brachial SBP vs			
PWV	570	0.23 (0.15 to 0.30)	<0.0001
eGFR	605	-0.13 (-0.21 to -0.05)	=0.001
LVMI-BSA	410	0.19 (0.09 to 0.28)	=0.0001
LVMI-$ht^{1.7}$	410	0.16 (0.06 to 0.25)	<0.005
LVMI-$ht^{2.7}$	410	0.15 (0.06 to 0.25)	<0.005
Brachial PP vs			
PWV	570	0.14 (0.06 to 0.22)	=0.0006
eGFR	605	-0.01 (-0.08 to 0.07)	=0.89
LVMI-BSA	410	0.22 (0.13 to 0.31)	<0.0001
LVMI-$ht^{1.7}$	410	0.19 (0.10 to 0.28)	=0.0001
LVMI-$ht^{2.7}$	410	0.18 (0.08 to 0.27)	<0.0005

CI, confidence intervals; SBP, systolic BP; PP, pulse pressure; PWV, aortic pulse wave velocity; eGFR, estimated glomerular filtration rate; LVMI, left ventricular mass index; BSA, body surface area; ht, height. *Adjustments are for age, sex, BMI, diabetes mellitus and/or an HbA1c>6.1%, regular tobacco intake, regular alcohol intake and pulse rate.

Table 4.3. Multivariate adjusted relationships between aortic blood pressures (BP) and target organ changes in normotensive participants (conventional BP<140/90 mm Hg) of the community sample.

	n	partial r (CI)	p-value	partial r (CI)	p-value	partial r (CI)	p-value
Aortic SBP vs		Adjusted for *		Adjusted for *+brachial SBP		Adjusted for * + brachial PP	
PWV	570	0.28 (0.20 to 0.35)	p<0.0001	0.19 (0.11 to 0.27)	p<0.0001	0.25 (0.17 to 0.32)	p<0.0001
eGFR	605	-0.14 (-0.22 to -0.07)	p<0.0005	-0.08 (-0.16 to -0.01)	p<0.05	-0.16 (-0.24 to -0.08)	p=0.0001
LVMI-BSA	410	0.28 (0.19 to 0.37)	p<0.0001	0.22 (0.12 to 0.31)	p<0.0001	0.21 (0.11 to 0.30)	p<0.0001
LVMI-$ht^{1.7}$	410	0.24 (0.15 to 0.33)	p<0.0001	0.18 (0.09 to 0.28)	p<0.0005	0.18 (0.08 to 0.27)	p<0.0005
LVMI-$ht^{2.7}$	410	0.26† (0.17 to 0.35)	p<0.0001	0.22 (0.12 to 0.31)	p<0.0001	0.21 (0.11 to 0.30)	p<0.0001
Aortic PP vs							
PWV	570	0.16 (0.08 to0.24)	p=0.0001	0.09 (0.004 to 0.17)	p<0.05	0.10 (0.02 to 0.18)	p=0.015
eGFR	605	-0.11† (-0.19 to -0.03)	p=0.0005	-0.07 (-0.15 to 0.01)	p=0.11	-0.14 (-0.21 to -0.06)	p=0.0008
LVMI-BSA	410	0.31† (0.21 to 0.39)	p<0.0001	0.26 (0.17 to 0.35)	p<0.0001	0.22 (0.13 to 0.31)	p<0.0001
LVMI-$ht^{1.7}$	410	0.24 (0.14 to 0.33)	p<0.0001	0.2 (0.1 to 0.29)	p<0.0001	0.16 (0.06 to 0.25)	p=0.0013
LVMI-$ht^{2.7}$	410	0.24 (0.15 to 0.33)	p<0.0001	0.21 (0.11 to 0.30)	p<0.0001	0.18 (0.08 to 0.27)	p<0.0005

CI, confidence intervals; SBP, systolic BP; PP, pulse pressure; PWV, aortic pulse wave velocity; eGFR, estimated glomerular filtration rate; LVMI, left ventricular mass index; BSA, body surface area; ht, height. *Adjustments are for age, sex, BMI, diabetes mellitus and/or an HbA1c>6.1%, regular tobacco intake, regular alcohol intake and pulse rate. †p<0.05 vs relationships between brachial SBP or PP and end organ changes given in Table 4.2 (z-statistics).

Table 4.4. Multivariate adjusted relationships between aortic forward (Pf) or backward (Pb) wave pressures and target organ changes in normotensive participants (conventional BP<140/90 mm Hg) of the community sample.

	n	partial r (CI)	p-value	partial r (CI)	p-value	partial r (CI)	p-value
		Adjusted for *		Adjusted for *+brachial SBP		Adjusted for * + brachial PP	
Aortic Pf vs							
PWV	570	0.09 (0.006 to 0.17)	p=0.03	-0.001 (-0.08 to 0.08)	p=0.97	0.007 (-0.08 to 0.09)	p=0.87
eGFR	605	-0.09 (-0.17 to -0.01)	p=0.02	-0.04 (-0.12 to 0.04)	p=0.29	-0.12 (-0.2 to -0.04)	p=0.0029
LVMI-BSA	410	0.25 (0.16 to 0.34)	p<0.0001	0.19 (0.09 to 0.28)	p=0.0001	0.13 (0.04 to 0.23)	p=0.007
LVMI-$ht^{1.7}$	410	0.22 (0.13 to 0.32)	p<0.0001	0.17 (0.07 to 0.27)	p=0.0005	0.13 (0.03 to 0.22)	p=0.01
LVMI-$ht^{2.7}$	410	0.19 (0.1 to 0.28)	p=0.0001	0.14 (0.04 to 0.23)	p=0.0057	0.09 (-0.004 to 0.19)	p=0.06
Aortic Pb vs							
PWV	570	0.16 (0.08 to 0.24)	p=0.0002	0.06 (-0.02 to 0.14)	p=0.15	$0.10^{\#}$ (0.02 to 0.18)	p=0.017
eGFR	605	-0.12 (-0.2 to -0.04)	p=0.0024	-0.07 (-0.15 to 0.01)	p=0.09	-0.15 (-0.23 to -0.07)	p=0.0003
LVMI-BSA	410	$0.36^{\#}$ (0.27 to 0.44)	p<0.0001	$0.31^{\dagger\#}$ (0.22 to 0.40)	p<0.0001	$0.29^{\#}$ (0.2 to 0.38)	p<0.0001
LVMI-$ht^{1.7}$	410	$0.26^{\dagger}$ (0.17 to 0.35)	p<0.0001	0.21 (0.12 to 0.30)	p<0.0001	0.19 (0.09 to 0.28)	p=0.0002
LVMI-$ht^{2.7}$	410	$0.28^{\dagger\#}$ (0.19 to 0.37)	p<0.0001	$0.24^{\#}$ (0.15 to 0.33)	p<0.0001	$0.23^{\#}$ (0.13 to 0.32)	p<0.0001

CI, confidence intervals; PWV, aortic pulse wave velocity; eGFR, estimated glomerular filtration rate; LVMI, left ventricular mass index; BSA, body surface area; ht, height. *Adjustments are for age, sex, BMI, diabetes mellitus and/or an HbA1c>6.1%, regular tobacco intake, regular alcohol intake and pulse rate. †p<0.05 vs relationships between brachial SBP or PP and end organ changes given in Table 4.2. $^{\#}$p<0.05 vs relationships between Pf and end organ changes.

Table 4.5. Multivariate adjusted relationships between the aortic reflection wave index (RI) and target organ changes in normotensive participants (conventional BP<140/90 mm Hg) of the community sample.

Aortic RI vs	n	partial r (CI)	p-value	partial r (CI)	p-value	partial r (CI)	p-value
		Adjusted for *		Adjusted for *+brachial SBP		Adjusted for * + brachial PP	
PWV	570	0.08 (-0.005 to 0.16)	p=0.07	0.005 (-0.08 to 0.09)	p=0.9	0.01 (-0.07 to 0.09)	p=0.82
eGFR	605	-0.1 (-0.18 to -0.02)	p=0.015	-0.06 (-0.14 to 0.02)	p=0.15	-0.12 (-0.19 to -0.04)	p=0.0045
LVMI-BSA	410	0.32 (0.23 to 0.4)	p<0.0001	0.28 (0.19 to 0.37)	p<0.0001	0.24 (0.15 to 0.33)	p<0.0001
LVMI-$ht^{1.7}$	410	0.21 (0.11 to 0.3)	p<0.0001	0.17 (0.07 to 0.26)	p=0.0007	0.13 (0.03 to 0.22)	p=0.01
LVMI-$ht^{2.7}$	410	0.23 (0.14 to 0.32)	p<0.0001	0.2 (0.1 to 0.29)	p<0.0001	0.16 (0.07 to 0.26)	p=0.0009

CI, confidence intervals; PWV, aortic pulse wave velocity; eGFR, estimated glomerular filtration rate; LVMI, left ventricular mass index; BSA, body surface area; ht, height. *Adjustments are for age, sex, BMI, diabetes mellitus and/or an HbA1c>6.1%, regular tobacco intake, regular alcohol intake and pulse rate.

between brachial BP and LVMI-BSA (data shown in Tables 4.3 and 4.4 as compared to data shown in Table 4.2 [z-statistics]). Furthermore, relationships between Pb and LVMI were greater than relations between Pf and LVMI (Table 4.4). After further adjustments for brachial SBP or PP, relationships between aortic SBP or PP and PWV or LVMI persisted (Table 4.3). Moreover, after further adjustments for brachial SBP or PP, relationships between aortic Pf, Pb (Table 4.4) or RI (Table 4.5) and LVMI, persisted.

4.4.4 Performance of measures of BP or aortic haemodynamics to detect target organ changes in normotensive participants.

In normotensives with all end-organ measurements 96 of 410 (23.4%), had LVH based on LVMI-BSA thresholds, 168 of 410 (41%), had LVH based on LVMI-$ht^{1.7}$ thresholds, 73 of 410 (17.8%), had LVH based on LVMI-$ht^{2.7}$ thresholds, 3 of 570 (0.5%) had an increases aortic PWV and 0 of 605 (0%) had a decreased eGFR. Hence, I assessed the performance of aortic versus brachial BP measurements for LVH detection, but not for the detection of increases in PWV or decreases in eGFR. All BP measurements and aortic haemodynamic values showed significant performance for LVH detection (Table 4.6). However, aortic SBP and PP as well as Pb showed a significantly greater performance for LVH detection than brachial SBP or PP (Table 4.6 and Figure 4.1). Importantly, neither Pf, nor RI showed a greater performance for LVH detection than either brachial SBP or PP (Table 4.6). Furthermore, Pb did not show a greater performance for LVH detection than either aortic SBP or PP (Table 4.6). The addition of Pb to either aortic SBP or PP failed to enhance the performance of either of these variables (Figure 4.2).

Table 4.6. Performance (area under the receiver operating curve [AUC]) of brachial and aortic haemodynamic variables for the detection of left ventricular hypertrophy (LVH) in normotensive participants (conventional BP<140/90 mm Hg) of the community sample.

	LVH detected using thresholds for					
	LVMI-BSA		LVMI-ht$^{1.7}$		LVMI-ht$^{2.7}$	
	96 of 410 (23.4%)		168 of 410 (41.0%)		73 0f 410 (17.8%)	
	AUC±SEM	p-value	AUC±SEM	p-value	AUC±SEM	p-value
Brachial systolic BP	0.586±0.034	=0.0072	0.595±0.029	=0.0010	0.618±0.037	=0.0014
Brachial pulse pressure	0.631±0.032	<0.0001	0.613±0.028	<0.0001	0.626±0.036	=0.0004
Aortic systolic BP	0.646±0.034*	<0.0001	0.652±0.028*	<0.0001	0.714±0.034***	<0.0001
Aortic pulse pressure	0.682±0.031*	<0.0001	0.693±0.026**	<0.0001	0.693±0.034*	<0.0001
Aortic Pf	0.629±0.031	<0.0001	0.593±0.028	=0.0016	0.614±0.036	=0.0018
Aortic Pb	0.674±0.031	=0.0002	0.672±0.027*	<0.0001	0.698±0.035*	<0.0001
Aortic RI	0.662±0.032	<0.0001	0.654±0.027*	<0.0001	0.663±0.036	<0.0001

LVMI, left ventricular mass index; BSA, body surface area; ht, height; BP, blood pressure; Pf, forward wave; Pb, backward wave, RI, reflected wave index. *p<0.05, **p<0.005, ***p<0.0005 for comparison with AUC values for brachial systolic blood pressure or pulse pressure.

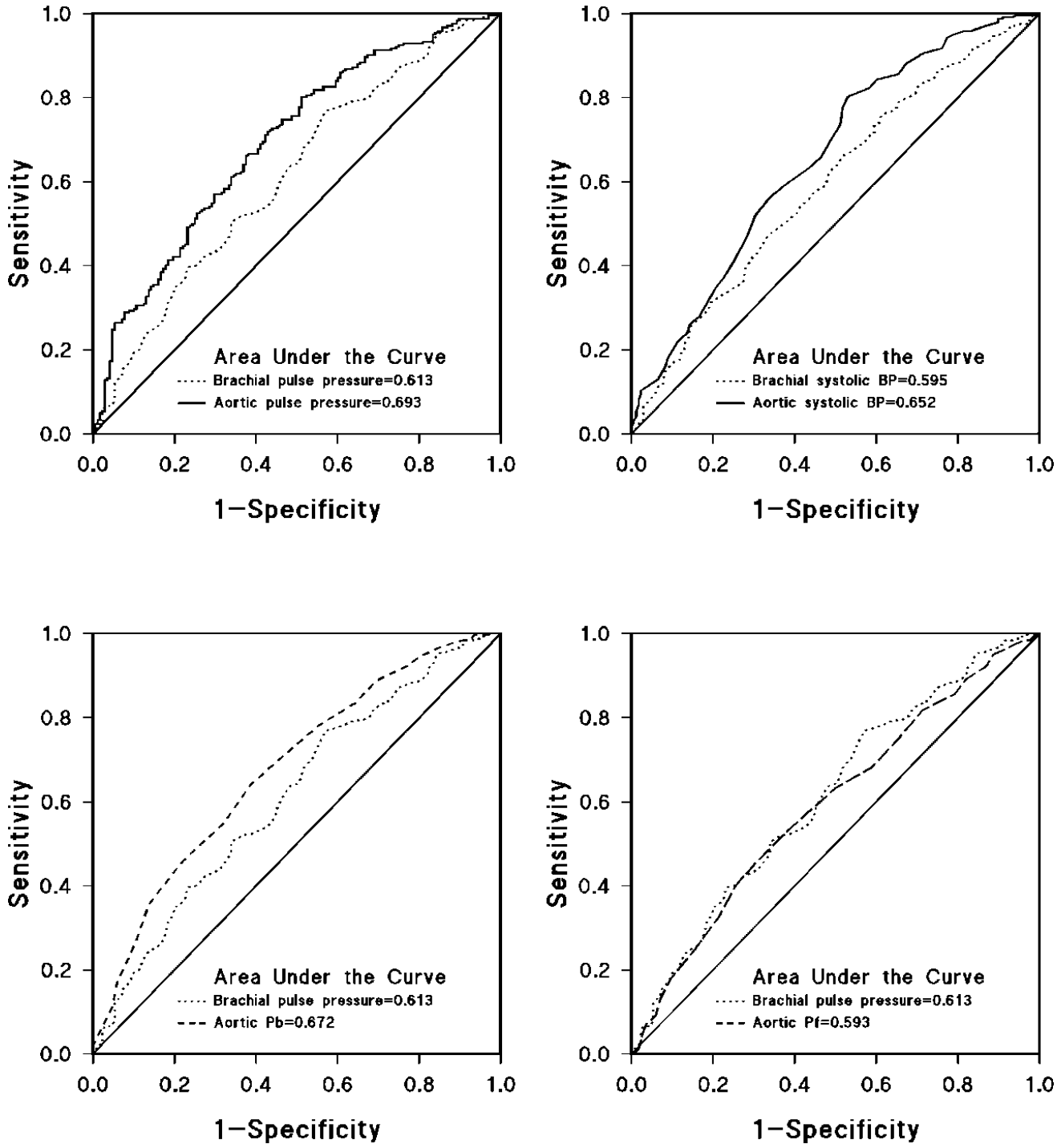
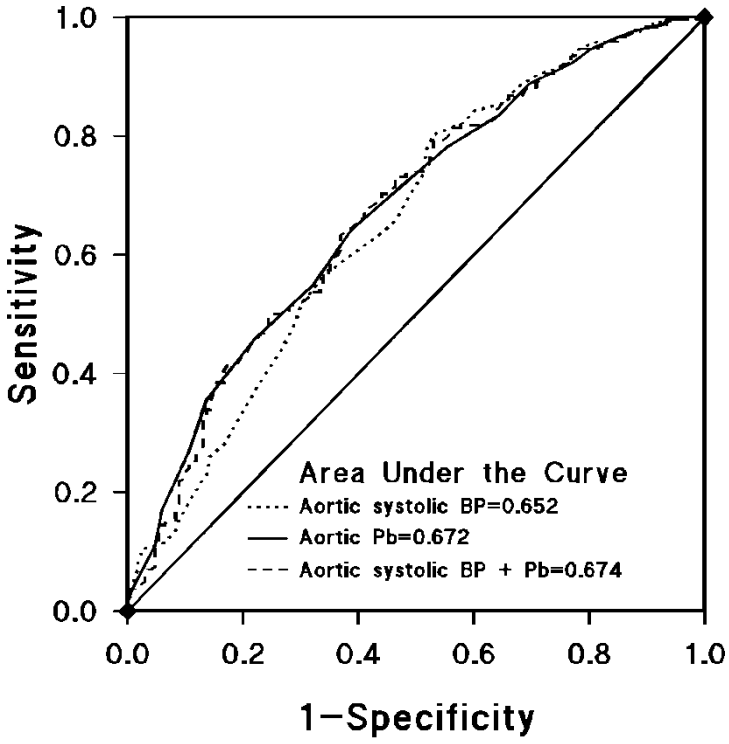


Figure 4.1. Receiver operating characteristic curves of brachial and aortic haemodynamic variables for the detection of left ventricular (LV) hypertrophy (168 of 410 participants [41%] with LV mass indexed to height$^{1.7}$ greater than thresholds) in normotensive participants (conventional BP<140/90 mm Hg) of the community sample. A comparison of the area under the receiver operating curves [AUC]) is made in Table 4.6.



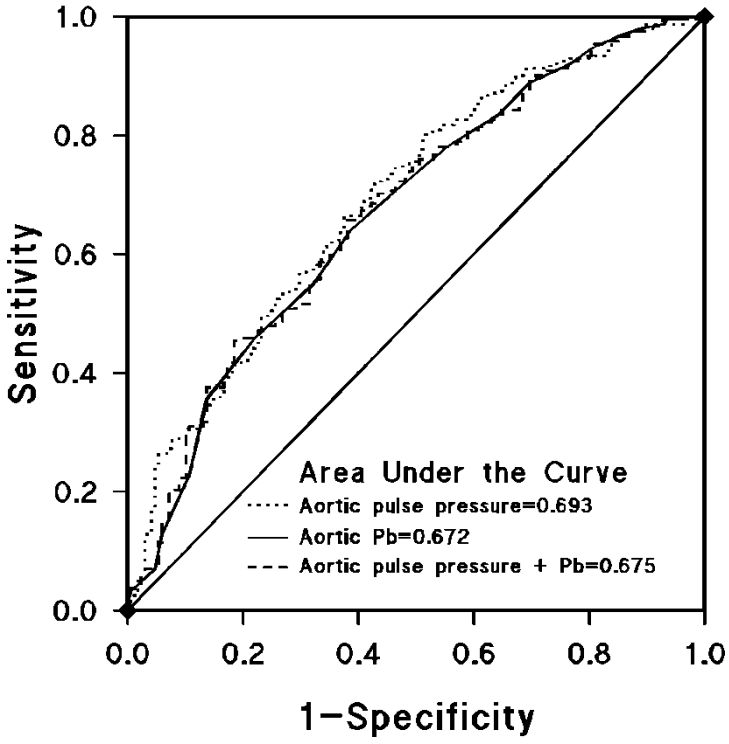


Figure 4.2. Impact on receiver operating characteristic curves for aortic systolic blood pressure or pulse pressure for the detection of left ventricular (LV) hypertrophy (168 of 410 participants [41%] with LV mass indexed to height$^{1.7}$ greater than thresholds) by the addition of aortic backward wave pressures (Pb) in normotensive participants (conventional BP<140/90 mm Hg) of the community sample. No differences in the area under the receiver operating curves (AUC) was noted.

4.5 Discussion

The main findings of the present study are as follows: In a large (n=1185), community-based sample of African ancestry, in those with normal brachial BP values (optimal, normal or high-normal BP), Pb was more closely related to LVMI than Pf, and Pb, but not Pf was better than brachial BP at LVH detection. Furthermore, in normotensives Pb, but not Pf was more closely associated with LVMI than brachial BP. However, in normotensives although aortic BP was associated with all end-organ changes independent of confounders and brachial BP, neither Pb, Pf, nor the reflection wave index (RI) were independently associated with all end-organ changes independent of confounders and brachial BP. In addition, although in normotensives Pb, but not Pf was more closely associated with LVMI than brachial BP and better than brachial BP at LVH detection, this effect was no better than aortic BP *per se* and the addition of Pb to aortic BP did not improve on the performance for LVH detection.

