Central Arterial Haemodynamics in the Normotensive Peripheral Blood Pressure Range

Bryan Hodson

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Abstract

Although hypertension is defined according to absolute blood pressure (BP) threshold levels, it is well recognised that the risk related to BP effects increases linearly from levels well below those currently identified. Therefore, international guidelines differ as to the BP level that requires antihypertensive therapy. Previous studies have identified the possibility that central arterial BP may refine the ability to identify those with BP levels within normotensive ranges who are at risk. In the present thesis I evaluated the determinants of central arterial BP that may enhance risk prediction within the normotensive BP range.

Prior reports on the contribution of aortic forward (Pf) and backward (Pb) wave pressures to age-related increases in aortic pulse pressure (PPc) have been confounded by the use of participants receiving antihypertensive therapy. Therefore, before assessing the changes in aortic function that occur in the normotensive BP range, I assessed the relative contribution of Pf and Pb to age-related increases in PPc in 892 community participants having never received antihypertensive therapy. On product of coefficient mediation analysis, in those participants <50 years of age, independent of several confounders and mean arterial pressure (MAP), Pb ($p<0.005$), but not Pf contributed to age-related increases in PPc. In contrast, in those participants ≥50 years of age, independent of several confounders and MAP, Pb ($p<0.005$) and Pf ($p<0.01$) contributed to age-related increases in PPc, and Pb effects were markedly diminished by adjustments for Pf (0.26±0.002 vs 0.52±0.003 mm Hg per year, $p<0.0001$ for comparison). Thus, independent of the effects of antihypertensive therapy, aortic backward waves contribute to age-related increases in aortic PPc across the adult lifespan, but at an older age, this effect may be attributed in-part to the impact of forward on backward wave pressures.

Whether age-related changes in aortic function occur in the normotensive BP range is unknown. I therefore evaluated the extent to which an abnormal brachial BP control accounts for age-related variations in aortic function in 1185 participants from a community sample (age>16 years)(36.4% uncontrolled BP). With adjustments for distending pressure (MAP), no increases in PPc, Pb, or aortic stiffness (pulse wave velocity [PWV]) and decreases in PP amplification (amp) were noted in those with an uncontrolled brachial BP younger than 50 years of age. In those older than 50 years of age with an uncontrolled brachial BP, MAP-adjusted aortic hemodynamic variables were only modestly different to those with a controlled brachial BP (PPc, 46±14 vs 42±15 mm Hg, $p<0.02$, Pb, 23±8 vs 21±8 mm Hg, PWV, 8.42±3.21 vs 8.19±3.37 m/sec, PPamp, 1.21±0.17 vs 1.21±0.14). Nonetheless, with adjustments for MAP, marked age-related increases in PPc, Pb and PWV and decreases in PPamp were noted in those with uncontrolled and controlled brachial BP across the adult lifespan ($p<0.0001$). Thus, brachial BP control in the general population fails to account for most distending pressure-independent, age-related changes in aortic hemodynamics across the adult lifespan. Age-related changes in aortic dysfunction therefore occur equally as strongly in the normotensive as

in the hypertensive brachial BP range.

In 1307 community participants I subsequently determined the extent to which the adverse effects of blood pressure (BP) are mediated by pulsatile haemodynamic changes across the normotensive as compared to the hypertensive adult brachial BP range. In normotensives (50.5%) independent of steady-state pressure (mean arterial pressure), significant relations between aortic backward wave pressure (Pb) and LVMI (partial $r=0.16$, $p<0.001$) or IMT (partial $r=0.15$, $p<0.005$) and between aortic pulse wave velocity (PWV) and eGFR (partial $r=-0.18$, $p<0.0001$) were noted, effects which in hypertensives were observed for LVMI and eGFR, but not IMT. In normotensives, as compared to brachial pulse pressure (PP) or systolic BP (SBP), Pb showed a greater slope (β-coefficient) of the relation with LVMI (0.99 ± 0.24 vs 0.47 ± 0.10 and 0.41 ± 0.09 mm Hg, $p<0.05$) and IMT (0.0045 ± 0.0013 vs 0.0013 ± 0.0006 and 0.0013 ± 0.0005 mm Hg, $p<0.05$) and a stronger association with left ventricular hypertrophy (Odds ratios [95% CI], 1.125 [1.059 to 1.195] vs 1.054 [1.027 to 1.082] and 1.042 [1.020 to 1.066, $p<0.05$). However, in hypertensives only the slope of the Pb-LVMI relationship was greater than that of PP- and SBP-LVMI relations. Thus, beyond brachial BP, pulsatile haemodynamics rather than steady-state pressures account for end-organ effects more consistently across the normotensive than the hypertensive BP range.

In conclusion, in the present thesis I show that age-related increases in both forward and backward wave pressures account for increases in aortic pulse pressure; that age-related increases in aortic backward wave pressures and stiffness as well as decreases in pulse pressure amplification are as striking in the normotensive as in the hypertensive brachial BP range; and that increases in aortic backward wave pressures and stiffness account for more end-organ changes beyond brachial BP in the normotensive than the hypertensive brachial BP range. These data suggest that the assessment of aortic function may identify those with brachial BP values in the normotensive BP range that are most at risk for a cardiovascular event.

Declaration

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

.....Bryan Hodson.....

Bryan Hodson/.....18th..... day of .....May....., 2021

I certify that all studies contained in this thesis have the approval of the Committee for Research on Humans of the University of the Witwatersrand (clearance numbers: M170769, M170401, M1604106).

.....Bryan Hodson.....

Bryan Hodson .....18th..... day of .....May....., 2021

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

Date.....04/06/2021..... Date..... 04/06/2021.....

Dedication**:**

I dedicate my thesis work to my family, friends, and partner. A special feeling of gratitude for my loving girlfriend for the support and time afforded to me for my work, for the constant push for excellence and encouragement.

I also dedicate my thesis to my many friends, my sports clubs, and my religious community for the encouragement and support they gave me in the transformative process of doing this work.

My final dedication is to all the patients and subjects across the globe, without whom the data presented in this work, and in the work referenced herein, would not be possible.

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Publications

In support of the present thesis, the work included has resulted in the following publications in international journals.

1. Hodson B, Norton GR, Ballim I, Libhaber CD, Sareli P, Woodiwiss AJ. Aortic rather than brachial pulsatile haemodynamics accounts for variations in end-organ measures in the normotensive blood pressure range. *J Hypertens.* 2017;35:2443-2453.
2. Hodson B, Norton GR, Ballim I, Sareli P, Woodiwiss AJ. Contribution of backward and forward wave pressures to age-related increases in aortic pressure in a community sample not receiving antihypertensive therapy. *J Am Soc Hypertens*. 2017;11:616-626.
3. Hodson B, Norton GR, Booysen HL, Sibiya MJ, Raymond A, Maseko MJ, Majane OHI, Libhaber E, Sareli P, Woodiwiss AJ. Brachial pressure control fails to account for most distending pressure-independent, age-related aortic hemodynamic changes in adults. *Am J Hypertens* 2016;29:605-613.

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List of Abbreviations

ACEI	angiotensin-converting enzyme inhibitor
AIx	augmentation index
BMI	body mass index
BP	blood pressure
cAIx	central aortic augmentation index
CCB	calcium channel blocker
CI	confidence Interval
CKD	chronic kidney disease
DBP	diastolic blood pressure
DM	diabetes mellitus
eGFR	estimated glomerular filtration rate
HbA_{1c}	glycated hemoglobin
IMT	intima media thickness
LVH	left ventricular hypertrophy
LVM	left ventricular mass
LVMI	left ventricular mass index
MAP	mean arterial pressure
MDRD	Modification of Diet in Renal Disease
mm Hg	millimeters mercury
Pa	augmented pressures
Pb	aortic backward wave pressure
Pf	aortic forward wave pressure
PI	central aortic pulsatility index
PP	pulse pressure
PPamp	pulse pressure amplification
PPc	aortic pulse pressure
PWV	pulse wave velocity
Q	aortic blood flow
RI	reflected wave index
RM	reflection magnitude
SBP	systolic blood pressure
ß-coeff	standardized ß coefficient
TPR	total peripheral resistance
Zc	characteristic impedance

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Preface

Cardiovascular disease presently accounts for the highest proportion of deaths world-wide. Most of these deaths occur in low and middle-income countries such as South Africa. Of all of the risk factors for cardiovascular disease, increases in blood pressure (BP) account for most population attributable risk. Although it is well accepted that the risk for cardiovascular events increases linearly from systolic BP values as low as 115 mm Hg, most guidelines presently advocate a systolic BP of 140 mm Hg as that threshold employed to diagnose and treat hypertension. With the completion of newer outcome-driven clinical trials however, there is an increasing recognition that thresholds well below 140 mm Hg systolic BP may be required. However, the use of lower BP thresholds would mean that a considerable proportion of any population may require therapy and this approach may be cost-ineffective for low and middle-income countries. Hence, additional approaches may be required to identify those most at risk for cardiovascular events within this BP range. In this regard, our group had previously identified that in the normotensive brachial BP range, central arterial as opposed to brachial BP thresholds may better identify those with cardiovascular damage. However, the extent to which aortic dysfunction occurs in the normotensive BP range and whether the determinants of central arterial BP best identify those with a normal brachial BP with cardiovascular damage, had not previously been assessed. Therefore, I embarked on the present thesis to attempt further explore the role of central arterial dysfunction in the normotensive BP range.

In chapter 1 of the present thesis I review the current understanding and controversies related to BP effects on the cardiovascular system in the normotensive BP range and the possibility that these effects are mediated by central arterial haemodynamic changes. In this chapter I thus arguing in favour of conducting the studies described herein. In chapters 2 - 4, I describe each of the studies, their results and the implications thereof. These chapters are constructed as semi-independent chapters and each includes its own abstract, introduction, methods, results and discussion sections. The present thesis concludes with a chapter (chapter 6), which provides a summary of the findings reported; highlights the novelty of these findings and places them in context of our current understanding of central arterial haemodynamic effects on the cardiovascular system in the normotensive BP range. In support of this thesis, the data provided in chapter 2 has been published in the *J Am Soc Hypertens* (Hodson *et al*., 2017; chapter 3 has been published in the *Am J Hypertens* (Hodson *et al.,* 2016); and chapter 4 has been published in the *J Hypertens* (Hodson *et al.,* 2017).

CHAPTER 1

Introduction

Alterations in Central Aortic Haemodynamics: A Possible Method of Enhancing Cardiovascular Risk Detection Across the Full Peripheral Blood Pressure Spectrum

1.0 Introduction

As compared to the previous century, the current burden of disease in the world today has dramatically changed. Whilst previously, infectious diseases dominated annual death rates, now death from noncommunicable disease by far exceeds that of communicable disease (McAloon et al 2016). The principal cause of noncommunicable disease is cardiovascular disease and this occurs in low, middle or high-income countries (Bhatia et al 2006; Bradshaw et al 2010; Mozaffarian et al 2015; Roth et al 2015). Cardiovascular disease is responsible for approximately 17 million deaths every year and accounts for 31 % of all deaths globally (McAloon et al 2016). The estimate is that by the year 2020, cardiovascular disease will be responsible for 25 million deaths every year (Yusuf et al 2001). Indeed, the Global Burden of Diseases study reported 18.6 million deaths due to CVD in 2019 (Roth et al 2020), which reflected a steady increase from 12.1 million in 1990. Moreover, 393.8 million (14.4 % of the total) disability adjusted life years are lost every year due to cardiovascular disease, with an increasing rather than decreasing trend noted each year (McAloon et al 2016; Moran et al 2014). The escalating prevalence of cardiovascular disease globally is mainly due to ageing populations, urbanisation and globalisation. In the previous century, cardiovascular disease primarily occurred in the developed world; however currently, 80% of deaths due to cardiovascular disease are in countries with low to middle income (Mendis et al 2007).

In South Africa, cardiovascular disease is the leading cause of death in the elderly; and in rural communities of African ancestry, it is the third highest reason for death in individuals of a younger age (Tollman et al 2008). Currently in South Africa it is estimated that the second highest reason for death is hypertensive heart disease and that the fifth highest reason for death is stroke (South African Medical Research Council (MRC) Causes of Death Report, 2014). In this regard, in people of black African ancestry in South Africa, hypertension is the salient risk factor for cardiovascular disease (Rayner 2010). Indeed, in South African individuals of African ancestry living in urban communities, hypertension is likely to be responsible for about one third of all of those presenting with heart failure (Stewart et al 2008). In addition, in these individuals there is a strong relationship between hypertension and myocardial infarction (Steyn et al 2005), and for strokes the predominant risk factor is hypertension (Conner et al 2009; O'Donnell et al 2010). Therefore, in order to prevent death in communities of black African ancestry in South Africa, a primary target is appropriate blood pressure (BP) control.

Currently, the diagnosis of hypertension and the decision to institute pharmacological therapy is founded on the thresholds of brachial BP which have been shown to be beneficial in predicting cardiovascular outcomes and to significantly diminish cardiovascular events as a consequence of decreasing BP to less than these thresholds. The current BP thresholds for most international guidelines are a systolic BP (SBP) of 140 mm Hg and a diastolic BP (DBP) of 90 mm Hg. Although several hypertension guideline committees advise higher thresholds for

elderly individuals and lower thresholds for those with diabetes mellitus or renal disease, the aforementioned thresholds have in the more recent past been recommended by most guidelines for the majority of patients (Kjeldsen et al 2014). However, based on more contemporary outcome-based studies (Wright et al 2015), recent guidelines for some developed countries have adopted even lower thresholds for the diagnosis of hypertension and its treatment using pharmacological therapy (Whelton et al 2018). In this regard however, the cost of instituting pharmacological therapy at these lower thresholds in any patient regardless of their co-morbidities or overall risk has not been universally accepted as outweighing the benefit gained. Although silent on this matter, because of the cost implications for low and middle-income countries, they are unlikely to adopt these lower thresholds. Moreover, guidelines committees from many high-income countries have been silent on whether they deem these lower thresholds to be of value. What are the possible solutions to the issue of appropriate BP thresholds?

One possible solution is to identify those whose BP values lie below the generally accepted thresholds, but who are indeed at risk of an event caused by haemodynamic disturbances associated with increases in BP. In this regard, our group have recently identified that central arterial BP assessments increase the ability to identify those individuals whose brachial BP is below acknowledged thresholds but who have end organ changes (Booysen et al 2013). Therefore, in the present thesis I identified those age-related central arterial haemodynamic alterations that may occur even in individuals whose brachial BP values are within a normotensive range (i.e, individuals whose brachial BP is controlled). I further explored to what extent these central arterial haemodynamic changes are responsible for end organ changes even in those whose brachial BP values lie below accepted thresholds for brachial BP. Therefore, in the present chapter I first outline the evidence to support or refute the notion that a single brachial BP threshold is appropriate for instituting antihypertensive therapy. Second, I discuss the differences in the determinants of central arterial versus peripheral (brachial artery) BP. In doing so I highlight the possibility that the main factor that determines alterations in central arterial BP, and that is an increasing age, may play as much of a role in individuals whose brachial BP values are considered to be in the normotensive range as it does in those individuals whose brachial BP values are in the hypertensive range.

1.1 The adverse effects of blood pressure may occur well below threshold values

Previously, the diagnosis of hypertension was made when an individual's brachial BP was above a systolic BP (SBP) of 160 mm Hg and a diastolic BP (DBP) of 100 mmHg. However, over the past 50 years, the threshold levels for the diagnosis of hypertension have been modified to an SBP of less than or equal to140 mm Hg or a DBP of less than or equal to 90 mm Hg (Ventura et al 2001). The uncertainty as to what is considered a normal BP is underscored

by the acknowledgement that the risk of cardiovascular events is enhanced in individuals whose SBP lies between 120 and 140 mm Hg or whose DBP lies between 80 and 90 mm Hg (Chobanian et al 2003). This BP category was given the term ‘pre-hypertension’ (Chobanian et al 2003) as hypertension is more likely to occur in individuals with BP values within this category (Moreira et al 2008) and the probability of developing hypertension in individuals with BP values within this category is decreased by reducing BP (Julius et al 2006; Luders et al 2008). The term ‘pre-hypertension’ has more recently been replaced by the term ‘normal BP’ for SBP≥120 mm Hg and <130 mm Hg and DBP≥80 mm Hg and <85 mm Hg, and the term ‘high-normal BP’ for SBP≥130 mm Hg and <140 mm Hg, and DBP≥85 mm Hg and <90 mm Hg (Williams et al 2018). The specific intention of the identification of the categories of normal BP and high-normal BP was to raise awareness amongst individuals whose BP is within these categories. Such individuals should be advised to modify their lifestyle to a healthier way of life so as to slow their rate of the development of hypertension, prevent them from developing hypertension or reduce their risk of having a cardiovascular event (Chobanian et al 2003; Williams et al 2018). Although some guidelines did not recommend the use of antihypertensive therapy in individuals whose BP values are in the normal or high-normal ranges (Chobanian et al 2003), other guidelines specifically recommended antihypertensive therapy in those individuals who have a high enough overall risk to necessitate BP to be reduced to lower values (Williams et al 2018). In this regard, specific reasons to commence antihypertensive therapy in individuals whose BP is in the normal or high-normal ranges include the presence of end organ changes, the metabolic syndrome, diabetes mellitus, renal disease or cardiovascular disease (Williams et al 2018). What is the evidence that has resulted in a continuing trend for reductions in the BP thresholds employed to diagnose hypertension?

Blood pressure is a continuous trait and as such earlier large, prospective observational studies demonstrated that cardiovascular outcomes were predicted by fairly low BP values, such as from an SBP/DBP of 115/75 mm Hg (Lewington et al 2002). Indeed, a two-fold increment in mortality was noted to occur for every 20 mm Hg increase in SBP above 115 mm Hg and/or for every 10 mm Hg increase in DBP above 75 mm Hg (Lewington et al 2002). Several subsequent large prospective, observational studies similarly showed an increased risk for cardiovascular events and death for individuals whose BP was in the normal and high-normal BP ranges in comparison to individuals whose BP was in the optimal BP range (Blake et al 2003; Butler et al 2011; Conen et al 2007; Dorjgochoo et al 2009; Gu et al 2009; Hsia et al 2007; Kshirsagar et al 2006; Liszka et al 2005; Mainous III et al 2004; Pednekar et al 2009; Qureshi et al 2005; Vasan et al 2001; Zhang et al 2006). Indeed, BP values in the normal or high-normal BP ranges have been demonstrated to predict stroke, myocardial infarction and heart failure beyond several confounders associated with normal or high-normal BP levels including age, body mass index, diabetes mellitus, smoking, drinking, high cholesterol concentrations, levels of education, levels of physical activity, geographic regions or inflammatory markers (Blake et al 2003; Butler et al

2011; Conen et al 2007; Gu et al 2009; Hsia et al 2007; Kshirsagar et al 2006; Liszka et al 2005; Qureshi et al 2005; Zhang et al 2006). Importantly, consistent with the adverse effect of an increased BP being a linear trait, the risk for cardiovascular disease is greater in individuals whose BP is in the high-normal range as opposed to individuals whose BP is in the normal BP range (Dorjgochoo et al 2010; Pednekar et al 2009; Vasan et al 2001). However, the capacity of BP values within the normal or high-normal BP ranges to predict risk has not been consistent. Indeed, in the National Health and Nutrition Examination Survey (NHANES) II and the NHANES II Mortality Study, a normal or high-normal BP was not an independent predictor of events (Mainous III et al 2004). Importantly, in addition to concerns regarding the lack of consistency of findings across studies, prospective observational studies also do not provide hard evidence for cause and effect. As will be discussed in subsequent sections, residual confounding may exist in these studies and hence events may have been predicted because of associated co-morbidities rather than because of the adverse effects of BP. To address these concerns the impact on events of BP lowering with pharmacological interventions requires consideration. What is the evidence from intervention studies?

A number of studies have discussed the effect of lowering BP in individuals with hypertension to BP values which are regarded as being substantially less than the current BP thresholds or the effect of BP lowering in normotensives to even less than accepted thresholds. In this regard, several randomized, controlled trials (Nissen et al. 2004; PROGRESS Collaborative Group 2001; Remme et al. 2009; Wright et al. 2015) and meta-analyses of such trials (Ettehad et al. 2016; Law et al. 2009; Thompson et al. 2011; Thomopoulos et al. 2016; Tumbull et al. 2003; Xie et al. 2016) have shown that the lowering of BP to less than the currently accepted BP thresholds in specific patients who are at high cardiovascular risk has beneficial effects on outcomes. A meta-analysis of 29 randomised clinical trials (a total of 162 341 individuals), showed that regardless of the BP level at the start of the study, a larger reduction in the risk of all major cardiovascular events was associated with a larger decrease in BP values to values less than the current thresholds of 140/90 mm Hg (Trialists Collaboration 2003). Furthermore, the largest meta-analysis completed to-date showed that a decrease in SBP of 10 mm Hg and a decrease in DBP of 5 mm Hg reduced the risk of coronary artery disease and stroke across all BP categories (Law et al 2009). However, only a few of these studies were designed to compare the impact of BP lowering in the normotensive BP range. Hence although baseline values were accounted for in multivariate adjustments, the impact on events may still be because of marked decreases in BP from very high to very low levels.

With regard to studies assessing the effect of antihypertensive treatment specifically in individuals who are normotensive, the Perindopril Protection Against Recurrent Stroke Study (PROGRESS), reported that antihypertensive therapy in non-hypertensive participants decreased the risk of having a stroke (Staessen and Jiguang 2001). The European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease' (EUROPA)

study, reported that the largest reduction in the risk for cardiovascular events occurred in patients whose BP was within the optimal BP range (Nissen et al 2004). Importantly, in normotensives in the EUROPA study, perindopril decreased the risk of non-fatal myocardial infarction, cardiac arrest in individuals who had a pre-existing history of coronary artery disease and cardiovascular death (Remme et al 2009), suggesting that this effect is beneficial in high risk patients. Many additional studies similarly report that the reduction of BP in the normotensive BP range decreases cardiovascular events (Nissen et al 2004; Patel 2007).

As indicated above, as with observational studies, contrary to the data suggesting that decreasing BP to values far less than 140/90 mm Hg results in beneficial effects, a number of studies have reported the absence of a decline in risk as a consequence of the use of antihypertensive treatment in individuals whose BP is within the pre-hypertensive category (Brunstrom et al 2016; Cooper-DeHoff et al 2010; Cushman et al 2010; McMurray et al 2010; Patel et al 2007; Schrier et al 2002; Yusuf et al 2008a; Yusuf et al 2008b; Yusuf et al 2008c; The SP3 Investigators 2013). Specifically, decreasing BP for 5 years, in individuals with pre-hypertension, showed no decline in the risk for angina pectoris, myocardial infarction, strokes, heart failure, arterial revascularization or cardiovascular death (McMurray et al 2010). Furthermore, antihypertensive therapy for 2.5 years in individuals with a BP in the normotensive range did not decrease the number of major cardiovascular events or repeated strokes (Yusuf et al 2008). Indeed, individuals in whom BP was lowered to less than 120/80 mm Hg were noted to have similar risks for major cardiovascular events as individuals in whom BP was reduced to less than 140/90 mm Hg (Cushman et al 2010). Further, when SBP was decreased to less than 130 mm Hg, cardiovascular outcomes were similar as compared to when SBP was reduced to less than 140 mm Hg (Cooper-DeHoff et al 2010).

In summary therefore, evidence has been provided by meta-analyses of a number of clinical studies to indicate that significant benefits can be gained from the lowering of BP regardless of the starting BP range and that individuals who have starting BP values that are in the pre-hypertensive BP category can experience these benefits. However, even though some randomised, controlled, clinical trials uphold the concept that there are benefits to the lowering of BP to values that are far lower than the current thresholds for an elevated BP (Law et al 2009; Nissen et al 2004; Patel 2007; Remme et al 2009; Schrier et al 2002; Staessen and Jiguang 2001; Trialists Collaboration 2003), not all intervention studies report the same benefits. Indeed, a number of clinical trials do not confirm that BP plays a causal role in cardiovascular disease in individuals with pre-hypertension (Brunstrom et al 2016; Cooper-DeHoff et al 2010; Cushman et al 2010; Patel et al 2007; McMurray et al 2010; Schrier et al 2002; The SP3 Investigators 2013; Yusuf et al 2008a; Yusuf et al 2008b; Yusuf et al 2008c). Thus, a number of interventional studies propose that pre-hypertensive brachial BP values are not likely to contribute significantly to overall cardiovascular risk in individuals whose BP values are in this range. However, it must be considered that the interventional studies conducted in individuals with BP in the pre-

hypertensive range have been of fairly short duration and hence it is possible that in those studies in which benefits were not shown, more prolonged BP lowering could have revealed beneficial effects on cardiovascular disease. Importantly, none of these studies were specifically designed to compare the impact of lowering BP to different threshold values. Is there evidence from studies designed to compare the impact of lowering BP to different thresholds?

The recent SPRINT study was designed to assess the impact of lowering BP to different BP thresholds (Wright et al 2015). The SPRINT study provided clear evidence that a threshold lower than 140/90 mm Hg was indeed more appropriate for risk reduction (Wright et al 2015). Although, as indicated above, several hypertension guideline committees in developed countries have thus adopted these lower thresholds (130/80 mm Hg)(Whelton et al 2018), there are several issues which confound the interpretation of the SPRINT study results. These issues include whether peripheral BP measurements performed in that study were comparable with other outcome-based studies (they were performed in quiet rooms without an observer present thus limiting alerting responses) and whether event reduction could be attributed to BP lowering or an impact of diuretic agents on heart failure (Wright et al 2015), issues that are beyond the scope of the present thesis. Irrespective of the arguments for and against lower BP thresholds, in any community there is nevertheless at least one quarter of individuals whose BP may be within the normal or the high-normal BP range and hence these individuals might have an increased risk of a cardiovascular event related to their BP. Importantly however, a possible reason why BP lowering is unable to consistently reduce events is that alternative factors account for the high risk of events in those with a normal or high-normal BP. What are these possible alternative risk factors?

1.2 Non-blood pressure-related factors in pre-hypertension

If in individuals with normal or high-normal BP values, brachial BP is not responsible for cardiovascular risk, what then may contribute to the well-described greater cardiovascular risk in some studies in this BP range? A number of studies provide consistent evidence that a normal or high-normal BP is related to alternative (non-BP) cardiovascular risk factors, examples of which are dyslipidaemia, obesity and diabetes mellitus. Indeed, in the National Health and Nutrition Examination Survey (NHANES) 1999-2000 study, 64% of participants with BP in the pre-hypertensive range and 94% of those over 60 years of age had as a minimum one of these alternative cardiovascular risk factors (Greenlund et al 2004). In addition, in the NHANES II mortality study, 90% of participants with BP in the pre-hypertensive range had as a minimum one of these alternative cardiovascular risk factors (Mainous III et al 2004). In a large study of 36 424 participants (of which 51% of males and 36% of females had pre-hypertensive BP values), body mass index was higher, blood concentrations of glucose, total cholesterol, low-density lipoprotein cholesterol and triglycerides were greater, and blood concentrations of high-

density lipoprotein cholesterol concentrations were lower in the individuals who had pre-hypertension (Grotto et al 2006). Moreover, after a 12 year period of follow-up, compared to individuals with BP within the optimal BP range, the development of diabetes mellitus was more frequent in individuals with BP within the pre-hypertensive range (Zhang et al 2006). In addition, individuals with pre-hypertension have elevated concentrations of the inflammatory markers that are related to an increased risk of cardiovascular disease (Chrysohoou et al 2004; King et al 2004). In particular, in the NHANES III and ATTICA (so-named as the study participants were enrolled from the Attica area of Greece) epidemiological studies, in comparison to individuals with BP values in the optimal BP range, individuals with pre-hypertension were noted to have greater blood concentrations of various inflammatory markers, such as C-reactive protein (Chrysohoou et al 2004; King et al 2004), tumour necrosis factor-α, homocysteine and amyloid-α, and greater counts of white blood cells (Chrysohoou et al 2004). There is therefore considerable data to indicate that alternative cardiovascular risk factors may account for the association between normal or high-normal BP levels and cardiovascular disease. However, is there data to indicate that a normal or high-normal BP is indeed related to cardiovascular damage through relationships with alternative cardiovascular risk factors?

Our group was the first to provide data to indicate that the noticeable cardiovascular end organ changes which were present in individuals with BP values in the normal or high-normal ranges were no longer evident following multivariate adjustments for alternative cardiovascular risk factors (Norton et al 2008). Although a later study suggested that end organ changes in individuals with normal or high-normal BP values were not totally explained by alternative cardiovascular risk factors, this study failed to report on the quality of their office BP measurements (Kim et al 2011). In comparison, our group has reported that the office BP measurements used to identify normal and high-normal BP values were of high quality (Norton et al 2008; Woodiwiss et al 2009). The data from our laboratory (Norton et al 2008) therefore propose a probable reason for the associations between normal and high-normal BP levels and cardiovascular end organ changes that are unlikely to be altered by therapy to lower BP. However, evidence to suggest that associations between normal or high-normal BP values and cardiovascular disease can be attributed to related risk factors is missing. The associations between a normal or high-normal BP and cardiovascular disease previously described, have mostly been adjusted for alternative cardiovascular risk factors, but few studies have adjusted for the elevated plasma concentrations of inflammatory markers that may be noted in individuals with a normal or high-normal BP. However, as mentioned above and as will be discussed in detail below, recent work from our laboratory suggests that relationships between normal or high-normal BP levels and end organ changes is markedly better when central rather than peripheral arterial haemodynamics are considered. This issue obviously raises the question as to whether the assessment of central arterial haemodynamics is one method that could be used to detect individuals with brachial BP values lower than 140/90 mm Hg, but who are

nevertheless at risk of having a cardiovascular event related to BP? Consequently, in the next section I will discuss the dissimilarity in the factors that determine central arterial as opposed to peripheral haemodynamics. I will then discuss the evidence to-date that central arterial haemodynamics enhance the capacity to identify individuals with peripheral BP values within the normal or high-normal BP ranges who are at risk of a cardiovascular event.

1.3 Central arterial versus peripheral blood pressure

Unlike DBP which remains relatively constant across the arterial tree, central arterial SBP, including SBP in the aorta, is lower than SBP measured in peripheral arteries including the brachial artery. These differences may be as much as 20-30 mm Hg. This effect is attributed to the amplification of pulse pressure (PP) from central to peripheral arteries There are two factors that explain central-to-peripheral PP amplification (Nichols et al 2011). In this regard, peripheral arteries are narrower in diameter and more muscular than central arteries such as the aorta, which are elastic in nature. Consequently, peripheral arteries generate a higher stiffness and hence impedance (resistance in a pulsatile system) to flow than do the central arteries. The consequent impedance mismatch between the central and peripheral arteries therefore amplifies PP as it is transmitted outward to the peripheral arteries (Nichols et al 2011). The second factor that may explain PP amplification is that the forward travelling pressure wave which is generated by ventricular ejection is transmitted to points of vascular tapering where wave reflection occurs and on their return to the proximal aorta, reflected waves summate with the forward travelling pressure wave (Nichols et al 2011). In the periphery the reflected wave returns at points of forward wave antinodes (pressure waves are oscillating waves around the arterial wall with both positive [antinodes] and negative [nodes] pressure wave components in the lumen) thus producing considerable overlap with positive waves and maximal summation. In contrast, the reflected wave returns sufficiently late in the aorta that overlap between the forward and reflected wave is more at forward wave pressure nodes and hence the extent of overlap of positive components of pressure waves and hence summation is considerably less (Nichols et al 2011) (Figure 1.1). The factors that explain SBP differences between peripheral and central arteries have varying effects at different ages and with different combinations of risk factors. Consequently, differences in SBP between central and peripheral arteries (PP amplification) vary considerably from person to person. Therefore, the question that arises is whether central and peripheral arterial SBP differ in their ability to detect cardiovascular damage?

1.3.1 Is central arterial better than peripheral blood pressure in detecting cardiovascular damage?

Several studies suggest that aortic SBP or aortic PP are related to measures of

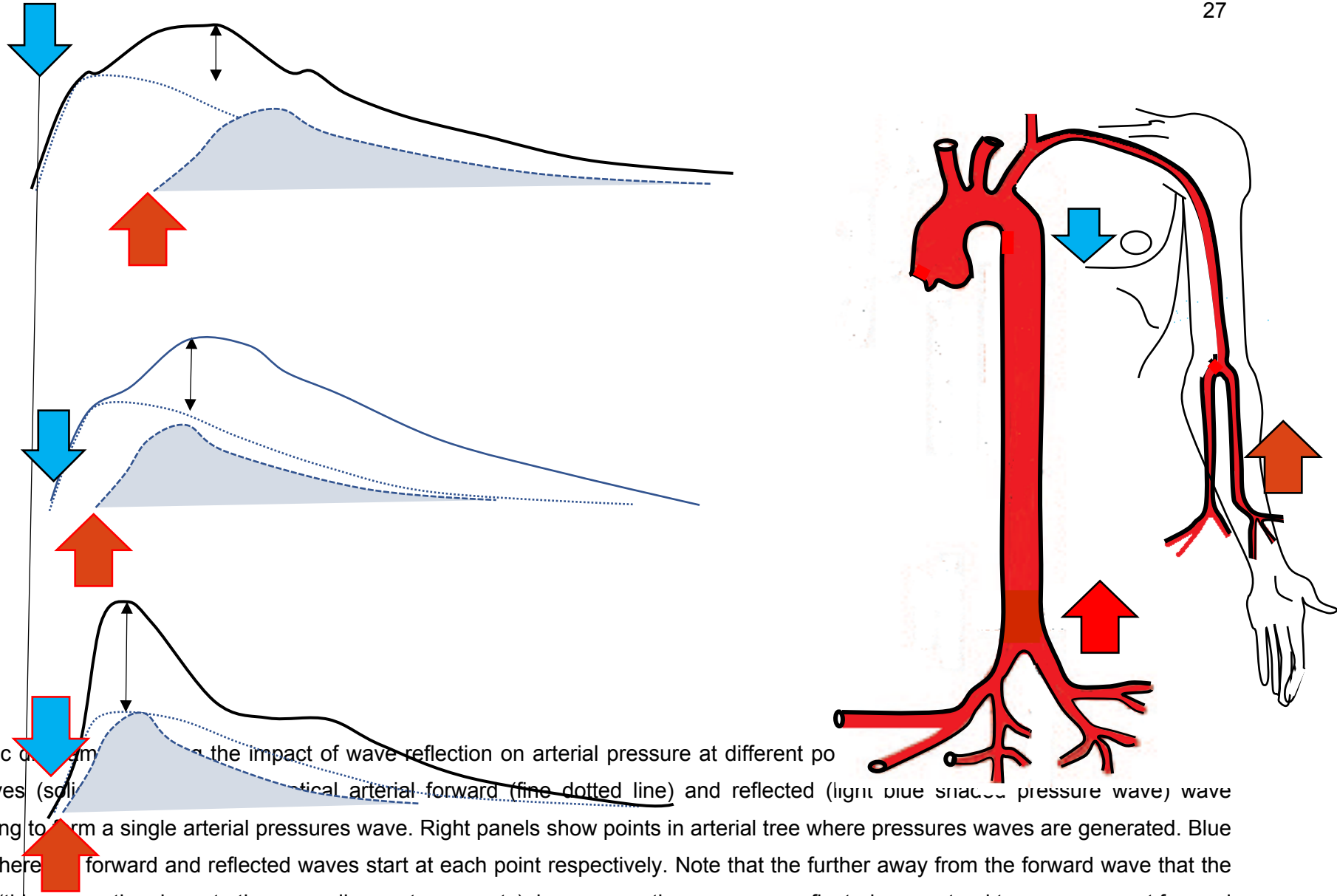

Figure 1.1. Schematic d[illegible] the impact of wave reflection on arterial pressure at different po[illegible] arterial pressure waves (soli[illegible] tical arterial forward (fine dotted line) and reflected (light blue shaded pressure wave) wave components summating to form a single arterial pressures wave. Right panels show points in arterial tree where pressures waves are generated. Blue and red arrows are where forward and reflected waves start at each point respectively. Note that the further away from the forward wave that the reflected wave starts (this occurs the closer to the ascending aorta one gets), less summation occurs as reflected waves tend to occur more at forward wave pressure nodes than antinodes.

cardiovascular end organ changes, including left ventricular mass index, left ventricular function, carotid intima-media thickness, and glomerular function more strongly than or beyond brachial BP (Boutouyrie et al 1999; Covic et al 2000; Neisius et al 2012; Norton et al 2012; Roman et al 2010; Wang et al 2009; Wohlfahrt et al 2011). In addition, Roman and Devereux (2014) have extensively reviewed this issue. More recently a meta-analysis of studies evaluating relationships between either central or peripheral SBP or PP and end organ measures suggests that aortic SBP or aortic PP are related to end organ changes beyond peripheral SBP or peripheral PP (Kollias et al 2016). Furthermore, several studies provide evidence that aortic SBP or aortic PP predict cardiovascular outcomes more strongly than or beyond brachial SBP or brachial PP (Benetos et al 2010; Benetos et al 2012; Jankowski et al 2008; Pini et al 2008; Regnault et al 2012; Roman et al 2007; Roman et al 2009; Safar et al 2002; Wang et al 2009; Williams et al 2006). In this regard, earlier studies suggested that independent of brachial BP, central aortic PP or central aortic SBP predicted cardiovascular events in the general population (Roman et al 2007 & 2009), in the elderly (Pini et al 2008), in patients undergoing coronary angiography (Jankowski et al 2008), and in individuals with end-stage renal disease (Safar et al 2002). However, some studies reported that cardiovascular events were predicted by brachial SBP but not central aortic SBP (Dart et al 2006). Importantly, in a meta-analysis of the studies published at that time, aortic SBP or PP did not show a significantly greater ability to predict risk than brachial BP, although a trend for a greater effect of aortic versus brachial BP was noted ($p=0.057$) (Vlachopoulos et al 2010). This meta-analysis was nevertheless criticised for several reasons including the inclusion of studies where the calibration of central pressure waveforms may have been inappropriate (Dart et al 2006). This meta-analysis also did not include data from the Conduit Artery Function Evaluation (CAFE) study which showed better relationships between cardiovascular outcomes and aortic compared to brachial BP (Williams et al 2006) in addition to data from a study conducted in Taiwan (only published just prior to the meta-analysis) (Wang et al 2009) which similarly showed that aortic BP predicted cardiovascular risk better than did brachial BP. Although, studies published after this meta-analysis were obviously also not included, data from the Framingham Heart Study nevertheless showed that aortic SBP failed to predict risk independent of brachial SBP (Mitchell et al 2010). However, it is important to note (and indeed I will discuss this subsequently), that the difference between aortic and brachial BP (termed PP amplification) was limited across the adult lifespan in the Framingham Heart Study, a finding which because of the generally excellent BP control in this community, could be attributed to the notably low brachial BP values reported in this study (Mitchell et al 2010). Hence, it is perhaps unsurprising that aortic SBP failed to provide prognostic information independent of brachial BP in the Framingham Heart Study.

The inconsistent findings in studies exploring the relative roles of central arterial BP versus peripheral BP in the prediction of cardiovascular risk has prompted several groups, including our own, to explore the possibility that the factors that determine central versus

peripheral SBP and PP may better associate with measures of cardiovascular end organ changes than SBP or PP *per se*. What are the determinants of central arterial PP and hence SBP and which of these determinants have been demonstrated to associate with cardiovascular damage?

1.3.2 Determinants of central arterial pulse pressure

As illustrated in Figure 1.1 and described in aforementioned sections, anywhere along the arterial tree, PP is generated by the sum of the forward and backward travelling pressure waves as they meet (Nichols et al 2011). As also indicated in the previous discussion, the forward travelling pressure wave is generated by the flow of blood ejected into the proximal aorta produced by contraction of the left ventricle (Nichols et al 2011). Thus ventricular function is a key determinant of forward wave pressures and hence PP. As with any conduit conducting pulsatile flow, the aorta (although it is not a resistance vessel) will produce resistance to blood flow during ventricular ejection (impedance), which in the absence of wave reflection is called characteristic impedance (Zc) (Nichols et al 2011). The pressure produced in the aorta by left ventricular contraction is thus the product of impedance to blood flow (Zc) and blood flow (Q) itself (Nichols et al 2011). However, as indicated the aorta is not a resistance vessel and hence the healthy aorta normally has a very low Zc. Thus, most of the pressure generated during ventricular contraction is produced by blood flow (Nichols et al 2011). Indeed, to some extent the peak forward wave pressure (Pf) (the peak of the forward pressure wave in Figure 1.1) is an index of the extent to which the aorta buffers load on the cardiovascular system during contraction. Furthermore, as the aorta stores energy during systole, which is then employed to drive blood flow when it recoils, Pf is also an index of the extent of aortic elastic recoil which contributes to diastolic blood flow in vessels (Nichols et al 2011). Thus, Pf is also an index of central arterial elastic mechanical properties (Nichols et al 2011).

Whilst aortic blood flow is influenced by many variables including any factor which determines cardiac contraction, Zc is determined mainly by two factors, an increased stiffness, which may be readily indexed by carotid-femoral pulse wave velocity (PWV) which is the current gold-standard assessment of aortic stiffness, and a decreased diameter of the aorta (Nichols et al 2011). In this regard, Q has seldom been demonstrated to increase in hypertension. Thus, the main determinant of forward wave pressures in hypertension may be an increased Zc. The principle determinant of Zc is an increased aortic stiffness which correlates well with the increases in Pf, PP and hence SBP with age, whilst the contribution of aortic diameter is controversial. Although aortic diameter also increases rather than decreases with age, this increase in diameter may not be as extensive in those with an increase in PP (Mitchell et al 2003). Moreover, an increase in aortic diameter may play a role in age-related increases in Pf and PP by increasing the degree of strain placed on collagen fibres in the aorta

and thus contributing to the impact of increases in stiffness (Nichols et al 2011). Importantly, the critical determinant of aortic stiffness is arteriosclerosis, which is produced by fragmentation of elastin fibres, an increase in collagen and its cross-linking and calcification of the aorta, all changes that are produced by uncontrolled cardiovascular risk factors (Kovacic et al 2011; Lam et al 2010; Wagenseil 2011; Mitchell 2015). In this regard, arteriosclerotic alterations in the aortic wall are produced through the increases in BP, through diabetic advanced glycation processes and through several alternative risk factors including smoking and dyslipidaemia as well as through associated inflammatory changes in the vascular wall. Risk factor-related arteriosclerotic changes are thought to be the main determinants of increases in aortic stiffness, Zc, and hence Pf with aging and with hypertension.

As discussed in the aforementioned section, as with any conduit which transmits flow in a pulsatile manner, where tapering occurs (such as at points of bifurcation or narrowing of vessels in the arterial system), forward travelling pressure waves will reflect and travel back to the point of origin (O'Rourke et al 1984) (Figure 1.1). As with the forward travelling pulsatile pressure waves, backward travelling pulsatile pressure waves travel at a very high speed in a normal aorta (around 3-6 m/sec). The high speed of wave travel of reflected waves will then result in the reflected wave returning to points in large arteries where the forward travelling pressure waves are at their antinodes and summation with the forward wave occurs (Figure 1.1). At points close to reflection sites summation is maximal (the two waves literally superimpose) (Figure 1.1). In this regard, in peripheral arteries (e.g, brachial, radial, femoral or dorsalis pedis) close to reflection points, reflected waves occur at pressure antinodes and hence markedly amplify the peripheral pulse (Figure 1.1). However, the further from reflection sites (such as the point of origin of the forward travelling pressure wave in the proximal aorta), the more chance that the reflected wave will reach the forward wave's pressure node and hence summation of the two waves will be less than in the periphery (Figure 1.1). The further from the aorta (i.e. the closer to reflection sites) where maximal overlap between the forward and the backward travelling wave antinodes occurs, summation will generate what appears to be a single pulse pressure wave (Figure 1.1). In comparison, the closer to the aorta (i.e. the further from reflection sites), where minimum overlap between the forward and the backward travelling waves occurs, the pulse will appear more as two discernible waves that have coincided with a first and second systolic shoulder (Figure 1.1). The degree of summation in the aorta will depend on the extent to which the reflected wave returns in phase (pressure antinode) or out of phase (pressure node) (Figure 1.1) with the forward wave. As the proximal aorta is far from the point of wave reflection, reflected waves arrive out of phase with the forward travelling wave (occur more at pressure nodes) (Figure 1.1). Thus in the aorta, summation with the forward wave is normally far less extensive than in the periphery (Figure 1.1).

If the speed of wave reflection is very slow then backward travelling pressure waves will arrive well after forward waves in the aorta and add to or augment diastolic more than systolic BP. This occurs in childhood and explains central arterial waveforms in some mammals with a very elastic aorta or where a longer distance for wave travel exists (Nichols et al 2011). The advantage of this system is that it will promote coronary blood flow which primarily occurs during the diastolic period of the cardiac cycle and which strongly depends on the pressure gradient across the coronary bed. However, in most human adults from as early as 16 years of age the speed of wave travel is fast enough that backward travelling pressure waves arrive during the systolic period of the cardiac cycle and thus summate with the forward travelling pressure waves. In this circumstance, backward travelling pressure waves thus augment aortic PP (Agabiti-Rosei et al 2007; Aviolo et al 2009; Nichols et al 2011). What are the determinants of backward wave pressures?

Because forward and subsequently backward waves travel through a system that dampens the force (the aorta), in the central and peripheral arteries reflected waves are by their nature smaller pressure waves than forward waves (Figure 1.2, left panel). Moreover, through Newton's 1st (inertial forces) and 3rd (for every action there is an equal and opposite reaction) Laws of Motion the major determinant of maximal backward wave pressure (Pb in Figure 1.2, left panel) is the maximal pressure generated by the forward travelling pressure wave (Pf in Figure 1.2, left panel). Thus, as Pf increases, so does Pb. The fact that Pb is always smaller than Pf and that Pb depends on Pf has rendered the opinion that the primary target to reduce PP should always be Pf as reductions in Pb will automatically follow and after all Pb is the minor pressure wave (in the magnitude of the pressure generated). However, there is now significant evidence that strong determinants of Pb are arteriolar tone (indexed by total peripheral resistance [TPR] and mean arterial pressure [MAP]) and vascular tone in more proximal arteries (Cecelja et al 2009; Liao et al 2011). In this regard, the role of vascular tone on wave reflection requires the exclusion of the effects of aortic forward pressure waves on wave reflection. To do this, reflection magnitude (RM) is calculated as the percentage of Pb/Pf. Importantly, as shall be discussed below, not only is there an increasing appreciation that with increasing years of age changes in Pb occur well beyond the effects of Pf on Pb, there is also a growing realisation that a significant proportion of Pf is in fact also driven by Pb.

1.3.3 Reappraisal of the relative contribution of reflected waves to load in central arteries

As highlighted above, through dampening effects in the aorta, Pb is lower than Pf (Figure 1.2, left panel). As maximal PP is the summation of the pressures generated by the two pressure waves at a point where overlap occurs, maximal PP is produced by a larger Pf (Figure

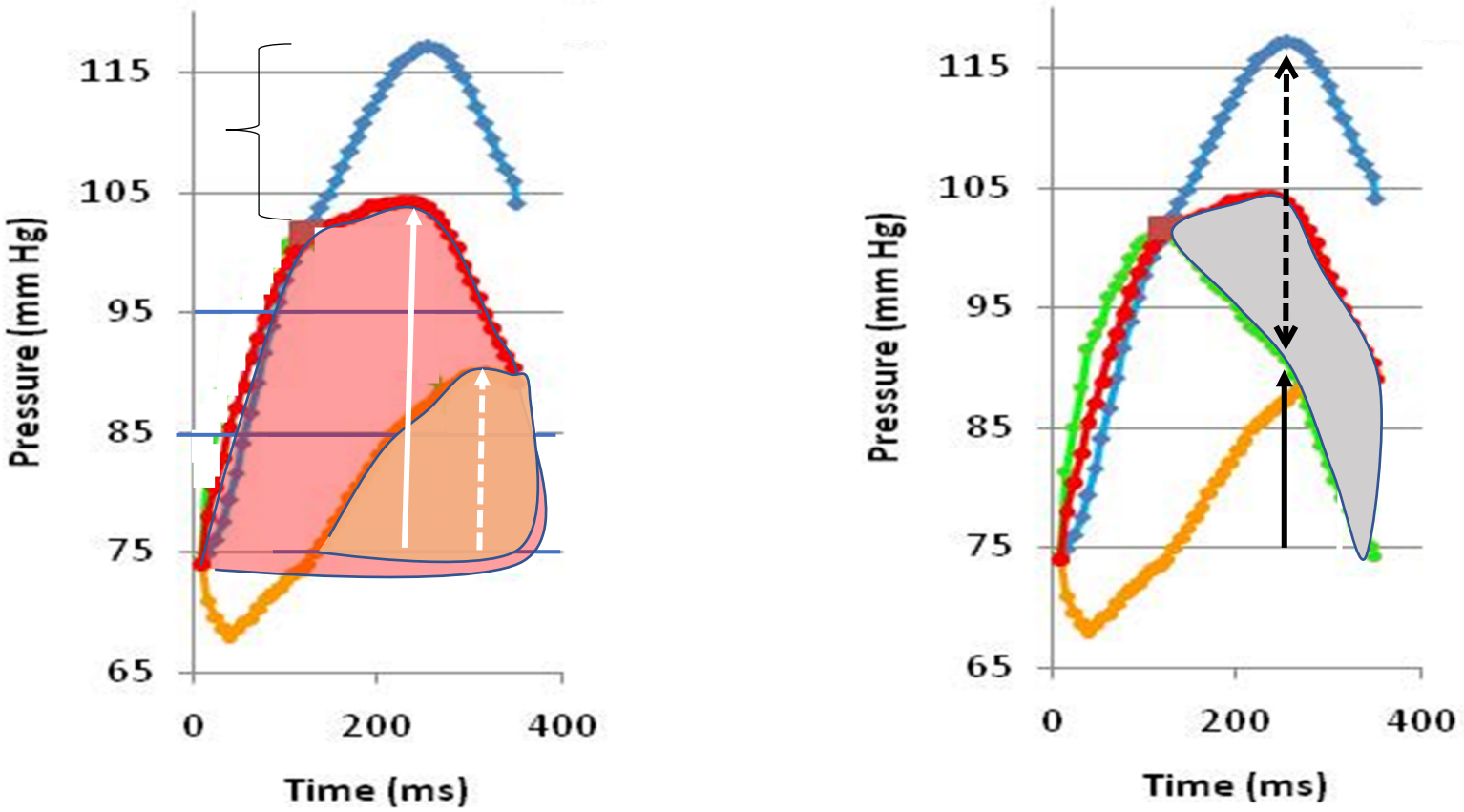

Figure 1.2. Aortic pressure wave (blue dots) and the forward (red dots and shading) and backward (orange dots and shading) pressure wave components (left panel) and the contribution of wave re-reflection (gray shading) and the pressure wave generated by the product of flow (Q) and characteristic impedance (Zc) (green dots) to aortic pulse pressure (right panel). Pf and Pb are peak aortic forward and backward pressure waves; A is the contribution of wave reflection + re-reflection and B the contribution of the pressure generated by Q x Zc to aortic pulse pressure. Data are generated from actual aortic pressure waves derived from a SphygmoCor recording and a flow wave generated from aortic velocity and diameter assessments in the aortic outlet tract (echocardiography). The forward and backward pressure waveforms are generated from wave separation analysis.

1.2, left panel) and a smaller Pb (Figure 1.2, left panel). Thus, it is logical to assume that the contribution of Pb to aortic PP is minor in comparison to that of Pf and that the extent to which Pb augments PP should be calculated as the pressure at the height of the second systolic shoulder minus the first (augmented pressures or Pa) (Nichols et al 2011) (Figure 1.2, left panel). The extent to which augmentation of central PP occurs through wave reflection is thus expressed as a percentage of Pa/PP (central aortic augmentation index [cAIx]). This approach to assessing wave reflection has been employed for several years and is incorporated in all major commercial software. As can be seen in Figure 1.2 (left panel) augmented pressures generally make a much smaller contribution to PP than those factors that influence pressure up until the inflection point (generally the maximal pressure produced by the product of Q and Zc). What this approach has not however considered is the contribution of wave re-reflection to both Pf and PP (Phan et al 2016).

As discussed in the aforementioned section, the forward pressure wave is thought to be driven primarily by the product of Q and Zc. However, the maximum pressure generated by Q x Zc is normally at a point close to the first systolic shoulder of the pressure wave (just before the inflection point) (Figure 1.2, right panel) and hence occurs well before peak Pf. Thus, as recently highlighted (Phan et al 2016) there is clearly an excess pressure in Pf that cannot be ascribed to either Q or Zc (shaded area in Figure 1.2, right panel). The presence of excess pressure in Pf makes sense as it appears in Figure 1.2 (left panel) that the peak of Pf and hence aortic PP occurs at a similar time as the peak of Pb, when in fact reflected waves in the aorta should occur closer to a pressure node than an antinode of the forward travelling pressure wave where minimal overlap with forward waves occurs. This is indeed the case if we consider the contribution of the pressure generated by Q x Zc at that time when the peak of the forward pressure wave occurs (Figure 1.2, right panel). In this regard, the contribution of the pressure produced by the product of Q and Zc to Pf is in fact only half of the peak pressure generated by the peak of Q x Zc (Figure 1.2, right panel). Importantly, the excess pressure in the forward wave is attributed to wave re-reflection (Phan et al 2016), where the backward travelling waves reflect forward on return to the proximal aorta and add to forward wave pressures. Once again, through Newton's 1st and 3rd Laws of Motion, the magnitude of the re-reflected wave is likely to be determined by the magnitude of wave reflection (Phan et al 2016). Importantly, when accounting for wave re-reflection, at the time point where maximal PP occurs, the sum of the contribution of the pressure produced by the backward travelling pressure wave and re-reflected waves (A in Figure 1.2, right panel) by far exceeds the contribution of the pressure produced by the product of Q and Zc (B in Figure 1.2, right panel). Thus in fact the contribution of reflected waves to peak PP exceeds that of the pressure produced by the product of Q and Zc. In short, Pf overestimates the impact of Q and Zc on aortic PP and Pa underestimates the total contribution of wave reflection to aortic PP.

1.3.4 Reflected waves and age-related increases in pulse pressure

The aforementioned continuing debate either in favor of or against an important role of backward wave pressures in determining PP is reflected in conflicting data addressing this issue. In this regard, many studies report on the relative roles of forward and backward wave pressures in determining age-related increases in PP across the adult lifespan. In some of these studies (Mitchell et al 2010; Segers et al 2007; Torjesen et al 2014) including the Framingham Heart Study, the authors reported that age-related increases in PP were largely ascribed to age-related increases in forward wave pressures with reflected wave pressures contributing to little of the age-related increases in PP. However, in one study age-related effects on aortic function were studied over a narrow range of age (Segers et al 2007) and in two of the studies (Mitchell et al 2010; Torjesen et al 2014) most hypertensive participants were receiving antihypertensive therapy and BP was in general very well controlled. This may indeed have modified the relative roles of each of the pressure waves. Moreover, how much of the Pf change could be attributed to wave re-reflection in these studies was not determined. Importantly, work performed in the Anglo-Cardiff Study demonstrated, using augmented pressures as an index of wave reflection and product of coefficient mediation analysis, that up until 50 years of age, reflected waves explain age-related increases in wave reflection and thereafter both incident pressure waves (an index of maximal pressures produced by the product of Q and Zc) and reflected waves contribute equally to age-related increases in PP (Namasivayam et al 2009). Subsequent work by the same group conducted in a large clinical sample similarly demonstrated using product of coefficient mediation analysis, that up until 50 years of age, reflected waves account for age-related increases in wave reflection and thereafter both forward and reflected pressure waves contribute equally to age-related increases in PP (Namasivayam et al 2016). Our group has subsequently shown in a large representative community-based sample of African ancestry, that with Pf and Pb in the same regression model, the most important determinant of variations in aortic PP across the adult lifespan is Pb, with Pf contributing to only a small extent (Booysen et al 2015). Indeed, independent of each other whilst maximal Pf only contributed 3% to the variability of aortic PP in individuals less than 50 years of age and 2% to the variability of aortic PP in individuals over 50 years of age (the age at which Pf begins to markedly increase), maximal Pb contributed 76% to the variability of aortic PP in individuals younger than 50 years of age and 94% to the variability of aortic PP in individuals over 50 years of age (Booysen et al 2015). Although co-linearity plays an important role in interpreting these results, this should be considered in context. Indeed, whilst Pb is determined by Pf and hence adjustments for Pf are through collinearity likely to markedly underestimate Pb effects, Pf is not meant to be determined by Pb and hence should not be confounded by collinearity. The greater role of Pb to age-related increases in PP in the study described by our group (Booysen et al 2015) is consistent with aortic wave reflection being an important determinant of PP. Thus, in the context of wave re-reflection (Phan et al 2016) and existing evidence (Booysen et al 2015) conducted in a community sample with much higher reflected wave function than alternative ethnic samples around the world (Chirinos et al 2011), reflected waves are likely to contribute far more than what was previously thought to variations in central arterial PP. This is despite the fact that reflected wave pressures are always lower than forward wave pressures and that reflected wave pressures are strongly dependent on forward wave pressures. However, in all of the aforementioned studies none of the authors excluded the impact of antihypertensive treatment on either forward wave pressures or on wave reflection. Thus, as will be discussed in the “problem statement” below as part of the present thesis prior to assessing changes in aortic haemodynamics and their impact on end organs in the individuals with BP in the normal or high-normal ranges, I first evaluated the relative roles of Pf versus Pb in determining age-related increases in PP in community participants who were not receiving antihypertensive treatment.