Several recent studies suggest that indices of aortic wave reflection, including Pb, but not forward wave pressures (Pf), may predict cardiovascular outcomes better than or independent of brachial BP (Wang et al 2010, Chirinos et al 2012, Weber et al 2012, Zamani et al 2014). Consistent with these data (Wang et al 2010, Chirinos et al 2012, Weber et al 2012, Zamani et al 2014), in the present study I also show that Pb, but not Pf is better than brachial BP at detecting LVH in those with brachial BP values in the normotensive range. However, in contrast to one previous study which reported a stronger relationship between reflected wave magnitude and cardiovascular outcomes than between PP amplification, an index of differences between aortic and brachial PP, and cardiovascular outcomes (Chirinos et al 2012), in the present study I show that RI and Pb are not more closely associated with end-organ changes than aortic BP *per se*, and that RI and Pb are no better than aortic PP at detecting LVH in normotensives. However, whether reflected wave magnitude predicted outcomes better than aortic pressure *per se* in this previous study (Chirinos et al 2012) was not reported on. Moreover, consistent with

backward wave pressures offering no further prognostic information than aortic BP *per se*, in one study adjustments for aortic BP eliminated the brachial BP-independent relationship between backward wave pressures and cardiovascular outcomes (Wang et al 2010) and in another study, backward wave and aortic pressures provided comparable prognostic information (Weber et al 2012).

The results of the present and previous studies (Wang et al 2010, Chirinos et al 2012, Weber et al 2012, Zamani et al 2014) demonstrating a stronger relationship between reflected as compared to forward wave pressures or indices and cardiovascular end-organ changes or outcomes, does not imply that forward wave pressures do not contribute to cardiovascular damage. Indeed, consistent with previous studies (Wang et al 2010, Weber et al 2012, Booysen et al 2015 [Chapter 3]) the present study shows that relationships between Pf and end-organ changes do occur and that Pf is important for LVH detection.

It may be argued that the more important role of Pb as compared to Pf in accounting for variations in LVMI and producing LVH in normotensives is consistent with the average age of those with normal and high-normal brachial BP values. In this regard, those with a normal or high-normal brachial BP are markedly younger than those with hypertension and as demonstrated in Chapter 3, Pb increases across the adult lifespan whilst Pf only begins to increase later in life (Booysen et al 2015). However, as also demonstrated in Chapter 3, Pf contributes to variations in LVMI in those younger rather than older than 50 years of age. Why Pf increases at 50 years of age, but plays no role in mediating LVH in this age group, whilst Pf remains unchanged prior to 50 years of age, but contributes to variations in LVMI over this age range cannot as yet be explained.

The clinical implications of the present study warrant consideration. First, the present study suggests that increases in Pb are likely to explain the ability of aortic BP to detect LVH beyond brachial BP in normotensives. Hence, therapeutic approaches that target aortic reflected waves are required in those with normal/high-normal BP values. In this regard, to the best of my knowledge, at present there are no studies that have

evaluated the impact of antihypertensive therapy or lifestyle modification on Pb and reflected wave magnitude or index derived from wave separation analysis. Hence, further studies are required. Second, although increases in Pb are likely to explain the ability of aortic BP to detect LVH beyond brachial BP in normotensives, the present study also suggests that the impact of Pb is no greater than aortic BP on end-organs. Thus, to enhance risk prediction beyond brachial BP in normotensives, aortic BP, which does not require wave separation analysis, may be all that is required.

The finding that Pb or RI are unable to show stronger associations with end-organ changes than aortic BP *per se*, does not exclude the possibility that measures of the factors that influence backward waves may not enhance risk prediction. For example, non-invasive measures of pressure and flow may allow for the derivation of ascending aortic impedance, a well-recognized determinant of backward wave function, and ascending aortic impedance may enhance risk prediction beyond aortic BP.

Although not an aim of the present study, the possible mechanisms responsible for increases in aortic backward waves in those with normotensive BP levels warrant consideration. In this regard, decreases in distensibility result in increases in characteristic impedance in the ascending aorta and through its effect on wave velocity cause a shift of impedance curves to higher frequencies (O'Rourke 1970). Although it is well recognized that the impedance modulus-frequency curve is shifted up and to the right in hypertension, an effect that is not attributed to change in vascular resistance (O'Rourke 1970), whether similar effects characterize pre-hypertension has not been described. Further work is therefore required to evaluate whether alterations in impedance modulus-frequency curves characterize increases in backward wave pressures in pre-hypertension. Moreover, the environmental (salt intake or obesity), neurohormonal (sympathetic activation or activation of the renin-angiotensin-aldosterone system), genetic (Djami-Tchatchou et al 2015) or molecular (factors that modify vascular structure and function) systems that influence characteristic impedance and hence possibly Pb and RI in pre-hypertension require further study. In this regard, galectin-3, a pro-fibrotic inflammatory

molecule has recently been demonstrated by our group to show independent relations with RI in men (Libhaber et al 2015).

There are several limitations to the present study that have largely been acknowledged in Chapters 2 and 3. First, 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 indices 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). Second, the present study was a cross-sectional design. Hence, conclusions regarding cause and effect cannot be drawn. Longitudinal studies are therefore required. Third, end-organ changes are surrogate measures of cardiovascular outcomes. Hence, whether aortic reflected wave indices predict cardiovascular outcomes better than aortic BP in normotensives requires further study.

In conclusion, in the present study I show that although increases in aortic wave reflection are likely to explain the ability of aortic BP to refine the ability to detect end-organ changes (LVH) in normotensives, measures of wave reflection are not more closely associated with end-organ changes than aortic BP. Furthermore, increases in aortic wave reflection do not detect LVH in normotensives better than aortic BP *per se*. Hence, indices of aortic wave reflection may not be more useful than aortic BP *per se* when refining the ability to risk predict in those with BP values in the normal/high-normal BP range.

Chapter 5

Imputation of Central Aortic Pulse Pressure from Simple Clinical Measurements: Validity and Ability to Detect End-Organ Changes in Normotensives

5.1 Abstract

Although arterial pulse wave analysis (PWA)-derived central aortic blood pressure (BP) may refine the ability to detect those with a normal/high-normal brachial BP at risk of BP-related cardiovascular damage, the cost of measurement devices precludes the use of this approach in resource-limited settings. Whether aortic BP may be imputed from simple clinical measures, is uncertain. An imputation equation for central aortic pulse pressure (PPc), incorporating brachial PP, age, mean arterial pressure and pulse rate was identified from multivariate modelling of the factors associated with radial applanation tonometry (PWA)-derived PPc (SphygmoCor) in 1179 community participants. Imputed PPc values closely approximated PPc determined from PWA in all participants of the community-based sample (r^2=0.96, slope=1.00±0.006, mean difference (±2xSD)=1.4±6.2 mm Hg) and in 351 patients from a clinical sample (r^2=0.943, slope=0.96±0.01, mean difference (±2xSD)=-2.17±7.44 mm Hg). In normotensives imputed aortic pulse pressure (PP) was associated with left ventricular mass index (n=410, partial r=0.17, p<0.001), aortic pulse wave velocity (n=570, partial r=0.09, p<0.05) and estimated glomerular filtration rate (n=605, partial r=-0.15, p<0.0005) independent of confounders and brachial BP. Independent relations with end-organ changes were similar for imputed and PWA-derived aortic BP. The area under the receiver operating curve (AUC) for the detection of left ventricular hypertrophy (n=168 of 410 normotensives) showed a greater performance of both imputed (AUC=0.656±0.027) and PWA-derived (AUC=0.678±0.027) aortic PP as compared to brachial PP (AUC=0.613±0.028) or systolic BP (AUC=0.595±0.029) (p<0.05 for comparisons of AUC). In conclusion, aortic BP imputed from simple clinical measures closely approximates PWA-derived aortic BP and refines the ability to detect normotensives at risk of BP-related sub-clinical cardiovascular disease.

5.2 Introduction

As highlighted in chapters 1, 2 and 4, prospective, observational studies indicate that those with BP values in the normal/high-normal range (120-139/80-89 mm Hg) are at an increased risk for cardiovascular events (Hsia et al 2007, Conen et al 2007, Dorjgochoo et al 2009, Qureshi et al 2005, Vasan et al 2001, Blake et al 2003, Liszka et al 2005, Gu et al 2009, Zhang et al 2006, Butler et al 2011, Kshirsagar et al 2006). In addition, some randomised, controlled trials (Nissen et al 2004, Remme et al 2009, Staessen and Jiguang 2001, Schrier et al 2002, Patel 2007) and meta-analyses of BP lowering trials (Trialists Collaboration 2003, Law et al 2009) in high risk patients support a view that treatment of those with a normal/high-normal BP has benefits for outcomes. In contrast, several more recent intervention studies suggest that antihypertensive treatment to thresholds lower than 140/90 mm Hg has no added benefit (Yusuf et al 2008, Cushman et al 2010, McMurray et al 2010). These studies (Yusuf et al 2008, Cushman et al 2010, McMurray et al 2010) highlight the markedly variable BP-related risk conferred by a normal/high-normal BP. Strategies are therefore required to better identify those with a normal/high-normal BP at risk for BP-related cardiovascular outcomes. Although, as recently demonstrated, aortic blood pressure (BP) may refine the ability to detect those with a normal/high-normal BP at risk of BP-related cardiovascular damage (Booysen et al 2013, Chapter 2), the current cost of devices employed for non-invasive aortic BP measurements precludes their routine use at a primary care level in resource-limited settings.

One possible solution to the potential high costs of non-invasive aortic BP measurement, may be to impute aortic pulse pressure (PPc) from routinely attained clinical measures (Camacho et al 2004). Indeed, the major determinants of PPc (Camacho et al 2004, Wilkinson et al 2001, McEniery et al 2008) are normally acquired as part of standard risk prediction. Thus, deriving an imputation equation from multivariate modelling (Camacho et al 2004) and applying this equation to routinely acquired clinical

measures may serve as an approximate of aortic PPc. In this regard, aortic BP imputed from simple clinical measurements closely correlates with pulse wave analysis-derived aortic BP with minimal mean differences (Benetos et al 2010, Regnault et al 2012). However, in these studies (Benetos et al 2010, Regnault et al 2012) imputed PPc was unable to predict outcomes beyond brachial BP. Nevertheless, mean arterial pressure (MAP) and pulse rate, two of the principal determinants of PPc (Camacho et al 2004, Wilkinson et al 2001, McEniery et al 2008) were not included in the imputation equation for PPc (Benetos et al 2010, Regnault et al 2012). I therefore aimed to identify an imputation equation that incorporates MAP and pulse rate that closely approximates PPc and subsequently to determine whether imputed aortic BP may refine the ability to detect those with a normal/high-normal BP at risk of BP-related sub-clinical cardiovascular disease.

5.3 Methods

5.3.1 Study samples.

The present study has been described in chapter 2, page 60. In the present analysis to derive the imputation equation 1179 participants were evaluated. Of these participants, 788 had 24-hour ambulatory BP measurements that met with pre-specified quality control criteria (see Chapter 2). To assess whether aortic BP derived from the imputation equation refines the ability to detect those with a normal/high-normal BP at risk of BP-related cardiovascular damage, 793 participants had echocardiography, 1030 aortic pulse wave velocity (PWV), and 1125 estimated glomerular filtration rate (eGFR). To validate the imputation equation in an external sample, 351 patients derived from several clinical samples (217 with critical limb ischaemia, 89 with renal failure requiring dialysis, 45 with severe or refractory hypertension), 248 of whom were of black African origins and 103 of whom were of European, Asian and mixed ancestry were evaluated.

5.3.2 Clinical, demographic and anthropometric measurements.

The clinical (including office and ambulatory BP), demographic and anthropometric measurements have been described in chapter 2, page 61.

5.3.3 Imputation of aortic pulse pressure.

To derive an appropriate imputation equation, aortic BP was first determined as described in Chapters 2-4 (pages 62 and 84). Central aortic systolic BP (SBPc) was determined both from the generalised transfer function (GTF) and from the peak pressure of the second pressure wave of the radial pulse wave (P2) (Norton et al 2012). Both GTF- and P2-derived PPc were calculated as SBPc-DBP. Both GTF- and P2-derived PPc were determined as P2-derived aortic BP does not depend on the use of a GTF and there is uncertainty as to whether the application of a GTF to derive central pressures is appropriate for both sexes and all disease groups (Norton et al 2012). Mean arterial pressure (MAP) was calculated as brachial diastolic BP (DBP) + (1/3 [brachial SBP-DBP]), or from the brachial form factor (MAP-DBP)/PPb, where MAP was obtained from SphygmoCor software and was derived from the area under the radial pulse wave calibrated to brachial BP. The brachial form factor was employed to determine the average of the brachial waveform independent of absolute BP (Camacho et al 2004). To assess the validity of the imputation equation, the equation was evaluated in a number of subgroups, including in those above and below the median for aortic augmentation index (AIx). 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.

To derive an appropriate imputation equation, multiple linear regression analysis was performed to identify the factors that account for most of the variation in radial pulse

wave-derived PPc. The β-coefficient for each factor was employed to derive the final equation. To determine the appropriateness of the imputation equation, the correlation coefficients and slopes of the imputed versus pulse wave-derived PPc relationships were evaluated and the mean±2SDs for the imputed versus pulse wave-derived PPc values were compared using Bland-Altman analysis in the population from which the equation was derived, subgroups of the population from which the equation was derived, and in the separate clinical population (external validation).

5.3.4 End-organ changes

End-organ changes were assessed as described in chapter 2, page 65 and chapter 4, page 111.

5.3.5 Data analysis.

To determine the factors that account for variations in SphygmoCor-derived PPc, multivariate linear regression analysis was performed with appropriate adjustments using SAS version 9.1 (SAS Institute, North Carolina, USA). Unadjusted means and proportions were compared by the large-sample z-test and the χ^2-statistic, respectively. Optimal thresholds for aortic BP were identified from upper 95% confidence intervals obtained in 311 participants with optimal conventional BP values and without diabetes mellitus, as described in chapter 2. The aortic systolic BP threshold was identified as 112 mm Hg. Differences in indices of organ changes between participants in categories of BP and independent relations between BP and target organ changes were determined using multivariate regression analysis with adjustments for age, sex, BMI, diabetes mellitus and/or an HbA1c>6.1%, regular tobacco use, regular alcohol intake and pulse rate in the models. 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). The performance of brachial BP, SphygmoCor-derived aortic BP and imputed aortic BP for LVH detection was determined from the area under the receiver operating characteristic (ROC) curves (area under the curve [AUC]). The performance of brachial and aortic BP for the detection of an increased PWV or decreased eGFR was not determined as too few participants had these end-organ changes which exceeded currently accepted thresholds.

5.4 Results

5.4.1 Characteristics of participants.

The clinical and demographic characteristics of community-based participants and participants from the clinical sample are shown in Table 5.1. In the community-based sample 1.5% had a history of cardiovascular disease. Of the community-based sample 27.8% of participants had either normal or high-normal BP. 17.1% had a normal BP and 10.7% had high-normal BP values. Age, BMI, waist circumference, and the frequency of participants who were overweight or obese were similar to that described in chapter 2, Table 2.1. Also, hypertensives, but not those with a normal or high-normal BP, had more diabetes mellitus and/or an impaired blood glucose control, and an increased total/HDL cholesterol (see Table 2.2 for representative data). No differences were noted between BP categories in regular alcohol and tobacco intake or pulse rate (see Table 2.2 for representative data).

5.4.2 Derivation of imputed aortic pulse pressure.

The factors most strongly associated with pulse wave-derived central aortic pulse pressure (PPc) were brachia PP (PPb), age, pulse rate (obtained from SpygmoCor), MAP and female gender (Table 5.2). Although PPb was closely correlated with pulse-wave

Table 5.1. Characteristics of study samples.

	Community-based study (±SD)	Clinical sample (±SD)
Sample size (% female)	1179 (65.1)	351 (51.3%)
Age (years)	43.5±18.1	55.9±14.8
Body mass index (kg/m^2)	29.5±8.1	26.5±6.1
Regular tobacco (% subjects)	14.9	35.9
Regular alcohol (% subjects)	21.3	48.5
Treated diabetes mellitus (% subjects)	6.8	29.3
Treated hypertension (% subjects)	24.1	73.5
Body height (cm)	161.1±8.7	167.5±10
Body weight (kg)	76.2±19.5	74.4±19.9
Pulse rate (Beats/min)	66±12	78±17
Measured BP and PP amplification		
Brachial SBP/DBP (mm Hg)	129±23/84±13	137±23/84±14
Brachial PP (mm Hg)	45±17	53±17
Aortic PP (mm Hg)	36±15	40±15
PP amplification	1.29±0.18	1.34±0.18
Brachial mean Arterial Pressure (mm Hg)	100±16	102±17
Imputed BP and PP amplification		
Aortic PP (mm Hg)	36±15	43±16
PP amplification	1.29±0.18	1.27±0.16
End organ values		
Left ventricular mass index (g/m$^{1.7}$)	67.7±24.2	-
Aortic pulse wave velocity (m/sec)	6.42±2.67	-
Estimated GFR (mls/min/1.73 m^2)	116±33	-

SBP/DBP, systolic/diastolic blood pressures; PP, pulse pressure; GFR, glomerular filtration rate. – indicates “not available”.

Table 5.2. Factors independently associated with central aortic pulse pressure (PPc) in 1179 participants from a community sample.

	partial r^2*	β-coefficient† ±SEM	p value
Aortic PPc vs			
Brachial PP	0.920	0.844±0.007	<0.0001
Age	0.014	0.146±0.008	<0.0001
Pulse rate	0.019	-0.159±0.006	<0.0001
MAP	0.006	0.101±0.007	<0.0001
Female gender	0.005	0.060±0.008	<0.0001
Body height	0.0007	-0.040±0.008	<0.0001
Treatment for HT	0.0005	-0.024±0.007	<0.0005
Regular tobacco use	0.0003	-0.017±0.006	=0.0001
Model r^2	0.97		

MAP, mean arterial pressure; HT, hypertension. *Additional factors included in the model which were not associated are body weight, regular alcohol intake, and diabetes mellitus or an HbA1c<6.1%. Probability values are further adjusted for non-independence of family members. †Standardized slopes of the relationships. #MAP determined using diastolic BP + (systolic-diastolic BP)/3.

derived PPc (Figure 5.1, upper left panel, Table 5.3), brachial PP consistently overestimated PPc with a greater bias toward a lower PPc as compared to brachial PP at higher PPc values (Figure 5.1, lower left panel). Imputing PPc from the size effects of PPb, age, pulse rate and MAP using the formula given in Table 5.3, generated a relationship between imputed PPc and pulse wave-derived PPc with an improved correlation coefficient, slope and intercept (Figure 5.1, upper right panel and Table 5.3), with a markedly reduced mean difference (Figure 5.1, lower right panel and Table 5.3) and no bias toward a lower PPc as compared to brachial PP at higher PPc values (Figure 5.1, lower right panel, Table 5.3).

The addition of sex to the PPc imputation equation resulted in a greater mean (±2SD) difference (-4.20±5.80) between imputed PPc and pulse wave-derived PPc than that achieved without the addition of sex to the model ($p<0.0001$ for comparisons of mean differences). The exclusion of pulse rate and MAP from the PPc imputation equation also generated a greater mean (±2SD) difference between imputed and pulse wave-derived PPc values (-6.5±7.9, $p<0.0001$ versus with pulse rate and MAP). The inclusion of the brachial form factor, rather than MAP failed to improve the mean (±2SDs) differences between pulse wave-derived and imputed PPc (-11.6±5.0 mm Hg). The addition of body height, treatment for hypertension or smoking failed to improve the correlation coefficients, or slopes of the imputed versus pulse wave-derived PPc relationships or the mean differences between these values (data not shown). The relationship between imputed PPc and P2-derived, rather than GTF-derived PPc showed a similar correlation coefficient (0.94), slope (0.99±0.007), intercept (-1.22±0.29) and mean difference ±2SD (-1.61±7.63).

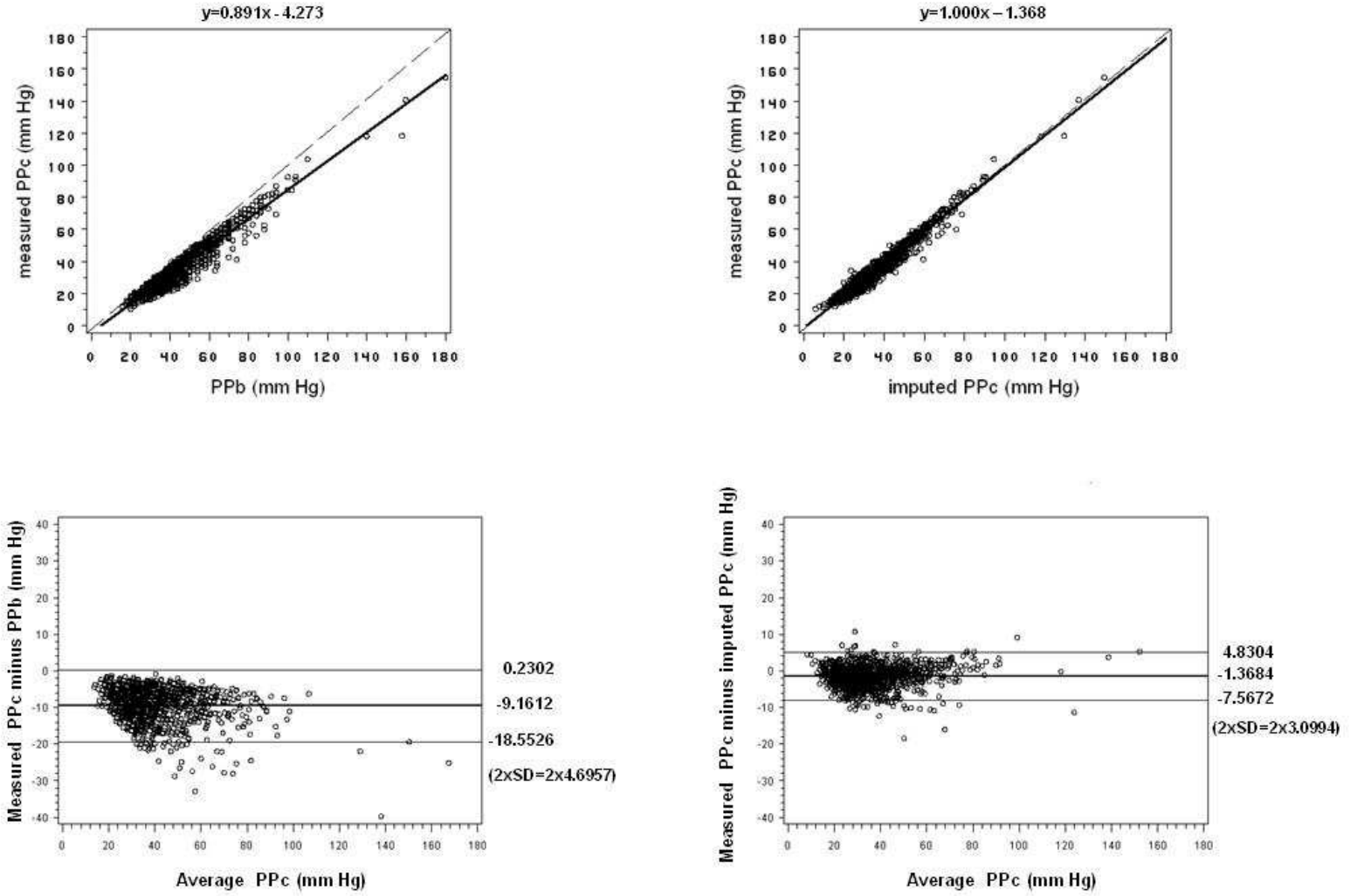


Figure 5.1. Correlations between radial pulse wave-derived central aortic pulse pressure (measured PPc) and either brachial PP (PPb) (left upper panel) or imputed PPc (right upper panel) and Bland Altman plots showing mean differences (±2 x SD) between pulse wave-derived PPc and PPb (left lower panel) or pulse wave-derived and imputed PPc (right lower panel) in the community sample.

Table 5.3. Characteristics of relationships between brachial or imputed aortic pulse pressure (PP) and pulse wave (PW)-derived central aortic PP (PPc) and the mean differences between these values in subgroups of the study sample.

Pulse wave-derived PPc vs	n=	r^2 (CI)	β-coefficient (slope)±SEM	Intercept±SEM (mm Hg)	Mean difference ±2SD (mm Hg)
Brachial PP (PPb)	1179	0.920 (0.911-0.929)	0.891±0.008	-4.27±0.37	-9.16±9.39
Imputed PPc					
All participants	1179	0.959* (0.954-0.964)	1.000±0.006*	-1.37±0.24*	-1.37±6.20*
Women	769	0.965 (0.961-0.970)	0.989±0.007	-0.21±0.26	-0.62±5.38
Men	410	0.962 (0.955-0.969)	1.030±0.010	-3.94±0.42	-2.77±6.64
Hypertensives	540	0.964 (0.958-0.970)	1.031±0.012	-2.93±0.41	-1.54±6.42
DM	165	0.961 (0.949-0.972)	0.990±0.016	-1.52±0.73	-1.97±6.54
Smokers	176	0.957 (0.945-0.969)	1.050±0.017	-3.36±0.67	-1.48±6.42
Increased WC	513	0.963 (0.957-0.969)	0.986±0.009	-0.47±0.36	-1.05±5.80
White-coat effect[†]	138	0.960 (0.944-0.971)	1.048±0.018	-3.68±0.84	-1.59±6.28
No white-coat effect	650	0.950 (0.942-0.957)	0.983±0.009	-0.73±0.34	-1.32±6.40
Office BP within 5 mm Hg day BP[‡]	104	0.932 (0.900-0.953)	0.936±0.025	1.03±0.83	-0.10±5.03
Office BP > 5 mm Hg of day BP[‡]	684	0.954 (0.947-0.960)	0.998±0.008	-1.36±0.34	-1.43±6.55
PW derived PPc≥50 mm Hg	185	0.950 (0.933-0.962)	1.002±0.017	-0.25±1.09	-0.11±6.62

Imputed PPc = (0.782 x PPb) + (0.115 x age) + (0.090 x MAP) – (0.184 x PR).

MAP, mean arterial pressure derived from brachial diastolic BP + 1/3(systolic BP- diastolic BP); PR, pulse rate; DM, diabetes mellitus defined as treatment or HbA1c>6.5%; increased WC, increased waist circumference defined as 102 in men and 88 in women. *p<0.0001 vs PW-derived PPc vs brachial PP. [†]indicates office systolic or diastolic BP > day systolic or diastolic BP, [‡]for systolic BP. All r^2 values, β-coefficients, intercepts and mean differences are significant at p<0.0001.

5.4.3 Validity of the imputation equation in subgroups of the community sample.

The characteristics of the relationships and mean (±2SD) differences between imputed PPc and pulse wave-derived PPc were similar in men and women, in those with an increased waist circumference, hypertensives, those with diabetes mellitus, and in smokers (Table 5.3). Furthermore, the characteristics of the relationships and mean (±2SD) differences between imputed PPc and pulse wave-derived PPc were similar to all participants in those with a PPc≥50 mm Hg (Table 5.3) where a greater bias toward a lower PPc as compared to brachial PP was noted (Figure 5.1, lower left panel). The mean (±2SD) differences between imputed PPc and pulse wave-derived PPc were similar below (-2.9.±6.14 mm Hg) and above (0.16±4.54 mm Hg) the median of AIx (140.2). However, the slope (β-coefficient) of the relationship between imputed PPc and pulse wave-derived PPc was reduced in those with an AIx below (0.86±0.01) as compared to above (1.00±0.006 mm Hg) the median value (140.2). Nevertheless this difference was largely attributed to the slope of the relationship between brachial PP and pulse wave-derived PPc being reduced in those with an AIx below (0.73±0.01) as compared to above (0.89±0.005 mm Hg) the median value (140.2) rather than an inability of the imputation equation to improve on the slope.

5.4.4 Validation of the imputation equation in clinical sample (external validation).

As with the community-based sample, in the clinical population, as indicated in Figure 5.2, brachial PP was closely correlated with pulse-wave derived PPc (r^2=0.882), but consistently overestimated PPc with a greater bias toward a lower PPc as compared to brachial PP at higher PPc values (slope=0.82±0.02, mean difference ± 2xSD = -12.46±12.30 mm Hg). Imputing PPc using the formula given in Table 5.3, generated a relationship between imputed PPc and pulse wave-derived PPc in the clinical sample with

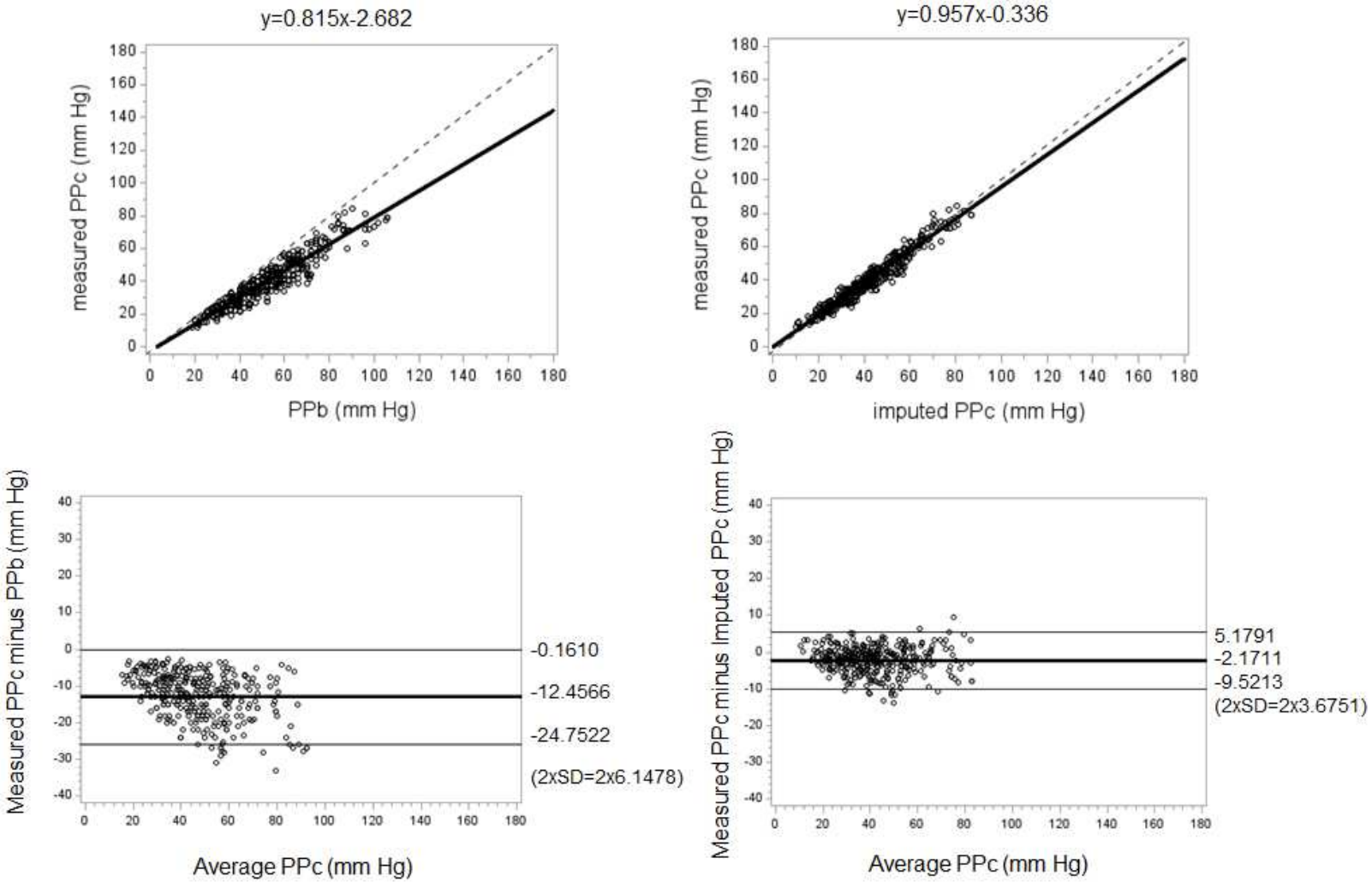


Figure 5.2. Correlations between radial pulse wave-derived central aortic pulse pressure (measured PPc) and either brachial PP (PPb) (left upper panel) or imputed PPc (right upper panel) and Bland Altman plots showing mean differences (±2 x SD) between pulse wave-derived PPc and PPb (left lower panel) or pulse wave-derived and imputed PPc (right lower panel) in the clinical sample.

an improved correlation coefficient (r^2=0.943), and slope (0.96±0.01) with a markedly reduced mean difference ± 2xSD (-2.17±7.36 mm Hg)($p<0.0001$ for comparisons of r^2, β-coefficient and mean difference) (Figure 5.2). The relationship between imputed PPc and pulse wave-derived PPc in those of European, Asian and mixed ancestry showed a similar correlation coefficient (r^2=0.946), slope (β-coefficient=0.964±0.023) and mean difference±2SD (-2.50± 7.54 mm Hg) as did the relationship between imputed PPc and pulse wave-derived PPc in those of black African ancestry (r^2=0.941, slope=0.957±0.015, mean difference ± 2xSD= -2.03±7.38 mm Hg).

5.4.5 Aortic blood pressures within BP categories.

Conventional and 24-hour BP values in the community sample are similar to that given in Chapter 2, Table 2.2. The mean imputed aortic SBP values across categories of brachial BP (imputed aortic SBP in mm Hg: optimal brachial BP=101±14 mm Hg, normal brachial BP=112±9 mm Hg, high-normal brachial BP=120±9 mm Hg, hypertensives=138±22 mm Hg $p<0.0001$ across BP categories) were similar to the mean SphygmoCor-derived aortic SBP values across categories of brachial BP (SphygmoCor-derived aortic SBP in mm Hg: optimal brachial BP=100±14 mm Hg, normal brachial BP=110±9 mm Hg, high-normal brachial BP=119±10 mm Hg, hypertensives=136±22 $p<0.0001$ across brachial BP categories) ($p>0.08$) for comparison of imputed and SphgmoCor-derived aortic SBP within brachial BP categories). Furthermore, the mean imputed aortic PP values across categories of brachial BP (imputed aortic PP in mm Hg: optimal brachial BP=28±12 mm Hg, normal brachial BP=31±8 mm Hg, high-normal brachial BP=35±9 mm Hg, hypertensives=45±16 mm Hg $p<0.0001$ across BP categories) were similar to the mean SphygmoCor-derived aortic PP values across categories of brachial BP (SphygmoCor-derived aortic PP in mm Hg: optimal brachial BP=27±11 mm Hg, normal brachial BP=29±8 mm Hg, high-normal brachial BP=34±9 mm Hg, hypertensives=43±17 mm Hg $p<0.0001$ across brachial BP categories) ($p>0.19$ for

comparison of imputed and SphgmoCor-derived aortic SBP within optimal, normal and high-normal brachial BP categories) and modestly greater (p=0.024) within the hypertensive brachial BP category. Importantly, in those with a normal/high-normal BP, 47.5% had an imputed aortic SBP and 53.7% had SphygmoCor-derived aortic SBP that did not exceed the upper 95% confidence intervals of healthy participants with an optimal BP.

5.4.6 Continuous relationships between various measures of PP and target organ changes in normotensive participants.

In normotensive participants (BP<140/90 mm Hg and no antihypertensive treatment) of the community sample, with adjustments for confounders, conventional, imputed central aortic and SphygmoCor-derived aortic PP (Table 5.4) and SBP (Table 5.5) were correlated with target organ changes. The relationships between imputed and SphygmoCor-derived aortic PP or SBP and LVMI-BSA were stronger than those between brachial PP or SBP and LVMI-BSA (Table 5.4). After further adjustments for aortic PP or SBP, the relationships between conventional PP or SBP and target organ changes in normotensives were abolished (Tables 5.4 and 5.5). In contrast, with further adjustments for conventional PP or SBP, imputed aortic and SphygmoCor-derived aortic PP or SBP retained independent relationships with target organ changes in normotensives (Tables 5.4 and 5.5). In addition, with further adjustments for 24-hour brachial PP, imputed aortic (PWV; partial r=0.15, confidence intervals=0.05 to 0.25, p=0.003, n=386; eGFR; partial r= -0.11, confidence intervals= -0.20 to -0.01, p<0.05, n=412; LVMI; partial r=0.25, confidence intervals=0.13 to 0.35, p<0.0001, n=290) and SphgmoCor-derived aortic (PWV; partial r=0.14, confidence intervals=0.04 to 0.24, p=0.006, n=386; eGFR; partial r= -0.10, confidence intervals= -0.20 to -0.006, p<0.05, n=412; LVMI; partial r=0.23, confidence intervals=0.12 to 0.34, p<0.0001, n=290) PP also retained independent

Table 5.4. Multivariate adjusted relationships between brachial and aortic pulse pressure (PP) and target organ changes in normotensive participants (conventional BP<140/90 mm Hg) of the community sample.

PP vs	n	partial r	CI	p-value	partial r	CI	p-value
		Brachial PP adjusted for*			Brachial PP adjusted for imputed aortic PP+*		
Pulse wave velocity	570	0.14	(0.06 to 0.22)	=0.0006	0.06	(-0.02 to 0.13)	=0.14
Estimated GFR	605	-0.01	(-0.08 to 0.07)	=0.89	0.09	(0.01 to 0.17)	<0.05
LVMI-BSA	410	0.22	(0.13 to 0.31)	<0.0001	0.03	(-0.07 to 0.12)	=0.58
LVMI-ht$^{1.7}$	410	0.19	(0.10 to 0.28)	=0.0001	0.05	(-0.05 to 0.14)	=0.35
LVMI-ht$^{2.7}$	410	0.18	(0.08 to 0.27)	<0.0005	0.04	(-0.06 to 0.13)	=0.18
		Imputed aortic PP adjusted for*			Imputed aortic PP adjusted for brachial PP+*		
Pulse wave velocity	570	0.16	(0.07 to 0.24)	=0.0002	0.09	(0.01 to 0.17)	<0.05
Estimated GFR	605	-0.12†	(-0.20 to -0.04)	<0.005	-0.15	(-0.23 to -0.07)	<0.0005
LVMI-BSA	410	0.32$^{\dagger\#}$	(0.23 to 0.41)	<0.0001	0.24	(0.14 to 0.33)	<0.0001
LVMI-ht$^{1.7}$	410	0.25$^{\#}$	(0.15 to 0.34)	<0.0001	0.17	(0.07 to 0.26)	=0.0008
LVMI-ht$^{2.7}$	410	0.24$^{\#}$	(0.14 to 0.33)	<0.0001	0.17	(0.07 to 0.26)	=0.0009
		SphygmoCor-derived aortic PP adjusted for*			SphygmoCor-derived aortic PP adjusted for brachial PP+*		
Pulse wave velocity	570	0.16	(0.08 to 0.24)	=0.0001	0.10	(0.02 to 0.18)	=0.015
Estimated GFR	605	-0.11†	(-0.19 to -0.03)	<0.01	-0.14	(-0.21 to -0.06)	=0.0008
LVMI-BSA	410	0.31$^{\dagger\#}$	(0.21 to 0.39)	<0.0001	0.22	(0.13 to 0.31)	<0.0001
LVMI-ht$^{1.7}$	410	0.24$^{\#}$	(0.14 to 0.33)	<0.0001	0.16	(0.06 to 0.25)	=0.0013
LVMI-ht$^{2.7}$	410	0.24$^{\#}$	(0.15 to 0.33)	<0.0001	0.18	(0.08 to 0.27)	<0.0005

CI, confidence intervals; GFR, glomerular filtration rate; LVMI, left ventricular mass index; BSA, body surface area; ht, height. *Adjustments are for age, sex, BMI, diabetes mellitus and/or an HbA1c>6.1%, regular tobacco intake, regular alcohol intake and pulse rate. †p<0.05 vs r values for brachial PP versus end-organ changes, $^{\#}$p<0.05 vs r values for brachial SBP versus end-organ changes (z-statistics).

Table 5.5. Multivariate adjusted relationships between brachial and aortic systolic blood pressure (SBP) and target organ changes in normotensive participants (conventional BP<140/90 mm Hg) of the community sample.

SBP vs	n	partial r	CI	p-value	partial r	CI	p-value
		Brachial SBP adjusted for*			Brachial SBP adjusted for imputed aortic SBP+*		
Pulse wave velocity	570	0.23	(0.15 to 0.30)	<0.0001	0.07	(-0.01 to 0.15)	=0.10
Estimated GFR	605	-0.13	(-0.21 to -0.05	=0.001	-0.05	(-0.13 to 0.03)	=0.20
LVMI-BSA	410	0.19	(0.09 to 0.28	=0.0001	0.01	(-0.09 to 0.11)	=0.84
LVMI-$ht^{1.7}$	410	0.16	(0.06 to 0.25)	=0.002	0.01	(-0.09 to 0.11)	=0.86
LVMI-$ht^{2.7}$	410	0.15	(0.06 to 0.25)	<0.002	-0.01	(-0.11 to 0.09)	=0.88
		Imputed aortic SBP adjusted for*			Imputed aortic SBP adjusted for brachial SBP+*		
Pulse wave velocity	570	0.28	(0.15 to 0.30)	<0.0001	0.18	(0.10 to 0.26)	<0.0001
Estimated GFR	605	-0.15	(-0.23 to -0.07)	=0.0002	-0.08	(-0.16 to -0.01)	<0.05
LVMI-BSA	410	0.29†	(0.20 to 0.38)	<0.0001	0.23	(0.13 to 0.32)	<0.0001
LVMI-$ht^{1.7}$	410	0.25	(0.16 to 0.34)	<0.0001	0.19	(0.10 to 0.29)	<0.0001
LVMI-$ht^{2.7}$	410	0.26†	(0.17 to 0.35)	<0.0001	0.21	(0.12 to 0.30)	<0.0001
		SphygmoCor-derived aortic SBP adjusted for*			SphygmoCor-derived aortic SBP adjusted for brachial SBP+*		
Pulse wave velocity	570	0.28	(0.20 to 0.36)	<0.0001	0.19	(0.11 to 0.27)	<0.0001
Estimated GFR	605	-0.14	(-0.22 to -0.07)	=0.0004	-0.08	(-0.16 to -0.01)	<0.05
LVMI-BSA	410	0.28	(0.19 to 0.37)	<0.0001	0.22	(0.12 to 0.31)	<0.0001
LVMI-$ht^{1.7}$	410	0.24†	(0.15 to 0.33)	<0.0001	0.18	(0.09 to 0.28)	=0.0002
LVMI-$ht^{2.7}$	410	0.26†	(0.17 to 0.35)	<0.0001	0.22	(0.12 to 0.31)	<0.0001

CI, confidence intervals; GFR, glomerular filtration rate; LVMI, left ventricular mass index; BSA, body surface area; ht, height. *Adjustments are for age, sex, BMI, diabetes mellitus and/or an HbA1c>6.1%, regular tobacco intake, regular alcohol intake and pulse rate. †p<0.05 vs r values for brachial SBP versus end-organ changes (z-statistics).

relationships with target organ changes in normotensives. Further, with adjustments for 24-hour brachial SBP, imputed aortic (PWV; partial r=0.24, confidence intervals=0.14 to 0.33, p<0.0001, n=386; eGFR; partial r= -0.12, confidence intervals= -0.21 to -0.02, p<0.05, n=412; LVMI; partial r=0.24, confidence intervals=0.13 to 0.35, p<0.0001, n=290) and SphgmoCor-derived aortic (PWV; partial r=0.23, confidence intervals=0.14 to 0.33, p<0.0001, n=386; eGFR; partial r= -0.11, confidence intervals= -0.21 to -0.01, p<0.05, n=412; LVMI; partial r=0.24, confidence intervals=0.11 to 0.33, p=0.0001, n=290) SBP also retained independent relationships with target organ changes in normotensives. Before or after adjustments for brachial BP, relations between end-organ changes and imputed aortic versus SphygmoCor-derived aortic BP were identical (Tables 5.4 and 5.5).