1.3.5 Reflected waves and end-organ measures or cardiovascular events

The concept of a significant impact of wave re-reflection on Pf (Phan et al 2016) clearly modifies our view of the factors that influence pulsatile load in central arteries. What is the

evidence for or against a relatively more important role of one pulsatile pressure wave as opposed to another in contributing to cardiovascular disease? Although a meta-analysis of several studies assessing the ability of cAIx to predict events demonstrated robust effects (Vlachopoulos et al 2010), subsequent studies published at a similar time failed to demonstrate similar effects beyond steady-state pressures (Mitchell et al 2010). However, as indicated in the aforementioned discussion, in the context of wave re-reflection, the effects of wave re-reflection (Phan et al 2016) and hence reflected waves (Booysen et al 2015) on aortic PP and end organs are likely to be markedly underestimated by cAIx. Thus, we turn to data on the role of Pf and Pb. In this regard, it is only in more recent years that several studies (Booysen et al 2015; Chirinos et al 2012; Cooper et al 2015; Kaess et al 2016; Sibiya at al 2015; Wang et al 2010; Weber et al 2012; Zamani et al 2014; Zamani et al 2015) have provided the data to show the effects of Pb relative to Pf on end organ measures and cardiovascular events beyond steady-state pressures.

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

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

As with end-organ measures, few large community-based or clinical studies have reported on the relative role of Pf and Pb as predictors of events beyond steady-state pressures and all confounders. In this regard, whilst the Framingham Heart Study reported that events were predicted by Pf, but not Pb (Cooper et al 2015), the MESA reported Pb and not Pf as a

predictor of events (Chirinos et al 2012; Zamani et al 2015). This is consistent with the differences noted between Framingham and MESA with respect to the relative impact of Pf and Pb on LVM (Booysen et al 2015; Kaess et al 2016; Sibiya at al 2015; Zamani et al 2014) and may be explained in the same way. That is, the lack of influence of wave reflection on events in the Framingham Heart Study may have simply been because the authors failed to take into account the role of wave re-reflection in determining Pf and hence PP. As highlighted in the aforementioned discussion the possibility also exists that in the Framingham Heart Study a better BP control overall than alternative studies may have been noted and hence fewer participants may have had increases in PP that are determined by Pb. Once again therefore, these contrasting results (Chirinos et al 2012; Cooper et al 2015; Zamani et al 2015) do not negate the importance of reflected waves, but rather emphasize the importance of accounting for wave re-reflection as a determinant of Pf, or the relatively greater role of reflected waves in the hypertensive as opposed to the normotensive BP range.

1.3.6 Importance of aortic stiffness beyond pulsatile loads

Meta-analyses (Ben-Shlomo et al 2014; Vlachopoulos et al 2010), which include an individual patient meta-analysis (Ben-Shlomo et al 2014) have showed that increases in carotid-femoral PWV (the current gold-standard index of aortic stiffness) predicted cardiovascular events independent of brachial BP. The relationship between PWV and cardiovascular events was noted across a number of different subgroups including in individuals of a younger age (Ben-Shlomo et al 2014). Therefore the measurement of aortic PWV is recommended by guidelines for the detection and management of hypertension to improve the prediction of cardiovascular risk (Mancia et al 2013; Williams et al 2018). The association between aortic PWV and cardiovascular events independent of brachial PP was originally thought to be partly due to brachial PP being a poor indicator of central aortic PP (as PP increases from the aorta to the periphery) as discussed above. However, as also highlighted in the aforementioned discussion several lines of evidence imply that cardiovascular events may not be predicted by aortic PP independent of brachial PP. Importantly, in the Framingham Heart Study, PWV but not aortic PP predicted cardiovascular events independent of brachial PP (Mitchell et al 2010). Hence, there is substantial data to indicate that aortic PWV can predict cardiovascular events independent of both brachial and aortic PP. However, whether aortic stiffness, as indexed by PWV, mediates effects beyond Pf or the peak pressure produced by the product of Zc and Q is presently unknown. Nevertheless, current evidence suggests that aortic stiffness mediates events beyond pulsatile loads. What are the mechanisms that may explain how aortic stiffness mediates events through an impact that is beyond pulsatile load?

Previously it was hypothesized that increases in large artery stiffness mediate atherosclerotic changes beyond pulsatile loads. This idea developed from a number of studies which suggested that there were effects on atherogenesis which occurred independent of pressure pulsatility. Indeed, when endothelial cells were plated into a conduit which was compliant as compared to a conduit which was stiff and then these two conduits were exposed to identical pulsatile loads, the function of the endothelial cells in the stiff conduit was worse

than the function of the endothelial cells in the compliant conduit (Peng et al 2003). In addition, endothelial cell adhesion molecules in the vascular wall are directly activated by collagen (which increases arterial stiffness); whereas endothelial function is enhanced by elastin (which improves aortic elasticity) (Gonzales-Santiago et al 2002; Orr et al 2009). Bearing in mind that the dysfunction of endothelial cells plays an important role in the pathology of atherosclerosis, the data discussed above (Gonzales-Santiago et al 2002; Orr et al 2009; Peng et al 2003) imply that atherosclerosis can be enhanced by arterial stiffness independent of pulsatile loads. As these data would suggest that atherosclerosis is more likely to occur in the vascular wall where there is increased stiffness, these data propose a means by which increases in aortic PWV may play a role in the formation of aortic aneurysms and related aortic dissection or aortic rupture. However, aortic PWV is an indicator of aortic stiffness and not stiffness in smaller arteries; hence these data cannot provide an explanation for either stroke or myocardial infarction, which are the consequence of atherosclerotic alterations in intra- or extracranial arteries or coronary arteries respectively.

More recently it has been suggested that enhanced aortic stiffness reduces the normal mismatch in impedance that is present in the aorta (low impedance) compared to the peripheral arterial beds (higher impedance). This reduction in impedance mismatch enhances the distribution of pulsatile energy from the aorta into the peripheral arterial beds (O'Rourke et al 2010; Smulyan et al 2016**).** Consequently, pulsatile flow will be increased in the miscrovasculature. This increase in pulsatile flow will damage the microvasculature particulary in low resistance organs such as the kidney and the brain. Evidence in support of this hypothesis are endothelial dysfunction in the microvasculature of the forearm, renal disease, white matter lesions and cognitive dysfunction, and dementia, (Cooper et al 2016; Hashimoto et al 2011; Mitchell et al 2011; Webb et al 2012; Woodard et al 2015). However, there is no evidence for stroke. Moreover, associations between aortic stiffness and coronary artery disease cannot be attributed to reductions in impedance mismatch, as coronary artery disease is a consequence of damage to major arteries and not due to damage to the microvasculature.

Alternatively, an enhanced proximal aortic stiffness may increase left ventricle loads independent of aortic PP or its component pressure waves through ventricular-vascular coupling. Such increases in left ventricular load would result in left ventricular hypertrophy and dysfunction (Bell et al 2015; Bello et al 2017; Ohyama et al 2016). Furthermore, as a consequence of left ventricular hypertrophy, an enhanced aortic stiffness may increase the chances of myocardial infarction independent of pulsatile pressure loads as left ventricular mass is a risk factor for myocardial infarction. The healthy aorta because of its elasticity has a high capacity to store energy during systole. This stored energy allows for recoil in diastole thus contributing to blood flow. In this regard, it is well known that as the aorta becomes stiffer its capacity for elastic recoil in diastole is reduced which would decrease the capacity of the aorta to augment systemic blood flow during diastole. It is therefore likely that an enhanced aortic

stiffness plays a role in decreased myocardial blood flow (coronary blood flow occurs mainly during diastole). Indeed, many studies have provided evidence to indicate that there is an association between enhanced aortic stiffness and dysfunction of the coronary microcirculation (Ikonomidis et al 2008; Watanabe et al 1993).

1.4 Central arterial haemodynamics in the normotensive blood pressure range

In view of the extensive evidence that several aspects of central arterial haemodynamics may account for adverse cardiovascular effects beyond BP measured in the periphery, an important question is whether some of the effects of normal or high-normal peripheral BP values on cardiovascular end organs can be explained by the adverse effects of these central arterial effects. If so, then the measurement of central arterial function may better risk stratify in normotensives who are at risk and hence who may benefit from antihypertensive therapy. In the present section I will review the evidence to support an adverse role of central as opposed to peripheral arterial pulsatile load as a cause of cardiovascular events in the individuals with normotensive peripheral BP values. In doing so, I will emphasize the evidence which is lacking to either support or refute this hypothesis that persuaded me to perform the work described in the present thesis.

1.4.1 Aortic blood pressure in the normal or high-normal BP range

The results of the recent SPRINT study (Wright et al 2015) underscore the importance of increases in systolic BP (the BP criteria for selection of participants) and hence PP as a cause of events in individuals with normotensive BP values. Thus, there is a strong possibility that pulsatile haemodynamic effects are more important than steady-state effects on cardiovascular end organs when peripheral BP is normal or high-normal. Importantly, substantial overlap in aortic systolic BP across the categories of optimal, normal, high-normal and hypertensive BP values has been shown (McEniery et al 2008). Those pre-hypertensives who have an aortic systolic BP within the BP range usually found in hypertensive individuals may have increased risk of cardiovascular events; whereas those pre-hypertensives with an aortic systolic BP within the BP range usually found in individuals with optimal BP values may be at a low risk of cardiovascular events. Furthermore, there may be different effects of antihypertensive treatment on aortic BP as compared to brachial BP (Agabiti-Rosei et al 2007). Hence, when using antihypertensive treatment to reduce brachial BP from hypertensive to high-normal or normal BP ranges, the decreases in brachial BP probably do not accurately reflect the impacts of the BP which probably accounts for cardiovascular end organ changes (i.e. aortic BP). Consequently, our group set out to assess whether aortic BP could enhance the identification of those with normal or high-normal BP values with end organ changes (Booysen et al 2013). What were the members of our group able to show and what are the implications of these findings?

In a large, randomly selected community-based sample, members of our group demonstrated that although 27% of the sample had a normal or high-normal BP, 45% of these individuals had central aortic BP values that were less than the upper 95% confidence interval of aortic BP values in healthy participants with optimal BP values (Booysen et al 2013). Second, members of our group demonstrated that normal and high-normal brachial BP categories did not identify those individuals with end organ changes; whereas individuals with either normal or high-normal brachial BP, but aortic BP values above “optimal” thresholds did have end organ changes (Booysen et al 2013). As discussed in that publication (Booysen et al 2013), and as indicated in hypertension guidelines (Mancia et al 2007), individuals with a brachial BP in the high-normal range who are at enough risk to necessitate the use of antihypertensive therapy may be recognized by the presence of end organ damage. Indeed, two prior studies had indicated that the addition of markers of subclinical end organ damage to traditional risk assessment considerably improved risk prediction (Sehestedt et al 2009; Sehestedt et al 2010). However, in the one study (Sehestedt et al 2010) the BP values in the individuals who had a cardiovascular event were high enough which would imply that at least one half of the participants had brachial BP in the hypertensive range, and in the other study (Sehestedt et al 2009), 42% of the participants were identified as having hypertension. Hence, conclusions regarding data in only those individuals with brachial BP in the normotensive range cannot be made from either of these studies (Sehestedt et al 2009; Sehestedt et al 2010). Furthermore, in these studies (Sehestedt et al 2009; Sehestedt et al 2010), the presence of end organ changes was inconsistent in that the identification of end organ changes using one measure, did not necessarily signify the presence of end organ changes using an alternative measure. This would imply that the benefits of end organ assessment could only be accrued if the damage in multiple end organs was assessed (Sehestedt et al 2009; Sehestedt et al 2010). However, the assessment of multiple end organs is impractical as it would incur substantial costs, it would require the services of trained technicians, and it would not necessarily detect BP-related as opposed alternative risk factor induced end organ changes. In comparison, measurements of aortic BP are simple, reproducible and reliable. Furthermore, the costs of aortic BP measurements are likely to be lower, and importantly aortic BP is more likely to indicate the effects of BP on end organs rather than the effects of alternative cardiovascular risk factors.

1.4.2 Can alternative aortic haemodynamic changes further refine risk prediction in the normotensive BP range?

Several important questions not addressed in the previous work performed by our group on the role of aortic BP in the normotensive BP range (Booysen et al 2013) had prior to the present thesis, not been addressed. The first question is whether pulsatile haemodynamic

effects are more important than steady-state effects in mediating cardiovascular damage in the normotensive BP range. In this regard, even though we had demonstrated that aortic systolic BP improved the ability to identify end organ changes independent of peripheral BP measurements (Booysen et al 2013), we had at this time not addressed the question of whether damage caused by haemodynamic loads in the normotensive peripheral BP range were attributed largely to steady-state or pulsatile pressure effects. The second question is whether alternative aortic haemodynamic assessments beyond just aortic systolic BP or PP either further refine or better identify the ability to detect the risk of a cardiovascular event in individuals with brachial BP in the normotensive range. As highlighted in the aforementioned discussion the role of aortic BP *per se* in the prediction of cardiovascular risk beyond brachial BP has been questioned. However, aortic PWV is now accepted as an index of risk prediction beyond both brachial and aortic BP. Furthermore, whilst still under investigation, there is a strong possibility that through aortic wave re-reflection, reflected waves may explain a considerable portion of the variation in aortic PP and end organ damage. Thus, one must consider the possibility that PWV and reflected wave function are strong determinants of cardiovascular damage in individuals with BP in the normotensive BP. Consequently, in the present thesis I explored several aspects of aortic function with a particular emphasis on their role in the normotensive BP range. What are the problems that I identified and what were the aims of the present thesis?

1.5 Problem statement

As highlighted in the aforementioned discussion, the strongest determinant of aortic dysfunction is age. As there are no data on age-related changes in aortic PWV and wave reflection throughout the adult lifespan in the normotensive BP range, in the present thesis I aimed to compare age-related alterations in several aortic functional changes in those individuals whose BP values were considered to be controlled and hence within the normotensive range. However, as discussed above, the contribution of forward and backward wave pressures to age-related increases in aortic PP have previously been confounded by the inclusion of participants who were receiving antihypertensive therapy. Thus, prior to comparing age-related differences in aortic function between normotensives and hypertensives, in the present thesis I first assessed the relative contribution of Pf and Pb to age-related increases in aortic PP in those participants of a community sample not receiving antihypertensive treatment. Importantly, following the “rule of halves” only half of all hypertensives in the community studied were receiving therapy. As I subsequently demonstrated that aortic PP is determined equally by both Pf and Pb, and that normotensives show considerable age-related changes in aortic dysfunction (including Pb and aortic PWV) even within BP ranges considered to be normotensive (controlled BP), I then evaluated the relative contribution of steady-state versus

aortic pulsatile haemodynamic changes including Pb and PWV to several end organ measures in those with peripheral BP values within normotensive BP ranges.

1.6 Aims

In the present thesis I therefore aimed to determine

1) the relative contribution of aortic forward and backward wave pressures to age-related increases in aortic pulse pressure in a community sample with a high prevalence of untreated hypertension. These data are described in chapter 2 and have been published in the *J Am Soc Hypertens* (Hodson et al 2017).
2) the extent to which brachial blood pressure control in the general population (systolic/diastolic BP<140/90 mm Hg) accounts for age-related aortic haemodynamic changes across the adult lifespan. These data are described in chapter 3 and have been published in the *Am J Hypertens* (Hodson et al 2016).
3) the extent to which the adverse effects of BP are mediated by pulsatile as compared to steady-state haemodynamic changes across the normotensive as compared to the hypertensive adult brachial BP range, and whether aortic rather than brachial pulsatile changes best index these effects. These data are described in chapter 4 and have been published in *J Hypertens* (Hodson et al 2017).

CHAPTER 2

Contribution of Backward and Forward Wave Pressures to Age-Related Increases in Aortic Pressure in a Community Sample Not Receiving Antihypertensive Therapy.

The data in this chapter have been published in

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Bryan Hodson, Gavin R Norton, Imraan Ballim, Pinhas Sareli, Angela J Woodiwiss.

Contribution of Backward and Forward Wave Pressures to Age-Related Increases in Aortic Pressure in a Community Sample Not Receiving Antihypertensive Therapy.

2.0 Abstract

Introduction: Reports on the contribution of aortic forward (Pf) and backward (Pb) wave pressures to age-related increases in aortic pulse pressure (PPc) have been confounded by the use of participants receiving antihypertensive therapy. We assessed the relative contribution of Pf and Pb to age-related increases in PPc.

Methods: Aortic PP was determined by radial applanation tonometry and SphygmoCor software using an assumed triangular wave for wave separation analysis, in 892 community participants not receiving antihypertensive therapy. We validated our results using aortic flow waves (echocardiography) for wave separation analysis in 254 of these participants.

Results: In multivariate regression models in those <50 years of age, adjustments for both Pb and a Pf-independent measure of reflected wave function (RM=Pb/Pf), but not Pf abolished the impact of age on PPc. However, in those older than 50 years of age, adjustments for Pf (β-coefficient: 0.25±0.06 vs 0.74±0.08 $p<0.0001$) and Pb (0.04±0.04 vs 0.74±0.08 $p<0.0001$), but not RM markedly decreased the relationship between age and PPc. On product of coefficient mediation analysis, whether assessed in men or in women, in those participants <50 years of age, independent of several confounders and mean arterial pressure (MAP), Pb ($p<0.005$), but not Pf contributed to age-related increases in PPc. In contrast, in those participants ≥50 years of age, independent of several confounders and MAP, Pb ($p<0.005$) and Pf ($p<0.01$) contributed to age-related increases in PPc, and Pb effects were markedly diminished by adjustments for Pf (0.26±0.002 vs 0.52±0.003 mm Hg per year, $p<0.0001$ for comparison).

Conclusion: Independent of the effects of antihypertensive therapy, aortic backward waves contribute to age-related increases in aortic PPc across the adult lifespan, but at an older age, this effect may be attributed in-part to the impact of forward on backward wave pressures.

Key words: Aortic pulse pressure, aortic forward waves, aortic backward waves.

2.1 Introduction

For several decades age-related increases in pulse pressure (PP) rather than steady-state pressures have been recognised as a critical determinant of cardiovascular risk in hypertension (Darné et al. 1989; Rudnichi et al. 1997; Madhavan et al. 1994; Mitchell et al. 1997; Celis et al. 2001). As aortic PP may often be considerably lower than peripheral PP and because of the proximity of the aorta to end-organs, aortic PP has on several occasions been suggested to be a better index of the adverse effects of PP. Indeed, aortic PP is more closely associated with end-organ measures than brachial PP (Roman et al. 2014; Kollias et al. 2016) and in some (Vlachopoulos et al. 2010; Williams et al. 2016), but not other (Mitchell et al 2010) studies aortic PP has been demonstrated to predict outcomes beyond brachial PP. Furthermore, more contemporary studies suggest that the aortic backward wave component of aortic PP, derived from wave separation analysis, is the main determinant of the impact of aortic PP on end-organ measures (Booysen et al. 2015; Sibiya et al. 2015; Zamani et al. 2015) and cardiovascular outcomes (Wang et al. 2010; Chirinos et al. 2012; Weber et al. 2012; Zamani et al. 2014). Although it is well recognised that age is an important determinant of either brachial or aortic PP, the factors that determine age-related increases in aortic PP have nevertheless been a matter of some debate.

Aortic PP is determined by both forward (Pf) and backward (Pb) pressure waves. Whilst ventricular ejection and aortic impedance largely determine Pf, Pb is governed by both the magnitude of Pf (Newton's 3rd Law of Motion) and several arterial changes that influence wave reflection from distal arterial sites. In this regard, reflected wave pressures identified from the extent to which aortic PP is augmented by reflected waves (augmentation pressure [Pa] or index [AIx]) was initially demonstrated in a select group of women, to contribute more than forward wave pressures to age-related increases in aortic PP (Cecelja et al. 2009) and this was supported by product of coefficient mediation analysis of data obtained in a large population based study (Namasivayam et al. 2009). However, these approaches (Pa and AIx) to assessing the relative impact of forward and backward wave pressures to aortic PP are confounded by marked underestimation of the peak of Pf and Pb. Subsequent work in the Framingham Heart Study employing wave separation analysis, which identifies actual Pf and Pb, demonstrated that Pf contributes far more than a Pf-independent index of wave reflection to age-related increases in aortic PP (Mitchel et al. 2010). Alternative studies assessing changes in Pf and Pb with age that have employed wave separation analysis have also shown a dominant age-related increase in Pf rather than Pb contributing to increases in aortic BP with age (Segers et al. 2007; Torjesen et al. 2014). However, one of these studies was conducted over a narrow age range (Segers et al 2007). In contrast, studies conducted in large community-based samples with a high prevalence of uncontrolled hypertension and over a wide age range show a marked age-related increase in Pb (Wang et al. 2010; Booysen et al 2015), at least equivalent to that of Pf

(Booysen et al. 2015) across the adult age range and in a clinical sample also employing wave separation analysis (Namasivayam et al. 2016), Pb only was noted to contribute in the young, whilst both Pf and Pb contributed equally in the elderly to age-related increases in aortic PP. As Pb is strongly determined by Pf, what is not clear in these studies (Namasivayam et al. 2016; Wang et al. 2010; Booysen et al 2015) is the extent to which the impact of Pb on PPc in the elderly was the result of an age-related increase in Pf. In addition to the lack of clarity on whether Pb effects on age-related increases in the PPc in the elderly are independent of Pf, in studies employing wave separation analysis to identify the major determinants of age-related increases in aortic PP (Mitchell et al. 2010; Torjesen et al. 2014; Namasivayam et al. 2016), a significant proportion of the study samples were participants receiving antihypertensive therapy, which is well recognised as decreasing several components of aortic PP (Agabiti-Rosei et al. 2007). Hence, in the present study sample we assessed, using wave separation analysis, the relative contribution of Pf and Pb to age-related increases in aortic PP in a community sample with a much lower prevalence of antihypertensive therapy use than these prior studies (Mitchell et al. 2010; Torjesen et al. 2014; Namasivayam et al. 2016). To exclude the confounding influence of antihypertensive therapy, we evaluated the relative contribution of Pf and Pb to age-related increases in aortic PP in only those not receiving therapy.

2.2 Methods

Study group. The present study was conducted according to the principles outlined in the Helsinki declaration. The Committee for Research on Human Subjects of the University of the Witwatersrand approved the protocol (approval number: M02-04-72 and renewed as M07-04-69, M12-04-108 and M17-04-01). Participants gave informed, written consent. The present study design has previously been described (Norton et al. 2008; Woodiwiss et al. 2009; Redelinghuys et al. 2010; Norton et al. 2012). Briefly 892 participants of 1173 randomly recruited participants (from the population census figures of 2001) of black African descent (Nguni and Sotho chiefdoms) from the South West Township (SOWETO) of Johannesburg, South Africa, with siblings older than 16 years of age who were not receiving antihypertensive therapy were evaluated. In a sub-study, 254 of 347 who had aortic velocity determined by echocardiography were not receiving antihypertensive therapy.

Clinical, demographic and anthropometric measurements. A questionnaire was administered to obtain demographic and clinical data (Norton et al. 2008; Woodiwiss et al. 2009; Redelinghuys et al. 2010; Norton et al. 2012). Height and weight were measured using standard approaches and participants were considered to be overweight if their body mass index (BMI) was ≥25 kg/m^2 and obese if their BMI was ≥30 kg/m^2. High quality brachial BP measurements were obtained in the seated position after 5 minutes of rest by a trained nurse-technician using a standard mercury sphygmomanometer according to guidelines (Woodiwiss

et al. 2009). The mean of 5 measurements obtained at least 30 seconds apart was taken as office BP. Hypertension was defined as a mean BP≥140/90 mm Hg. Laboratory blood tests of renal function, liver function, blood glucose, hematological parameters, and percentage glycated hemoglobin (HbA_{1c}) were performed. Diabetes mellitus (DM) or an abnormal blood glucose control was defined as the use of insulin or oral hypoglycemic agents or an HbA_{1c} value greater than 6.1%.

Pulse wave analysis. Central aortic hemodynamics were estimated using pulse wave and wave separation analysis as previously described (Booysen et al. 2015; Sibiya et al. 2015; Redelinghuys et al. 2010; Norton et al 2012). After participants had rested for 15 minutes in the supine position, arterial waveforms at the radial (dominant arm) pulse were recorded by applanation tonometry during an 8-second period using a high-fidelity SPC-301 micromanometer (Millar Instrument, Inc., Houston, Texas) interfaced with a computer employing SphygmoCor, version 9.0 software (AtCor Medical Pty. Ltd., West Ryde, New South Wales, Australia). The pulse wave was calibrated by manual measurement (auscultation) of brachial BP taken immediately before the recordings. The peripheral pressure waveform was converted into a central aortic waveform using a validated generalized transfer function incorporated in SphygmoCor software. Recordings where the systolic or diastolic variability of consecutive waveforms exceeded 5% or the amplitude of the pulse wave signal was less than 80 mV were discarded. Central aortic PP (PPc) was determined as the difference between aortic systolic BP (SBP) and diastolic BP (DBP). Mean arterial pressure (MAP) was derived from SphygmoCor software. Aortic Pf and backward wave pressure (Pb) were determined from wave separation analysis of the SphygmoCor-derived aortic waveform using a ‘triangular flow wave’ (also from SphygmoCor software) (Westerhof et al. 2006). To determine reflected wave effects independent of Pf, the reflected wave magnitude (RM=Pb/Pf) was determined. In 254 participants that were not receiving antihypertensive therapy we also separated the forward and backward waves using aortic flow waveforms derived from aortic velocity and diameter measurements obtained using echocardiography (five-chamber view). To perform wave separation analysis using an aortic velocity waveform, the leading (outer) edge or the most dense, or brightest, portion of the spectral image of the velocity waveform was outlined using graphics software and using aortic diameter measurements employed to construct a flow waveform. Characteristic impedance (Zc) was calculated in the time domain as change in pressure/change in flow from the foot of the pulse wave up until 95% of peak flow (Mitchell et al., 2010b). Using Zc values and the flow and pressure waveforms, wave separation analysis was performed based on the following formulae: Forward wave pressure=(PPc + QxZc)/2 and Backward wave pressure=(PPc – QxZc)/2 (Murgo et al., 1981; Westerhof et al., 2006), where Q is flow. Wave separation analysis was performed in the time domain based upon the consensus that wave separation analysis can be done in either the time or the frequency domain (Segers et al., 2017).

Data analysis. For database management and statistical analysis, SAS software, version 9.4 (SAS Institute Inc., Cary, NC) was employed. Multiple linear regression analysis was performed to determine the independent relations between aortic Pf or Pb (in the same regression models) and aortic PP or between age and aortic PP or Pb. To determine the yearly contribution of the forward and backward waves to aortic PP, multivariate adjusted product of coefficient mediation analysis was performed (Namasivayam et al 2009, 2016). In both regression analysis and in mediation analysis, adjustments were for MAP, age (regression analysis), sex (when evaluated in both sexes together), regular alcohol intake, regular tobacco intake, height, weight, heart rate and diabetes mellitus and/or an HbA_{1c}>6.1%, all of which were correlated with aortic PP on univariate analysis. As Pb may contribute more to aortic pressures in women than in men (Tade et al. 2017), analysis was conducted in men and women separately. In addition analysis was conducted in those <50 and ≥50 years of age. Although prior studies have employed 60 years of age as the threshold for age-specific analysis (Namasivayam et al 2009, 2016), in the present study, based on nonparametric smoothing (LOESS fit) to identify breakpoints (inflection points) in the age-Pf relationship, a threshold of 50 years of age was noted as that point when Pf begins to increase. Relationships were compared using z-statistics.

2.3 Results

Characteristics of the participants. The clinical and demographic characteristics of the participants and the aortic hemodynamic values are given in Table 2.1. The characteristics of the group in whom wave separation analysis was determined from aortic flow waves was similar to the remaining participants (Table 2.2). More women than men volunteered for the study. Women were more obese than men. Importantly, although treated hypertensives were not included in the analysis, of the remaining individuals, 27.6% were noted to be hypertensive. In both younger and older age groups, men had a higher brachial BP. In addition, in the older age group men had a higher Pb, Pf and aortic PP. However, in the younger age group, women had a higher RM. With adjustments for mean arterial pressure and additional confounders, women had a higher Pb in the younger age group and a higher RM in those both younger and older than 50 years of age (Table 2.3).

Age-related increases in aortic hemodynamic parameters. Across deciles of age, age was independently associated with increases in aortic PP, Pf and Pb (Figure 2.1). However, in both women and in men while these increases were noted to occur for Pb and aortic PP across the adult lifespan, Pf only began to increase from age 50 years (Figure 2.1, Tables 2.4 and 2.5). In those younger than 50 years of age, a relatively weak correlation between Pf and Pb was noted (r^2=0.34, p<0.0001). However in those over 50 years of age Pb showed a stronger correlation with Pf (r^2=0.61 p<0.0001). Hence, in those older than 50 years of age we explored

Table 2.1. Characteristics of study participants

	<50 years of age		≥50 years of age	
	Women	Men	Women	Men
Sample size	407	245	140	100
Age (years)	31.5±9.9	29.5±9.6†	60.2±8.4***	61.4±9.5**
Body mass index (kg/m^2)	28.9±7.4	23.5±4.6†††	34.2±7.9**	26.5±5.0**†††
Hypertensive n, (%)	61 (15.0)	58 (23.7)††	66 (47.1)**	61 (61)**†
DM or HbA1c>6.1% n, (%)	45 (11.1)	24 (9.8)	49 (35.5)**	29 (29)**
Regular alcohol n, (%)	65 (16.0)	89 (36.5)†††	12 (8.6)	38 (38)†††
Regular smoking n, (%)	26 (6.4)	88 (36.1)†††	7 (5.0)	32 (32)†††
Brachial SBP (mm Hg)	117±16	121±15††	135±24**	144±24**††
Brachial DBP (mm Hg)	79±11	82±12†††	86±12**	90±13**†
MAP (mm Hg)	93±13	96±12†	105±16**	109±16**†
Brachial PP (mm Hg)	38±10	38±10	49±16**	54±17**†
Heart rate (beats/min)	67.6±10.2	60.6±9.4†††	66.6±10.9	64.2±11.8*
Aortic SBP (mm Hg)	109±17	111±15	128±22*	136±23*†
Aortic PP (mm Hg)	29.1±9.0	27.8±8.4	40.9±13.6*	45.7±16.0*†
Aortic Pb (mm Hg)	13.9±5.2	13.2±4.8	20.3±7.1*	23.2±9.0*††
Aortic Pf (mm Hg)	20.9±5.6	21.5±5.2	25.0±8.8*	28.9±9.2*††
RM (%)	66.9±19.7	60.9±15.2††	83.3±21.3*	80.0±20.2*

Data are shown as mean±SD or proportions. DM, diabetes mellitus; HbA1c, glycated haemoglobin; SBP, systolic blood pressure; DBP, diastolic BP; MAP, mean arterial pressure; PP, pulse pressure; Pb backward wave pressure; Pf, forward wave pressure; RM, reflected wave magnitude (Pb/Pf). *p<0.01, **p<0.0001 vs <50 years of age within each gender. †p<0.05, ††p<0.005, †††p<0.0005 vs men within each age group.

Table 2.2. Characteristics of study participants with and without aortic forward and backward waves separated using actual aortic flow wave rather than an assumed aortic triangular flow wave.

	<50 years of age		≥50 years of age	
	With	Without	With	Without
Sample size	187	467	67	171
% Women	58	64	61	58
Age (years)	32.4±9.7	31.2±9.8	61.0±8.7*	61.0±9.3*
Body mass index (kg/m^2)	26.7±7.0	26.9±7.0	31.0±7.6*	31.1±7.9*
Hypertensive (%)	17	18	42*	58*
DM or HbA1c>6.1% (%)	8	11	23*	37*
Regular smoking (%)	22	17	19	15
Regular alcohol (%)	23	25	16	23
Brachial SBP (mm Hg)	117±15	120±18	132±25*	139±24*
Brachial DBP (mm Hg)	80±12	81±11	84±13*	88±12*
MAP (mm Hg)	93±13	95±13	107±17*	109±16*
Brachial PP (mm Hg)	37±9	39±13	47±16*	51±15*
Heart rate (beats/min)	64±10	65±11	64±10	66±12
Aortic SBP (mm Hg)	108±15	110±18	125±24*	133±23*
Aortic PP (mm Hg)	27±7	29±11	40±15*	43±14*
Pf and Pb separated using triangular flow wave				
Aortic Pb (mm Hg)	13.0±4.3	13.9±5.6	19.5±8.1*	21.9±7.5*
Aortic Pf (mm Hg)	20.7±4.9	21.6±7.3	25.2±9.2*	26.7±8.5*
RM	63.2±17.9	65.0±18.5	78.8±19.3*	82.8±21.4*
Pf and Pb separated using aortic flow wave				
Aortic Pb (mm Hg)	10.6±3.2		15.4±5.4*	
Aortic Pf (mm Hg)	20.8±4.8		26.6±9.3*	
RM	51.1±12.1		58.6±10.7*	

Data are shown as mean±SD or proportions. For abbreviations see Table 2.1. *p<0.0001 vs <50 years of age.

Table 2.3. Multivariate adjusted aortic pulsatile hemodynamic values.

	<50 years of age		≥50 years of age	
	Women	Men	Women	Men
Sample size	407	245	140	100
Aortic PP (mm Hg)	30.2±10.1†	27.7±11.7	43.5±9.8**	45.4±12.7**
Aortic Pb (mm Hg)	14.7±4.8†††	12.6±5.5	21.7±5.0**	22.6±6.5**
Aortic Pf (mm Hg)	21.3±7.4	21.8±8.5	26.8±7.0*†	29.9±9.1**
RM (%)	69.5±16.1†††	59.5±18.8	83.7±14.2**††	75.6±18.0**

Data are shown as multivariate adjusted mean±SD. Adjustors included age, mean arterial pressure, heart rate, body weight, body height, regular alcohol intake, regular smoking, and the presence of diabetes mellitus or an HbA1c>6.1%. *p<0.01, **p<0.0001 vs <50 years of age within each gender. †p<0.05, ††p<0.005, †††p<0.0001 vs men within each age group.

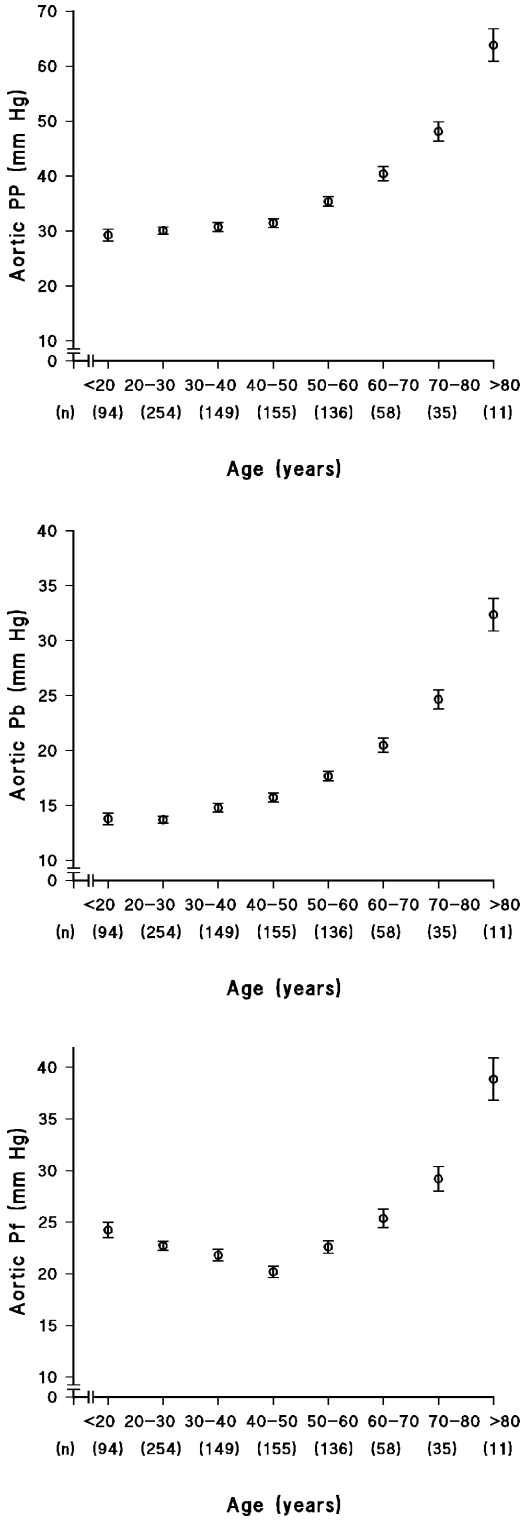

Figure 2.1. Multivariate adjusted age-related increases in aortic pulse pressure (PP) and aortic forward (Pf) and backward (Pb) wave pressures across the adult lifespan in participants from a community sample not receiving antihypertensive therapy. Adjustments are for variations in age, sex, mean arterial pressure, body weight, body height, pulse rate, regular smoking, regular alcohol intake, diabetes mellitus or an HbA_{1c}>6.1% within each 10 year period of age.

Table 2.4. Multivariate adjusted relationships between age and aortic pressures derived from wave separation analysis using a triangular aortic flow wave to separate the forward and backward waves.

	<50 years of age				≥50 years of age		
Adjustments	β-coeff±SEM	partial r (95% CI)	p value		β-coeff±SEM	partial r (95% CI)	p value
Age versus aortic	n=407			Women	n=140		
PP: *	0.09±0.04	0.10 (0.006 to 0.200)	<0.05		0.69±0.12	0.44 (0.284 to 0.562)	<0.0001
Pf: *	-0.15±0.03	-0.23 (-0.321 to -0.135)	<0.0001		0.37±0.08	0.38 (0.217 to 0.511)	<0.0001
Pb: *	0.08±0.02†	0.17 (0.076 to 0.266)	=0.0005		0.38±0.06	0.47 (0.322 to 0.590)	<0.0001
Pb: *+Pf	0.15±0.02‡	0.39 (0.303 to 0.470)‡	<0.0001		0.17±0.05‡†	0.30 (0.139 to 0.451)‡	<0.0005
Age versus aortic	n=245			Men	n=100		
PP: *	0.18±0.09	0.13 (0.004 to 0.254)	<0.05		0.80±0.12	0.58 (0.425 to 0.700)	<0.0001
Pf: *	-0.02±0.06	-0.02 (-0.145 to 0.109)	=0.78		0.41±0.08	0.50 (0.324 to 0.635)	<0.0001
Pb: *	0.12±0.04†	0.20 (0.074 to 0.319)†	<0.005		0.42±0.07	0.55 (0.383 to 0.673)	<0.0001
Pb: *+Pf	0.13±0.03	0.26 (0.140 to 0.377)	<0.0001		0.20±0.06‡†	0.32 (0.118 to 0.489)‡	<0.005

β-coeff, β-coefficient, See table 2.1 for additional abbreviations. *Adjustments are for variations in mean arterial pressure, body weight, body height, pulse rate, regular smoking, regular alcohol intake, diabetes mellitus or an HbA_{1c}>6.1%, and Pf as indicated. Probability values are further adjusted for the non-independence of family members. †p<0.05 versus age-Pf relationship, ‡p<0.05 as compared to age-Pb relationship before adjustments for Pf.

Table 2.5. Multivariate adjusted relationships between age and aortic pressures derived from wave separation analysis using an actual aortic flow wave to separate the forward and backward waves.

		<50 years of age			≥50 years of age		
Adjustments		β-coeff±SEM	partial r (95% CI)	p value	β-coeff±SEM	partial r (95% CI)	p value
Age versus aortic			n=108	Women		n=41	
PP:	*	0.07±0.08	0.09 (-0.114 to 0.276)	=0.40	0.57±0.19	0.48 (0.140 to 0.714)	<0.01
Pf:	*	-0.19±0.06	-0.32 (-0.485 to -0.131)	=0.001	0.36±0.17	0.38 (0.015 to 0.647)	<0.05
Pb:	*	0.09±0.04†	0.20 (0.004 to 0.381)	<0.05	0.25±0.09	0.45 (0.102 to 0.694)	<0.05
Pb:	*+Pf	0.19±0.03	0.50 (0.329 to 0.630)‡	<0.0001	0.09±0.07	0.27 (-0.115 to 0.574)	=0.16
Age versus aortic			n=79	Men		n=26	
PP:	*	0.18±0.09	0.23 (-0.006 to 0.444)	=0.05	0.74±0.20	0.66 (0.283 to 0.854)	<0.005
Pf:	*	0.01±0.07	0.02 (-0.222 to 0.251)	=0.90	0.45±0.15	0.59 (0.173 to 0.819)	<0.01
Pb:	*	0.16±0.05	0.35 (0.117 to 0.537)	<0.005	0.35±0.10	0.65 (0.259 to 0.847)	<0.005
Pb:	*+Pf	0.15±0.04	0.42 (0.204 to 0.600)	<0.0005	0.15±0.10	0.37 (-0.130 to 0.707)	=0.13

β-coeff, β-coefficient, See table 2.1 for additional abbreviations. *Adjustments are for variations in mean arterial pressure, body weight, body height, pulse rate, regular smoking, regular alcohol intake, diabetes mellitus or an HbA_{1c}>6.1% and Pf as indicated. Probability values are further adjusted for the non-independence of family members. †p<0.05 versus age-Pf relationship. ‡p<0.05 versus age-Pb relationship before adjustments for Pf.

whether age-related increases in Pb could in-part be attributed to the impact of Pf. In this regard, although the relationship between age and Pb was unchanged by further adjustments for Pf in those younger than 50 years of age, the age-Pb relationship was markedly decreased by further adjustments for Pf in those over 50 years of age (Tables 2.4 and 2.5). Importantly, before adjustments for Pf, the slope (β-coefficient) of the age-Pb relationship was similar to that of the age-Pf relationship (Tables 2.4 and 2.5). However, after adjustments for Pf the age-Pb relationship was less than that of the age-Pf relationship (Table 2.4).

Contribution of the aortic forward and backward waves to age-related increases in aortic PP as assessed from product of coefficient mediation analysis. Using multivariate adjusted product of coefficient analyses, Pb was noted to make a significant contribution in both men and women to age-related increases in aortic PP both before and after 50 years of age (Figure 2.2). However, in both women and men Pf made a significant contribution to age-related increases in aortic PP after 50 years of age, whilst before this age, Pf failed to significantly contribute to age-related increases in aortic PP (Figure 2.2). Nevertheless, although the contribution of Pb to age-related increases in aortic PP was unchanged by further adjustments for Pf in those younger than 50 years of age, the contribution of Pb to age-related increases in aortic PP was markedly diminished by further adjustments for Pf in those older than 50 years of age (Figure 2.2). Indeed, the residual effect of Pb on age-related increases in aortic PP after adjustments for Pf in those older than 50 years of age was markedly lower than the impact of Pf (Figure 2.2).

Contribution of the aortic forward and backward waves to age-related increases in aortic PP as assessed from multivariate regression analysis. In multivariate adjusted regression analysis, independent relations between age and aortic PP in those less than 50 years of age were abolished by adjustments for Pb and RM (Pf-independent index of wave reflection), but not Pf (Figure 2.3, Tables 2.6 and 2.7). In contrast, in multivariate adjusted regression analysis independent relations between age and aortic PP in those older than 50 years of age although abolished by adjustments for Pb, were also markedly attenuated by adjustments for Pf and adjustments for RM failed to attenuate age-PP relations (Figure 2.3, Tables 2.6 and 2.7).

Figure 2.2. Multivariate adjusted contribution (product of coefficient mediation analysis) of aortic forward (Pf, cross-hatched bars) and backward (Pb, open bars) wave pressures to age-related increases in aortic pulse pressure (PP) in women and men younger or older than 50 years of age. Upper panels show results from “triangular aortic flow”-derived wave separation analysis and the lower panels from actual aortic flow-derived wave separation analysis. Adjustments are for variations in mean arterial pressure, body weight, body height, pulse rate, regular smoking, regular alcohol intake, and diabetes mellitus or an HbA_{1c}>6.1% and for Pf when assessing Pb effects (hatched bars). *p<0.0001 versus before adjustments for Pf, †p<0.0001 versus <50 years of age, ‡p<0.0001 versus Pf effects.

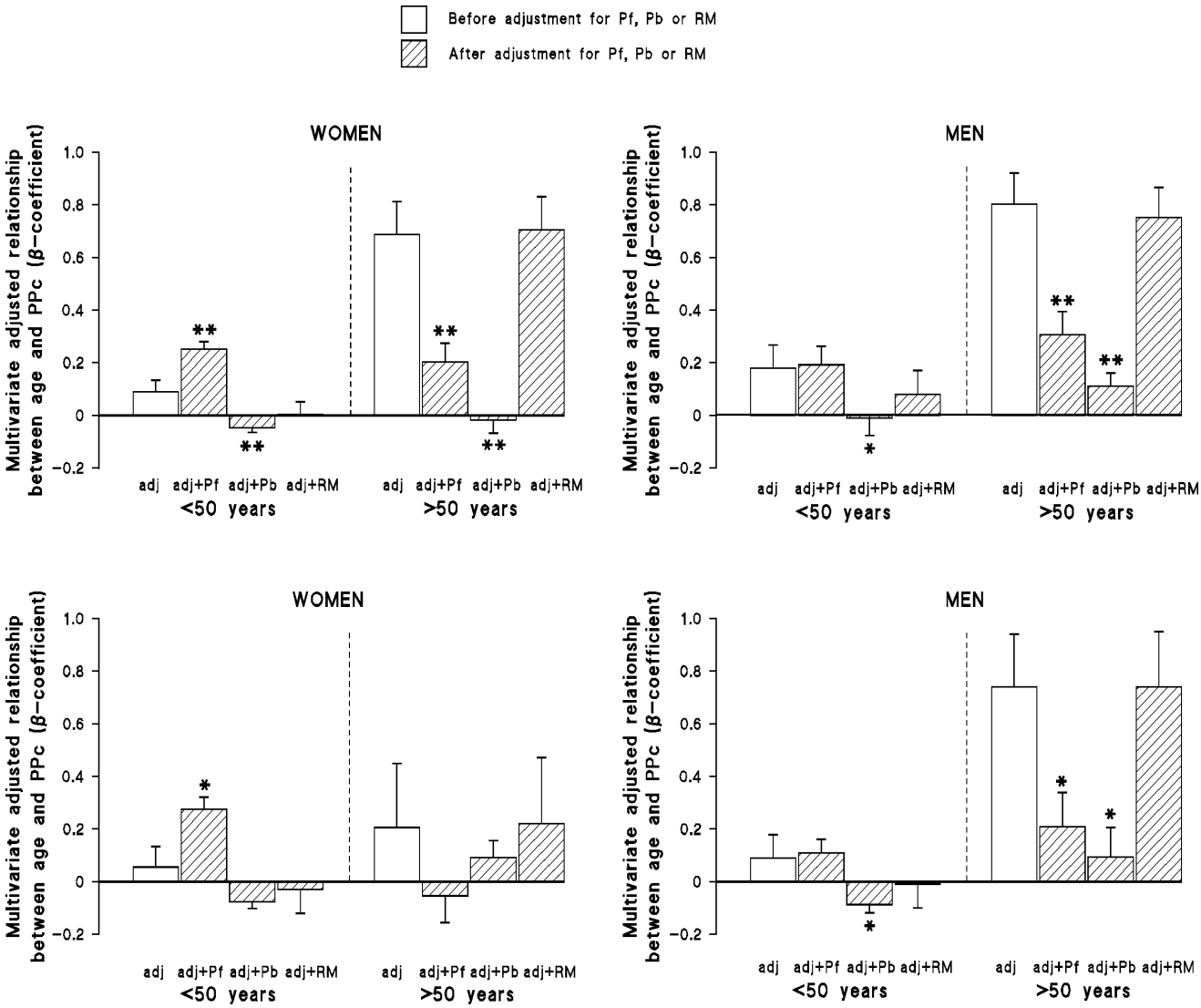

Figure 2.3. Impact of adjustments for aortic forward (Pf) or backward (Pb) wave pressures or a Pf-independent index of backward wave pressure (RM=Pb/Pf) on the slope (β-coefficient) of the multivariate adjusted age relations with aortic pulse pressure (PP) in women and men younger or older than 50 years of age. Upper panels show results from "triangular aortic flow"-derived wave separation analysis and the lower panels from actual aortic flow-derived wave separation analysis. Adjustments (adj) are for variations in mean arterial pressure, body weight, body height, pulse rate, regular smoking, regular alcohol intake, and diabetes mellitus or an HbA_{1c}>6.1% and Pf, Pb or RM in separate models as indicated. *p<0.05, **p<0.005 versus before adjustments for Pf, Pb or RM. See Figure 2.2 for sample sizes.

Table 2.6. Impact of adjustments for aortic forward (Pf) or backward (Pb) wave pressures on the strength (partial r) of the multivariate adjusted age relations with aortic pulse pressure (PP) in women.

	<50 years of age		≥50 years of age	
Adjustments	partial r (95% CI)	p value	partial r (95% CI)	p value
"Triangular flow wave"				
Age versus aortic PP	n=407		n=140	
*	0.10 (0.006 to 0.200)	<0.05	0.44 (0.284 to 0.562)	<0.0001
* + Pb	-0.13 (-0.229 to -0.037)†	<0.01	-0.03 (-0.201 to 0.140)†	=0.72
* + Pf	0.42 (0.340 to 0.501)	<0.0001	0.24 (0.068 to 0.391)†	<0.01
* + RM	0.0004 (-0.098 to 0.099)	=0.99	0.44 (0.291 to 0.568)	<0.0001
"Actual flow wave"				
Age versus aortic PP	n=108		n=41	
*	0.09 (-0.114 to 0.276)	=0.40	0.48 (0.140 to 0.714)	<0.01
* + Pb	-0.32 (-0.482 to -0.125)†	=0.001	0.19 (-0.193 to 0.517)	=0.32
* + Pf	0.55 (0.395 to 0.674)	<0.0001	0.38 (0.007 to 0.650)	<0.05
* + RM	-0.02 (-0.217 to 0.177)	=0.84	0.51 (0.169 to 0.735)	=0.005

See table 2.1 for abbreviations. *Adjustments are for variations in mean arterial pressure, body weight, body height, pulse rate, regular smoking, regular alcohol intake, and diabetes mellitus or an HbA_{1c}>6.1%. Probability values are further adjusted for the non-independence of family members. †p<0.05 as compared to age-PPc relationship before adjustments for Pb or Pf.

Table 2.7. Impact of adjustments for aortic forward (Pf) or backward (Pb) wave pressures on the strength (partial r) of the multivariate adjusted age relations with aortic pulse pressure (PP) in men.

	<50 years of age		≥50 years of age	
Adjustments	partial r (95% CI)	p value	partial r (95% CI)	p value
"Triangular flow wave"				
Age versus aortic PP	n=245		n=100	
*	0.13 (0.004 to 0.254)	<0.05	0.58 (0.425 to 0.700)	<0.0001
* + Pb	-0.01 (-0.138 to 0.117)†	=0.87	0.24 (0.033 to 0.421)†	<0.05
* + Pf	0.16 (0.034 to 0.282)	<0.05	0.35 (0.152 to 0.515)†	<0.001
* + RM	0.06 (-0.070 to 0.184)	=0.38	0.57 (0.406 to 0.689)	<0.0001
"Actual flow wave"				
Age versus aortic PP	n=79		n=26	
*	0.23 (-0.006 to 0.444)	=0.05	0.66 (0.283 to 0.854)	<0.005
* + Pb	-0.26 (-0.471 to -0.026)†	<0.05	0.20 (-0.299 to 0.607)†	=0.42
* + Pf	0.36 (0.133 to 0.551)	<0.005	0.37 (-0.123 to 0.711)	=0.13
* + RM	0.10 (-0.140 to 0.332)	=0.41	0.66 (0.267 to 0.858)	<0.005

See table 2.1 for abbreviations. *Adjustments are for variations in mean arterial pressure, body weight, body height, pulse rate, regular smoking, regular alcohol intake, and diabetes mellitus or an HbA_{1c}>6.1%. Probability values are further adjusted for the non-independence of family members. †p<0.05 as compared to age-PPc relationship before adjustments for Pb or Pf.

2.4 Discussion

The main findings of the present study are as follows: In a community sample with a high prevalence of hypertension, but in which only half of the hypertensives were receiving treatment, in all participants not receiving treatment we noted that although aortic backward wave pressures (Pb) contributed to age-related increases in aortic PP across the adult lifespan, aortic forward wave pressures (Pf) only contributed in those over 50 years of age. However, because Pb was strongly correlated with Pf in those over 50 years of age, we further explored whether in this age group, a significant proportion of Pb effects on age-related increases in aortic PP could be accounted for by the impact of Pf. Indeed, in product of coefficient mediation analysis, we noted that the contribution of Pb to age-related increases in aortic PP in this age category was markedly attenuated by adjustments for Pf. Moreover, consistent with Pf effects explaining a significant proportion of Pb effects on age-related increases in aortic PP, relations between age and aortic PP in those older than 50 years of age were markedly attenuated by adjustments for Pf. As age-related increases in aortic PP were quantitatively far greater in those over as compared to under 50 years of age, these data suggest a relatively more important role of Pf as compared to Pb in accounting for age-related increases in aortic PP.