5.4.7 Target organ changes in those with a normal or high-normal BP irrespective of aortic BP.

Before adjustments for confounders, as compared to participants with optimal BP values, hypertensives and those with either normal or high-normal BP values had a markedly increased PWV, LVMI and eGFR (Table 5.6). However, after adjustments for confounders, only modest target organ changes were noted in those with a normal or high-normal BP (Table 5.6). Moreover, with the exception of eGFR which was higher in these with a high-normal BP, normal versus high-normal BP categories failed to distinguish between those with and without target organ changes (Table 5.6).

5.4.8 Imputed aortic BP distinguishes target organ changes in those with a normal/high-normal BP.

As compared to those with an optimal BP, both unadjusted and multivariate adjusted target organ changes were consistently noted in those with a normal/high-normal BP with, but not in those without imputed aortic systolic BP values≥upper 95% confidence

Table 5.6. Unadjusted and multivariate adjusted indices of target organ changes of study participants of the community sample.

BP categories	Optimal	Normal	High-normal	Hypertensives
BP range (mm Hg)	<120/80	≥120/80 and <130/85	≥130/85 and <140/90	≥140/90 or Treatment
Unadjusted values				
PWV (m/sec)(n)	4.86(285)	5.36(178)	6.11(107)*** †	7.87(459)*** †††###
eGFR (mls/min/1.73 m^2)(n)	131.8(296)	123.6(190)*	114.1(117)*** †	104.8(518)*** †††#
LV mass index (g/m^2)(n)	65.9(197)	75.8(133)*	74.8(80)	81.9(367)***
LV mass index ($g/m^{1.7}$)(n)	57.2(197)	66(133)**	65.9(80)*	74.3(367)*** ††#
LV mass index ($g/m^{2.7}$)(n)	35.4(197)	39.7(133)*	40.8(80)*	46.5(367)*** †††##
Multivariate adjusted values				
PWV (m/sec)(n)	5.92(285)	6.21(178)	6.37(107)	6.82(459)*** †
eGFR (mls/min/1.73 m^2)(n)	121.2(296)	115.2(190)	111.2(117)*	114.6(518)
LV mass index (g/m^2)(n)	71.4(197)	78.8(133)	75.5(80)	77.7(367)
LV mass index ($g/m^{1.7}$)(n)	64.5(197)	69.7(133)	66(80)	69(367)
LV mass index ($g/m^{2.7}$)(n)	40(197)	42.4(133)	41.1(80)	43(367)

BP, blood pressure; PWV, aortic pulse wave velocity; eGFR, estimated glomerular filtration rate; LV, left ventricle. Adjustments are for age, sex, BMI, diabetes mellitus and/or an HbA1c>6.1%, regular tobacco use, regular alcohol intake and pulse rate. *p<0.05, **p<0.005, ***p<0.0001 vs optimal; †p<0.05, ††p<0.005, †††p<0.0005 vs normal; #p<0.05, ##p<0.005, ###p<0.0001 vs high-normal.

interval for healthy participants with optimal BP values (Table 5.7). Importantly, even those with a normal as opposed to high-normal conventional BP values, but whom had an imputed aortic SBP that exceeded “optimal” values had multivariate adjusted increases in PWV, LVMI and decreases in eGFR.

5.4.9 Performance of measures of BP to detect target organ changes in normotensive participants.

In normotensives with all end-organ measurements 96 of 410 (23.4%) had LVH based on LVMI-BSA thresholds, 168 of 410 (41%) had LVH based on LVMI-$ht^{1.7}$ thresholds, 73 of 410 (17.8%) had LVH based on LVMI-$ht^{2.7}$ thresholds, 3 of 570 (0.5%) had an increases aortic PWV and 0 of 605 (0%) had a decreased eGFR. Hence, I assessed the performance of aortic versus brachial BP measurements for LVH detection, but not for the detection of increases in PWV or decreases in eGFR. All BP measurements showed significant performance for LVH detection (Table 5.8). However, SphygmoCor-derived and imputed aortic SBP and PP showed a greater performance for LVH detection than brachial SBP or PP (Table 5.8 and Figure 5.3). Imputed aortic SBP and PP showed a similar performance for LVH detection as SphygmoCor-derived aortic BP (Table 5.8 and Figure 5.3).

5.5 Discussion

The main findings of the present study are as follows: In a large community-based sample I identified an equation that incorporates the simple clinical measures of age, PPb, MAP and pulse rate and which generates imputed PPc values that closely approximate pulse wave analysis (PWA)-derived PPc values. Second, this equation was validated when applied to a clinical sample consisting of patients with severe and refractory hypertension, critical limb ischaemia and renal failure and performed equally as well in those of black African

Table 5.7. Unadjusted and multivariate adjusted indices of target organ changes of prehypertensives of the community sample with (Yes) or without (No) imputed aortic systolic blood pressures (SBP) greater than thresholds (112 mm Hg) defined in those with optimal conventional BP values.

Blood pressure categories Blood pressure range (mm Hg)	Optimal <120/80	Normal/high-normal ≥120/80 and <140/90 with aortic SBP≥112 mm Hg No	 Yes	Hypertensives ≥140/90 or Treatment
Unadjusted values				
PWV (m/sec)(n)	4.86(285)	4.99(112)	6.06(173)*** ††	7.87(459)*** †††###
eGFR (mls/min/1.73 m^2)(n)	131.8(296)	128.2(117)	114.9(190)*** ††	104.8(518)*** †††##
LV mass index (g/m^2)(n)	65.9(197)	66.9(79)	80.4(134)*** †	82(367)*** †††
LV mass index (g/$m^{1.7}$)(n)	57.2(197)	59.1(79)	70(134)*** ††	74.3(367)*** †††
LV mass index (g/$m^{2.7}$)(n)	35.4(197)	36(79)	42.5(134)*** †	46.5(367)*** †††#
Multivariate adjusted values				
PWV (m/sec)(n)	5.54(285)	5.67(112)	6.07(173)**	6.51(459)*** †††#
eGFR (mls/min/1.73 m^2)(n)	121.4(296)	117.1(117)	111.7(190)**	114.5(518)*
LV mass index (g/m^2)(n)	70.8(197)	71(79)	81.1(134)*	78.2(367)
LV mass index (g/$m^{1.7}$)(n)	64.1(197)	63.8(79)	70.7(134)*	69.3(367)
LV mass index (g/$m^{2.7}$)(n)	39.8(197)	39.3(79)	43.2(134)	43.2(367)

PWV, aortic pulse wave velocity; eGFR, estimated glomerular filtration rate LV, left ventricle. Adjustments are for age, sex, BMI, diabetes mellitus and/or an HbA1c>6.1%, regular tobacco use, regular alcohol intake and pulse rate. *p<0.05, **p<0.005, ***p<0.0001 vs optimal; †p<0.05, ††p<0.005, †††p<0.0005 vs aortic BP<112 mm Hg; #p<0.05, ##p<0.005, ###p<0.0001 vs aortic BP≥112 mm Hg.

Table 5.8. Performance (area under the receiver operating curve [AUC]) of brachial blood pressures (BP), SphygmoCor-derived aortic BP, or imputed aortic BP for left ventricular hypertrophy detection in normotensive participants (conventional BP<140/90 mm Hg) of the community sample.

	LVH detected using thresholds for					
	LVMI-BSA		LVMI-ht$^{1.7}$		LVMI-ht$^{2.7}$	
	96 of 410 (23.4%)		168 of 410 (41.0%)		73 0f 410 (17.8%)	
	AUC±SEM	p-value	AUC±SEM	p-value	AUC±SEM	p-value
Brachial systolic BP	0.586±0.034	=0.0072	0.595±0.029	=0.0010	0.618±0.037	=0.0014
Brachial pulse pressure	0.631±0.032	<0.0001	0.613±0.028	<0.0001	0.626±0.036	=0.0004
SphygmoCor† SBPc	0.646±0.034*	<0.0001	0.652±0.028*	<0.0001	0.714±0.034***	<0.0001
SphygmoCor† PPc	0.682±0.031*	<0.0001	0.693±0.026**	<0.0001	0.693±0.034*	<0.0001
Imputed SBPc	0.652±0.033*	<0.0001	0.645±0.028*	<0.0001	0.714±0.034***	<0.0001
Imputed PPc	0.682±0.032*	<0.0001	0.657±0.028*	<0.0001	0.683±0.036*	=0.0001

LVMI, left ventricular mass index; BSA, body surface area; ht, height; BP, blood pressure; SBPc, central aortic systolic BP; PPc, central aortic pulse pressure. †Refers to values obtained using radial applanation tonometry and SphygmoCor software. *p<0.05, **p<0.005, ***p<0.0005 for comparison with AUC values for brachial systolic blood pressure or pulse pressure.

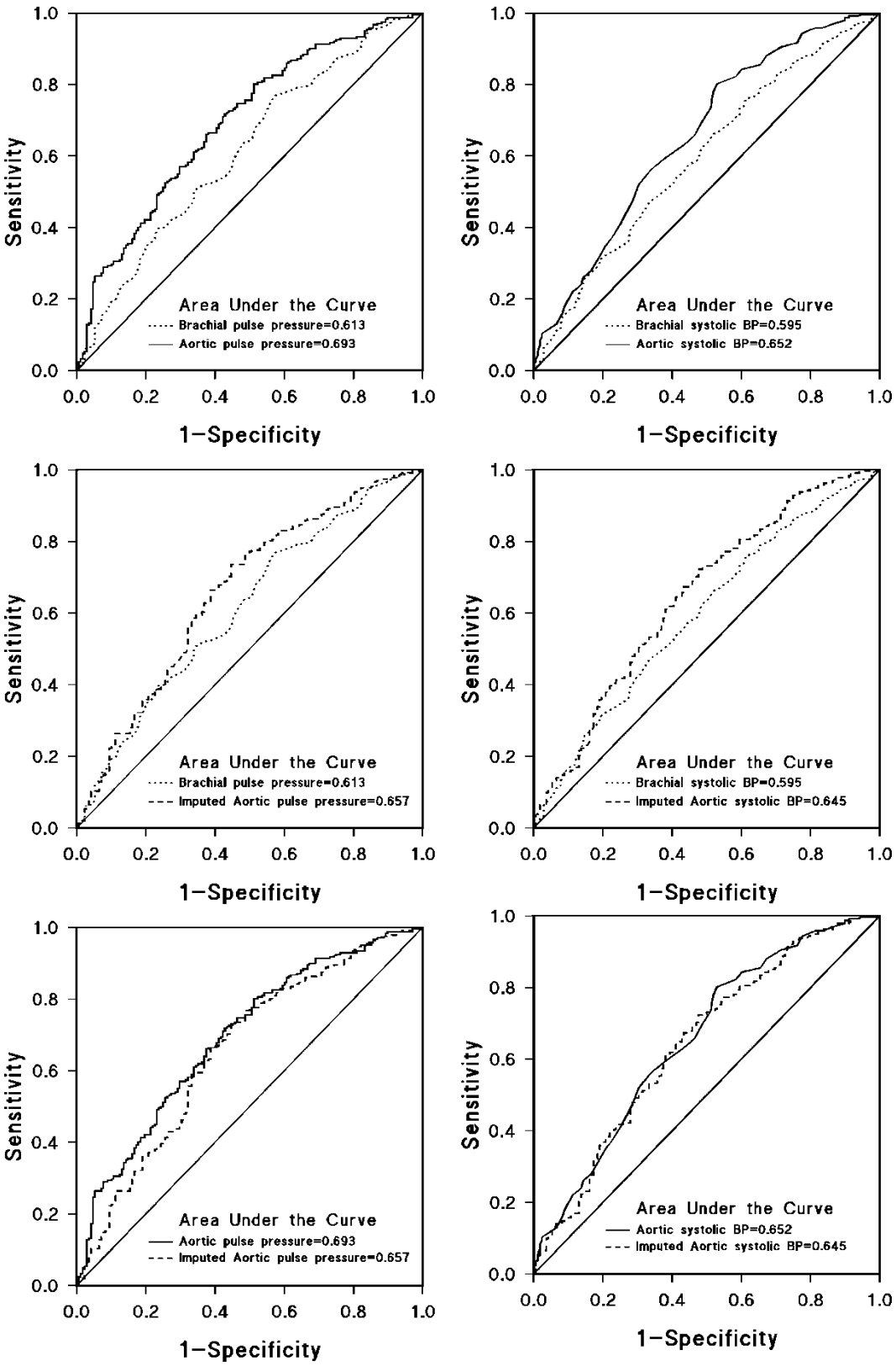


Figure 5.3. Performance of brachial blood pressures (BP), SphygmoCor-derived aortic BP, or imputed aortic BP for left ventricular hypertrophy detection (168 of 410 participants [41%] with LV mass indexed to height$^{1.7}$ greater than thresholds) in normotensive participants (conventional BP<140/90 mm Hg) of the community sample. A comparison of the area under the curves is made in Table 5.8.

origins as in those of other ethnic groups. Third, when applying this imputation equation to those with normal-high normal BP values of the community sample, as compared to those with an optimal BP, both unadjusted and multivariate adjusted target organ changes were consistently noted in those with a normal/high-normal BP with, but not in those without imputed aortic SBP values≥upper 95% confidence interval for healthy participants with optimal BP values. In contrast, normal and high-normal brachial BP categories failed to consistently identify those with target organ changes. Furthermore, in normotensives independent of brachial BP, imputed aortic BP was just as strongly associated with end-organ changes as PWA-derived aortic BP; imputed and PWA-derived aortic BP both showed similarly stronger relations with LVMI-BSA than brachial BP; and in comparison to PWA-derived aortic BP, imputed aortic BP showed a similarly improved ability (area under the receiver operating curve) to detect LVH than brachial BP.

Prior studies where PPc was imputed from an equation which did not incorporate pulse rate and MAP, although demonstrating independent relationships between imputed PP amplification and outcomes, failed to show that imputed PPc predicts outcomes beyond brachial PP (Benetos et al 2010, Regnault et al 2012). Furthermore, the imputation equation derived by Benetos et al (2010), failed to predict outcomes in alternative populations (unpublished data). These findings (Benetos et al 2010, Regnault et al 2012) may be attributed to an inability to generate an optimal imputation equation for estimating PPc, in-part because of the exclusion of MAP and pulse rate from the imputation equation. Indeed, in contrast to these studies (Benetos et al 2010, Regnault et al 2012) where only 85.8% of the variation in PPc could be accounted for, in the present study I could account for 97.5% of the variation in aortic BP, 96% of which was attributed to brachial PP, age, pulse rate and MAP. Importantly, in the present study I show that without pulse rate and MAP included in the model, imputed PPc remained markedly lower than pulse wave-derived PPc. The present study therefore underscores the importance of pulse rate and MAP as determinants of central aortic BP. Indeed, prior studies have demonstrated that the differential effects of β-adrenoreceptor blocker-based as compared

to alternative antihypertensive therapy on cardiovascular outcomes, may be attributed in-part to an attenuated beneficial effect of heart rate-lowering therapy on aortic BP (Williams et al 2006, Williams et al 2009).

An important caveat of the present study is that the present results do not suggest that imputed PPc may replace non-invasively measured PPc in enhancing risk-prediction in those with normal-high normal BP values. In this regard, although 96% of the variation of PPc was attributed to brachial PP, age, pulse rate and MAP, and these factors were included in the imputation equation, the unaccounted for 4% of the variability of PPc may translate into a 6.2 mm Hg (2xSD) difference in PPc, which may have potentially important effects on cardiovascular risk. Furthermore, in those with a lower augmentation index (younger individuals), largely because the slope of the relationship between brachial PP and PPc is reduced, the slope (β-coefficient) of the relationship between imputed PPc and PWA-derived PPc is further from unity (0.86) than that desired. Hence, in younger individuals with a lower augmentation index, the imputation equation is not ideal. The clinical importance of the present study is that in resource-limited settings where the devices for the non-invasive assessment of aortic BP may not be cost-effective methods of risk assessment, the use of an imputation equation as applied to simple clinical measurements may be a reasonable alternative with no cost implications.

Several limitations of the present study require consideration: First, the present study was conducted in a community sample of black African ancestry. Hence, whether similar data occur in other ethnic groups requires confirmation. However, in the clinical cohort employed for external validation I noted that the imputation equation applied equally as well in a small group of European, Asian and mixed ancestry as it did in the group of black African origins. Second, the present study was a cross-sectional design. Hence, conclusions regarding cause and effect cannot be drawn. Longitudinal studies are therefore required. Third, end-organ changes are surrogate measures of cardiovascular outcomes. Hence, whether imputed aortic BP predicts cardiovascular outcomes as well as PWA-derived-aortic BP in normotensives requires further study. In this regard, although

not conducted specifically in normotensives, in 4795 patients from a Mid-Eastern population in Israel referred for ambulatory BP monitoring, where 648 patients died over 20 years, independent of awake brachial PP, the hazards ratio for all-cause mortality per SD of ambulatory awake imputed PPc was 2.02 (95% CI:1.19-3.41, $p<0.01$). Similarly, independent of awake brachial systolic BP, imputed awake PPc predicted survival ($p<0.0001$) (Bursztyn et al, *PLoS One,* under-review).

In conclusion, in the present study I show that aortic PP can be imputed from an equation that employs simple clinical measures (age, brachial PP, MAP and pulse rate) and that imputed aortic PP produces values that closely approximate non-invasively determined aortic PP (applanation tonometry and SphygmoCor software). In addition, I show that aortic PP imputed from this equation may refine the ability to detect those with a normal/high-normal BP at risk of BP-related sub-clinical cardiovascular disease. In view of the cost of devices designed to measure aortic BP non-invasively, aortic BP imputed from simple clinical measures may be of value when risk-predicting in those individuals with normotensive office BP values (<140/90 mm Hg) in resource-limited settings.

Chapter 6

Contextual Narrative and Conclusions

In the present thesis I explored the possibility that the use of various measures of central aortic haemodynamics may enhance the ability to identify cardiovascular end-organ changes in those individuals with a normal/high-normal brachial BP. Although these individuals are well-recognised as being at risk for a cardiovascular event, whether this risk is attributed to the effects of BP has generated considerable debate. Although the findings of the present thesis have largely been discussed in each data chapter (chapters 2 to 5), the present chapter provides an overarching view of the data provided in the context of our current understanding of the field. The present chapter has therefore been provided to lead the reader through a series of arguments which support the final conclusions and hence raise the possibility of future studies.

6.1 Pre-hypertension: Is the risk increased because of a high brachial BP?

As extensively outlined in chapter 1, and again in chapters 2, 4 and 5, there is no question that a considerable proportion of those with normal/high-normal BP values (120-139/80-89 mm Hg) are at risk of a cardiovascular event. This notion is supported by several prospective, observational studies (Hsia et al 2007, Conen et al 2007, Dorjgochoo et al 2009, Qureshi et al 2005, Vasan et al 2001, Blake et al 2003, Liszka et al 2005, Gu et al 2009, Zhang et al 2006, Butler et al 2011, Kshirsagar et al 2006), some randomised, controlled trials (Nissen et al 2004, Remme et al 2009, Staessen and Jiguang 2001, Schrier et al 2002, Patel 2007) and meta-analyses of BP lowering trials (Trialists Collaboration 2003, Law et al 2009). In this regard, as highlighted in the present thesis, approximately 27% of the SOWETO community may be at risk of a cardiovascular event, because they have normal/high normal BP values. This represents a substantial population attributable risk. The question that obviously arises from these data is whether antihypertensive therapy should be employed to treat those with normal/high-normal BP values? Because of the proportion of any population with BP values within this range, this question has major cost implications to any country, but particularly to resource-limited

countries such as South Africa. Nonetheless, several intervention studies have demonstrated that antihypertensive treatment to thresholds lower than 140/90 mm Hg produced no added benefit to risk reduction (Yusuf et al 2008, Cushman et al 2010, McMurray et al 2010). These findings (Yusuf et al 2008, Cushman et al 2010, McMurray et al 2010) have challenged the paradigm that normal/high-normal brachial BP values represent risk for a cardiovascular event caused by BP *per se* and provide the evidence to indicate that pre-hypertension should not be treated with antihypertensive drug therapy. However, the obvious question that arises is if it is not BP causing excessive cardiovascular events in persons with a normal/high-normal brachial BP, what then could explain the higher risk?