Although several prior studies have evaluated the relative contribution of aortic forward and reflected waves to age-related increases in aortic PP (Segers et al., 2007; Cecelja et al. 2009; Namasivayam et al. 2009; Mitchell et al 2010; Torjesen et al. 2014; Namasivayam et al. 2016), these studies have produced conflicting results. In this regard, several of these studies showed a more important contribution of aortic reflected as opposed to forward waves to age-related increases in aortic PP (Cecelja et al. 2009; Namasivayam et al. 2009; Namasivayam et al. 2016), whilst the Framingham Heart Study (Mitchell et al 1010) and alternative studies (Segers et al 2007; Torjesen et al. 2014) showed a substantially greater contribution of the forward as compared to the backward wave to age-related increases in aortic PP. There are several possible differences between studies that could explain these discrepancies. Two studies employed aortic augmented pressures as an index of reflected wave pressures and the pressure at the point of wave inflection as the height of the forward wave (Cecelja et al. 2009; Namasivayam et al. 2009), an approach which underestimates the peak of both the forward and backward wave pressures. In contrast, the Framingham Heart Study (Mitchell et a; 2010) and alternative studies (Segers et al 2007; Torjesen et al. 2014) performed wave separation analysis which provides an accurate assessment of peak forward and backward wave pressures. Nevertheless, one study only assssed age-related changes over a narrow adult age range (Segers et al 2007) and in the Framingham Heart Study (Mitchell et al 2010), 44% of those over 60 years of age were receiving antihypertensive therapy and antihypertensive therapy produces marked effects on either forward or reflected waves (Agabiti-Rosei et al. 2007). Moreover, in other studies (Torjesen et al. 2014) the proportion of hypertensives

receiving antihypertensive therapy and controlled to target levels is uncertain. Although in a subsequent study (Namasivayam et al 2016), using wave separation analysis in a clinical cohort attending a cardiology clinic, the authors showed a greater contribution of Pb to age-related increases in aortic PP than Pf, although not specified, it is likely that a similarly high proportion of participants were receiving antihypertensive therapy. Although it may be argued that antihypertensive therapy could reduce aortic forward and backward wave pressures to a similar degree (Manisty et al. 2012), the incorporation of those on therapy is likely to markedly diminish the contribution of aortic forward wave to backward wave pressure effects on age-related increases in aortic PP, a possibility not explored in this prior study (Namasivayam et al. 2016). Moreover, in that study (Namasivayam et al. 2016) wave separation analysis was only performed using an assumed "triangular" shaped flow wave and there is some question as to the reliability of this approach (Kips et al. 2009). Hence, the relative contribution of Pb versus Pf to age-related increases in aortic PP is uncertain. In contrast to prior studies (Segers et al 2007; Cecelja et al. 2009; Namasivayam et al. 2009; Mitchell et al. 2010; Torjesen et al. 2014; Namasivayam et al. 2016), the present study was not confounded by the impact of antihypertensive therapy on either Pf or Pb, and although wave separation analysis was performed using a "triangular" flow wave, the results were confirmed in a cohort in whom aortic flow was employed to separate the forward and backward waves. Using this approach, our data agree with those studies (Cecelja et al. 2009; Namasivayam et al. 2009; Namasivayam et al. 2016) that suggest that the backward wave contributes to age-related increases in aortic PP across the adult lifespan, whilst the forward wave only contributes in the elderly. The consistency of these findings across these prior (Cecelja et al. 2009; Namasivayam et al. 2009; Namasivayam et al. 2016) and the present study highlights the robust nature of these results. However, our results also agree with the Framingham Heart Study (Mitchell et al. 2010) in that the impact of the backward wave on aortic PP in the elderly may be attributed to a large extent to effects of forward on backward wave pressures. As age-related increases in aortic PP were quantitatively far greater in those over as compared to under 50 years of age, as noted in the Framingham Heart Study (Mitchell et al. 2010), the impact of Pf is likely to account for more of the age-related increase in aortic PP than Pb.

It is well recognised that independent of MAP, the main factor that determines Pb is Pf (Newton's 3rd Law of Motion). Hence it is also assumed that if Pb increases in parallel with Pf, that the change in Pb is likely to be attributed to alterations in Pf (Nichols et al. 2011). To identify Pb effects that are independent of Pf, reflected wave function is expressed as the reflection magnitude (RM=Pb/Pf) or the reflection index (Nichols et al. 2011). Alternatively, Pb effects can be adjusted for Pf effects. In this regard, in the Framingham Heart Study (Mitchell et al. 2010), the less important contribution of reflected as compared to forward waves to age-related increases in aortic PP was identified using the reflection index as a Pf-independent marker of the impact of reflected wave function on aortic PP. In contrast, in the present study

we employed both RM as a Pf-independent index of reflected wave effects in simple regression analysis as well as adjusting for Pf effects on Pb in product of coefficient mediation analysis, with both approaches demonstrating a less important contribution of reflected as compared to forward waves to age-related increases in aortic PP in those over 50 years of age.

In the present study, whilst Pb increased linearly across the adult lifespan, based on nonparametric smoothing to identify breakpoints (inflection points) in the age-Pf relationship, Pf began to increase at around 50 years of age. Hence, we assessed the contribution of Pf and Pb to age-related increases in aortic PP in those younger or older than 50 years of age. This is in contrast to several studies which employed 60 years of age as the breakpoint for analysis (Namasivayam et al. 2009; Namasivayam et al. 2016). Despite employing different age thresholds for analysis, in the present as compared to previous studies (Namasivayam et al. 2009; Namasivayam et al. 2016) all of these studies provided essentially the same results where the backward wave was noted to contribute to age-related increases in aortic PP across the adult lifespan, whilst the forward wave only contributed in the elderly. However, not examined in these prior studies (Namasivayam et al. 2009; Namasivayam et al. 2016) was the extent to which backward wave pressure effects may be accounted for by the impact of forward on backward wave pressures. In this regard the present study provides clear evidence that the impact of aortic backward wave pressures on age-related increases in aortic PP is highly dependent on the effect of the forward wave (in those over 50 years of age where most age-related increases in aortic PP occurred). Indeed, in those over 50 years of age, although both forward and backward wave pressures contributed to age-related increases in aortic PP, adjustments for Pf markedly attenuated the contribution of Pb to age-related increases in aortic PP.

It is important that the present results are interpreted with caution. Even if age-related increases in aortic PP are accounted for largely by increases in forward wave pressures, this does not imply that therapy should target forward as opposed to backward wave pressures. In this regard a clear distinction needs to be made between the contribution of Pf and Pb to age-related increases in aortic PP, or to simply variations in aortic PP (independent of age). Indeed, there are several studies that have demonstrated that the contribution of the backward wave to variations in aortic PP is far greater than forward waves in both the young and the elderly (Booysen et al 2015; Namasivayam et al. 2016). This information, together with data that show that the contribution of aortic backward wave pressures to variations in end-organ changes (Booysen et al. 2015; Sibiya et al. 2015) and to cardiovascular outcomes (Zamani et al 2015), are greater than the forward wave, emphasises the need to target the aortic backward wave across the adult lifespan, whilst targeting the forward wave may only be of benefit to the elderly.

There are several limitations to the present study which require consideration. First, as with all studies that have investigated the determinants of age-related changes in PP, the present study is cross-sectional in design, and hence a prospective observational study is

required to determine whether age effects on aortic hemodynamics are indeed cause and effect. Second, the exclusion of hypertensives receiving antihypertensive therapy may have influenced the conclusions to the present study. However, obtaining an untreated community or population-based sample is unlikely to be possible and in the present study we included almost a half of all hypertensives, participants whose hypertension was undiagnosed at the time. Third, although we adjusted relations for several potential confounders, whether aging effects of Pf or Pb on PPc in-part represent residual confounding is unknown.

2.5 Conclusions

In the present study conducted in a community sample of participants not receiving antihypertensive therapy, although backward waves contribute to age-related increases in aortic PPc across the adult lifespan, at an older age, this effect may be attributed in-part to the impact of forward on backward wave pressures. These findings lend further insights into possible aortic BP targets at different ages at a community level.

CHAPTER 3

Brachial Pressure Control Fails to Account for Most Distending Pressure-Independent, Age-Related Aortic Hemodynamic Changes in Adults.

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Bryan Hodson, Gavin R Norton, Hendrik L Booysen, Moekanyi J Sibiya, Andrew Raymond, Muzi J Maseko, Olebogeng HI Majane, Elena Libhaber, Pinhas Sareli, Angela J Woodiwiss.

Brachial Pressure Control Fails to Account for Most Distending Pressure-Independent, Age-Related Aortic Hemodynamic Changes in Adults.

3.0 Abstract

Introduction: Although several characteristics of aortic function, which are largely determined by age, predict outcomes beyond brachial blood pressure (BP), the extent to which brachial BP control accounts for age-related variations in aortic function is uncertain. We aimed to determine the extent to which brachial blood pressure (BP) control in the general population (systolic/diastolic BP<140/90 mm Hg) accounts for age-related aortic hemodynamic changes across the adult lifespan.

Methods: Central aortic pulse pressure (PPc), backward wave pressure (Pb), pulse wave velocity (PWV) and PP amplification (PPamp) (applanation tonometry and SphygmoCor software) were determined in 1185 participants from a community sample (age>16 years)(36.4% uncontrolled BP).

Results: With adjustments for distending pressure (mean arterial pressure, MAP), no increases in PPc, Pb, or PWV and decreases in PPamp were noted in those with an uncontrolled brachial BP younger than 50 years of age. In those older than 50 years of age with an uncontrolled brachial BP, MAP-adjusted aortic hemodynamic variables were only modestly different to those with a controlled brachial BP (PPc, 46±14 vs 42±15 mm Hg, $p<0.02$, Pb, 23±8 vs 21±8 mm Hg, PWV, 8.42±3.21 vs 8.19±3.37 m/sec, PPamp, 1.21±0.17 vs 1.21±0.14). Nonetheless, with adjustments for MAP, marked age-related increases in PPc, Pb and PWV and decreases in PPamp were noted in those with uncontrolled and controlled brachial BP across the adult lifespan ($p<0.0001$).

Conclusion: Brachial BP control in the general population fails to account for most distending pressure-independent, age-related changes in aortic hemodynamics across the adult lifespan.

Key words: Central blood pressure, aortic pulse pressure, reflected waves, age.

3.1 Introduction

Systolic (SBP) is superior to diastolic blood pressure in cardiovascular risk prediction (Nichols et al. 2011a). Aortic SBP may be markedly lower than brachial SBP (Avolio et al. 2009) and several characteristics of aortic BP have been demonstrated to be more closely or independently associated with end-organ measures and cardiovascular outcomes beyond brachial BP (Roman et al. 2014; Vlachopoulos et al. 2010; Wang et al. 2009; Wang et al. 2010; Chirinos et al. 2012; Weber et al. 2012; Vlachopoulos et al. 2010; Ben-Shlomo et al. 2014; Benetos et al. 2010; Regnault et al. 2012; Benetos et al. 2012). In this regard, central aortic pulse pressure (PPc) (Vlachopoulos et al. 2010; Wang et al. 2009), backward (reflected) wave pressures (Pb) or index (RI) (Wang et al. 2010; Chirinos et al. 2012; Weber et al. 2012), pulse wave velocity (PWV) (Vlachopoulos et al. 2010; Ben-Shlomo et al. 2014) and aortic-to-brachial PP amplification (PPamp) (Benetos et al. 2010; Regnault et al. 2012; Benetos et al. 2012) have all been demonstrated to predict cardiovascular outcomes beyond brachial BP. Moreover, aortic BP adds to the ability of brachial BP to predict treatment-induced improvements in end-organ measures (Shimizu et al. 2014).

Although age is the most important determinant of aortic function (Nichols et al 2011b), it is also well-recognised that antihypertensive therapy modifies several aspects of age-related aortic changes including increases in PPc, reflected waves and decreases in PPamp (Agabiti-Rosei et al. 2007). Hence, it is possible that achieving brachial BP control may be sufficient to counter many of the adverse effects of age on risk-related aortic functional changes. However, the extent to which brachial BP control accounts for age-related changes in PPc, Pb, RI, PWV and PPamp is uncertain. In the present study we therefore evaluated the extent to which brachial BP control accounts for age-related aortic hemodynamic changes across the adult lifespan in a community sample of African ancestry with a high prevalence of uncontrolled hypertension.

3.2 Methods

Study group. The present study was conducted according to the principles outlined in the Helsinki declaration. The Committee for Research on Human Subjects of the University of the Witwatersrand approved the protocol (approval number: M02-04-72 and renewed as M07-04-69 and M12-04-108). Participants gave informed, written consent. The present study design has previously been described (Redelinghuys et al. 2010; Norton et al. 2012; Booysen et al. 2015). Briefly, 1185 of 1194 participants from families of black African descent (Nguni and Sotho chiefdoms) with siblings older than 16 years with central hemodynamic measurements were randomly recruited from the South West Township (SOWETO) of Johannesburg, South Africa (SOWETO Hypertension Study).

Clinical, demographic and anthropometric measurements. A standardized questionnaire was administered to obtain demographic and clinical data (Redelinghuys et al. 2010; Norton et al. 2012; Booysen et al. 2015). Height and weight were measured using standard approaches and participants were identified as being overweight if their body mass index (BMI) was ≥25 kg/m^2 and obese if their BMI was ≥30 kg/m^2. Standard laboratory blood tests of renal function, liver function, blood glucose, hematological parameters, and percentage glycated hemoglobin (HbA_{1C}) were performed. Diabetes mellitus (DM) or an abnormal blood glucose control was defined as the use of insulin or oral hypoglycemic agents or an HbA_{1C} value greater than 6.1%.

Brachial BP. High quality brachial BP measurements were obtained as previously described (Redelinghuys et al. 2010; Norton et al. 2012; Booysen et al. 2015) after 10 minutes of rest in the seated position by a trained nurse using a mercury sphygmomanometer and an appropriate sized cuff according to the European Society of Hypertension guidelines (O'Brien et al. 2003). Korotkov phases I and V were employed to identify SBP and DBP respectively and care was taken to avoid auscultatory gaps. Five consecutive BP readings were obtained 30 to 60 seconds apart. The average of the five readings was taken as the BP. Only 0.84% of visits had fewer than the planned BP recordings. The frequency of identical consecutive recordings was 0.26% for systolic BP (SBP) and 1.21% for diastolic BP (DBP). No BP values were recorded as an odd number. Hypertension was defined as a mean SBP≥140 or DBP≥90 mm Hg, or both, or the use of antihypertensive medication. Uncontrolled BP was defined as an SBP≥140 mm Hg or a DBP≥90 mm Hg, irrespective of the presence of antihypertensive therapy.

Pulse wave analysis. Central aortic systolic BP (SBPc), pulse pressure (PPc), aortic forward wave pressures (Pf), Pb and RI were estimated from applanation tonometry determined at the radial artery and SphygmoCor software as previously described (Redelinghuys et al. 2010; Norton et al. 2012; Booysen et al. 2015). Briefly, after participants had rested for 15 minutes in the supine position, arterial waveforms at the radial (dominant arm) pulse were recorded by applanation tonometry during an 8-second period using a high-fidelity SPC-301 micromanometer (Millar Instrument, Inc., Houston, Texas) interfaced with a computer employing SphygmoCor, version 9.0 software (AtCor Medical Pty. Ltd., West Ryde, New South Wales, Australia) (Redelinghuys et al. 2010; Norton et al. 2012; Booysen et al. 2015). The radial pulse wave was calibrated by manual measurement (auscultation) of brachial BP taken immediately before the recordings. The radial pressure waveform was converted into a central aortic waveform using a validated generalized transfer function incorporated in SphygmoCor software. Recordings where the systolic or diastolic variability of consecutive waveforms exceeded 5% or the amplitude of the pulse wave signal was less than 80 mV were discarded. PPc was determined as the difference between SBPc and diastolic BP (DBP). Mean arterial pressure (MAP) was obtained from SphygmoCor software and was derived from the area under the radial pulse wave calibrated to brachial BP. Pb and Pf were determined using

SphygmoCor software which separates the aortic waveform using a triangular flow wave (Westerhof et al. 2006). The reflected wave index (RI) was calculated as Pb/Pf x 100.

Aortic PWV was determined from sequential waveform measurements at carotid and femoral sites and SphygmoCor software. The time delay in the pulse waves between the carotid and femoral sites was determined using an electrocardiograph-derived R wave as a fiducial point. Pulse transit time was taken as the average of 10 consecutive beats. The distance which the pulse wave travels was determined as the difference between the distance from the femoral sampling site to the suprasternal notch, and the distance from the carotid sampling site to the suprasternal notch. Aortic PWV was calculated as the ratio of the distance to the transit time (m/sec).

Data analysis. For database management and statistical analysis, SAS software, version 9.3 (SAS Institute Inc., Cary, NC) was employed. To exclude the impact of distending pressures on relationships between uncontrolled BP and aortic hemodynamics, adjustments for MAP were performed. 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 PWV occurred between 40 and 50 years of age, relationships between an uncontrolled BP and hemodynamic variables were evaluated in participants < or ≥50 years of age.

3.3 Results

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 an uncontrolled BP. The proportion of participants older than 50 years with an uncontrolled BP was greater than the proportion less than 50 years of age (Table 3.1).

Of those receiving antihypertensive therapy, 61.0% were receiving hydrochlorothiazide monotherapy, 4.5% long acting calcium channel blocker (CCB) monotherapy, 2.1% angiotensin-converting enzyme inhibitor (ACEI) monotherapy and 1.4% monotherapy with other antihypertensive agents (0.35% β-blockers). 6.3% of participants were receiving diuretic/CCB, 9.1% diuretic/ACEI and 6.6% diuretic combinations with other antihypertensive agents (dual therapy). 9.1% of participants were receiving more than 2 agents.

Table 3.1. Characteristics of the study sample.

Characteristics	All (n=1185)	<50 years (n=703)	≥50 years (n=482)
% Female	65.1	64.6	65.9
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	58.6
Regular tobacco (% subjects)	15.2	17.1	12.5
Regular alcohol (% subjects)	20.9	23.6	17.1
% with DM or HbA_{1C}>6.1%	25.8	12.4	45.5
% Hypertensive*	45.9	24.0	77.7
% Treated for hypertension	24.2	6.3	50.3
% Hypertensives controlled to target BP	20.6	13.0	24.0
% of all with uncontrolled BP	36.4	20.9	59.1
Pulse rate (beats/min)	69±10	70±11	69±10
Brachial SBP (mm Hg)	130±22	121±17	143±23
Brachial DBP (mm Hg)	84±13	81±12	88±12
Brachial pulse pressure (mm Hg)	46±16	39±10	55±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
Reflected wave index (RI) (%)	72±22	66±19	81±22
Pulse pressure amplification (PPamp)	1.30±0.18	1.35±0.18	1.21±0.13
Aortic pulse wave velocity (m/sec)	6.42±2.67	5.16±1.31	8.33±3.04

Data expressed as mean ± SD or proportions. DM, diabetes mellitus; HbA_{1C}, glycosylated haemoglobin; BP, blood pressure; SBP, systolic BP; DBP, diastolic BP. *Hypertension defined as a mean SBP≥140 or DBP≥90 mm Hg, or both, or the use of antihypertensive medication. Sample size for PWV=1030 for all participants, 621 for participants <50 years of age and 409 for participants ≥50 years of age.

Brachial BP in those with an uncontrolled versus controlled BP across the adult lifespan. Brachial SBP, DBP and MAP were higher in those with an uncontrolled as compared to those with a controlled brachial BP across the adult lifespan (Figure 3.1).

Aortic pressures in those with an uncontrolled versus controlled BP across the adult lifespan. Without adjustments, aortic PPc, Pb, and Pf were higher (Figure 3.2, left panels, Table 3.2) and PPamp was lower (Table 3.2) in those with an uncontrolled versus controlled BP across much of the adult lifespan. Aortic Pf and Pb were increased to a similar extent in those with an uncontrolled as compared to those with a controlled BP (Figure 3.2, left panels, Table 3.2). However, after adjustments for MAP, only residual increases in PPc, Pf and Pb were noted in those with an uncontrolled versus controlled BP and these differences occurred only in those over 50 years of age (Figure 3.2, right panels, Table 3.2).

Aortic reflected wave index and PWV in those with an uncontrolled versus controlled BP across the adult lifespan. Aortic RI and PWV were higher in those with an uncontrolled versus controlled BP (Figure 3.3, left panels, Table 3.2), effects which achieved significance when considering participants grouped according to whether they were < or ≥50 years of age (Table 3.2). These differences were noted in those younger and older than 50 years of age (Table 3.2). However, with adjustments for MAP, increases in aortic RI and PWV in those with an uncontrolled versus controlled BP were abolished (Figure 3.3, right panels, Table 3.2).

Age-related changes in aortic hemodynamics. Although adjustments for MAP abolished or markedly attenuated differences in aortic hemodynamic variables between those with an uncontrolled versus controlled BP (Figures 3.2 and 3.3 and Table 3.2), strong age versus aortic hemodynamic relationships were retained across the adult age range (Table 3.3, Figures 3.2 and 3.3, right panels). Indeed, after adjustments for MAP, those older than 50 years of age had markedly different aortic hemodynamic data as compared to those younger than 50 years of age irrespective of whether they had an uncontrolled or controlled BP (Table 3.2, Figures 3.2 and 3.3, right panels).

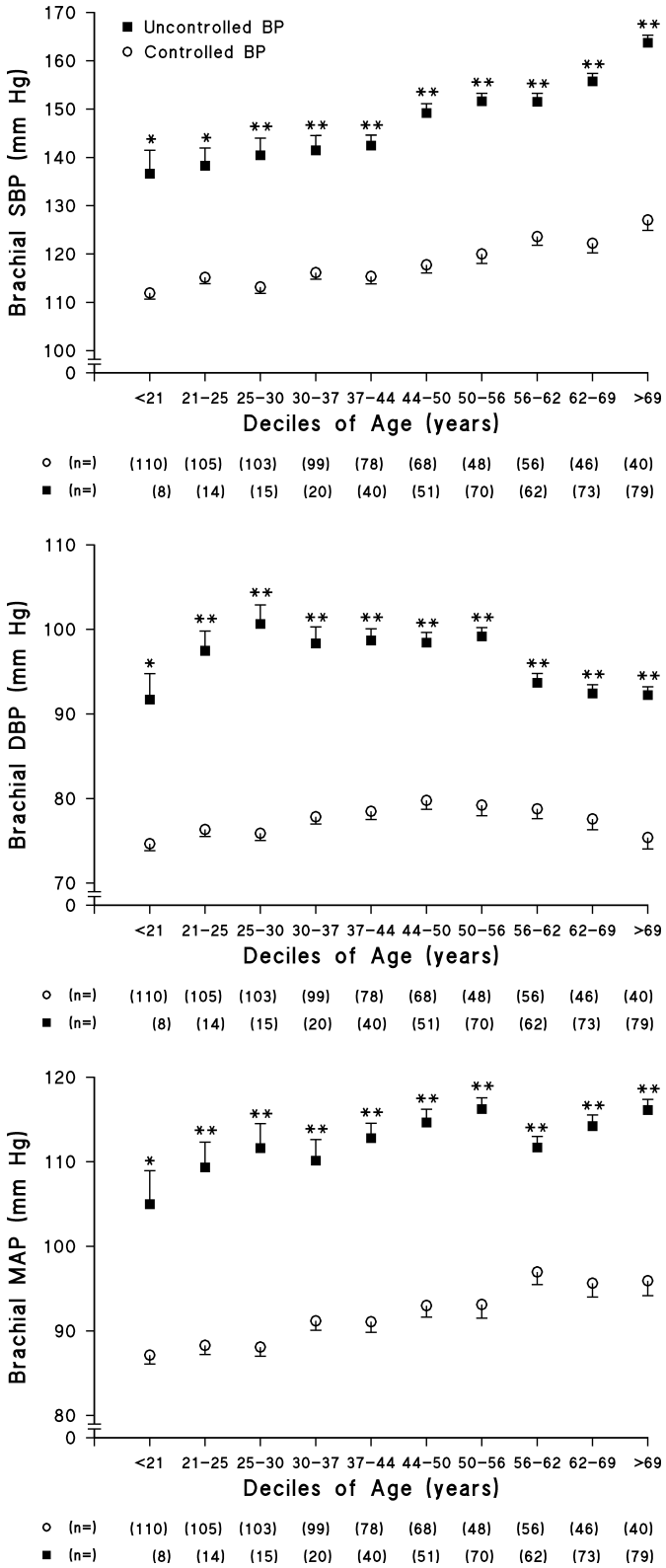

Figure 3.1. Brachial blood pressure (BP) differences in adults with uncontrolled versus controlled brachial BP across the lifespan. SBP, systolic BP; DBP, diastolic BP; MAP, mean arterial pressure derived from the area under the radial pulse wave calibrated to brachial BP. *p<0.001, **p<0.0001 vs controlled brachial BP.

Figure 3.2. Aortic blood pressure (BP) differences in adults with uncontrolled versus controlled brachial BP across the lifespan before (left panels) and after (right panels) adjusting for distending pressures (mean arterial pressure-MAP). PPc, central aortic pulse pressure; Pf, aortic forward wave pressures; Pb, aortic backward wave pressures; PPamp, pulse pressure amplification. *p<0.01, **p<0.001, ***p<0.0001 vs controlled brachial BP.

Table 3.2. Aortic hemodynamic differences between adults with uncontrolled (Uncontr.) versus controlled (Contr.) brachial blood pressure in age-specific categories.

	Age range→		<50 years	≥50 years	<50 years	≥50 years
	Adjustments→		None	None	MAP	MAP
Aortic Hemodynamics		n=	Mean (±SD)	Mean (±SD)	Mean (±SD)	Mean (±SD)
Aortic PP	Contr.	753	28±11	36±14	30±10	42±15†††
(mm Hg)	Uncontr.	432	35±11***	50±15***	25±12***†††	46±14*††
Aortic Pf	Contr.	753	21±7	23±9	21±7	26±10††
(mm Hg)	Uncontr.	432	24±7***	31±10***	22±9††	29±10**†
Aortic Pb	Contr.	753	13±5	18±8	14±5†††	21±8†††
(mm Hg)	Uncontr.	432	18±5***	25±8***	13±6**†††	23±8††
Aortic PP amp	Contr.	753	1.38±0.16	1.23±0.13	1.34±0.20††	1.21±0.14
	Uncontr.	432	1.27±0.18***	1.19±0.12**	1.39±0.20*†††	1.21±0.17†
Aortic RI	Contr.	753	63.5±18.8	78.4±21.9	67.1±17.4††	82.3±25.3
	Uncontr.	432	73.0±18.9***	82.3±12.6*	59.4±20.7**†††	79.7±25.3
Aortic PWV	Contr.	667	4.98±1.41	7.43±3.23	5.19±1.18†	8.19±3.37†
(m/sec)	Uncontr.	363	5.91±1.33*	8.94±3.21*	5.01±1.58†††	8.42±3.21†

MAP, mean arterial pressure; PP, pulse pressure; Pf, forward wave pressure; Pb, backward wave pressure; PPamp, aortic-to-brachial PP amplification; RI, reflected wave index; PWV, pulse wave velocity. *p<0.05, **p<0.005, ***p<0.0001 vs contr, †p<0.05, ††p<0.005, †††p<0.0001 vs before MAP adjustment. All data above 50 years of age are different from corresponding data below 50 years of age (p<0.0001).

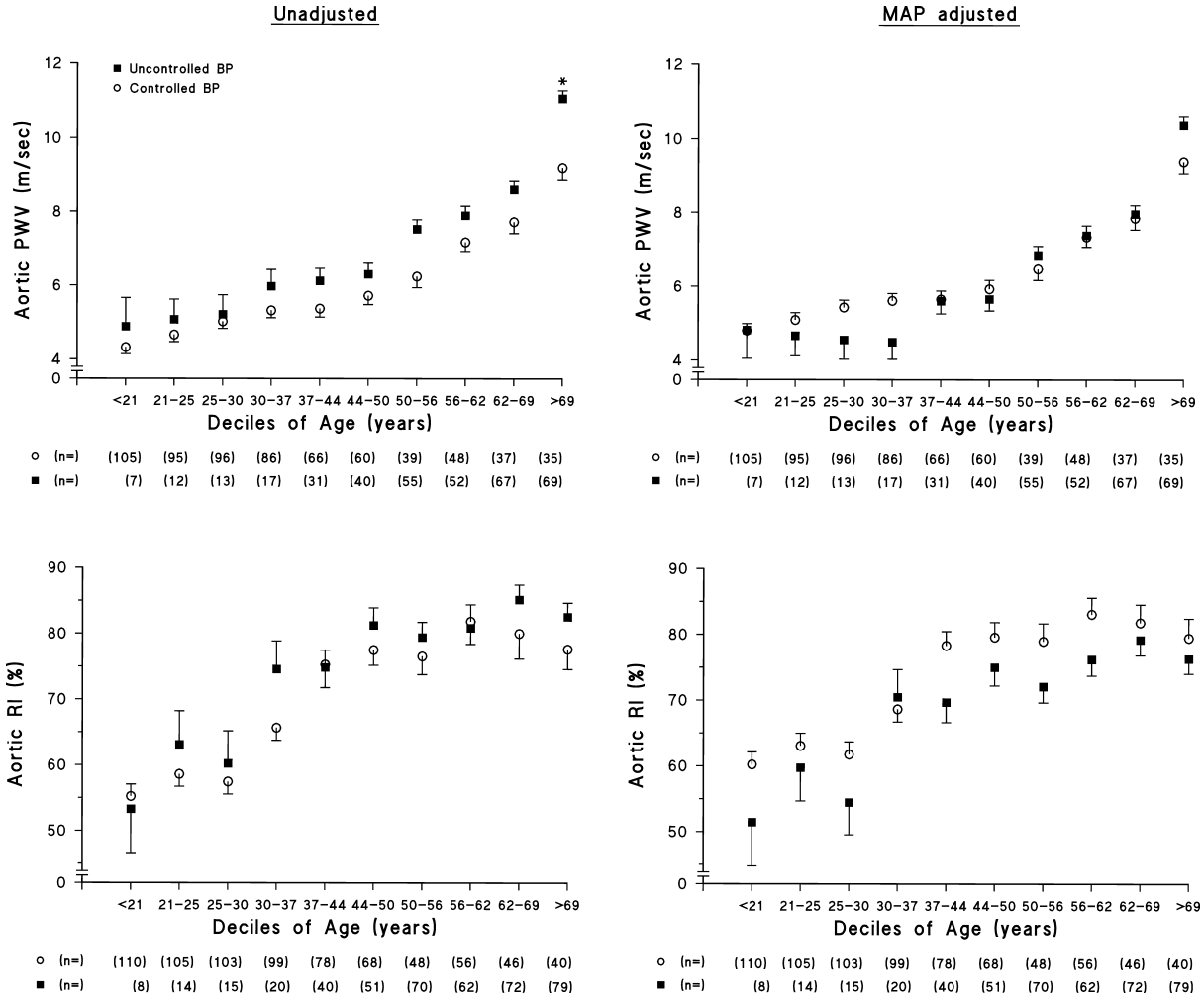

Figure 3.3. Differences in aortic reflected wave index (RI) and pulse wave velocity (PWV) between adults with uncontrolled versus controlled brachial blood pressure (BP) across the lifespan before (left panels) and after (right panels) adjusting for distending pressures (mean arterial pressure-MAP). *p<0.0001 vs controlled brachial BP.