As first pointed out by our group (Norton et al 2008), although those with a normal/high-normal BP have marked cardiovascular end-organ changes, these end-organ changes are eliminated with adjustments for associated cardiovascular risk factors. Hence, the concept arose that perhaps the high cardiovascular risk related to normal/high-normal BP values may be attributed to associated risk factors such as age, obesity, diabetes mellitus and dyslipidaemia. Indeed, several studies provide the evidence to show that a high proportion of those with pre-hypertension have at least one other associated risk factor or are at an increased risk of developing associated cardiovascular risk factors (Greenlund et al 2004, Mainous III et al 2004, Grotto et al 2006, Zhang et al 2006, King et al 2004, Chrysohoou et al 2004). In the present study I also show that in SOWETO, those with a normal/high-normal BP are indeed older and more obese. However, until the time of the present thesis, little consideration had been given to the possibility that although brachial BP may not be an accurate indicator of BP-related cardiovascular damage in pre-hypertension that BP may still be responsible for excess cardiovascular events in the normal/high-normal brachial BP range. In this regard, I considered the possibility that aortic BP may better herald the presence of cardiovascular damage. What was the evidence to suggest this possibility and how has the present thesis added to our understanding of cardiovascular risk related to pre-hypertension?

6.2 Pre-hypertension: Is the risk increased because of a high aortic BP?

The initial suggestion that normal/high-normal brachial BP values may signal the presence of a wide range of aortic BP values came from the findings of the Anglo-Cardiff Study which demonstrated considerable overlap in aortic BP across categories of optimal, pre-hypertensive (normal or high-normal) and hypertensive BP ranges (McEniery et al 2008). As several studies have demonstrated that aortic BP is more closely associated with end-organ changes than brachial BP or that the ratio of aortic-to-brachial PP predicts outcomes beyond brachial BP (Safar et al 2002, Roman et al 2007, Roman et al 2009, Jankowski et al 2008, Pini et al 2008, Wang et al 2010, Benetos et al 2010, Regnault et al 2012, Benetos et al 2012), overlap in aortic BP across categories of optimal, pre-hypertensive (normal or high-normal) and hypertensive BP ranges (McEniery et al 2008), raised the possibility that a considerable proportion of pre-hypertensives are not at risk of a BP-related cardiovascular event. This possibility may explain why several clinical trials have failed to show that antihypertensive treatment to thresholds lower than 140/90 mm Hg add no benefit to risk reduction (Yusuf et al 2008, Cushman et al 2010, McMurray et al 2010). In this regard, a high proportion of those treated may have had aortic BP values within optimal BP ranges. The overlap in aortic BP across categories of optimal, pre-hypertensive (normal or high-normal) and hypertensive BP ranges (McEniery et al 2008) raised the question of whether non-invasively determined aortic BP may further refine the ability to detect those pre-hypertensives at risk of a cardiovascular event. What is the evidence to suggest that a high proportion of pre-hypertensives treated with antihypertensive therapy may have had aortic BP values within optimal BP ranges and what is the evidence to show that non-invasively determined aortic BP may further refine the ability to detect those pre-hypertensives at risk of a cardiovascular event?

In chapter 2, data published in 2013 (Booysen et al 2013), I provide the evidence to show that 46% of those with normal/high-normal brachial BP values living in SOWETO

have aortic BP values that lie within optimal BP ranges. Hence, in keeping with the Anglo-Cardiff study (McEniery et al 2008) in a population of African ancestry across the adult age-range, a considerable proportion of pre-hypertensives are unlikely to be at risk of a BP-related cardiovascular event. In this same study, whilst only 39% of those with a normal brachial BP had an aortic BP higher than the upper 95% confidence intervals for optimal brachial BP values, 80% of those with a high-normal brachial BP had an aortic BP higher than the upper 95% confidence intervals for optimal brachial BP values. Hence, the question arose as to whether the brachial BP threshold that separates normal from high normal brachial BP categories (130/95 mm Hg) is not sufficient to identify those at risk? In this regard, one must consider whether it is worth treating 39% of those with a normal brachial BP whom have aortic BP values greater than optimal BP thresholds. This would represent 6.4% of any adult sample and in my opinion would be a significant chance to limit cardiovascular events, if indeed aortic BP above optimal thresholds does identify those at risk. Are those with normal/high-normal brachial BP values and an aortic BP above optimal thresholds at risk?

In chapter 2 (Booysen et al 2013), I also provide the first evidence to show that aortic BP may refine the ability to detect end-organ changes (sub-clinical cardiovascular disease) beyond brachial BP in the normotensive (optimal, normal and high-normal) BP range. These data provide the first direct evidence to suggest that a considerable proportion of pre-hypertensives both are, and are not at risk of a cardiovascular event through BP-related mechanisms and also suggest that the identification of pre-hypertensives whom may warrant antihypertensive therapy may be refined by non-invasively determined aortic BP measurements. Although there are clearly a number of limitations to this study (Booysen et al 2013, chapter 2) including the cross-sectional design and the lack of cardiovascular outcomes data, these data nevertheless provide a possible explanation as to why intervention studies have failed to support the paradigm that brachial BP in pre-hypertension is causally related to cardiovascular risk in some studies (Yusuf et al 2008, Cushman et al 2010, McMurray et al 2010). The data described

in the present thesis (Booysen et al 2013, chapter 2) also suggest that studies should be conducted to evaluate whether specifically targeting pre-hypertensives with aortic BP values above optimal thresholds with BP lowering drug therapy could benefit cardiovascular risk. Unfortunately, as causes of death in South Africa are poorly reported, and verbal autopsy data have far too many limitations to be reliable, this study is not feasible in this country.

An important consideration of the finding that aortic BP is able to refine the ability to detect end-organ changes in pre-hypertension beyond brachial BP is the mechanisms responsible for this effect? This question is important for several reasons. The first reason of which is whether these mechanisms can be targeted by current antihypertensive therapy. Second, is whether other measurements of aortic BP which specifically describe these mechanism, may predict end-organ changes in pre-hypertension better than aortic BP *per se*. What are the possible mechanisms responsible for the ability of aortic BP to refine the detection of end-organ changes in pre-hypertension?

6.3 What are the possible mechanisms that explain the ability of aortic BP to refine the identification of end-organ changes in pre-hypertension?

Aortic SBP is generally considered to be lower than brachial SBP and because of the proximity of the aorta to cardiovascular end-organs, aortic BP is thought to enhance risk prediction beyond brachial BP. Indeed, a number of studies support this notion (Safar et al 2002, Roman et al 2007, Roman et al 2009, Jankowski et al 2008, Pini et al 2008, Wang et al 2009, Benetos et al 2010, Regnault et al 2012, Benetos et al 2012). Several possibilities explain differences between aortic and brachial BP and these have been extensively reviewed in chapter 1 (section 1.3.2). Briefly, with the effects of ageing and cardiovascular risk factors, the aorta stiffens, whilst brachial artery stiffness increases to a lesser extent. Hence, with ageing aortic BP increases much more than brachial BP. With ageing aortic reflected waves derived largely from the lower limbs and the visceral bed are

thought to increase. Thus on return to the proximal aorta, these waves enhance aortic SBP. However, because reflected waves are transmitted to the brachial artery much later than aortic forward waves, thus producing a second systolic shoulder, and because reflected wave pressures are lower than forward wave pressures, changes in reflected waves are generally not detected by brachial BP measurements.

In short aortic, but not brachial BP closely mirrors the effects on BP of increases in aortic stiffness (which determines the aortic forward and backward wave) and/or wave reflection (which determines the aortic backward wave). Hence, the question which arises is whether it is increases in aortic forward or backward wave pressures which explain the ability of aortic BP to refine the detection of end-organ changes in pre-hypertension? In this regard, before I could address this question in the present thesis, I first needed to provide clarity on the best method of assessing the role of aortic forward and backward wave effects on aortic pressure and cardiovascular damage. What were the important questions to address on this topic and how has the work described in the present thesis advanced our knowledge of this field?

6.3.1 How best should aortic forward and backward wave effects be evaluated?

As extensively described in chapter 1, section 1.3.3, the relative contribution of aortic forward and backward waves to variations in aortic BP and cardiovascular damage continues to elicit heated debate. In this regard, a number of earlier studies indicate that across the adult age range, reflected waves, assessed from indices of pressure augmentation, dominate age-related increases in aortic pressure (McEniery et al 2008, Namasivayam et al 2009, Cecelja et al 2009) and predict cardiovascular damage (Hashimoto et al 2007, Hashimoto et al 2006, Weber et al 2006, Westerbacka et al 2005, Sibiya et al 2014), and cardiovascular outcomes (Chirinos et al 2005b, London et al 2001, Ueda et al 2004, Weber et al 2005) beyond brachial BP. Further, a meta-analysis of these and other outcome studies provided clear evidence that indices of pressure augmentation

predict outcomes beyond brachial BP (Vlachopoulos et al 2010). In contrast however, the Framingham Heart Study failed to show that indices of aortic pressure augmentation predict outcomes independent of brachial BP (Mitchell et al 2010a). Nevertheless, in the Framingham Heart Study, in contrast to the expected 5-15 mm Hg difference between aortic and brachial BP (PP amplification), little difference was noted across the adult lifespan (Mitchell et al 2010b). This has been explained on the basis of the application of tonometry at a site where the principles of tonometry cannot be achieved (brachial artery to calibrate the carotid artery pulse) and the use of an inaccurate mean pressure for calibrating carotid artery pressures (O'Rourke et al 2010). In this regard, the brachial artery, with tendon aponeurosis superficial to it, and with no bone to support it, cannot be reliably applanated, so that the theory of Drzewiecki et al (1983), cannot be relied upon. This error resulted in an assumption that little carotid to brachial amplification occurs, but that marked brachial-to-radial amplification occurs. In addition, although in several of these studies (Davies et al 2010, Hughes et al 2013, Fok et al 2014), the method of wave intensity analysis has been seriously questioned on methodological and theoretical grounds (Segers et al 2015), and Fok et al (2014) report an impossible flow-frequency response, apparently hand-drawn representative waves are shown, and control impedance values are given that differ markedly from Yaginuma et al (1985), the use of Pa or AIx as measures of aortic wave reflection have recently been criticised (Davies et al 2010, Cheng et al 2012, Hughes et al 2013, Fok et al 2014, Torjesen et al 2014, Schultz et al 2013). Indeed, marked overlap between aortic forward and reflected waves may confound Pa and AIx (Cheng et al 2012, Fok et al 2014, Torjesen et al 2014, Schultz et al 2013) and hence these measures may be poor indices of wave reflection. Increases in the timing or magnitude of Pf or Pi, and left ventricular systolic function may in fact 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, Fok et al 2014, Torjesen et al 2014, Schultz et al 2013). More recently, wave separation analysis has been employed to identify aortic backward wave effects, thus excluding confounding effects on wave reflection. What have

these studies demonstrated and how has data from the present thesis added to this debate?

Several recent studies suggest an important contribution of wave reflection, determined from wave separation analysis, to aortic BP and cardiovascular damage (Wang et al 2010, Chirinos et al 2012, Weber et al 2012, Zamani et al 2014). However, in these studies (Wang et al 2010, Chirinos et al 2012, Weber et al 2012, Zamani et al 2014) the extent to which indices of wave reflection determined from wave separation analysis were more closely associated with aortic BP or sub-clinical cardiovascular disease than indices of aortic pressure augmentation is uncertain (Wang et al 2010, Chirinos et al 2012, Weber et al 2012, Zamani et al 2014). In this regard in these studies, relations with end-organ changes were not adjusted for confounders (Wang et al 2010, Weber et al 2012); discrepancies in the index of wave reflection that was better associated with end-organ changes beyond forward wave pressures were noted (Wang et al 2010, Weber et al 2012); and whether the increase in forward wave pressures at 50 years of age impacts on these relations was not considered (Wang et al 2010, Chirinos et al 2012, Weber et al 2012). Moreover, although conducted either in a sample where little difference in aortic and brachial BP was noted across the adult lifespan (Mitchell et al 2010b), an effect that has been explained on the basis of the application of tonometry at a site where the principles of tonometry cannot be achieved (brachial artery to calibrate the carotid artery pulse) (O'Rourke et al 2010), forward rather than backward wave pressures have been reported to be the main determinant of aortic BP (Mitchell et al 2010b). However, in the present thesis I provide strong evidence accepted for publication in the journal *Hypertension* (Booysen et al 2015), that in a group of African ancestry living in SOWETO with a high prevalence of uncontrolled hypertension, with adjustments for confounders, across the adult lifespan (younger and older than 50 years of age), reflected waves contribute more than forward waves to variations in aortic BP and left ventricular mass index. Hence, these data suggest the possibility that aortic wave reflection could largely explain the ability of aortic BP to refine the detection of end-organ changes in pre-hypertension and hence that

measures of aortic reflected wave function may improve on the ability of aortic BP *per se* to risk predict in those with normal/high-normal BP values. These questions were addressed as part of the present thesis in chapter 4. What did these data show and what are the implications?

6.3.2 Aortic backward waves in pre-hypertension

In chapter 4 of the present thesis I show that in normotensives (optimal, normal, and high-normal brachial BP) backward wave pressures were indeed more closely associated with LVMI and better at detecting LVH than forward wave pressures. However, I also demonstrated that despite aortic BP being associated with all end-organ changes independent of confounders and brachial BP, neither backward, nor forward wave pressures were independently associated with all end-organ changes independent of confounders and brachial BP. In addition, although in normotensives backward wave, but not forward wave pressures were better than brachial BP at LVH detection and backward wave, but not forward wave pressures were more strongly associated with LVMI, these effects of backward wave pressures were no better than aortic BP *per se*. What are the implications of these findings?

First, the finding that in normotensives backward wave, but not forward wave pressures were better than brachial BP at LVH detection suggests that to reduce risk in pre-hypertensives, therapeutic approaches should target backward wave pressures. As discussed in chapter 4 however, although most antihypertensive agents are thought to reduce wave reflection, to the best of my knowledge, in these studies this conclusion has been reached without wave separation analysis (i.e, with the use of indices of aortic pressure augmentation alone). Hence, further studies are required to test the hypothesis that antihypertensive agents reduce wave reflection and which agents are best at producing these effects.

A second finding that requires consideration is that although aortic BP was associated with end-organ changes independent of brachial BP, neither backward, nor forward wave pressures were independently associated with all end-organ changes independent of confounders and brachial BP. In this regard, these data suggest that backward wave pressures are not the only factor explaining end-organ changes in pre-hypertensives. Indeed, although backward wave, but not forward wave pressures were better than brachial BP at LVH detection, forward wave pressures did indeed detect LVH, at least as well as brachial BP. Hence, therapeutic approaches to risk reduction in those with normal/high-normal brachial BP values should also target forward wave pressures. As acknowledged by consensus documents (Agabiti-Rosei et al 2007), there is unfortunately little evidence to indicate that current therapy modifies the structural aortic changes responsible for increases in aortic forward wave pressures.

The third finding that requires consideration is that although in normotensives, backward wave, but not forward wave pressures were better than brachial BP at LVH detection, this effect was no better than aortic BP *per se*. These data suggest that indices of wave reflection are unlikely to improve on risk prediction in normotensives beyond aortic BP *per se*. Hence, the more complicated measures of aortic wave reflection may not be required to replace aortic BP when risk predicting in normotensives. This has major implications with regard to the final question that I answered in the present thesis and that is whether in the absence of sufficient resources for routine risk prediction in normotensives using valid devices to non-invasively assess aortic BP, is there a reasonable alternative? The finding that Pb or RI may offer no prognostic information beyond aortic BP in normotensives, suggests that when risk predicting, surrogate measures of aortic PP or SBP may be sufficient, at least in normotensives. Hence, the question is whether reasonable alternatives to non-invasively measured aortic PP or SBP may be employed to enhance risk prediction beyond brachial BP? This question was answered in chapter 5 of the present thesis. What were the findings of this study and what are the potential implications?

6.4 Imputing aortic BP in pre-hypertension from simple clinical measures

As first suggested some years ago (Camacho et al 2004) aortic BP may be imputed from simple clinical measures. Indeed, in a recent study 85.8% of the variation in pulse wave analysis (PWA)-derived aortic PP could be accounted for by simple clinical measures (Benetos et al 2010). However, in this (Benetos et al 2010) and a subsequent (Regnault et al 2012) study, although PP amplification predicted outcomes beyond brachial BP, aortic BP *per se* was unable to predict outcomes beyond brachial BP. These findings (Benetos et al 2010, Regnault et al 2012) may be attributed to an inability to generate an optimal imputation equation for estimating aortic PP, in-part because of the exclusion of MAP and pulse rate from the imputation equation. Indeed, in contrast to these studies (Benetos et al 2010, Regnault et al 2012) where only 85.8% of the variation in aortic PP could be accounted for, as described in chapter 5 of the present thesis I could account for 97.5% of the variation in aortic BP, 96% of which was attributed to brachial PP, age, pulse rate and MAP. Importantly, in the present study I show that without pulse rate and MAP included in the model, imputed aortic PP remained markedly lower than pulse wave-derived aortic PP.

Not only did the imputation equation identified in the present thesis account for a significant proportion of the variability of PWA-derived aortic BP, but the equation markedly reduced the difference between brachial and aortic PP, and corrected the intrinsic bias toward lower aortic as compared to brachial PP values at higher BP values. Furthermore, in contrast to previous studies which failed to validate the equation in a separate study sample (Benetos et al 2010, Regnault et al 2012), in the present thesis I externally validated the equation in a clinical sample; demonstrated the validity of the equation across a number of subgroups of the community sample; and demonstrated in the clinical sample that the equation was equally as valid in patients of black African ancestry as it was for other ethnic groups. As in all instances the equation proved to be valid, in the

present thesis I therefore evaluated whether imputed aortic BP provides similar information as PWA-derived aortic BP when assessing relations with end-organ changes. What did these analyses show?

In chapter 5, I show that in normotensives, independent of brachial BP, imputed aortic BP is as closely associated with end-organ changes as PWA-derived aortic BP and that both imputed aortic BP and PWA-derived aortic BP are more strongly associated with end-organ changes than brachial BP. I also demonstrate that in normotensives, imputed aortic BP detects LVH better than brachial BP (area under the receiver operating characteristic curve) and as well as PWA-derived aortic BP. Hence, these data provide proof of principle that in resource-limited settings where valid devices to non-invasively assess aortic BP for routine risk prediction in normotensives would be cost-prohibitive, that the use of simple clinical data to impute aortic BP may be a useful approximate. However, again further outcome-driven studies are warranted to address this question.

6.5 Challenges and further limitations

Although the limitations of the present study have largely been addressed in the discussion section of each chapter and further highlighted in the present chapter, limitations of adequately indexing LVM to account for the non-pathological effects on the left ventricle require further discussion. In this regard, there is still considerable debate as to whether LVM should be indexed to allometric signals of body surface area, thus largely excluding the impact of obesity on cardiac growth, or to allometric signals of height, which recognise the ill-effect of obesity on cardiac growth. As discussed in a recent review of the topic (Woodiwiss and Norton, 2015), recent guidelines have now recognised the use of allometric signals to height in obese individuals (a high proportion of the present community sample were overweight or obese). Nevertheless, debate still remains as to whether indexation to height$^{2.7}$ or height$^{1.7}$ should be employed (Woodiwiss and Norton 2015). At the time of analysing the data for chapter 2, the debate as to whether indexation

to height$^{2.7}$ or height$^{1.7}$ should be employed had only recently begun based on the work of Chirinos et al (2010) who demonstrated that the use of height$^{2.7}$ may markedly overestimate the prevalence of LVH in women. Hence, in this chapter LVM was indexed to the power of 2.7, the accepted index at this point. Nevertheless, in subsequent chapters, I employed a range of indexation approaches including LVM indexed to body surface area, height$^{2.7}$ and height$^{1.7}$. The range of approaches adopted were largely employed to satisfy the fact that the ill-effects of BP and not obesity were being studied as well as the fact that no consensus has yet been achieved as to whether indexation to height$^{2.7}$ and height$^{1.7}$ should be employed (Woodiwiss and Norton 2015). Nevertheless, irrespective of whether LVM was indexed to body surface area, height$^{2.7}$ or height$^{1.7}$, in the present thesis I was able to show that aortic pressure, either determined from pulse wave analysis or imputed from simple clinical measures, was more closely associated with LVMI in pre-hypertensives than brachial BP, that this was largely accounted for by backward wave pressure effects, but that the association between backward wave pressures and LVMI was no better than associations between aortic BP *per se* and LVMI.

6.6 Conclusions

Hence, in conclusion, in the present thesis I provide evidence to support a possible solution to the conundrum of how best to identify normotensives who may be at risk of a BP-related cardiovascular event. In this regard I show that PWA-derived aortic BP may refine the ability to detect cardiovascular damage in normotensives. Second, I show that although aortic wave reflection, determined using 'wave-separation analysis' in-part accounts for the ability of aortic BP to detect end-organ damage better than brachial BP in normotensives, that these effects are no better than aortic BP *per se*. Third, I show that aortic BP imputed from simple clinical measures closely approximates PWA-derived aortic BP and performs as well as PWA-derived aortic BP in the detection of cardiovascular damage in normotensives. All of these findings have generated hypotheses that require

testing in longitudinal outcome-based studies and in intervention studies where the effects in normotensives of targeting aortic as compared to brachial BP with antihypertensive therapy are compared.