Table 3.3. Relations between age and central aortic hemodynamics.

Adjustments→		None			MAP		
Age vs	n=	β-coefficient ±SEM	1xSD age (years)	1xSD effect	β-coefficient ±SEM	1xSD age (years)	1xSD effect
Aortic PP	1185	0.469±0.020	18.3	8.6 mm Hg	0.298±0.019**	18.3	5.4 mm Hg
Aortic Pf	1185	0.190±0.013	18.3	3.5 mm Hg	0.112±0.014* *	18.3	2.0 mm Hg
Aortic Pb	1185	0.261±0.011	18.3	4.8 mm Hg	0.172±0.010* *	18.3	3.1 mm Hg
PP amp	1185	-0.0050±0.0002	18.3	-0.09	-0.039±0.0003*	18.3	-0.07
Aortic RI	1185	0.522±0.010	18.3	3.2%	0.401±0.011*	18.3	2.4%
Aortic PWV	1030	0.096±0.003	18.3	1.76 m/sec	0.082±0.004*	18.3	1.50 m/sec

MAP, mean arterial pressure; PP, pulse pressure; Pf, forward wave pressure; Pb, backward wave pressure; PPamp, aortic-to-brachial PP amplification; RI, reflected wave index; PWV, pulse wave velocity. All β-coefficients are significant at $p<0.0001$. *$p<0.005$, **$p<0.0001$ vs before MAP adjustment.

3.4 Discussion

The main findings of the present study are as follows: Across the adult lifespan in a community sample of African descent with a high prevalence of uncontrolled BP, brachial BP control fails to account for most MAP-independent, age-related changes in aortic function, including increases in PPc, Pb, RI, and PWV, and decreases in PPamp. Indeed, only modest MAP-adjusted increases in PPc, Pf and Pb were noted in those with an uncontrolled versus controlled BP older than 50 years of age.

Although several indexes of aortic function, including PPc, Pb, RI, PWV, and PPamp add to cardiovascular risk prediction (Vlachopoulos et al. 2010; Wang et al. 2009; Wang et al. 2010; Chirinos et al. 2012; Weber et al. 2012; Vlachopoulos et al. 2010; Ben-Shlomo et al. 2014; Benetos et al. 2010; Regnault et al. 2012; Benetos et al. 2012), the extent to which brachial BP control accounts for these age-related aortic hemodynamic abnormalities is unknown. In this regard, the present study suggests that brachial BP control accounts for little of the age-related changes in aortic function that confer cardiovascular risk. Indeed, with adjustments for MAP, only modest differences in PPc, Pb, Pf, PPamp, RI and PWV occurred between those with uncontrolled and controlled brachial BP values, but marked age-related increases in PPc, Pb, Pf, RI and PWV and decreases in PPamp were noted across the adult age range. These data are consistent with the age-related changes in aortic hemodynamics reported in several prior studies (Mitchell et al. 2010; Namasivayam et al. 2009; Cecelja et al. 2009), but add to these studies by indicating that these age-related changes are not accounted for by brachial BP control in the general population. The present data therefore support the notion that in the general population, aortic hemodynamic abnormalities may occur irrespective of brachial BP control.

Although it is well-accepted that targeting brachial BP with BP lowering therapy modifies several aspects of age-related aortic functional changes, including increases in PPc and Pb or RI and decreases in PPamp (Agabiti-Rosei et al. 2007), the present study suggests that most age-related aortic hemodynamic changes remain unaccounted for when brachial BP is controlled. The present study therefore supports the views that the identification of thresholds for PPc, Pb, RI, PWV, and PPamp may enhance risk prediction beyond brachial BP (Townsend et al. 2015) and that targeting aging-induced aortic hemodynamic changes in either normotensives or hypertensives may produce further reductions in cardiovascular events. These effects may include approaches which decrease age-related increases in aortic stiffness or in wave reflection. In this regard, at present, the antihypertensive classes that best target age-related increases in aortic stiffness or wave reflection have not as yet been identified.

In the present study, 61.0% of hypertensives receiving therapy were receiving a low dose thiazide diuretic agent as monotherapy and there is uncertainty as to whether thiazide diuretic agents are able to modify aortic hemodynamic variables as well as other agents. Hence,

it is possible that the marked age-related hemodynamic changes in those with a controlled brachial BP could in-part be attributed to an inability of thiazide diuretic agents to appropriately influence aortic BP. However, only 15% of all participants with a controlled brachial BP were receiving antihypertensive therapy, but participants with a controlled BP had marked age-related aortic functional changes.

In the present study, we were interested in identifying whether brachial BP-thresholds account for the impact of chronic age-related changes in the vessel wall on aortic function. Hence, we adjusted for the well-recognised influence of aortic distension, which is largely driven by MAP, on age-related changes in aortic function. In this regard, MAP is closely associated with SBP and DBP and hence the question of co-linearity arises (whether adjustments for MAP are in-part adjusting for BP thresholds). However, this argument does not explain why even before adjustments for MAP, marked age-related changes in all aortic hemodynamic changes were noted in participants with a controlled BP and that the age-related changes in PP amplification, RI and PWV were as striking as in participants with an uncontrolled BP.

Studies assessing changes in Pf and Pb with either age or hypertension and that have employed wave separation analysis (thus avoiding the considerable overlap between these pressure waves), have demonstrated discrepant findings. In this regard, several studies show a dominant age-related increase in Pf rather than Pb contributing to increases in aortic BP with age (Segers et al. 2007; Torjesen et al. 2014) or hypertension (Fok et al. 2014). However, these studies have been conducted in either small samples (Fok et al. 2014), over a narrow age range (Segers et al 2007), or in community samples with mean BP values that reflect a well-controlled BP (Torjesen et al. 2014). In contrast, studies conducted in large community-based samples with a high prevalence of uncontrolled hypertension and over a wide age range show a marked age-related increase in Pb (Wang et al. 2010; Booysen et al 2015), at least equivalent to that of Pf (Booysen et al. 2015) across the adult age range. The present study adds to these studies (Wang et al. 2010; Booysen et al. 2015), by demonstrating marked age-related increases in aortic Pf and Pb in all participants irrespective of brachial BP control.

The present study in-part explains the findings that brachial BP measurements have a limited capacity to detect a raised central aortic BP (sensitivity of only 49%) (Cheng et al. 2014). In this regard, as demonstrated in the present study, age-related increases in aortic PP and hence SBP are largely discounted when considering brachial BP thresholds only as an index of BP control. As a consequence, the use of brachial BP alone to identify thresholds below which BP should be lowered, may exclude many patients with a raised aortic BP who may benefit from antihypertensive therapy. Further intervention studies assessing the impact on cardiovascular damage when targeting aortic as compared to brachial BP are required to assess this hypothesis.

There are several limitations to the present study. The elderly and very elderly were under-represented in the present community sample. Hence, it is possible that in the elderly and

very elderly brachial BP control may better account for age-related aortic hemodynamic changes. Second, the assumptions intrinsic to the use of the 'triangulation method' of aortic wave separation are not ideal (Kips et al. 2009). Hence, we may have over or underestimated the contribution of brachial BP control in the general population to increases in Pf, Pb, or RI. Third, the present study was a cross-sectional design and requires corroboration with longitudinal and intervention studies. Fourth, PWV measurements were obtained from pulse transit distance using subtracted distances (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), prior to the recommendation that a standardized approach of 80% of the direct carotid-femoral distance be used (Van Bortel et al. 2012). Hence, our PWV values may be marginally different from actual invasive measurements.

3.5 Conclusions

The present results suggest that across the adult lifespan, most MAP-independent, age-related increases in PPc, Pb, RI and PWV and decreases in PPamp are not accounted for by brachial BP control. These findings further highlight the need to identify and employ aortic hemodynamic thresholds that add to risk prediction, and to develop therapeutic interventions that are able to target age-related changes in aortic function.

CHAPTER 4

Impact of Aortic Rather Than Brachial Pulsatile Haemodynamics on Variations in End-Organ Measures Across the Full Adult Blood Pressure Range.

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Bryan Hodson, Gavin R Norton, Imraan Ballim, Carlos D Libhaber, Pinhas Sareli, Angela J Woodiwiss.

Impact of Aortic Rather Than Brachial Pulsatile Haemodynamics on Variations in End-Organ Measures Across the Full Adult Blood Pressure Range.

4.0 Abstract

Aims: To determine the extent to which the adverse effects of blood pressure (BP) are mediated by pulsatile haemodynamic changes across the normotensive as compared to the hypertensive adult brachial BP range, and whether aortic rather than brachial pulsatile changes best index these effects.

Methods: In 1307 community participants the contribution of pulsatile haemodynamics (applanation tonometry and SphygmoCor software) to variations in left ventricular mass index (LVMI)(echocardiography) (n=920), carotid intima-media thickness (IMT)(n=712) and estimated glomerular filtration rate (eGFR)(n=1164) were assessed.

Results: In normotensives (50.5%) independent of steady-state pressure (mean arterial pressure), significant relations between aortic backward wave pressure (Pb) and LVMI (partial $r=0.16$, $p<0.001$) or IMT (partial $r=0.15$, $p<0.005$) and between aortic pulse wave velocity (PWV) and eGFR (partial $r=-0.18$, $p<0.0001$) were noted, effects which in hypertensives were observed for LVMI and eGFR, but not IMT. With adjustments for brachial PP or SBP and confounders, Pb and PWV showed independent relations with LVMI, IMT or eGFR in normotensives, but only with LVMI or eGFR in hypertensives. In normotensives, as compared to brachial pulse pressure (PP) or systolic BP (SBP), Pb showed a greater slope (β-coefficient) of the relation with LVMI (0.99±0.24 vs 0.47±0.10 and 0.41±0.09 mm Hg, $p<0.05$) and IMT (0.0045±0.0013 vs 0.0013±0.0006 and 0.0013±0.0005 mm Hg, $p<0.05$) and a stronger association with left ventricular hypertrophy (Odds ratios [95% CI], 1.125 [1.059 to 1.195] vs 1.054 [1.027 to 1.082] and 1.042 [1.020 to 1.066, $p<0.05$). However, in hypertensives only the slope of the Pb-LVMI relationship was greater than that of PP- and SBP-LVMI relations.

Conclusions: Beyond brachial BP, pulsatile haemodynamics rather than steady-state pressures account for end-organ effects more consistently across the normotensive than the hypertensive BP range. Hence, targeting aortic pulsatile haemodynamic changes may best limit BP-related cardiovascular risk within the normotensive BP range.

Key words: Aortic stiffness, aortic pressure, left ventricular mass, carotid intima-media thickness, estimated glomerular filtration rate.

4.1 Introduction

Current hypertension guidelines generally recommend threshold blood pressure (BP) values of 140/90 mm Hg for the diagnosis and management of hypertension. However, BP is continuously associated with cardiovascular outcomes from values of 115/75 mm Hg (Lewington et al. 2002) and in prospective, observational studies the risk for cardiovascular events increases from 120/80 mm Hg (Vasan et al. 2001; Hsia et al. 2007; Butler et al. 2011). Several randomized, controlled trials (Nissen et al. 2004; Remme et al. 2009; PROGRESS Collaborative Group 2001; Wright et al. 2015) and meta-analyses of such trials (Tumbull et al. 2003; Law et al. 2009; Thompson et al. 2011; Thomopoulos et al. 2016; Ettehad et al. 2016; Xie et al. 2016) indicate that BP lowering to below currently accepted thresholds in select (high risk) patients has benefits for outcomes. In contrast, alternative studies suggest otherwise (Schrier et al. 2002; Patel et al. 2007; Yusuf et al. 2008a; Yusuf et al 2008b; Yusuf et al 2008c; Cushman et al. 2010; Cooper-DeHoff et al. 2010; McMurray et al. 2010; Brunstrom et al 2016; The SP3 Investigators 2013). These conflicting results (Nissen et al. 2004; Remme et al. 2009; PROGRESS Collaborative Group 2001; Wright et al. 2015) and meta-analyses of such trials (Tumbull et al. 2003; Law et al. 2009; Thompson et al. 2011; Thomopoulos et al. 2016; Ettehad et al. 2016; Xie et al. 2016; Schrier et al. 2002; Patel et al. 2007; Yusuf et al. 2008a; Yusuf et al 2008b; Yusuf et al 2008c; Cushman et al. 2010; Cooper-DeHoff et al. 2010; McMurray et al. 2010; Brunstrom et al 2016; The SP3 Investigators 2013) highlight the need for strategies to better identify those within a normotensive BP range at risk for BP-related cardiovascular events.

Recent evidence indicates that an increased systolic BP (SBP) within normotensive ranges is causally related to outcomes (Wright et al. 2015). As SBP is determined by both steady-state (mean arterial [MAP]) as well as pulse (PP) pressure, the question arises as to what extent an increased PP and the haemodynamic origins thereof contribute toward the adverse effects of SBP within normotensive ranges. In this regard, several studies indicate that aortic PP and its determinants predict cardiovascular events beyond MAP (Vlachopoulos et al. 2010a; Ben-Shlomo et al. 2014; Vlachopoulos et al 2010b; Wang et al. 2010; Chirinos et al. 2012; Weber et al. 2012; Zamani et al. 2014) and there is some evidence that select determinants of aortic PP (aortic pulse wave velocity) may predict risk in normotensives beyond brachial BP (Ben-Shlomo et al. 2014). However, the extent to which pulsatile haemodynamic changes versus steady-state pressures determine cardiovascular damage within the normotensive as opposed to the hypertensive SBP range and whether aortic haemodynamic variables best index these effects is unknown. In this regard, at a lower SBP (e.g. normotensive range), PP and the determinants thereof are markedly less than at a higher SBP (hypertensive range). However, independent of steady-state pressures, similar age-induced increases in brachial and aortic pulsatile haemodynamic changes occur in those within normotensive as

compared to hypertensive BP ranges (Hodson et al. 2016). These data (Hodson et al. 2016) raise the question of the extent to which aortic pulsatile haemodynamic changes contribute to cardiovascular damage within the normotensive as compared to the hypertensive BP range. If the contribution is at least as extensive in the normotensive as in the hypertensive BP range, then targeting pulsatile haemodynamics in otherwise normotensive individuals may be an important strategy to reduce the risk of BP-related cardiovascular events in normotensives. To address this question, in a relatively large, community-based study, we compared the contribution of steady-state versus pulsatile pressures or their determinants, to several end-organ measures in those with BP within normotensive as opposed to hypertensive ranges. We also evaluated to what extent the contribution of pulsatile haemodynamic effects can be adequately detected using brachial BP measurements or whether the assessment of aortic function is required.

4.2 Methods

Study group. The present study was conducted according to the principles outlined in the Helsinki declaration. The Committee for Research on Human Subjects of the University of the Witwatersrand approved the protocol (approval number: M02-04-72 and renewed as M07-04-69 and M12-04-108). Participants gave informed, written consent. The present study design has previously been described (Booysen et al 2015). Briefly, 1307 participants from randomly recruited (from the population census figures of 2001) families of black African descent (Nguni and Sotho chiefdoms) from the South West Township (SOWETO) of Johannesburg, South Africa, with siblings older than 16 years were evaluated. In sub-studies, 920 had left ventricular mass index (LVMI) determined by echocardiography and 712 carotid intima-media thickness (IMT) assessments. The majority of participants had serum creatinine measurements for the assessment of estimated glomerular filtration rate (eGFR).

Clinical, demographic and anthropometric measurements. A questionnaire was administered to obtain demographic and clinical data (Booysen et al. 2015). Height and weight were measured using standard approaches and participants were considered to be overweight if their body mass index (BMI) was ≥25 kg/m^2 and obese if their BMI was ≥30 kg/m^2. High quality brachial BP measurements were obtained in the seated position after 5 minutes of rest by a trained nurse-technician using a standard mercury sphygmomanometer according to guidelines. The mean of 5 measurements obtained at least 30 seconds apart was taken as office BP. Hypertension was defined as a mean BP≥140/90 mm Hg or the use of antihypertensive medication. Laboratory blood tests of renal function, liver function, blood glucose, haematological parameters, and percentage glycated haemoglobin (HbA_{1c}) were performed. Diabetes mellitus (DM) or an abnormal blood glucose control was defined as the use of insulin or oral hypoglycaemic agents or an HbA_{1c} value greater than 6.1%.

Pulse wave analysis. Central aortic haemodynamics were estimated using pulse wave and wave separation analysis as previously described (Booysen et al. 2015). After participants had rested for 15 minutes in the supine position, arterial waveforms at the radial (dominant arm) pulse were recorded by applanation tonometry during an 8-second period using a high-fidelity SPC-301 micromanometer (Millar Instrument, Inc., Houston, Texas) interfaced with a computer employing SphygmoCor, version 9.0 software (AtCor Medical Pty. Ltd., West Ryde, New South Wales, Australia). The pulse wave was calibrated by manual measurement (auscultation) of brachial BP taken immediately before the recordings. The peripheral pressure waveform was converted into a central aortic waveform using a validated generalized transfer function incorporated in SphygmoCor software. Recordings where the systolic or diastolic variability of consecutive waveforms exceeded 5% or the amplitude of the pulse wave signal was less than 80 mV were discarded. Central aortic PP (PPc) was determined as the difference between aortic SBP and diastolic BP (DBP). Aortic forward (Pf) and backward wave (Pb) pressures was determined from wave separation analysis of the SphygmoCor-derived aortic waveform using a 'triangular flow wave' (also from SphygmoCor software) (Westerhof et al. 2006). The aortic pulsatility index was determined as aortic PP/DBP expressed as a percentage.

Aortic pulse wave velocity (PWV) was successfully determined in 1128 participants from sequential waveform measurements at carotid and femoral sites using applanation tonometry and SphygmoCor software. The time delay in the pulse waves between the carotid and femoral sites was determined using an electrocardiograph-derived R wave as a fiducial point. Pulse transit time was obtained from the average of 10 consecutive beats. The distance which the pulse wave travels was determined as the difference between the distance from the femoral sampling site to the suprasternal notch, and the distance from the carotid sampling site to the suprasternal notch.

End organ measures. Echocardiographic measurements were recorded and analysed off-line by experienced investigators (CDL and AJW) who were unaware of the clinical data of the participants (Booysen et al. 2015). Left ventricular mass index (LVMI) was determined from transthoracic two-dimensional targeted M-mode echocardiography obtained in the long axis parasternal view. Variables were analysed according to the American Society of Echocardiography convention (Sahn et al. 1978). Left ventricular mass was determined using a standard formula (Devereux et al. 1986) and indexed (LVMI) to height$^{1.7}$. Left ventricular hypertrophy (LVH) was identified as an LVMI-ht$^{1.7}$>80 g/m$^{1.7}$ for men and >60 g/m$^{1.7}$ for women. 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). Chronic kidney disease (CKD) was identified as eGFR <90 ml/min/1.73 m^2. Carotid intima-media thickness (IMT) was determined using high resolution B-mode ultrasound (SonoCalc IMT, Sonosite Inc, Bothell, Washington) employing a linear array 7.5 MHz probe. Images of at least 1cm length of the far

wall of the distal portion of the right common carotid artery from an optimal angle of incidence (defined as the longitudinal angle of approach where both branches of the internal and external carotid artery are visualized simultaneously) at least 1 cm proximal to the flow divider were obtained. Carotid IMT measurements were determined using semi-automated border-detection and quality control software. An increased IMT was identified as >0.90 mm.

Data analysis. For database management and statistical analysis, SAS software, version 9.3 (SAS Institute Inc., Cary, NC) was employed. Multiple linear regression analysis was performed to determine the independent relations between aortic hemodynamic parameters and end-organ measures (continuous data). Multivariate adjusted logistic regression analysis was performed to determine the independent relations between aortic hemodynamic parameters and LVH (discrete data). Due to the low prevalence of an increased IMT (4.2%) and CKD (20.6%) in normotensives, no relations between haemodynamic factors and an increased IMT or CKD were determined. Adjustments included in multivariate models were those correlated with central haemodynamic variables and end organ measures in bivariate analysis. To determine probability values, further adjustments for non-independence of family members was performed using non-linear regression analysis (mixed procedure as defined in the SAS package). Regression coefficients and Odds ratios were compared with z statistics. To ensure that antihypertensive therapy did not produce a marked impact on the results obtained in hypertensives, sensitivity analysis was conducted in hypertensives not receiving antihypertensive therapy. In addition, in analysis conducted in hypertensives receiving antihypertensive therapy adjustments were made for drug classes which included low dose thiazide diuretic monotherapy, calcium channel blocker (CCB) mono- or dual therapy with alternative agents (mostly low dose thiazide diuretic), angiotensin-converting enzyme inhibitor (ACEI) mono- or dual therapy (mostly low dose thiazide diuretic), and other classes of agents.

4.3 Results

Participant characteristics. Tables 4.1 and 4.2 show that the demographic and clinical characteristics of participants with versus without LVMI (Table 4.1) or IMT (Table 4.2) measurements were similar. Table 4.3 gives the demographic and clinical characteristics of normotensives and hypertensives. Only 2.4% of participants had a history of cardiovascular disease. A significant proportion of hypertensives were not receiving therapy. Moreover, 77.4% of hypertensives had uncontrolled hypertension. Hypertensives were older, more obese, had higher steady-state as well as pulsatile haemodynamic values, and had a higher prevalence of LVH, CKD and an increased IMT.

Pulsatile haemodynamics across the full adult SBP range. Increases in SBP across the full adult BP range, including BP values within normotensive ranges, were associated with stepwise increases in pulsatile haemodynamic factors (brachial PP, PPc, Pb, Pf, and

Table 4.1. Characteristics of participants with and without echocardiography.

	With echocardiography	Without echocardiography
Sample size (% Female)	920 (66.2%)	387 (65.4)
Age (years)	46.1±18.2	43.0±18.6
Body mass index (kg/m^2)	30.3±13.7	29.4±8.6
% Obese	46.2	41.3
Regular tobacco (% subjects)	14.6	16.3
Regular alcohol (% subjects)	19.6	23.0
% with DM or HbA_{1c}>6.1%	23.6	25.3
% Hypertensive	51.7	44.2
% Treated for hypertension	28.7	19.9
% diuretic/CCB†/ACEI†/other	15.4/6.4/2.9/4.0	14.5/2.0/1.8/1.6
Pulse rate (beats/min)	66±11	66±12
Brachial SBP/DBP (mm Hg)	128±22/84±12	128±21/84±12
Brachial pulse pressure (mm Hg)	45±16	44±14
Mean arterial pressure (mm Hg)	100±15	100±21
Central aortic SBP (mm Hg)	120±22	119±21
Central aortic PP (mm Hg)	36±14	34±13
Central aortic pulsatility index (PI)(%)	42±16	41±15
Aortic forward wave pressure (mm Hg)	24±9	24±7
Aortic backward wave pressure (mm Hg)	17±8	17±8
Aortic pulse wave velocity (m/sec)	6.02±2.68 (n=792)	6.67±2.43 (n=336)

Data expressed as mean ± SD or proportions. DM, diabetes mellitus; HbA_{1c}, glycosylated hemoglobin; CCB, calcium channel blocker; ACEI, angiotensin-converting enzyme inhibitor; BP, blood pressure; SBP, systolic BP; DBP, diastolic BP; PP, pulse pressure; PI=PPc/DBP. †These include patients on monotherapy or drug combinations as given in the analysis section.

Table 4.2. Characteristics of participants with and without carotid intima-media thickness (IMT).

	With IMT	Without IMT
Sample size (% Female)	712 (66.4%)	595 (65.4)
Age (years)	46.7±18.3	43.4±18.3
Body mass index (kg/m^2)	30.6±15.1	29.3±7.9
% Obese	46.9	42.2
Regular tobacco (% subjects)	15.3	14.8
Regular alcohol (% subjects)	20.5	20.7
% with DM or HbA_{1c}>6.1%	23.3	25.0
% Hypertensive	50.7	48.1
% Treated for hypertension	29.5	22.0
% diuretic/CCB†/ACEI†/other	17.1/5.9/3.5/3.0	12.8/4.4/1.1/3.7
Pulse rate (beats/min)	66±12	66±12
Brachial SBP/DBP (mm Hg)	126±20/83±12	131±23/85±13
Brachial pulse pressure (mm Hg)	44±15	46±15
Mean arterial pressure (mm Hg)	99±15	101±16
Central aortic SBP (mm Hg)	118±20	122±23
Central aortic PP (mm Hg)	35±14	36±14
Central aortic pulsatility index (PI)(%)	42±17	42±15
Aortic forward wave pressure (mm Hg)	24±9	25±8
Aortic backward wave pressure (mm Hg)	17±7	18±8
Aortic pulse wave velocity (m/sec)	5.90±2.52 (n=634)	6.62±2.69 (n=494)

Data expressed as mean ± SD or proportions. DM, diabetes mellitus; HbA_{1c}, glycosylated hemoglobin; CCB, calcium channel blocker; ACEI, angiotensin-converting enzyme inhibitor; BP, blood pressure; SBP, systolic BP; DBP, diastolic BP; PP, pulse pressure; PI=PPc/DBP. †These include patients on monotherapy or drug combinations as given in the analysis section.

PWV)(Figures 4.1 and 4.2). Importantly, pulsatile haemodynamic variables in normotensives considerably overlapped with values in hypertensives (Figure 4.1). However, neither aortic nor brachial PP, or Pf varied across DBP values; only modest increases in Pb and PWV were noted across incremental DBP values; and aortic Pi decreased across the adult range of DBP values (Figures 4.3 and 4.4). In contrast, as with SBP, increases in MAP across the full adult BP range, including BP values within normotensive ranges, were associated with stepwise increases in pulsatile haemodynamic factors (brachial PP, PPc, Pb, Pf, and PWV)(Figures 4.5 and 4.6).

Contribution of steady-state and pulsatile haemodynamics to variations in LVMI and LVH. Both brachial and aortic haemodynamic variables correlated with and were independently associated with LVMI and LVH (Tables 4.4 and 4.5). In the normotensives, but not the hypertensives, the relations between Pb and LVH were stronger than the relations between brachial PP or SBP and LVH (Table 4.5). With MAP and either PPc or Pb in the same regression models, PPc and Pb, but not MAP were independently associated with LVMI and LVH in normotensives and hypertensives (Tables 4.6, 4.7, 4.8 and 4.9). With the inclusion of MAP and either Pf or brachial PP in the same regression models, Pf was independently associated with LVMI and LVH in normotensives, but not hypertensives (Tables 4.6, 4.7, 4.8 and 4.9); and brachial PP was independently associated with LVMI and LVH in both normotensives (LVMI and LVH) and hypertensives (LVMI) (Tables 4.6, 4.7, 4.8 and 4.9). However, in these models MAP retained trend effects for independent associations with LVMI in normotensives (Table 4.6). Aortic PWV was not independently associated with LVMI or LVH in either normotensives or hypertensives (Tables 4.6, 4.7, 4.8 and 4.9). Without MAP included in regression models, the slope of the relationship between Pb and LVMI was greater than the slope of the relationship between brachial PP or SBP and LVMI (Figures 4.6 and 4.7). Moreover, the relationship between Pb and LVH was greater in normotensives than in hypertensives (Tables 4.7 and 4.9).