Appendix 1

Ethic clearance certificates

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

UNIVERSITY OF THE WITWATERSRAND
PROF PE CLEATON-JONES
HREC (MEDICAL)
2007-05-09
JOHANNESBURG

DECISION OF THE COMMITTEE *

Approved unconditionally

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

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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

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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

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Appendix 2

Booysen, H. L., Norton, G. R., Maseko, M. J., Libhaber, C. D., Majane, O. H., Sareli, P., & Woodiwiss, A. J. (2013). Aortic, but not brachial blood pressure category enhances the ability to identify target organ changes in normotensives. *Journal of Hypertension* 31(6), 1124-1130.

Original Article

Aortic, but not brachial blood pressure category enhances the ability to identify target organ changes in normotensives

Hendrik L. Booysen[a,*], Gavin R. Norton[a,*], Muzi J. Maseko[a], Carlos D. Libhaber[b], Olebogeng H.I. Majane[a], Pinhas Sareli[a], and Angela J. Woodiwiss[a,*]

Aims: We sought to determine whether within normal/high-normal blood pressure (BP) ranges (120–139/80–89 mmHg), aortic BP may further refine BP-related cardiovascular risk assessment, as determined from target organ changes.

Methods: In 1169 participants from a community sample of African ancestry, 319 (27%) of whom had a normal/high-normal BP, aortic BP was determined using radial applanation tonometry and SphygmoCor software, and target organ changes assessed from carotid-femoral pulse wave velocity (PWV) ($n = 1025$), estimated glomerular filtration rate (eGFR) ($n = 944$), and left ventricular mass indexed to height$^{2.7}$ (LVMI) ($n = 690$).

Results: Normal versus high-normal BP categories failed to differentiate between those participants with a BP above optimal values with versus without multivariate-adjusted target organ changes. However, in those with a normal/high-normal BP with aortic SBP values that were less than 95% confidence interval of healthy participants with optimal BP values (45% of those with a normal/high-normal BP), no unadjusted or multivariate adjusted target organ changes were noted. In contrast, those with a normal/high-normal BP with aortic SBP values that exceeded optimal thresholds, demonstrated unadjusted and multivariate adjusted increases in PWV and LVMI and decreases in eGFR ($P < 0.05$ to $P < 0.005$ after multivariate adjustments).

Conclusion: In contrast to normal versus high-normal BP categories which do not clearly distinguish normotensives with from those without organ damage, noninvasively determined aortic BP measurements may refine the ability to detect those with a normal/high-normal BP at risk of BP-related cardiovascular damage.

Keywords: aortic BP, normal/high-normal BP, risk factors, target organ changes

Abbreviations: BP, blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated haemoglobin; HDL, high density lipoprotein; LV, left ventricular; LVMI, left ventricular mass indexed to height$^{2.7}$; PWV, pulse wave velocity

INTRODUCTION

Although guidelines recommend threshold blood pressure (BP) values of 140/90 mmHg for the diagnosis of hypertension, BP is continuously associated with cardiovascular outcomes from values as low as 115/75 mmHg [1]. Prospective, observational studies indicate that those with BP values in the normal/high-normal range (120–139/80–89 mmHg) are at an increased risk for cardiovascular events [2–9]. In addition, some randomized, controlled trials [10–12] and meta-analyses of BP-lowering trials [13–15] in high-risk patients support a view that treatment of those with a normal/high-normal BP has benefits for outcomes. In contrast, several more recent intervention studies suggest that antihypertensive treatment to thresholds lower than 140/90 mmHg has no added benefit [16–23]. Contrasting results of intervention studies in normal/high-normal BP ranges [10–23] highlight the markedly variable BP-related risk conferred by a normal/high-normal BP. Strategies are, therefore, required to better identify those with a normal/high-normal BP at risk for BP-related cardiovascular outcomes.

One possible reason for the variable BP-related cardiovascular risk in those with a normal/high-normal BP is that brachial BP measurements may be insufficiently accurate for risk determination. In this regard, prior studies indicate that a number of those with a normal/high-normal BP may have aortic BP values that are more consistent with either an optimal or hypertensive BP range [24]. As aortic BP as assessed using easy and reproducible non-invasive measurements is more closely associated with

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[a]Cardiovascular Pathophysiology and Genomics Research Unit, School of Physiology and [b]School of Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

Correspondence to Angela J. Woodiwiss, Cardiovascular Pathophysiology and Genomics Research Unit, School of Physiology, University of the Witwatersrand Medical School, 7 York Road, Parktown, 2193, Johannesburg, South Africa. Tel: +27 11 717 2363; fax: +27 11 717 2153; e-mail: angela.woodiwiss@wits.ac.za

*Hendrik L. Booysen, Gavin R. Norton and Angela J. Woodiwiss contributed equally to the writing of this work.

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cardiovascular outcomes than brachial BP [25–29], non-invasive aortic BP measurement may further refine cardiovascular risk in those with a normal/high-normal BP. To test this hypothesis, in the present study we, therefore, assessed whether aortic BP enhances the ability to identify independent relationships between BP and target organ changes in the normotensive range and whether 'optimal' aortic BP thresholds may refine the ability to identify organ damage in the normal/high-normal BP range.

METHODS

The study protocol was approved by the University of the Witwatersrand Committee for Research in Humans (approval numbers: M02-04–72 renewed as M07-04–69 and M12-04–108). Participants gave informed, written consent. The study design has previously been described [30–32]. Briefly, nuclear families of black African ancestry consisting of siblings with a minimum age of 16 years were randomly recruited from the South West Township (SOWETO) of Johannesburg, South Africa. Of the 1191 participants enrolled, 1169 had central aortic BP measurements and in these participants, carotid-femoral pulse wave velocity (PWV) was available in 1025 participants, estimated glomerular filtration rate (eGFR) in 944 participants, and in a substudy, echocardiographic data in 690 participants. Seven hundred and eighty-two participants had ambulatory BP recordings that met with prespecified quality control criteria (longer than 20 h and more than 10 and five readings for the computation of daytime and night-time means, respectively).

Clinical, demographic and anthropometric measurements

A standardized questionnaire was administered to obtain demographic data and information on each participant's medical history, smoking habits, intake of alcohol, use of medication and menopausal status [30–32]. Participants were identified as being overweight if their BMI was at least 25 kg/m^2 and obese if their BMI was at least 30 kg/m^2. Laboratory blood tests of renal function, liver function, blood glucose, haematological parameters, lipid profiles and percentage glycated haemoglobin (HbA_{1C}) (Roche Diagnostics, Mannheim, Germany) were performed. Diabetes mellitus was defined as the use of insulin or oral hypoglycaemic agents and an impaired blood glucose control was identified from an HbA_{1C} more than 6.1% [33].

Conventional and 24-h blood pressure

Details as previously described [30,31] of nurse-derived conventional BP and 24-h BP measurements and the quality of these measurements are provided in the on-line supplement (see on-line supplement for details, http://links.lww.com/HJH/A249). Hypertension was defined as the presence of antihypertensive treatment or a mean conventional BP at least 140/90 mmHg; a high-normal BP as a conventional BP at least 130/85 and less than 140/90 mmHg; a normal BP as a conventional BP at least 120/80 and less than 130/85 mmHg; and an optimal BP as less than 120/80 mmHg.

Aortic blood pressure and target organ changes

Aortic BP and carotid-femoral PWV were determined using applanation tonometry and SphygmoCor software as previously described [30–32] (see on-line supplement for details, http://links.lww.com/HJH/A249). eGFR was determined using the abbreviated Modification of Diet in Renal Disease study group equation: $186.3 \times (\text{serum creatinine in mg//decilitre}^{-1.154}) \times (\text{age in years}^{-0.203}) \times 1.212 \times 0.742$ (if female) [34]. Echocardiographic measurements of left ventricular (LV) diastolic dimensions were performed using previously described methods [30–32] (see on-line supplement for interobserver and intraobserver variability, http://links.lww.com/HJH/A249). Left ventricular mass was derived according to an anatomically validated formula [35] and indexed to height$^{2.7}$ (LVMI).

Data analysis

For database management and statistical analysis, SAS software, version 9.1 (SAS Institute Inc., Cary, North Carolina, USA) was employed. Unadjusted means and proportions were compared by the large-sample z-test and the χ^2-statistic, respectively. Optimal thresholds for aortic and 24-h BP were identified from upper 95% confidence intervals (CI) obtained in 311 participants with optimal conventional BP values and without diabetes mellitus, 212 of whom had 24-h BP measurements that met with prespecified quality control criteria. The aortic SBP threshold was identified as 112 mmHg and the 24-h SBP and DBP thresholds as 123 and 78 mmHg, respectively. Differences in indices of organ changes between participants in categories of BP and independent relations between BP and target organ changes were determined using multivariate regression analysis with adjustments for age, sex, BMI, diabetes mellitus and/or an HbA_{1c} more than 6.1%, regular tobacco use, regular alcohol intake and pulse rate in the models. To determine probability values, further adjustments for nonindependence of family members was performed using nonlinear regression analysis (mixed procedure as defined in the SAS package).

RESULTS

Characteristics of participants in categories of blood pressure

Of the total sample, 27.3% of participants had either normal or high-normal BP; 16.5% had a normal BP and 10.8% had high-normal BP values. Age, BMI, waist circumference and the frequency of participants who were overweight or obese were intermediate in those with a normal or high-normal BP between values noted in persons with an optimal BP and in hypertensives (Table 1). Hypertensives, but not those with a normal or high-normal BP, had more diabetes mellitus and/or an impaired blood glucose control, and an increased total/HDL cholesterol (Table 1). No differences were noted between BP categories in regular alcohol and tobacco intake or pulse rate (Table 1). The distribution of antihypertensive medication given to treated hypertensives is given in Supplemental Table S1, http://links.lww.com/HJH/A249. The characteristics of the sample

TABLE 1. Characteristics of study participants

BP categories BP range (mmHg)	Optimal <120/80	Normal ≥120/80 and <130/85	High-normal ≥130/85 and <140/90	Hypertensives ≥140/90 or treatment
Sample size (% female)	311 (69.1)	193 (62.7)	126 (61.1)	539 (64.9)
Age (years)	30.7 ± 12.4	34.0 ± 13.6	40.2 ± 16.8***,††	55.1 ± 15.0$^{***,\dagger\dagger\dagger,\#\#}$
BMI (kg/m^2)	25.3 ± 6.3	28.0 ± 8.1**	29.6 ± 8.0***,†	32.4 ± 7.9$^{***,\dagger\dagger\dagger,\#\#}$
Waist circumference (cm)	80.6 ± 13.9	86.2 ± 15.5**	89.2 ± 15.1***	97.6 ± 15.4$^{***,\dagger\dagger\dagger,\#\#}$
% Overweight/obese	21.2/22.5	22.8/32.6*	22.2/43.7**	23.9/57.9$^{***,\dagger\dagger\dagger,\#}$
Regular tobacco intake (%)	13.8	18.7	16.7	14.3
Regular alcohol intake (%)	18.7	21.8	25.4	21.9
% With DM or HbA_{1C}>6.1%	10.0	15.0	10.3	41.4$^{***,\dagger\dagger\dagger,\#\#}$
Pulse rate (beats/min)	69.5 ± 11.3	69.5 ± 10.9	69.0 ± 11.0	69.4 ± 10.3
Total/HDL cholesterol	3.13 ± 1.17	3.22 ± 1.06	3.60 ± 1.53	3.84 ± 1.26***,††

BP, blood pressure; DM, diabetes mellitus; HbA_{1C}, glycosylated haemoglobin; HDL:, high density lipoprotein.
$^{*}P<0.05$.
$^{**}P<0.005$.
$^{***}P<0.0001$ versus optimal.
$^{\dagger}P<0.05$.
$^{\dagger\dagger}P<0.005$.
$^{\dagger\dagger\dagger}P<0.0005$ versus normal.
$^{\#}P<0.005$.
$^{\#\#}P<0.0001$ versus high-normal.

with and without echocardiography were similar (Supplemental Table S2, http://links.lww.com/HJH/A249).

Blood pressures and proportions with elevated aortic or ambulatory blood pressure within blood pressure categories

Conventional, 24 h and central aortic BP values were intermediate in those with a normal or high-normal BP between values noted in persons with an optimal BP and in hypertensives (Table 2). A greater proportion of hypertensives as well as those with a normal or high-normal BP had aortic SBP values that exceeded that of the upper 95% CI of healthy participants with an optimal BP (Table 2). Of those with a normal/high-normal BP, 45% had an aortic SBP that did not exceed the upper 95% CI of healthy participants with an optimal BP. A greater proportion of hypertensives and those with high-normal BP values, but not those with normal BP values had 24-h SBP and DBP values that exceeded that of the upper 95% CIs of healthy participants with an optimal BP (Table 2).

Continuous relationships between various measures of blood pressure and target organ changes in normotensive participants

In normotensive participants (BP <140/90 mmHg and no antihypertensive treatment), with adjustments for confounders, conventional and central aortic BP were correlated with target organ changes (Table 3). After further adjustments for aortic BP, the relationship between conventional BP and target organ changes in normotensives was abolished. In contrast, with further adjustments for conventional BP, aortic BP retained independent relationships with target organ changes in normotensives (Table 3). In addition, with further adjustments for 24-h SBP, aortic BP also retained independent relationships with target organ changes in normotensives (PWV; partial $r=0.18$,

TABLE 2. Blood pressures of study participants

BP categories BP range (mmHg)	Optimal <120/80	Normal ≥120/80 and <130/85	High-normal ≥130/85 and <140/90	Hypertensives ≥140/90 or treatment
Sample size	311	193	126	539
Conventional SBP/DBP (mmHg)	108 ± 7/72 ± 6	119 ± 7/80 ± 4***	128 ± 8/86 ± 4***,†††	146 ± 22/92 ± 13$^{***,\dagger\dagger\dagger,\#\#\#}$
Aortic SBP (mmHg)	100 ± 13	110 ± 7***	119 ± 8***,†††	136 ± 22$^{***,\dagger\dagger\dagger,\#\#\#}$
Aortic pulse pressure (mmHg)	26.6 ± 11.0	29.1 ± 7.5	33.6 ± 8.8*	43.5 ± 16.7$^{***,\dagger\dagger\dagger,\#\#\#}$
24-h SBP (mmHg) (*n*)	109 ± 9 (212)	113 ± 9* (134)	117 ± 11***,††† (84)	127 ± 16$^{***,\dagger\dagger\dagger,\#\#\#}$ (352)
24-h DBP (mmHg) (*n*)	67 ± 7 (212)	69 ± 7 (134)	72 ± 7* (84)	78 ± 11$^{***,\dagger\dagger\dagger,\#\#\#}$ (352)
n (%) with aortic SBP >threshold[a]	16 (5)	75 (39)***	99 (80)***,†††	471 (88)$^{***,\dagger\dagger\dagger,\#}$
n (%) with 24-h SBP >threshold[b]	12 (6)	16 (12)	21 (25)*,†	201 (57)$^{***,\dagger\dagger\dagger,\#\#\#}$
n (%) with 24-h DBP >threshold[b]	11 (5)	10 (8)	18 (21)**,††	147 (42)$^{***,\dagger\dagger\dagger,\#\#}$

[a]Upper threshold for aortic SBP in those with an optimal conventional BP = 112 mmHg.
[b]Upper threshold for 24-h SBP/DBP in those with an optimal conventional BP = 123/78 mmHg.
$^{*}P<0.05$.
$^{**}P<0.005$.
$^{***}P<0.0001$ versus optimal.
$^{\dagger}P<0.05$.
$^{\dagger\dagger}P<0.005$.
$^{\dagger\dagger\dagger}P<0.0005$ versus normal.
$^{\#}P<0.05$.
$^{\#\#}P<0.005$.
$^{\#\#\#}P<0.0001$ versus high-normal.

TABLE 3. Multivariate adjusted relationships between SBP and target organ changes in normotensive participants (conventional BP <140/90 mmHg)

BP versus	*n*	Partial r	CI	*P*	Partial r	CI	*P*
		SBPc adjusted for[a]			SBPc adjusted for aortic SBP+[a]		
Pulse wave velocity	568	0.24	0.16 to 0.32	<0.0001	0.05	−0.03 to 0.13	=0.24
Estimated GFR	501	−0.10	−0.19 to −0.01	<0.05	0.06	−0.03 to 0.14	=0.22
LV mass index	372	0.20	0.10 to 0.30	<0.0001	−0.05	−0.15 to 0.06	=0.36
		Aortic SBP adjusted for[a]			Aortic SBP adjusted for SBPc+[a]		
Pulse wave velocity	568	0.26	0.18 to 0.34	<0.0001	0.12	0.04 to 0.20	<0.005
Estimated GFR	501	−0.17	−0.25 to −0.08	<0.0005	−0.15	−0.23 to −0.06	=0.001
LV mass index	372	0.28	0.18 to 0.37	<0.0001	0.20	0.10 to 0.30	=0.0001

CI, confidence intervals; GFR, glomerular filtration rate; LV, left ventricle; SBPc, conventional SBP.
[a]Adjustments are for age, sex, BMI, diabetes mellitus and/or an HbA_{1c}>6.1%, regular tobacco intake, regular alcohol intake and pulse rate.

CI = 0.08–0.28, $P < 0.0005$, $n = 389$; eGFR; partial $r = -0.15$, CI = −0.25 to −0.04, $P < 0.01$, $n = 342$; LVMI; partial $r = 0.22$, CI = 0.10–0.33, $P < 0.0005$, $n = 265$).

Target organ changes in those with a normal or high-normal blood pressure irrespective of aortic blood pressure

Before adjustments for confounders, as compared to participants with optimal BP values, hypertensives and those with either normal or high-normal BP values had a markedly increased PWV and LVMI and decreased eGFR (Table 4). However, after adjustments for confounders, only modest target organ changes were noted in those with a normal or high-normal BP (Table 4). Moreover, normal versus high-normal BP categories failed to distinguish between those with and without target organ changes (Table 4).

Aortic blood pressure distinguishes target organ changes in those with a normal/high-normal blood pressure

As compared to those with an optimal BP, both unadjusted and multivariate adjusted target organ changes were consistently noted in those with a normal/high-normal BP with, but not in those without aortic SBP values at least upper 95% CI for healthy participants with optimal BP values (Table 5). Importantly, even those with a normal as opposed to high-normal conventional BP values, but whom had an aortic BP that exceeded 'optimal' values had multivariate adjusted decreases in eGFR (ml/min per 1.73 m^2) (108 ± 4 versus 116 ± 2, $P < 0.05$) and increases in LVMI (g/$m^{2.7}$) (46.7 ± 1.8 versus 40.8 ± 1.2, $P < 0.005$).

DISCUSSION

The main findings of the present study are as follows: First, in a randomly selected community sample, although a normal/high-normal BP was noted in 27% of the sample, 45% of these participants had central aortic BP values that did not exceed the upper 95% CI of aortic BP values in healthy participants with optimal BP values. Second, normal and high-normal BP categories failed to identify those with target organ changes. In contrast, in those with either a normal or high-normal BP, aortic BP values above 'optimal' thresholds clearly identified those with target organ changes.

Persons with a BP in the normal/high-normal range are considered at sufficient risk to warrant antihypertensive therapy if in-part they have diabetes mellitus, or established

TABLE 4. Unadjusted and multivariate adjusted indices of target organ changes of study participants

BP categories BP range (mmHg)	Optimal <120/80	Normal ≥120/80 and <130/85	High-normal ≥130/85 and <140/90	Hypertensives ≥140/90 or treatment
Unadjusted values				
PWV (m/s) (*n*)	4.83 ± 1.24 (289)	5.36 ± 1.55* (172)	6.09 ± 1.97** (107)	7.90 ± 2.99***,†††,### (457)
eGFR (ml/min per 1.73 m^2) (*n*)	128 ± 32 (244)	122 ± 29* (153)	111 ± 28** (104)	103 ± 28***,†††,# (443)
LV mass index (g/$m^{2.7}$) (*n*)	35.5 ± 10.2 (181)	41.1 ± 11.2** (117)	42.2 ± 13.3** (74)	47.5 ± 15.8***,†††,## (318)
Multivariate adjusted values				
PWV (m/s) (*n*)	5.89 ± 2.21 (289)	6.15 ± 1.97 (172)	6.34 ± 1.97 (107)	6.87 ± 2.35***,†††,# (457)
eGFR (ml/min per 1.73 m^2) (*n*)	117 ± 31 (244)	113 ± 28 (153)	108 ± 27* (104)	113 ± 31 (443)
LV mass index (g/$m^{2.7}$) (*n*)	40.3 ± 14.4 (181)	43.6 ± 13.0* (117)	42.4 ± 12.6 (74)	43.8 ± 14.6* (318)

BP, blood pressure; eGFR, estimated glomerular filtration rate; LV, left ventricle; PWV, aortic pulse wave velocity. Adjustments are for age, sex, BMI, diabetes mellitus and/or an HbA_{1c}>6.1%, regular tobacco use, regular alcohol intake and pulse rate.
*$P < 0.05$.
**$P < 0.005$.
***$P < 0.0001$ versus optimal.
†$P < 0.05$.
††$P < 0.005$.
†††$P < 0.0005$ versus normal.
#$P < 0.05$.
##$P < 0.005$.
###$P < 0.0001$ versus high-normal.

TABLE 5. Unadjusted and multivariate adjusted indices of target organ changes of prehypertensives with (Yes) or without (No) aortic SBP greater than thresholds (112 mmHg) defined in those with optimal conventional blood pressure values

Blood pressure categories	Optimal	Normal/high-normal		Hypertensives
		≥120/80 and <140/90 with aortic SBP≥112 mmHg		
Blood pressure range (mmHg)	<120/80	No	Yes	≥140/90 or treatment
Unadjusted values				
PWV (m/s) (*n*)	4.83 ± 1.24 (289)	5.07 ± 1.30 (128)	6.12 ± 1.94***,††† (151)	7.90 ± 2.99$^{***,\dagger\dagger\dagger,\#\#\#}$ (457)
Estimated GFR (ml/min per 1.73 m^2) (*n*)	128 ± 32 (244)	126 ± 32 (108)	111 ± 26***,††† (149)	103 ± 28$^{***,\dagger\dagger\dagger,\#\#}$ (443)
LV mass index (g/$m^{2.7}$) (*n*)	35.5 ± 10.2 (181)	38.2 ± 11.0 (82)	44.0 ± 12.1***,††† (109)	47.5 ± 15.8$^{***,\dagger\dagger\dagger,\#}$ (318)
Multivariate adjusted values				
Pulse wave velocity (m/s) (*n*)	5.89 ± 2.21 (289)	6.09 ± 2.05 (128)	6.30 ± 1.95* (151)	6.87 ± 2.29$^{***,\dagger\dagger\dagger,\#\#}$ (457)
eGFR (ml/min per 1.73 m^2) (*n*)	118 ± 29 (244)	115 ± 27 (108)	108 ± 26**,† (104)	112 ± 30* (443)
LV mass index (g/$m^{2.7}$) (*n*)	40.0 ± 14.3 (181)	40.7 ± 13.2 (82)	44.5 ± 12.6**,† (109)	44.0 ± 14.6* (318)

eGFR, estimated glomerular filtration rate LV, left ventricle; PWV, aortic pulse wave velocity. Adjustments are for age, sex, BMI, diabetes mellitus and/or an HbA_{1c}>6.1%, regular tobacco use, regular alcohol intake and pulse rate.
$^{*}P < 0.05$.
$^{**}P < 0.005$.
$^{***}P < 0.0001$ versus optimal.
$^{\dagger}P < 0.05$.
$^{\dagger\dagger}P < 0.005$.
$^{\dagger\dagger\dagger}P < 0.0005$ versus aortic BP <112 mmHg.
$^{\#}P < 0.05$.
$^{\#\#}P < 0.005$.
$^{\#\#\#}P < 0.0001$ versus aortic BP≥112 mmHg.

cardiovascular or renal disease [36]. However, intervention studies targeting high-risk patients with preexisting cardiovascular disease or diabetes mellitus, have produced discrepant outcomes [10–23]. This approach nevertheless assumes that most high-risk patients with normal/high-normal conventional BP values would benefit from BP-lowering therapy. In contrast, as indicated in the present study, in those participants with normal/high-normal BP values who also had 'optimal' aortic BP values (45% of participants), no evidence of target organ changes were noted. Thus, a high proportion of persons with a normal/high-normal BP are not at risk for BP-related cardiovascular damage.

As suggested by guidelines [36], the presence of organ damage may identify persons with a BP in the high-normal range at sufficient risk to warrant antihypertensive therapy. Indeed, two recent studies indicate that by adding markers of subclinical organ damage to traditional risk assessment, risk prediction may be considerably improved [37,38]. However, the mean BP values in those experiencing a cardiovascular event in the one study [37] suggest that almost half of these participants were hypertensive. Moreover, in the other study [38], 42% were hypertensives. Thus, in neither of these studies [37,38] can conclusions be drawn from data obtained only in the normotensive range. Moreover, in these studies [37,38], the presence of organ damage identified using one measure of target organ change, did not necessarily imply the presence of organ damage using another measure of target organ change. Thus, the benefit of target organ assessment would require the evaluation of damage in multiple organs [37,38]. This combined approach would incur considerable costs, necessitate the use of trained technicians and not necessarily identify organ damage attributed to BP effects as opposed to alternative risk factors. In contrast, aortic BP measurements are simple, reliable and reproducible, are likely to incur considerably lower costs and reflect the impact of BP rather than alternative risk factors.

In the present study, 39% of those with a BP in the normal conventional BP range as compared to 80% in the high-normal BP range had aortic BP values that exceeded 'optimal' values. Rather than measure aortic BP, a more cost-effective approach could, therefore, be to treat those with a high normal, but not a normal BP. However, 75 of the total sample of 319 participants with a normal or high-normal conventional BP had a normal conventional, but an increased aortic BP. Importantly, these individuals had multivariate adjusted decreases in eGFR and increases in LVMI. Hence, approximately one-quarter of all those with a normal/high-normal BP at risk of cardiovascular damage would be excluded from potentially necessary antihypertensive therapy if treatment were withheld from those with a normal BP. Clearly, this dilemma would be avoided if aortic BP rather than normal versus high-normal conventional BP categories were employed to identify at-risk persons.

In the present study, in those with normal/high-normal BP values, aortic BP was associated with an increased PWV, an index of aortic stiffness. This relationship may be explained, not only by an effect of BP on aortic stiffness, but also by an impact of aortic stiffness on central BP. If increases in aortic stiffness mediate aortic BP changes in those with normal/high normal BP values, therapeutically targeting aortic stiffness may prevent the progression to hypertension. In this regard, a normal/high-normal BP is a risk factor for the development of hypertension and progression to hypertension may occur within 10 years in 80% of those with a normal/high-normal BP [39].

The present results suggest that assessing the impact of BP-lowering therapy on cardiovascular outcomes in those with normal/high-normal BP values may warrant the selection of only those participants with central aortic BP values that exceed optimal values. If this approach were adopted, a decrease in the heterogeneity of the impact of BP-lowering therapy on outcomes may occur in those with a normal/high-normal BP, which as recent outcome studies have demonstrated [16–23], is large.

In normotensives from the present randomly selected community sample, only 14% had day BP values that exceeded 135/85 mmHg (masked hypertension). In contrast, in employees of a university hospital or private company [40] or in referrals to a hypertension clinic [41] 34 and 24.7%, respectively, of those with a normal/high-normal BP had masked hypertension and only those with masked hypertension had target organ changes. As masked hypertension is independently associated with cardiovascular outcomes, it is possible that ambulatory BP monitoring also has an important role to play in further refining risk in those with a normal/high-normal BP, at least in groups with a high prevalence of masked hypertension.

The limitations of the present study include the cross-sectional design that prevents us from drawing conclusions regarding cause and effect, and the use of target organ changes as surrogates for risk. Prospective studies are, therefore, required to assess whether aortic BP measurements identify earlier separation of curves describing cardiovascular outcomes in those with a normal/high-normal BP as compared to those with an optimal BP. In this regard, those persons with a normal/high-normal BP may experience significantly more cardiovascular events only 10–15 years after detection [42]. Moreover, the present study was conducted only in a group of black African ancestry. Corroboration of the present findings is required in other ethnic groups. Last, as thresholds for central aortic BP values have not been identified from outcome-based studies we identified thresholds from participants with optimal brachial BP values.

In conclusion, in contrast to the lack of ability of normal or high-normal BP categories to identify normotensives with target organ changes, in the present study we show that in normotensives, 'optimal' central aortic BP values clearly identify the presence of target organ changes. Thus, the use of aortic BP measurements may enhance the ability to risk stratify those with a normal/high-normal brachial BP.

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Conflicts of interest

None of the authors have any conflicts of interests to declare.

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Reviewers' Summary Evaluations

Reviewer 1

The authors studied the relationship between aortic SBP and target organ damage in a normotensive population of 1169 participants to the SOWETO study, remarkable for their black African ancestry, and individualized those with normal and high-normal BP. They conclude that aortic SBP was better correlated with target organ damage than brachial SBP. These findings provide additional evidence for the pathophysiological importance of central BP and wave reflections (increasing aortic SBP), and their better relationship with target organ damage than peripheral (brachial) BP, in line with the concept that the true damaging SBP is local SBP, i.e. the maximum hemodynamic load that the target organ 'sees'.

Reviewer 2

The study investigates to what extent high aortic blood pressure is present in individuals with normal/high-normal blood pressure, and will reclassify individuals at low risk to high risk.

Individuals with normal/high-normal blood pressure and high aortic systolic blood pressure show increases in pulse wave velocity, left ventricular mass index and decreases in estimated glomerular infiltration rate.

The limitation is a cross-sectional design. Long-term follow-up is needed to clarify absolute risk. Neither does the study define whether aortic blood pressure is superior to, e.g. 24-h blood pressure for risk prediction.

The study adds to our understanding of the relationship between various measures of subclinical target organ damage.

Appendix 3

Booysen, H.L., Woodiwiss, A. J., Moekanyi, J. S., Hodson, B., Raymond, A., Libhaber, E., Sareli, P., Norton, G. R. (2015) Indexes of aortic pressure augmentation markedly underestimates the contribution of reflected waves toward variations in aortic pressure and left ventricular mass. *Hypertension,* 65(3), 540-546.

Indexes of Aortic Pressure Augmentation Markedly Underestimate the Contribution of Reflected Waves Toward Variations in Aortic Pressure and Left Ventricular Mass

Hendrik L. Booysen,* Angela J. Woodiwiss,* Moekanyi J. Sibiya,* Bryan Hodson, Andrew Raymond, Elena Libhaber, Pinhas Sareli, Gavin R. Norton*

Abstract—Although indexes of wave reflection enhance risk prediction, the extent to which measures of aortic systolic pressure augmentation (augmented pressures [Pa] or augmentation index) underestimate the effects of reflected waves on cardiovascular risk is uncertain. In participants from a community sample (age >16), we compared the relative contribution of reflected (backward wave pressures and the reflected wave index [RI]) versus augmented (Pa and augmentation index) pressure wave indexes to variations in central aortic pulse pressure (PPc; n=1185), and left ventricular mass index (LVMI; n=793). Aortic hemodynamics and LVMI were determined using radial applanation tonometry (SphygmoCor) and echocardiography. Independent of confounders, RI and backward wave pressures contributed more than forward wave pressures, whereas Pa and augmentation index contributed less than incident wave pressure to variations in PPc (P<0.0001 for comparison of partial r values). In those <50 years of age, while backward wave pressures (partial r=0.28, P<0.0001) contributed more than forward wave pressures (partial r=0.15, P<0.001; P<0.05 for comparison of r values), Pa (partial r=0.13, P<0.005) contributed to a similar extent as incident wave pressure (partial r=0.22, P<0.0001) to variations in LVMI. Furthermore, in those ≥50 years of age, backward wave pressures (partial r=0.21, P<0.0001), but not forward wave pressures (P=0.98), while incident wave pressure (partial r=0.23, P<0.0001), but not Pa (P=0.80) were associated with LVMI. Pa and augmentation index underestimated the effect of wave reflection on PPc and LVMI in both men and women. Thus, as compared with relations between indexes of aortic pressure augmentation and PPc or LVMI, strikingly better relations are noted between aortic wave reflection and PPc or LVMI. **(*Hypertension*. 2015;65:540-546. DOI: 10.1161/HYPERTENSIONAHA.114.04582.)** ● **Online Data Supplement**

Key Words: aortic blood pressure ■ aortic pulse pressure ■ left ventricular hypertrophy

Although pulse pressure measured at the brachial artery is closely correlated with central aortic pulse pressure (PPc), pulse pressure may be considerably higher in brachial arteries as compared with the aorta.[1,2] 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.[1,2] 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), augmentation index (AIx), and indexes of wave reflection are associated with cardiovascular outcomes[3–7] and end-organ damage[8–12] independent of brachial BP. However, more recently the use of Pa or AIx as indexes of wave reflection in risk prediction has been challenged.[13–18]

Marked overlap between aortic forward and reflected waves may confound Pa and AIx[14,16–18] and hence these measures may be poor indexes of wave reflection. Indeed, there is 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 forward (Pf) or incident (Pi) wave pressures, and left ventricular systolic function playing a more important role than wave reflection in contributing to variations in Pa and AIx.[13–18] More recent studies have, therefore, focussed 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.[19–22] However, in these studies[19–22] 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;[19,21] discrepancies in the index of wave reflection that was better associated with end-organ damage beyond Pf were noted[19,21]; whether the increase in Pf at

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From the Cardiovascular Pathophysiology and Genomics Research Unit, Schools of Physiology (H.L.B., A.J.W., M.J.S., B.H., A.R., P.S., G.R.N.) and Medicine (E.L.), Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa.

*These authors contributed equally to this study.

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Correspondence to Angela J. Woodiwiss, Cardiovascular Pathophysiology and Genomics Research Unit, School of Physiology, University of the Witwatersrand Medical School, 7 York Rd, Parktown, 2193 Johannesburg, South Africa. E-mail angela.woodiwiss@wits.ac.za

50 years of age affects these relations was not considered[19–21]; and Pf 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.[22] To clarify the extent to which indexes of aortic systolic pressure augmentation underestimate the effect of wave reflection on cardiovascular disease, in this study we, therefore, aimed to evaluate, in a large community-based sample with a high prevalence of uncontrolled BP, the degree to which Pb or RI are more closely related to multivariate adjusted increases in PPc and left ventricular mass index (LVMI) beyond Pf than Pa or AIx, and whether these effects are age- or sex-specific.

Methods

Study Group and Clinical, Demographic, and Anthropometric Measurements

This 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. Briefly, 1185 participants from families of black African descent (Nguni and Sotho chiefdoms) with siblings >16 years with central hemodynamic measurements were randomly recruited from the South West Township (Soweto) of Johannesburg, South Africa. In a substudy, 793 participants had LVMI determined using echocardiography. For clinical, demographic, and anthropometric measurements see online-only Data Supplement for further details.

Pulse Wave Analysis

Central aortic systolic BP, PPc, Pi, Pa, and AIx were estimated using radial applanation tonometry and SphygmoCor software as previously described.[12] See online-only Data Supplement for further details. Pb and Pf were determined using SphygmoCor software, which separates the aortic waveform using a triangular flow wave.[23] RI was determined as previously described.[15]

Echocardiography

Left ventricular mass and stroke volume were determined from transthoracic 2-dimensional targeted M-mode echocardiographic images obtained in the parasternal long-axis view as previously described[12] (see online-only Data Supplement for further details).

Data Analysis

For database management and statistical analysis, SAS software, version 9.1 (SAS Institute Inc, Cary, NC) was used. 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.[22] To determine probability values, further adjustments for nonindependence of family members was performed using nonlinear regression analysis (mixed procedure as defined in the SAS package). As a sharp age-related increase in Pf and Pi occurred between 40 and 50 years of age, relationships between aortic hemodynamic variables and PPc or LVMI were evaluated in participants < or ≥50 years of age. 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.

Table 1. Characteristics of the Study Sample

Characteristics	All (n=1185)	<50 yr (n=703)	≥50 yr (n=482)
% Female	65.0	64.6	65.8
Age, yr	44.3±18.3	31.4±10.0	63.0±9.2
Body mass index, kg/m^2	29.6±8.1	27.4±7.4	32.7±8.0
% Obese	43.3	32.9	58.5
Regular tobacco (% subjects)	15.2	17.1	12.5
Regular alcohol (% subjects)	20.9	23.6	17.0
% With DM or HbA1c >6.1%	25.8	12.4	45.4
% Hypertensive	45.9	24.0	77.8
% Treated for hypertension	24.2	6.3	50.4
% Hypertensives controlled to target BP	20.8	13.0	24.3
% Of all with uncontrolled BP	36.4	20.9	58.9
Pulse rate, bpm	66±12	65±11	67±13
Brachial SBP/DBP, mm Hg	130±22/84±13	121±17/81±12	143±23/88±12
Brachial pulse pressure, mm Hg	46±16	39±13	53±18
Brachial mean arterial pressure, mm Hg	100±16	95±14	108±16
Central aortic SBP, mm Hg	120±23	111±18	133±23
Central aortic pulse pressure (PPc), mm Hg	35±15	29±11	44±16
Aortic forward wave pressure (Pf), mm Hg	24±9	21±7	28±10
Aortic reflected wave pressure (Pb), mm Hg	17±8	14±6	22±9
Aortic reflected wave index	0.16±0.06	0.13±0.04	0.19±0.06
Aortic augmented pressure (Pa)	11±8	7±6	15±8
Aortic Pi	25±9	22±7	29±10
Aortic augmentation index (AIx), %	142±25	135±24	153±23
Stroke volume, mL (n)	63±17 (793)	61±16 (468)	65±18 (325)
Left ventricular mass index, g/m^2 (n)	76±31 (793)	70±27 (468)	84±34 (325)
Left ventricular mass index, g/m$^{1.7}$ (n)	67±24 (793)	61±20 (468)	76±27 (325)

Data expressed as mean±SD or proportions. Pi=PPc−Pa. BP indicates blood pressure; DBP, diastolic BP; DM, diabetes mellitus; HbA1c, glycosylated hemoglobin; Pi, incident wave pressure; PPc, central aortic pulse pressure; and SBP, systolic BP.

Results

Characteristics of the Participants

The clinical and demographic characteristics of the participants are shown in Table 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

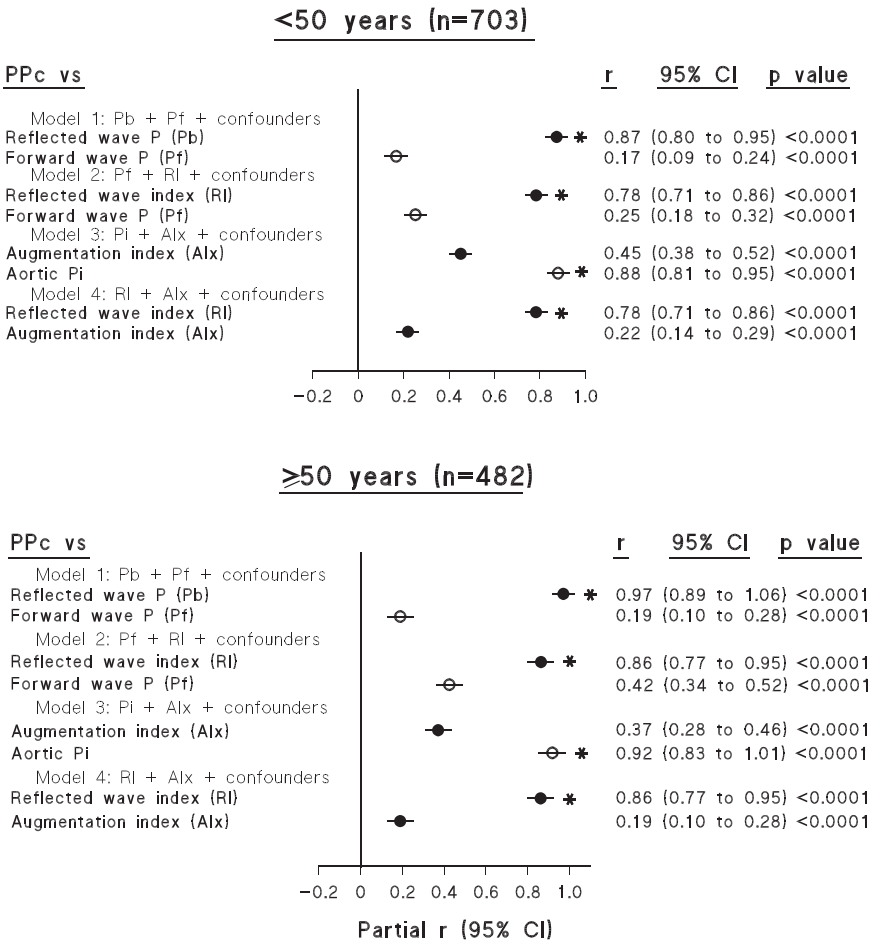

Figure 1. Relative contribution of aortic hemodynamic variables to variations in central aortic pulse pressure (PPc) in age-specific categories in a group of African descent. Closed circles indicate indexes of wave reflection and open circles indicate indexes of forward (Pf) or incident (Pi) wave pressures. Data show multivariate adjusted correlation coefficients (partial *r*) derived from stepwise regression analysis with Pf and backward wave pressures (Pb; model 1), Pf and reflected wave index (RI; model 2), Pi and augmentation index (AIx; model 3), or RI and AIx (model 4)+confounders included in the same regression models. Potential confounders included in the model are age, sex, mean arterial pressure, body height, body weight, pulse rate, diabetes mellitus or a glycosylated hemoglobin>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). CI indicates confidence interval; and Pa, augmented pressures.

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.

Age-Related Increases in Aortic Hemodynamics

See online-only Data Supplement .

Relative Independent Contribution of Reflected Versus Forward Waves to Variations in PPc

When included in separate models (Table S4 in the online-only Data Supplement) or in the same multivariate stepwise models (Figure 1) in participants either < or ≥50 years of age, a stronger relationship was noted between RI and PPc or Pb and PPc than between Pf and PPc or AIx and PPc. In contrast, a stronger relationship was noted between Pi and PPc, than between Pa and PPc (Table S4) or between AIx and PPc (Table S4; Figure 1). 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 1). Similar differences in the relative contribution of reflected versus forward wave indexes to variations in PPc were noted in women and men (Table 2; Table S5). Similar findings were noted in participants not receiving antihypertensive therapy (Tables S6 and S7). 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 S8).