Contribution of steady-state and pulsatile haemodynamics to variations in IMT. Both brachial and aortic haemodynamic variables correlated with and were independently associated with IMT (Table 4.10). With MAP and either PPc, Pb or brachial PP in the same regression models, PPc, Pb, and brachial PP, but not MAP were independently associated with IMT in normotensives, but not hypertensives (Tables 4.11 and 4.12). With the inclusion of MAP and either Pf or PWV in the same regression models, neither Pf, nor PWV were independently associated with IMT in either normotensives or hypertensives (Tables 4.11 and 4.12). Without MAP included in regression models, the slope of the relationship between Pb and IMT was greater than the slope of the relationship between brachial PP or SBP and IMT (Figure 4.7).

Contribution of steady-state and pulsatile haemodynamics to variations in eGFR. Both brachial and aortic haemodynamic variables correlated with and were independently associated with eGFR (Table 4.13). In unadjusted models, the relationship between PWV and eGFR was stronger than the relationship between brachial PP or SBP and eGFR in normotensives, but not

Table 4.3. Characteristics of normotensive and hypertensive study participants.

	Normotensives	Hypertensives
Sample size (% Female)	660 (66.2)	647 (65.7)
Age (years)	34.8±14.9	55.7±15.3*
Body mass index (kg/m^2)	27.2±7.3	32.9±15.4*
% Obese	31.2	58.6*
Regular tobacco (% subjects)	15.8	14.4
Regular alcohol (% subjects)	21.4	19.8
% with DM or HbA_{1c}>6.1%	11.5	36.9*
% Treated for hypertension	0	52.7*
% Treated to target BP	-	22.6
% diuretic/CCB†/ACEI†/other	-	30.6/10.5/5.1/6.5
Pulse rate (beats/min)	65±11	67±12
Brachial SBP/DBP (mm Hg)	114±11/77±7	142±21/91±12*
Brachial pulse pressure (PP)(mm Hg)	38±9	51±17*
Mean arterial pressure (MAP) (mm Hg)	90±8	110±14*
Central aortic SBP (mm Hg)	106±11	134±20*
Central aortic PP (PPc) (mm Hg)	28±7	42±16*
Central aortic pulsatility index (PI) (%)	37±10	47±19*
Aortic forward wave pressure (Pf) (mm Hg)	21±5	27±10*
Aortic backward wave pressure (Pb) (mm Hg)	13±4	21±8*
Aortic pulse wave velocity (PWV) (m/sec)	5.10±1.53 (n=587)	7.43±2.99* (n=541)
Left ventricular mass index (LVMI)(g/m$^{1.7}$)	60.6±20.4 (n=444)	73.3±25.4* (n=476)
Carotid intima-media thickness (IMT) (mm)	0.59±0.11 (n=351)	0.71±0.15* (n=361)
Estimated GFR (mls/min/1.73 m^2)	127±33 (n=606)	105±29* (n=558)
Left ventricular hypertrophy (%)	38	57*
IMT>0.90 (%)	1.4	6.9*
Estimated GFR<90 mls/min/1.73 m^2	10.9	31.2*

Data expressed as mean ± SD or proportions. DM, diabetes mellitus; HbA_{1c}, glycosylated hemoglobin; BP, blood pressure; CCB, calcium channel blocker; ACEI, angiotensin-converting enzyme inhibitor; SBP, systolic BP; DBP, diastolic BP; GFR, glomerular filtration rate. PI=PPc/DBP. *p<0.0005 vs normotensives. †These include patients on monotherapy or drug combinations as given in the analysis section.

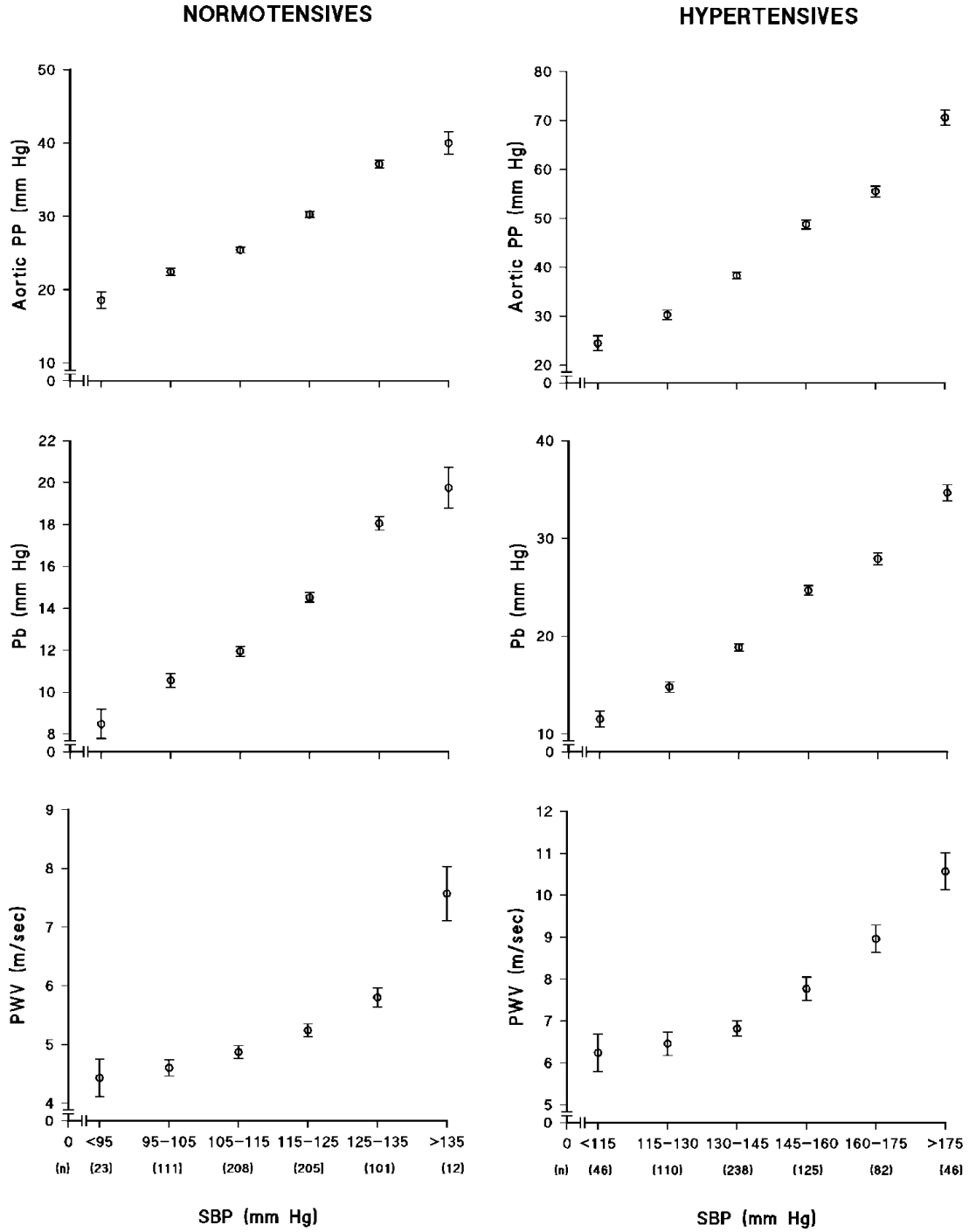

Figure 4.1. Aortic pulsatile haemodynamic changes over a range of brachial systolic blood pressures (SBP) in normotensives and hypertensives of a community sample. PP, pulse pressure; Pb, aortic forward wave pressures; PWV, aortic pulse wave velocity. p<0.0001 for a trend for an increase in aortic haemodynamics across normotensives and hypertensives.

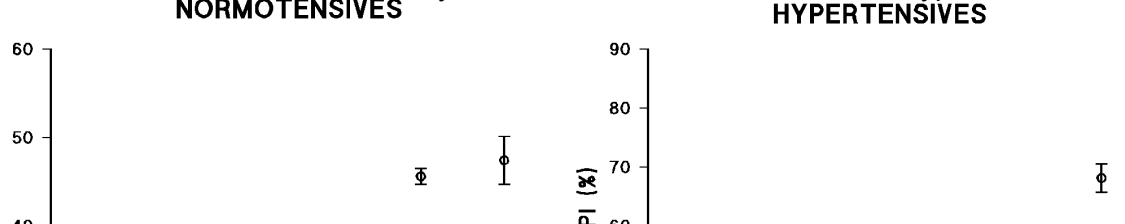

Figure 4.2. Aortic pulsatile haemodynamic changes over a range of brachial systolic blood pressures (SBP) in normotensives and hypertensives of a community sample. Aortic PI, aortic pulsatility index; PP, pulse pressure; Pf, aortic forward wave pressures. p<0.0001 for a trend for an increase in aortic haemodynamics across normotensives and hypertensives.

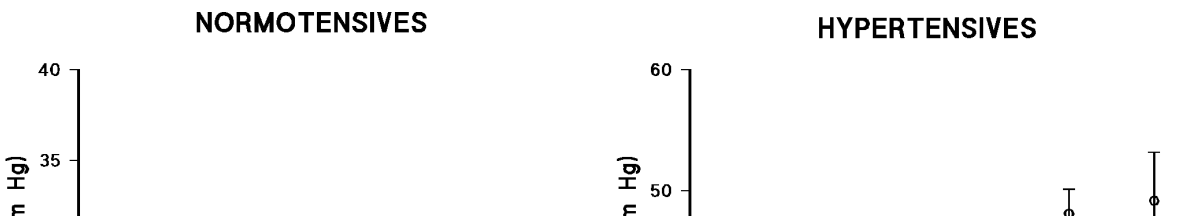

Figure 4.3. Aortic pulsatile haemodynamic changes over a range of brachial diastolic blood pressures (DBP) in normotensives and hypertensives of a community sample. PP, pulse pressure; Pb, aortic forward wave pressures; PWV, aortic pulse wave velocity. $p<0.0001$ for a trend for an increase in aortic haemodynamics across normotensives and hypertensives.

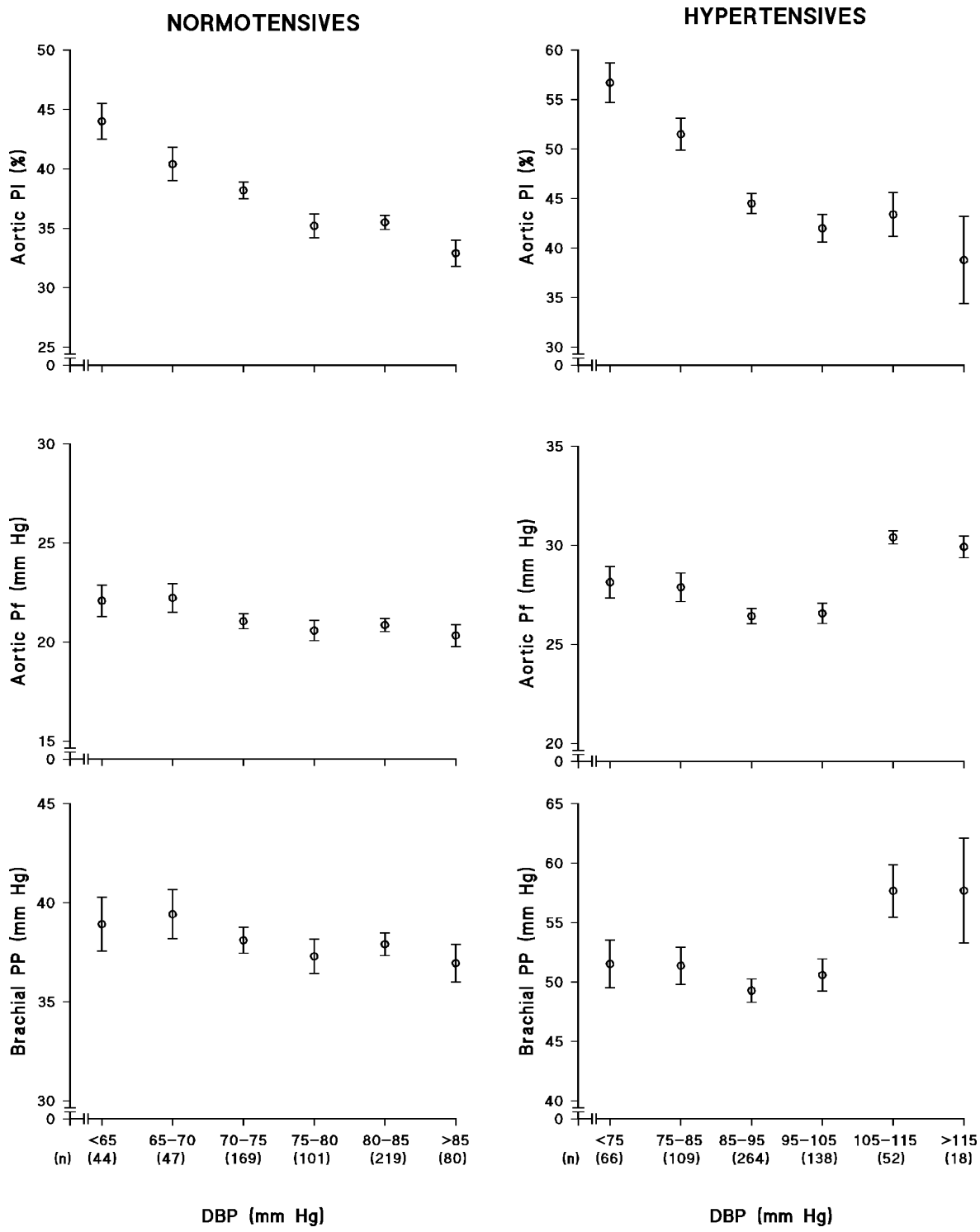

Figure 4.4. Aortic pulsatile haemodynamic changes over a range of brachial diastolic blood pressures (DBP) in normotensives and hypertensives of a community sample. Aortic PI, aortic pulsatility index; PP, pulse pressure; Pf, aortic forward wave pressures. $p<0.0001$ for a trend for an increase in aortic haemodynamics across normotensives and hypertensives.

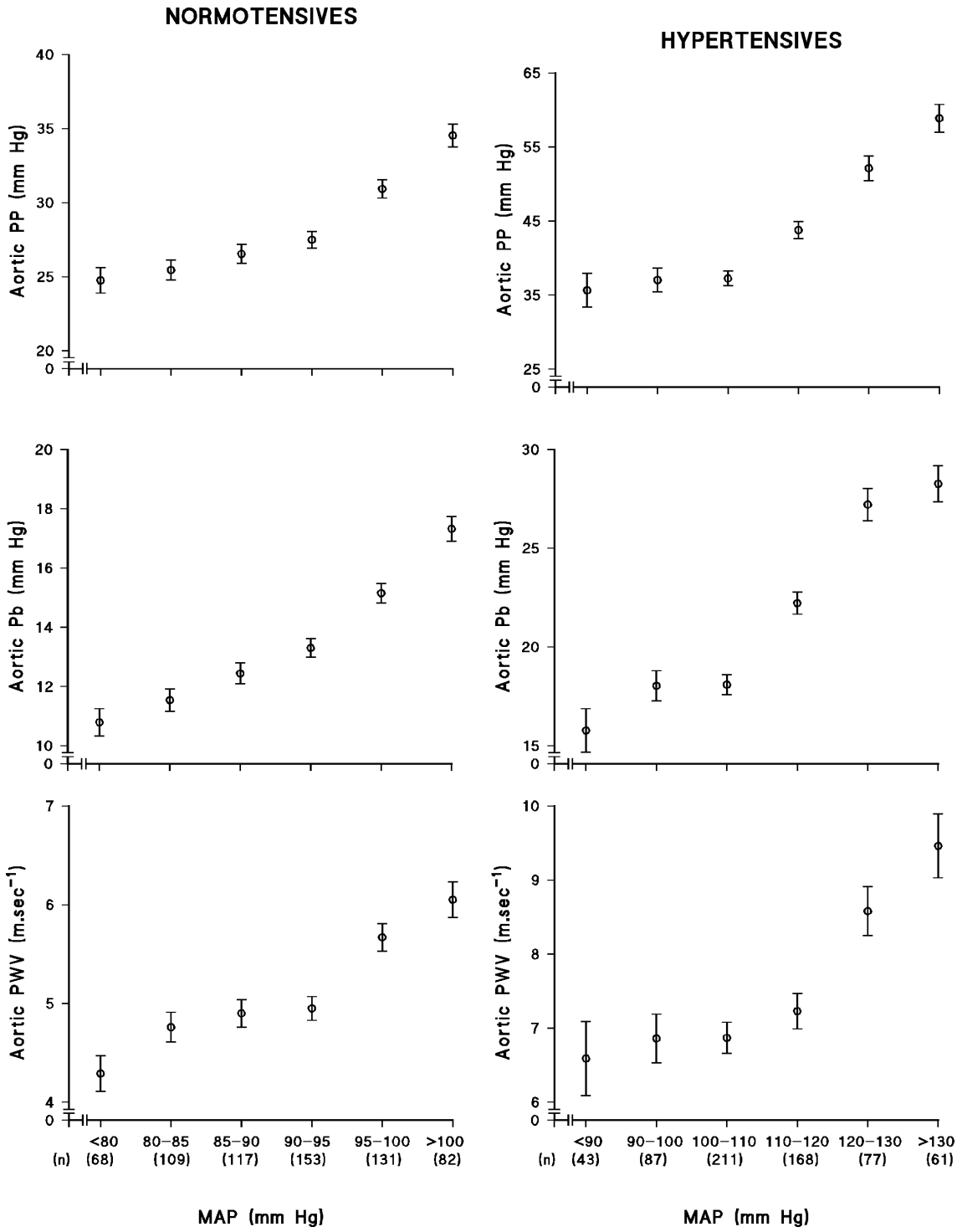

Figure 4.5. Aortic pulsatile haemodynamic changes over a range of mean arterial blood pressures (MAP) in normotensives and hypertensives of a community sample. PP, pulse pressure; Pb, aortic forward wave pressures; PWV, aortic pulse wave velocity. $p<0.0001$ for a trend for an increase in aortic haemodynamics across normotensives and hypertensives.

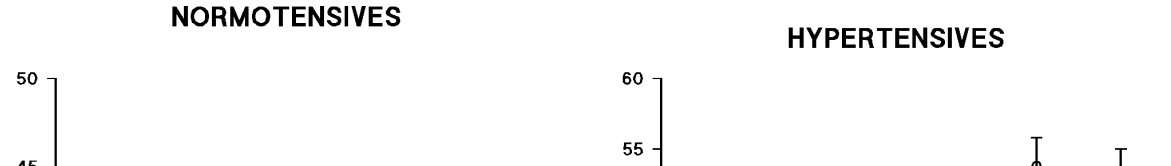

Figure 4.6. Aortic pulsatile haemodynamic changes over a range of mean arterial pressures (MAP) in normotensives and hypertensives of a community sample. Aortic PI, aortic pulsatility index; PP, pulse pressure; Pf, aortic forward wave pressures. $p<0.0001$ for a trend for an increase in aortic haemodynamics across normotensives and hypertensives.

Table 4.4. Univariate and multivariate-adjusted relations between haemodynamic variables and left ventricular mass index (LVMI) in normotensives and hypertensives of a community sample.

	Bivariate relations				Multivariate adjusted relations			
	Normotensives (n=444)		Hypertensives (n=476)		Normotensives (n=444)		Hypertensives (n=476)	
LVMI versus	r (95% CI)	p value	r (95% CI)	p value	Partial r (95% CI)	p value	Partial r (95% CI)	p value
MAP	0.22 (0.13 to 0.31)	<0.0001	0.08 (-0.01 to 0.17)	=0.08	0.13 (0.03 to 0.22)	<0.01	0.10 (0.01 to 0.19)	<0.05
Brachial PP	0.25 (0.16 to 0.34)	<0.0001	0.22 (0.13 to 0.30)	<0.0001	0.22 (0.12 to 0.30)	<0.0001	0.17 (0.08 to 0.25)	<0.0005
Brachial SBP	0.30 (0.22 to 0.39)	<0.0001	0.17 (0.08 to 0.26)	<0.0005	0.22 (0.13 to 0.31)	<0.0001	0.16 (0.07 to 0.24)	<0.001
Aortic PP	0.27 (0.18 to 0.35)	<0.0001	0.22 (0.13 to 0.30)	<0.0001	0.21 (0.12 to 0.30)	<0.0001	0.18 (0.09 to 0.26)	=0.0001
Aortic PI	0.20 (0.11 to 0.28)	<0.0001	0.21 (0.13 to 0.30)	<0.0001	0.16 (0.07 to 0.25)	<0.001	0.17 (0.08 to 0.26)	<0.001
Aortic Pf	0.19 (0.10 to 0.28)	<0.0001	0.15 (0.06 to 0.24)	<0.001	0.18 (0.08 to 0.26)	<0.0005	0.09 (-0.003 to 0.18)	=0.06
Aortic Pb	0.25 (0.16 to 0.33)	<0.0001	0.22 (0.13 to 0.30)	<0.0001	0.20 (0.10 to 0.28)	<0.0001	0.18 (0.10 to 0.27)	<0.0001
Aortic PWV	0.22 (0.12 to 0.31)	<0.0001	0.22 (0.12 to 0.31)	<0.0001	0.12 (0.02 to 0.21)	<0.05	0.12 (0.02 to 0.21)	<0.05

See table 4.3 for additional abbreviations. Adjustments are for age, age2, sex, body weight, regular smoking, regular alcohol intake, diabetes mellitus or an HbA1c>6.1%, pulse rate and type of antihypertensive drug treatment in hypertensives. For aortic PWV, n=395 for normotensives and 397 for hypertensives.

Table 4.5. Univariate and multivariate-adjusted relations between haemodynamic factors and left ventricular hypertrophy (LVH) in normotensives and hypertensives of a community sample.

	Bivariate relations				Multivariate-adjusted relations			
	Normotensives (n=169 of 444)		Hypertensives (n=269 of 476)		Normotensives (n=169 of 444)		Hypertensives (n=269 of 476)	
LVH versus	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
MAP	1.039 (1.013 to 1.065)*	<0.005	1.008 (0.995 to 1.021)	=0.23	1.027 (0.998 to 1.056)	=0.07	1.015 (0.999 to 1.031)	=0.07
Brachial PP	1.051 (1.027 to 1.075)*	<0.0001	1.014 (1.003 to 1.025)	<0.02	1.054 (1.027 to 1.082)*	<0.0001	1.014 (1.001 to 1.028)	<0.05
Brachial SBP	1.042 (1.022 to 1.062)*	<0.0001	1.009 (1.000 to 1.018)	=0.06	1.042 (1.020 to 1.066)*	<0.0005	1.013 (1.002 to 1.024)	<0.05
Aortic PP	1.078 (1.049 to 1.109)*	<0.0001	1.017 (1.004 to 1.029)	<0.01	1.068 (1.034 to 1.104)*	<0.0001	1.018 (1.003 to 1.034)	<0.05
Aortic PI	1.045 (1.025 to 1.066)*	<0.0001	1.013 (1.003 to 1.024)	<0.02	1.038 (1.015 to 1.062)	<0.002	1.012 (1.000 to 1.025)	=0.06
Aortic Pf	1.050 (1.011 to 1.089)	<0.02	1.014 (0.996 to 1.033)	=0.13	1.069 (1.025 to 1.116)	<0.005	1.011 (0.987 to 1.035)	=0.36
Aortic Pb	1.134 (1.081 to 1.190)*†	<0.0001	1.038 (1.014 to 1.062)	<0.005	1.125 (1.059 to 1.195)*†	=0.0001	1.051 (1.016 to 1.087)	<0.005
Aortic PWV	1.204 (1.050 to 1.381)	<0.01	1.098 (1.023 to 1.177)	<0.01	1.168 (0.987 to 1.383)	=0.07	1.103 (1.004 to 1.211)	<0.05

See table 4.3 for additional abbreviations. Adjustments are for age, age2, sex, body weight, regular smoking, regular alcohol intake, diabetes mellitus or an HbA1c>6.1%, pulse rate and type of antihypertensive drug treatment in hypertensives. *p<0.05 versus relationship in hypertensives. †p<0.05 versus relations of brachial PP and SBP. For aortic PWV, n=395 in normotensives and 397 for hypertensives.

Table 4.6. Relative independent contribution (relationships) of steady-state (mean arterial pressure [MAP]) versus pulsatile haemodynamic factors to variations in left ventricular mass index (LVMI) in normotensives and hypertensives of a community sample.

		Normotensives (n=444)		Hypertensives (n=476)	
LVMI versus		Partial r (95% CI)	p value	Partial r (95% CI)	p value
Models					
1.	MAP	0.087 (-0.007 to 0.180)	=0.07	0.024 (-0.066 to 0.115)	=0.60
	Brachial PP	0.195 (0.103 to 0.284)	<0.0001	0.138 (0.048 to 0.226)	<0.005
2.	MAP	-0.082 (-0.175 to 0.012)	=0.09	-0.092 (-0.18 to -0.01)	=0.05
	Brachial SBP	0.196 (0.104 to 0.285)	<0.0001	0.154 (0.064 to 0.241)	<0.001
3.	MAP	0.052 (-0.043 to 0.145)	=0.28	0.009 (-0.082 to 0.099)	=0.85
	Aortic PP	0.177 (0.085 to 0.267)	<0.0005	0.149 (0.059 to 0.237)	<0.005
4.	MAP	0.126 (0.032 to 0.217)	=0.009	0.077 (-0.014 to 0.166)	=0.097
	Aortic PI	0.164 (0.071 to 0.254)	<0.001	0.160 (0.070 to 0.247)	<0.001
5.	MAP	0.098 (0.004 to 0.190)	<0.05	0.071 (-0.020 to 0.160)	=0.13
	Aortic Pf	0.156 (0.063 to 0.247)	<0.005	0.059 (-0.032 to 0.149)	=0.20
6.	MAP	0.049 (-0.046 to 0.142)	=0.31	0.004 (-0.087 to 0.095)	=0.93
	Aortic Pb	0.158 (0.065 to 0.248)	<0.001	0.158 (0.068 to 0.245)	<0.0005
7.	MAP	0.115 (0.015 to 0.212)	<0.05	0.119 (0.020 to 0.216)	<0.05
	Aortic PWV	0.091 (-0.009 to 0.189)	=0.07	0.088 (-0.012 to 0.186)	=0.09

See table 4.3 for additional abbreviations. Models 1-7 include MAP and pulsatile hemodynamic factors or brachial SBP and additional covariables (age, age2, sex, body weight, regular smoking, regular alcohol intake, diabetes mellitus or an HbA1c>6.1%, pulse rate and type of antihypertensive drug treatment in hypertensives). For model 7, n=395 for normotensives and 397 for hypertensives.

Table 4.7. Relative independent contribution (relationships) of steady-state (mean arterial pressure [MAP]) versus pulsatile haemodynamic factors to left ventricular hypertrophy (LVH) in normotensives and hypertensives of a community sample.