Comparison of Independent Relations Between Aortic Hemodynamics and LVMI

In participants <50 years of age, Pb was more closely associated with LVMI (Figure 2, upper panel; Table S9) than Pf and in a multivariate model with Pb and Pf in the same model, Pb (partial r=0.31, confidence interval=0.24–0.38, P<0.0001), but not Pf (partial r=0.01, confidence interval=−0.06 to 0.08, P=0.72) was independently associated with LVMI. In contrast, however, Pa showed similar associations with LVMI as did Pi (Figure 2, upper panel; Table S9). In addition, RI was more closely associated with LVMI than AIx (Figure 2, upper panel; Table S9). In participants ≥50 years of age, Pb, but not Pf was independently associated with LVMI (Figure 2, lower panel; Table S9). In contrast, however, Pi, but not Pa was independently associated with LVMI (Figure 2, lower panel; Table S9). In participants ≥50 years of age RI, but not AIx was independently associated with LVMI-height$^{1.7}$ (Table S9), but neither RI nor AIx were independently associated with LVMI-body surface area (Figure 2, lower panel). Similar differences in the relative contribution of reflected versus forward wave indexes and LVMI were noted in men and women (Table 3). Importantly, although the relations between Pa or AIx and LVMI were stronger in men than in women (P=0.01 to 0.0002 for comparison of r values; Table 3), these differences were

not attributed to reflected wave effects. Indeed, Pb or RI-LVMI relations were similar in men and women (Table 3). Similar findings were also noted in participants <50 years of age not receiving antihypertensive therapy (Table S10). There were too few participants (n=151) ≥50 years of age not receiving antihypertensive therapy to compare relationships between aortic hemodynamics and LVMI. 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 S11).

Discussion

The main findings of this study are as follows: In a large (n=1185), community-based sample of African ancestry, independent of confounders including mean arterial pressure (distending pressures), reflected waves (RI or Pb) accounted for more of the variation in PPc and LVMI than did Pf, whereas Pi accounted for more of the variation in PPc and LVMI than did aortic systolic pressure augmentation (AIx or Pa). The marked contrasting contributions of indexes of reflected waves, RI or Pb and AIx or Pa, as compared with Pf and Pi toward variations in PPc and LVMI were noted below as well as above the age threshold (50 years) when Pf or Pi began to increase as well as in women and men considered separately.

Several previous studies have reported on a relatively greater contribution of Pa as compared with Pi to age-related increases in PPc.[24–26] However, it is now recognized 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.[13–18] Indeed, Pa may be determined in large part by Pf.[16] Nevertheless, studies which have used approaches to separate Pb from Pf, suggest that Pb contributes little to age-related increases in PPc.[22,27] These studies were nonetheless conducted either in a sample where BP values were largely well-controlled[22] or in a sample with a narrow age range.[27] In contrast, using wave separation analysis in this study conducted in a community sample with a wide age range and with a high prevalence of uncontrolled hypertension, we show that Pb has a far stronger relationship with PPc than Pf, and that these associations occurred irrespective of age and independent of sex. Hence, this study provides the first direct evidence to show that across the adult lifespan of a community sample with poorly controlled hypertension, in both women and men reflected waves account for more of the variation in PPc than do Pf and that indexes of aortic pressure augmentation underestimate the contribution of aortic wave reflection to variations in PPc.

A few previous 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 Pa indexes (Pa and AIx).[19,21] However, in neither study were these comparisons made with adjustments for confounders. Hence, the differences reported on[19] may be attributed to confounders including distending pressures and heart rate. Moreover, in neither study[19,21] were comparisons of relations made in age-specific categories, despite increases in Pf occurring only later in life. Furthermore, in 1 study[21] no comparisons were made between correlation coefficients and similar relations were noted between reflected wave indexes derived from wave separation analysis and end-organ changes as compared with relations between indexes of aortic systolic pressure augmentation and end-organ changes.[21] In this study, we provide clear evidence that relations between indexes of wave reflection and LVMI were markedly stronger than Pf effects, whereas indexes of aortic systolic pressure augmentation considerably underestimated the contribution of reflected as compared with Pf.

As age-related increases in AIx occurred in those less than, but not greater than 50 years of age, a lack of relationship between AIx and LVMI in those >50 years of age is not unexpected. However, Pa increased across the full adult age range, and yet, in those >50 years, reflected, but not augmented wave pressures accounted for variations in LVMI. Thus, without the use of wave separation analysis, even when indexes of pressure augmentation that increase with age across the full adult lifespan are used, the effect of reflected wave function on end-organ changes may be markedly underestimated.

As previously demonstrated,[28] 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

Table 2. Independent Relationships Between Aortic Hemodynamics and PPc in Sex-Specific Categories in a Group of African Ancestry

	Women (n=771)		Men (n=414)	
PPc vs	Partial r (CI)*	P Value	Partial r (CI)*	P Value
Model with Pb and Pf included together				
Pb	0.97 (0.90–1.04)†	<0.0001	0.92 (0.82–1.02)†	<0.0001
Pf	0.19 (0.12–0.26)	<0.0001	0.10 (0.02–0.20)	<0.0001
Model with RI and Pf included together				
RI	0.88 (0.81–0.95)†	<0.0001	0.86 (0.76–0.96)†	<0.0001
Pf	0.39 (0.32–0.46)	<0.0001	0.18 (0.08–0.28)	<0.0001
Model with AIx and Pi included together				
AIx	0.41 (0.34–0.48)	<0.0001	0.34 (0.24–0.44)	<0.0001
Pi	0.90 (0.83–0.97)‡	<0.0001	0.93 (0.83–1.03)‡	<0.0001
Model with RI and AIx included together				
RI	0.88 (0.81–0.95)‡	<0.0001	0.86 (0.76–0.96)‡	<0.0001
AIx	0.19 (0.12–0.26)	<0.0001	0.18 (0.08–0.28)	<0.0001

AIx indicates augmentation index; CI, confidence intervals; Pb, backward wave pressures; Pf, forward wave pressures; Pi, incident wave pressures; PPc, central aortic pulse pressure; and RI, reflected wave index.

*Adjustors are age, mean arterial pressure, body height, body weight, pulse rate, diabetes mellitus or a glycosylated hemoglobin >6.1%, regular smoking, and regular alcohol intake.

†P<0.0001 for comparisons of partial r values with Pf.

‡P<0.0001 for comparison of partial r values with AIx (z statistics).

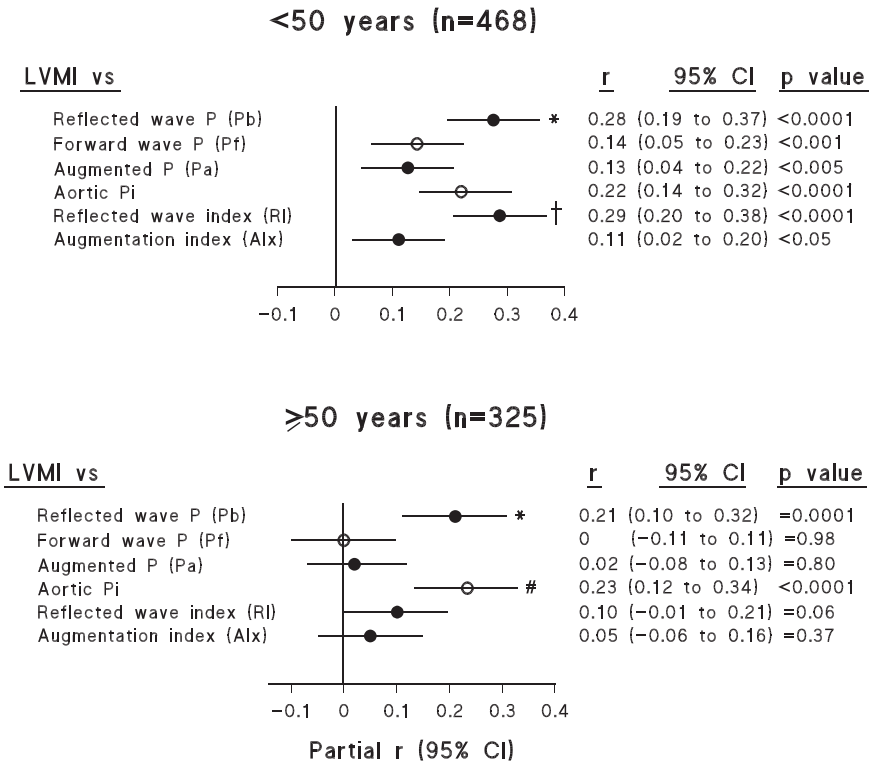

Figure 2. Contribution of aortic hemodynamic variables to variations in left ventricular mass indexed (LVMI) to body surface area in age-specific categories in a group of African descent. Closed circles indicate indexes of wave reflection and open circles indicate indexes of forward (Pf) or incident (Pi) wave pressures. Potential confounders included in the model are age, sex, mean arterial pressure, pulse rate, body height, pulse rate, diabetes mellitus or a glycosylated hemoglobin>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 augmentation index (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). CI indicates confidence interval; Pa, augmented pressures; Pb, backward wave pressures; and RI, reflected wave index.

flow waveforms (r^2=0.34).[28] Thus, the triangulation method of wave separation is better than augmentation indexes at identifying reflected wave effects. Despite using a relatively imprecise method of identifying reflected wave magnitude and index, we were still able to show that indexes of aortic wave reflection were more closely associated with PPc and LVMI than Pf, whereas indexes of aortic pressure augmentation showed weaker associations than Pf with PPc and LVMI. Hence, this 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 Pf.[29] In contrast, norepinephrine, which augments PPc through marked vasoconstriction, mainly increases Pb but does not produce as much of an increase in PPc.[29] Furthermore, increases in Pf may account for more of the increment in PPc in hypertensives than reflected wave pressures.[29] It has, therefore, been suggested that Pf, mediated by increases in stroke volume may be more important than reflected wave pressures in determining variations in PPc in hypertension.[29] However, as in this and previous[26,27] studies where no increase[27] or only modest increases (this study) in stroke volume were noted with increasing age, or where stroke volume contributed little to variations in PPc,[26] increases in stroke volume are unlikely to explain a significant proportion of age-related increases in PPc. Moreover, norepinephrine-induced effects on aortic reflected waves[29] are more likely to represent the hypertensive state where a major effect on BP is through increases in vascular smooth muscle tone. Furthermore, in this study the greater effect of Pb as compared with Pf on variations in PPc and LVMI were replicated even when stroke volume was included in multivariate-adjusted analysis.

Previous studies have demonstrated that the effect of aortic pressure augmentation on end-organ changes[12] or cardiovascular outcomes[19] is attenuated in women as compared with men. In this study, we similarly show that relations between

Table 3. Independent Relationships Between Aortic Hemodynamics and LVMI-BSA in Women and Men of African Ancestry

LVMI-BSA vs	Women (n=515)		Men (n=278)	
	Partial *r* (CI)*	*P* Value	Partial *r* (CI)*	*P* Value
Pb	0.32 (0.23 to 0.41)†	<0.0001	0.33 (0.21 to 0.45)‡	<0.0001
Pf	0.08 (−0.01 to 0.17)	0.07	0.13 (0.01 to 0.25)	<0.05
Pa	0.04 (−0.05 to 0.13)	0.40	0.31 (0.19 to 0.43)	<0.0001
Pi	0.29 (0.20 to 0.38)§	<0.0001	0.29 (0.17 to 0.41)	<0.0001
RI	0.30 (0.21 to 0.39)‖	<0.0001	0.34 (0.22 to 0.46)¶	<0.0001
AIx	−0.07 (−0.16 to 0.02)	0.08	0.12 (0.01 to 0.24)	=0.04

AIx indicates augmentation index; CI, confidence intervals; LVMI, left ventricular mass index; Pa, augmented pressures; Pb, backward wave pressures; Pf, forward wave pressures; Pi, incident wave pressure; and RI, reflected wave index.

*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*<0.0005 for comparisons of partial *r* values with Pf.

‡*P*<0.02.

§*P*<0.0001 for comparisons of partial *r* values with Pa.

‖*P*<0.0001 for comparisons of partial *r* values with AIx (*z* statistics).

¶*P*<0.01.

Pa or AIx and LVMI were diminished in women as compared with 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 with women. Hence, the weaker associations between augmentation indexes and cardiovascular damage in women as compared with men[12,19] are likely to be attributed to a greater degree of inaccuracy of pressure augmentation as an index of wave reflection in women as compared with men, effects which may be attributed to sex differences in the width of the forward wave peak and the slope of the backward wave upstroke.[17]

Additional limitations of this study are as follows: This study was a cross-sectional design. Therefore, we cannot determine whether the age-related changes reported on are attributed to the long-term effect 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 this 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.

Perspectives

Although indexes of aortic systolic pressure augmentation (Pa and AIx) have been demonstrated in various populations to be independent predictors of outcomes,[3–7] the use of these indexes as surrogate measures of aortic wave reflection has been challenged.[13–18] However, the extent to which reflected waves derived from wave separation analysis are more strongly related to PPc and end-organ damage than indexes of aortic systolic pressure augmentation is unclear. In this study conducted in a community sample with a high prevalence of uncontrolled hypertension, we show that reflected waves are more closely associated with PPc and LVMI than forward waves, but that indexes 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 PPc, effects which nonetheless cannot be accurately detected using indexes of aortic systolic pressure augmentation. Moreover, given the high prevalence of hypertension and related cardiovascular events in urban communities in Africa, this study suggests that approaches to decreasing age-related increases in aortic wave reflection may produce a major effect on the burden of disease in these communities.

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Disclosures

None.

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Novelty and Significance

What Is New?

- The extent to which measures of aortic systolic pressure augmentation (augmented pressure or augmentation index) underestimate the effects of reflected waves on cardiovascular risk is uncertain.

What Is Relevant?

- As marked overlap between aortic forward and reflected waves may confound aortic augmented pressure and augmentation index, these measures may be poor indexes of wave reflection. Hence, recent studies have recommended the use of approaches to separate the forward and backward pressure waves.

Summary

In a community sample, with a high prevalence of uncontrolled hypertension, strikingly better relations were noted between aortic wave reflection, derived from wave separation analysis, and aortic pulse pressure or left ventricular mass index as compared with relations between aortic systolic pressure augmentation and aortic pulse pressure or left ventricular mass index. Hence, indexes of aortic systolic pressure augmentation may markedly underestimate relationships between wave reflection and cardiovascular risk.

Appendix 4

Independent relationships between aortic haemodynamics and central aortic pulse pressure (PPc) in age-specific categories in a group of African ancestry, with brachial form factor instead of mean arterial pressure as an adjustor.

Appendix 4. Independent relationships between aortic haemodynamics and central aortic pulse pressure (PPc) in age-specific categories in a group of African ancestry, with brachial form factor instead of mean arterial pressure as an adjustor.

PPc vs	<50 years (n=703)		≥50 years (n=482)	
	partial r (CI)*	p value	partial r (CI)*	p value
Pb	0.87 (0.80 to 0.95)[†]	<0.0001	0.97 (0.88 to 1.10)[†]	<0.0001
Pf	0.65 (0.58 to 0.72)	<0.0001	0.80 (0.71 to 0.89)	<0.0001
Pa	0.80 (0.72 to 0.87)	<0.0001	0.88 (0.79 to 0.97)	<0.0001
Pi	0.88 (0.81 to 0.96)[‡‡]	<0.0001	0.92 (0.83 to 1.01)[‡]	<0.0001
RI	0.79 (0.71 to 0.86)[§]	<0.0001	0.86 (0.77 to 0.95)[§]	<0.0001
AIx	0.38 (0.31 to 0.45)	<0.0001	0.31 (0.22 to 0.40)	<0.0001

CI, confidence intervals; Pb, reflected wave pressure; Pf, forward wave pressure; Pa, aortic augmented pressure; Pi=Aortic pulse pressure-Pa; RI, reflected wave index; AIx, aortic augmentation index. *Adjustors are age, sex, brachial form factor, 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<0.0001 for comparisons of partial r values with Pa, [§]p<0.0001 for comparison of partial r values with AIx (z-statistics).

Appendix 5

Independent relationships between aortic haemodynamics and central aortic pulse pressure (PPc) in age-specific categories in a group of African ancestry, with brachial form factor instead of mean arterial pressure as an adjustor.

Appendix 5. Independent relationships between aortic haemodynamics and central aortic pulse pressure (PPc) in age-specific categories in a group of African ancestry, with brachial form factor instead of mean arterial pressure as an adjustor.

PPc vs	<50 years (n=703)		≥50 years (n=482)	
	partial r (CI)*	p value	partial r (CI)*	p value
	Model with Pb and Pf included together			
Pb	0.87 (0.80-0.95)†	<0.0001	0.97 (0.89-1.06)†	<0.0001
Pf	0.17 (0.09-0.24)	<0.0001	0.19 (0.10-0.28)	<0.0001
	Model with RI and Pf included together			
RI	0.78 (0.71-0.86)†	<0.0001	0.86 (0.77-0.95)†	<0.0001
Pf	0.33 (0.25-0.40)	<0.0001	0.42 (0.34-0.52)	<0.0001
	Model with AIx and Pi included together			
AIx	0.45 (0.38-0.52)	<0.0001	0.37 (0.28-0.46)	<0.0001
Pi	0.88 (0.81-0.95) ‡	<0.0001	0.92 (0.83-1.01) ‡	<0.0001
	Model with RI and AIx included together			
RI	0.78 (0.71-0.86) ‡	<0.0001	0.86 (0.77-0.95) ‡	<0.0001
AIx	0.05 (0.01-0.13)	=0.022	0.08 (0.01-0.15)	<0.0001

CI, confidence intervals; Pb, reflected wave pressure; Pf, forward wave pressure; Pa, aortic augmented pressure; Pi=Aortic pulse pressure-Pa; RI, reflected wave index; AIx, aortic augmentation index. *Adjustors are age, sex, brachial form factor, 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<0.0001 for comparison of partial r values with AIx (z-statistics).

Appendix 6

Independent relationships between aortic haemodynamics and left ventricular mass indexed to body surface area (LVMI) in participants of African ancestry, with brachial form factor instead of mean arterial pressure as an adjustor.

Appendix 6. Independent relationships between aortic haemodynamics and left ventricular mass indexed to body surface area (LVMI) in participants of African ancestry, with brachial form factor instead of mean arterial pressure as an adjustor.

	<50 years (n=468)		≥50 years (n=325)	
LVMI vs	partial r (CI)*	p value	partial r (CI)*	p value
Pb	0.28 (0.19 to 0.37)[†]	<0.0001	0.21 (0.10 to 0.32)[†]	=0.0001
Pf	0.14 (0.05 to 0.23)	<0.001	0.05 (-0.06 to 0.13)	=0.25
Pa	0.13 (0.04 to 0.22)	<0.005	0.11 (0.001 to 0.22)	<0.05
Pi	0.22 (0.14 to 0.32)	<0.0001	0.23 (0.12 to 0.34)[‡]	<0.0001
RI	0.29 (0.20 to 0.38)[§]	<0.0001	0.10 (-0.01 to 0.21)	=0.06
AIx	0.08 (-0.01 to 0.17)	<0.05	0.05 (-0.06 to 0.16)	=0.35

CI, confidence intervals; Pb, reflected wave pressure; Pf, forward wave pressure; Pa, aortic augmented pressure; Pi=Aortic pulse pressure-Pa; RI, reflected wave index; AIx, aortic augmentation index. *Adjustors are age, sex, brachial form factor, 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, [‡]$p<0.05$ for comparison of partial r values with Pa and AIx, [§]$p<0.05$ for comparison of partial r values with AIx (z-statistics).

Appendix 7

Independent relationships between aortic haemodynamics and left ventricular mass indexed to height$^{1.7}$ (LVMI-ht$^{1.7}$) in participants of African ancestry, with brachial form factor instead of mean arterial pressure as an adjustor.

Appendix 7. Independent relationships between aortic haemodynamics and left ventricular mass indexed to height$^{1.7}$ (LVMI-ht$^{1.7}$) in participants of African ancestry, with brachial form factor instead of mean arterial pressure as an adjustor.

	<50 years (n=468)		≥50 years (n=325)	
LVMI-ht$^{1.7}$ vs	partial r (CI)*	p value	partial r (CI)*	p value
Pb	0.20 (0.11 to 0.29)†	<0.0001	0.20 (0.09 to 0.31)†	<0.0005
Pf	0.08 (-0.01 to 0.17)	=0.07	0.08 (-0.03 to 0.19)	=0.06
Pa	0.17 (0.08 to 0.26)	=0.0001	0.12 (0.01 to 0.13)	<0.05
Pi	0.15 (0.06 to 0.24)	=0.0005	0.25 (0.14 to 0.36)‡	<0.0001
RI	0.19 (0.10 to 0.29)§	<0.0001	0.13 (0.02 to 0.24)	<0.02
AIx	0.07 (-0.02 to 0.16)	=0.15	0.04 (-0.07 to 0.15)	=0.47

CI, confidence intervals; Pb, reflected wave pressure; Pf, forward wave pressure; Pa, aortic augmented pressure; Pi=Aortic pulse pressure-Pa; RI, reflected wave index; AIx, aortic augmentation index. *Adjustors are age, sex, brachial form factor, 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<0.05 for comparison of partial r values with Pa, §p<0.05 for comparison of partial r values with AIx (z-statistics).

Appendix 8

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