		Normotensives (n=169 of 444)			Hypertensives (n=269 of 476)		
LVH versus		Odds ratio (95% CI)	Wald X2	p value	Odds ratio (95% CI)	Wald X2	p value
Models							
1.	MAP	1.017 (0.988 to 1.047)	1.25	=0.26	1.010 (0.992 to 1.027)	1.14	=0.29
	Brachial PP	1.052 (1.024 to 1.080)*	14.11	<0.0005	1 .010 (0.995 to 1.025)	1.84	=0.17
2.	MAP	0.952 (0.908 to 0.999)	3.99	=0.05	0.993 (0.961 to 1.027)	0.15	=0.70
	Brachial SBP	1.074 (1.035 to 1.114)*	14.34	<0.0005	1.017 (0.994 to 1.041)	2.02	=0.15
3.	MAP	1.006 (0.976 to 1.038)	0.15	=0.70	1.008 (0.990 to 1.027)	0.79	=0.37
	Aortic PP	1.066 (1.029 to 1.104)*	12.50	<0.0005	1.021 (1.001 to 1.042)	4.29	<0.05
4.	MAP	1.028 (0.999 to 1.058)	3.46	=0.06	1.016 (1.000 to 1.033)	3.83	=0.05
	Aortic PI	1.038 (1.015 to 1.062)	10.54	<0.005	1.017 (1.002 to 1.033)	4.91	<0.05
5.	MAP	1.020 (0.991 to 1.050)	1.77	=0.18	1.015 (0.997 to 1.032)	2.69	=0.10
	Aortic Pf	1.064 (1.019 to 1.112)*	7.99	<0.005	1.002 (0.974 to 1.031)	0.02	=0.88
6.	MAP	1.004 (0.972 to 1.036)	0.05	=0.82	1.004 (0.986 to 1.022)	0.19	=0.66
	Aortic Pb	1.122 (1.050 to 1.199)*	11.57	<0.001	1.047 (1.008 to 1.087)	5.54	<0.05
7.	MAP	1.030 (0.998 to 1.063)	3.41	=0.07	1.018 (0.999 to 1.037)	3.49	=0.06
	Aortic PWV	1.123 (0.945 to 1.335)	1.73	=0.19	1.082 (0.984 to 1.190)	2.65	=0.10

See table 4.3 for additional abbreviations. Models 1-7 include MAP and pulsatile hemodynamic factors or brachial SBP as indicated and additional covariables (age, age2, sex, body weight, regular smoking, regular alcohol intake, diabetes mellitus or an HbA1c>6.1%, pulse rate and rate and type of antihypertensive drug treatment in hypertensives). *p<0.05 versus relationship in hypertensives. For model 7, n=395 in normotensives and 397 for hypertensives.

Table 4.8. Relative independent contribution (relationships) of steady-state (mean arterial pressure [MAP]) versus pulsatile haemodynamic factors to variations in left ventricular mass index (LVMI) in hypertensives not receiving antihypertensive therapy (n=214).

LVMI versus		Partial r (95% CI)	p value
Models			
1.	MAP	0.133 (-0.004 to 0.265)	=0.06
	Brachial PP	0.137 (0.000 to 0.269)	=0.05
2.	MAP	0.012 (-0.125 to 0.149)	=0.87
	Brachial SBP	0.129 (-0.008 to 0.261)	=0.06
3.	MAP	0.116 (-0.022 to 0.249)	=0.10
	Aortic PP	0.153 (0.016 to 0.284)	<0.05
4.	MAP	0.177 (0.040 to 0.306)	<0.02
	Aortic PI	0.140 (0.003 to 0.272)	<0.05
5.	MAP	0.182 (0.046 to 0.311)	<0.01
	Aortic Pf	0.115 (-0.022 to 0.248)	=0.10
6.	MAP	0.136 (-0.002 to 0.268)	=0.05
	Aortic Pb	0.133 (-0.004 to 0.265)	=0.06
7.	MAP	0.180 (0.027 to 0.323)	<0.05
	Aortic PWV	0.054 (-0.100 to 0.205)	=0.49

See table 4.3 for additional abbreviations. Models 1-7 include MAP and pulsatile haemodynamic factors or brachial SBP and additional covariables (age, age^2, sex, body weight, regular smoking, regular alcohol intake, diabetes mellitus or an HbA_{1c}>6.1%, and pulse rate). For model 7, n=174).

Table 4.9. Relative independent contribution (relationships) of steady-state (mean arterial pressure [MAP]) versus pulsatile haemodynamic factors to left ventricular hypertrophy (LVH)(n=102) in hypertensives not receiving antihypertensive therapy (n=214).

LVH versus	Odds ratio (95% CI)	Wald X^2	p value
Models			
1. MAP	1.041 (1.006 to 1.077)	5.19	<0.05
Brachial PP	0.994 (0.969 to 1.018)	0.27	=0.61
2. MAP	1.049 (0.991 to 1.111)	2.74	=0.10
Brachial SBP	0.991 (0.955 to 1.028)	0.24	=0.62
3. MAP	1.037 (1.001 to 1.073)	4.07	<0.05
Aortic PP	1.000 (0.973 to 1.027)	0.00	=0.99
4. MAP	1.037 (1.005 to 1.070)	5.10	<0.05
Aortic PI	0.999 (0.980 to 1.019)	0.00	=0.94
5. MAP	1.038 (1.005 to 1.072)	5.17	<0.05
Aortic Pf	0.993 (0.945 to 1.043)	0.09	=0.77
6. MAP	1.034 (1.000 to 1.070)	3.82	=0.05
Aortic Pb	1.010 (0.950 to 1.073)	0.10	=0.75
7. MAP	1.035 (1.000 to 1.072)	3.82	=0.05
Aortic PWV	1.043 (0.882 to 1.232)	0.24	=0.62

See table 4.3 for additional abbreviations. Models 1-7 include MAP and pulsatile hemodynamic factors or brachial SBP as indicated and additional covariables (age, age^2, sex, body weight, regular smoking, regular alcohol intake, diabetes mellitus or an HbA_{1c}>6.1%, and pulse rate). *p<0.05 versus relationship in normotensives (see table 3). For model 7, n=77/174.

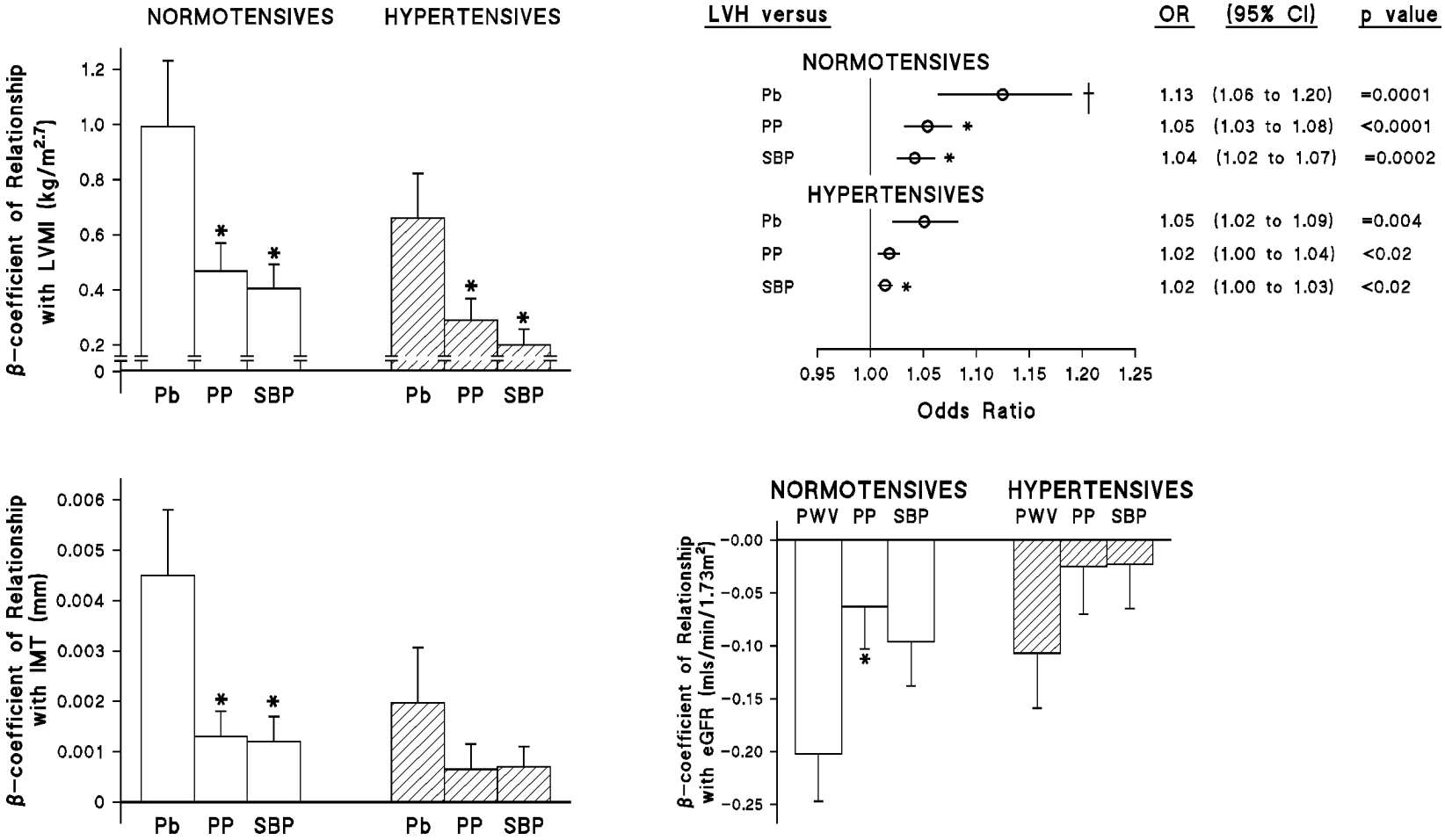

Figure 4.7. Slope (β-coefficient) of the relationships between aortic or brachial haemodynamic variables and end-organ measures and odds (Odds ratios [OR]) of left ventricular hypertrophy (LVH) associated with aortic or brachial haemodynamic variables in normotensives and hypertensives of a community sample. PP, brachial pulse pressure; SBP, brachial systolic blood pressure; Pb, aortic backward wave pressure; PWV, aortic pulse wave velocity; LVMI, left ventricular mass index; IMT, carotid intima-media thickness; eGFR, estimated glomerular filtration rate. β-coefficients for haemodynamics versus eGFR relations are standardized. Adjustments are given in Tables 2-5. *p<0.05 versus brachial PP or SBP vs end-organ relations. †p<0.05 versus relations in hypertensives.

Table 4.10. Univariate and multivariate-adjusted relations between haemodynamic factors and carotid intima-media thickness (IMT) in normotensives and hypertensives of a community sample.

	Bivariate relations				Multivariate adjusted relations			
	Normotensives (n=351)		Hypertensives (n=361)		Normotensives (n=351)		Hypertensives (n=361)	
IMT versus	r (95% CI)	p value	r (95% CI)	p value	r (95% CI)	p value	r (95% CI)	p value
MAP	0.30 (0.21 to 0.40)*	<0.0001	0.03 (-0.07 to 0.14)	=0.54	0.11 (0.006 to 0.22)	<0.05	0.08 (-0.03 to 0.18)	=0.15
Brachial PP	0.18 (0.08 to 0.28)	<0.001	0.27 (0.17 to 0.36)	<0.0001	0.13 (0.02 to 0.23)	<0.02	0.07 (-0.03 to 0.18)	=0.17
Brachial SBP	0.29 (0.19 to 0.38)	<0.0001	0.18 (0.07 to 0.27)	<0.001	0.14 (0.04 to 0.24)	<0.01	0.10 (-0.007 to 0.20)	=0.07
Aortic PP	0.32 (0.23 to 0.41)	<0.0001	0.28 (0.18 to 0.37)	<0.0001	0.18 (0.07 to 0.28)	<0.001	0.08 (-0.02 to 0.18)	=0.13
Aortic PI	0.22 (0.12 to 0.32)	<0.0001	0.27 (0.17 to 0.36)	<0.0001	0.15 (0.04 to 0.25)	<0.01	0.05 (-0.05 to 0.16)	=0.34
Aortic Pf	0.09 (-0.02 to 0.19)*	=0.11	0.26 (0.16 to 0.35)	<0.0001	0.10 (-0.005 to 0.21)	=0.06	0.11 (0.007 to 0.21)	<0.05
Aortic Pb	0.33 (0.23 to 0.42)	<0.0001	0.31 (0.21 to 0.40)	<0.0001	0.19 (0.08 to 0.29)	<0.001	0.10 (-0.007 to 0.20)	=0.07
Aortic PWV	0.41 (0.31 to 0.49)	<0.0001	0.32 (0.21 to 0.41)	<0.0001	0.12 (0.01 to 0.23)	<0.05	0.02 (-0.10 to 0.13)	=0.80

See table 4.3 for additional abbreviations. Adjustments are for age, age^2, sex, body weight, body height, regular smoking, regular alcohol intake, diabetes mellitus or an HbA_{1c}>6.1%, pulse rate and type of antihypertensive drug treatment in hypertensives. *p<0.05 versus relationship in hypertensives. Aortic PWV, n=323 in normotensives and 311 for hypertensives.

Table 4.11. Relative independent contribution (relationships) of steady-state (mean arterial pressure [MAP]) versus pulsatile haemodynamic factors to variations in carotid intima-media thickness (IMT) in normotensives and hypertensives of a community sample.

		Normotensives (n=351)		Hypertensives (n=361)	
IMT versus		Partial r (95% CI)	p value	Partial r (95% CI)	p value
Models					
1.	MAP	0.088 (-0.018 to 0.192)	=0.11	0.052 (-0.053 to 0.156)	=0.33
	Brachial PP	0.108 (0.002 to 0.212)	<0.05	0.047 (-0.058 to 0.151)	=0.38
2.	MAP	-0.001 (-0.107 to 0.106)	=0.99	-0.015 (-0.120 to 0.090)	=0.78
	Brachial SBP	0.085 (-0.021 to 0.189)	=0.12	0.061 (-0.044 to 0.165)	=0.25
3.	MAP	0.050 (-0.057 to 0.155)	=0.36	0.045 (-0.060 to 0.149)	=0.40
	Aortic PP	0.148 (0.043 to 0.250)	<0.01	0.051 (-0.054 to 0.155)	=0.34
4.	MAP	0.110 (0.004 to 0.214)	<0.05	0.072 (-0.033 to 0.175)	=0.18
	Aortic PI	0.143 (0.038 to 0.246)	<0.01	0.042 (-0.063 to 0.146)	=0.44
5.	MAP	0.096 (-0.011 to 0.200)	=0.08	0.050 (-0.055 to 0.154)	=0.35
	Aortic Pf	0.083 (-0.024 to 0.187)	=0.13	0.095 (-0.010 to 0.198)	=0.07
6.	MAP	0.035 (-0.071 to 0.141)	=0.51	0.036 (-0.070 to 0.140)	=0.50
	Aortic Pb	0.153 (0.047 to 0.254)	<0.005	0.070 (-0.035 to 0.173)	=0.19
7.	MAP	0.124 (0.013 to 0.231)	<0.05	-0.005 (-0.118 to 0.108)	=0.93
	Aortic PWV	0.104 (-0.007 to 0.212)	=0.07	0.016 (-0.098 to 0.129)	=0.79

See table 4.3 for additional abbreviations. Models 1-7 include MAP and pulsatile hemodynamic factors or brachial SBP and additional covariables (age, age^2, sex, body weight, body height, regular smoking, regular alcohol intake, diabetes mellitus or an HbA_{1c}>6.1%, pulse rate and type of antihypertensive drug treatment in hypertensives). For model 7, n=323 in normotensives and 311 for hypertensives.

Table 4.12. Relative independent contribution (relationships) of steady-state (mean arterial pressure [MAP]) versus pulsatile haemodynamic factors to variations in carotid intima-media thickness (IMT) in hypertensives not receiving antihypertensive therapy (n=153).

IMT versus		Partial r (95% CI)	p value
Models			
1.	MAP	0.09 (-0.08 to 0.25)	=0.31
	Brachial PP	0.008 (-0.16 to 0.17)	=0.93
2.	MAP	0.04 (-0.13 to 0.20)	=0.67
	Brachial SBP	0.03 (-0.14 to 0.19)	=0.73
3.	MAP	0.09 (-0.07 to 0.25)	=0.26
	Aortic PP	0.02 (-0.18 to 0.15)	=0.84
4.	MAP	0.10 (-0.07 to 0.26)	=0.24
	Aortic PI	-0.02 (-0.18 to 0.15)	=0.83
5.	MAP	0.09 (-0.07 to 0.25)	=0.27
	Aortic Pf	0.02 (-0.15 to 0.18)	=0.84
6.	MAP	0.10 (-0.06 to 0.26)	=0.23
	Aortic Pb	-0.03 (-0.20 to 0.13)	=0.71
7.	MAP	-0.004 (-0.18 to 0.17)	=0.96
	Aortic PWV	0.05 (-0.13 to 0.23)	=0.57

See table 4.3 for additional abbreviations. Models 1-7 include MAP and pulsatile haemodynamic factors or brachial SBP and additional covariables (age, age^2, sex, body weight, body height, regular smoking, regular alcohol intake, diabetes mellitus or an HbA_{1c}>6.1%, and pulse rate). For model 7, n=133.

in hypertensives (Table 4.13). With MAP and PWV in the same regression models, PWV, but not MAP was independently associated with eGFR in normotensives and hypertensives (Tables 4.14 and 4.15). With the inclusion of MAP and Pf in the same regression models, Pf showed independent relations with eGFR in normotensives, but not hypertensives; but importantly, in this model MAP retained independent associations with eGFR. With the inclusion of MAP and either brachial PP, PPc, Pb, or Pf in the same regression models, none of these pulsatile haemodynamic changes were independently associated with eGFR (Tables 4.14 and 4.15). In normotensives, without MAP included in regression models, a greater standardized slope of the relationship between PWV and eGFR was noted as compared to the standardized slope of the relationship between brachial PP and eGFR, and a trend effect was noted for the comparison with the relationship between brachial SBP and eGFR (Figure 4.7).

Do aortic pulsatile haemodynamic factors associate with end-organ measures independent of brachial BP? With brachial SBP or PP included in the same regression model as either Pb or PWV, in normotensives Pb and PWV retained independent relations with LVMI (Pb), LVH (Pb), IMT (Pb) or eGFR (PWV), whilst relations between brachial PP or SBP and end-organ measures were largely eliminated (Table 4.16). With brachial SBP or PP included in the same regression model as either Pb or PWV, in hypertensives, independent relations between Pb were noted with LVMI and between PWV were noted with eGFR, whilst relations between brachial SBP or PP and end-organ measures were eliminated (Table 4.16). In contrast to the brachial BP-independent relations between Pb or PWV and LVMI, IMT or eGFR, alternative aortic haemodynanmic parameters were either not associated with or only modestly associated with LVMI, IMT or eGFR independent of brachial BP in either the normotensive or hypertensive BP range (Tables 4.17, 4.18 and 4.19).

4.4 Discussion

The main findings of the present study are as follows. In a randomly selected community sample, across a wide range of brachial BP values within the normotensive range (<140 mm Hg), stepwise increases in PP and the major determinants thereof (backward and forward wave pressures and pulse wave velocity) were noted. This translated into significant relations between several pulsatile haemodynamic changes and end-organ measures (LVMI, LVH, IMT,

Table 4.13. Univariate and multivariate-adjusted relations between haemodynamic factors and estimated glomerular filtration rate (eGFR) in normotensives and hypertensives of a community sample.

	Bivariate relations				Multivariate-adjusted relations			
	Normotensives (n=606)		Hypertensives (n=558)		Normotensives (n=606)		Hypertensives (n=558)	
eGFR versus	r (95% CI)	p value	r (95% CI)	p value	Partial r (95% CI)	p value	Partial r (95% CI)	p value
MAP	-0.21 (-0.29 to -0.14)*	<0.0001	0.003 (-0.08 to 0.09)	=0.95	-0.12 (-0.20 to -0.04)	<0.005	-0.01 (-0.10 to 0.07)	=0.79
Brachial PP	-0.13 (-0.21 to -0.05)	<0.005	-0.19 (-0.27 to -0.11)	<0.0001	-0.09 (-0.17 to -0.008)	<0.05	-0.02 (-0.10 to 0.06)	=0.65
Brachial SBP	-0.21 (-0.28 to -0.13)	<0.0001	-0.11 (-0.19 to -0.02)	<0.02	-0.13 (-0.21 to -0.05)	<0.002	-0.02 (-0.11 to 0.06)	=0.60
Aortic PP	-0.25 (-0.32 to -0.17)	<0.0001	-0.17 (-0.25 to -0.09)	<0.0001	-0.11 (-0.19 to -0.03)	<0.01	0.01 (-0.07 to 0.10)	=0.79
Aortic PI	-0.19 (-0.26 to -0.11)	<0.0001	-0.19 (-0.26 to -0.10)	<0.0001	-0.08 (-0.16 to 0.002)	=0.06	0.02 (-0.07 to 0.10)	=0.72
Aortic Pf	-0.11 (-0.18 to -0.03)	<0.01	-0.11 (-0.20 to -0.03)	<0.01	-0.12 (-0.20 to -0.04)	<0.005	0.01 (-0.07 to 0.10)	=0.74
Aortic Pb	-0.25 (-0.33 to -0.18)	<0.0001	-0.18 (-0.26 to -0.10)	<0.0001	-0.10 (-0.18 to -0.02)	<0.02	0.01 (-0.07 to 0.10)	=0.75
Aortic PWV	-0.33 (-0.40 to -0.25)†	<0.0001	0.30 (-0.38 to -0.22)	<0.0001	-0.19 (-0.27 to -0.11)#	<0.0001	-0.10 (-0.18 to -0.005)	<0.05

See table 4.3 for additional abbreviations. Adjustments are for age, age^2, sex, body weight, body height, regular smoking, regular alcohol intake, diabetes mellitus or an HbA_{1c}>6.1, pulse rate and type of antihypertensive drug treatment in hypertensives.*p<0.05 versus relationship in hypertensives. †p<0.05 versus relations of brachial PP and SBP. #p<0.05 versus relations of brachial PP. For PWV, n=544 in normotensives and 478 for hypertensives.

Table 4.14. Relative independent contribution (relationships) of steady-state (mean arterial pressure [MAP]) versus pulsatile haemodynamic factors to variations in estimated glomerular filtration rate (eGFR) in normotensives and hypertensives of a community sample.

		Normotensives (n=606)		Hypertensives (n=558)	
eGFR versus		Partial r (95% CI)	p value	Partial r (95% CI)	p value
Models					
1.	MAP	-0.104 (-0.183 to -0.024)	=0.011	-0.003 (-0.087 to 0.081)	=0.94
	Brachial PP	-0.069 (-0.148 to 0.011)	=0.09	-0.016 (-0.100 to 0.068)	=0.71
2.	MAP	-0.023 (-0.103 to 0.058)	=0.58	0.018 (-0.066 to 0.102)	=0.67
	Brachial SBP	-0.059 (-0.138 to 0.022)	=0.15	-0.026 (-0.110 to 0.058)	=0.54
3.	MAP	-0.086 (-0.166 to -0.006)	<0.05	-0.020 (-0.104 to 0.064)	=0.64
	Aortic PP	-0.070 (-0.150 to 0.010)	=0.09	0.020 (-0.064 to 0.104)	=0.64
4.	MAP	-0.121 (-0.199 to -0.041)	<0.005	-0.014 (-0.097 to 0.070)	=0.75
	Aortic PI	-0.083 (-0.162 to -0.002)	<0.05	0.017 (-0.067 to 0.101)	=0.69
5.	MAP	-0.102 (-0.181 to -0.022)	<0.05	-0.017 (-0.101 to 0.067)	=0.69
	Aortic Pf	-0.107 (-0.186 to -0.027)	<0.01	0.019 (-0.065 to 0.103)	=0.65
6.	MAP	-0.086 (-0.165 to -0.006)	<0.05	-0.021 (-0.105 to 0.063)	=0.62
	Aortic Pb	-0.055 (-0.135 to 0.025)	=0.18	0.022 (-0.062 to 0.106)	=0.60
7.	MAP	-0.053 (-0.137 to 0.032)	=0.21	0.025 (-0.066 to 0.115)	=0.60
	Aortic PWV	-0.178 (-0.259 to -0.095)	<0.0001	-0.098 (-0.187 to -0.007)	<0.05

See table 4.3 for additional abbreviations. Models 1-7 include MAP and pulsatile hemodynamic factors or brachial SBP and additional covariables (age, age^2, sex, body weight, body height, regular smoking, regular alcohol intake, diabetes mellitus or an HbA_{1c}>6.1, pulse rate and type of antihypertensive drug treatment in hypertensives). For model 7, n=544 in normotensives and 478 for hypertensives.

Table 4.15. Relative independent contribution (relationships) of steady-state (mean arterial pressure [MAP]) versus pulsatile haemodynamic factors to variations in estimated glomerular filtration rate (eGFR) in normotensives and hypertensives not receiving antihypertensive therapy (n=278).

eGFR versus		Partial r (95% CI)	p value
Models			
1.	MAP	0.05 (-0.07 to 0.17)	=0.38
	Brachial PP	0.02 -0.10 to 0.14)	=0.75
2.	MAP	0.008 (-0.11 to 0.13)	=0.89
	Brachial SBP	0.04 (-0.09 to 0.15)	=0.57
3.	MAP	0.04 (-0.08 to 0.16)	=0.51
	Aortic PP	0.04 (-0.08 to 0.16)	=0.47
4.	MAP	0.06 (-0.06 to 0.18)	=0.32
	Aortic PI	0.04 (-0.08 to 0.16)	=0.55
5.	MAP	0.07 (-0.05 to 0.19)	=0.27
	Aortic Pf	0.005 (-0.12 to 0.13)	=0.94
6.	MAP	0.03 (-0.10 to 0.14)	=0.69
	Aortic Pb	0.08 (-0.03 to 0.20)	=0.18
7.	MAP	0.10 (-0.07 to 0.23)	=0.13
	Aortic PWV	-0.07 (-0.20 to 0.06)	=0.28

See table 4.3 for additional abbreviations. Models 1-7 include MAP and pulsatile haemodynamic factors or brachial SBP and additional covariables (age, age^2, sex, body weight, body height, regular smoking, regular alcohol intake, diabetes mellitus or an HbA_{1c}>6.1, and pulse rate). For model 7, n=237.

Table 4.16. Independent contribution (relationships) of brachial versus aortic haemodynamic factors to variations in end-organ measures in normotensives and hypertensives of a community sample.

		Normotensives		Hypertensives	
		Partial r* (95% CI)	p value	Partial r* (95% CI)	p value
Models					
LVMI versus					
1.	Aortic Pb	0.11 (0.019 to 0.206)	<0.02	0.09 (0.001 to 0.182)	<0.05
	Brachial PP	0.06 (-0.038 to 0.155)	=0.20	0.03 (-0.056 to 0.126)	=0.45
2.	Aortic Pb	0.10 (0.006 to 0.194)	<0.05	0.10 (0.013 to 0.193)	<0.05
	Brachial SBP	0.11 (0.017 to 0.204)	<0.05	0.03 (-0.061 to 0.120)	=0.52
IMT versus					
1.	Aortic Pb	0.14 (0.029 to 0.238)	<0.02	0.06 (-0.041 to 0.168)	=0.23
	Brachial PP	-0.01 (-0.120 to 0.092)	=0.79	0.001 (-0.104 to 0.105)	=0.99
2.	Aortic Pb	0.12 (0.017 to 0.226)	<0.05	0.04 (-0.065 to 0.144)	=0.46
	Brachial SBP	0.02 (-0.088 to 0.124)	=0.74	0.04 (-0.066 to 0.143)	=0.46
eGFR versus					
1.	Aortic PWV	-0.19 (-0.267 to -0.103)	<0.0001	-0.09 (-0.180 to -0.001)	<0.05
	Brachial PP	-0.05 (-0.133 to 0.036)	=0.26	-0.001 (-0.092 to 0.089)	=0.98
2.	Aortic PWV	0.18 (-0.257 to 0.093)	<0.0001	0.10 (-0.184 to -0.005)	<0.05
	Brachial SBP	-0.06 (-0.145 to 0.024)	=0.16	0.011 (-0.080 to 0.101)	=0.81
Models		OR (95% CI)	p value	OR (95% CI)	p value
LVH versus					
1.	Aortic Pb	1.10 (1.001 to 1.211)	=0.047	1.07 (1.003 to 1.139)	=0.041
	Brachial PP	1.03 (0.992 to 1.073)	=0.12	0.99 (0.966 to 1.023)	=0.68
2.	Aortic Pb	1.11 (1.022 to 1.212)	=0.014	1.05 (1.002 to 1.105)	=0.043
	Brachial SBP	1.03 (0.994 to 1.056)	=0.11	1.00 (0.986 to 1.019)	= 0.79

OR, Odds ratio; CI, confidence interval. See table 4.3 for additional abbreviations and tables 2-5 for sample sizes. Models 1 and 2 include Pb or PWV and brachial PP (model 1) or brachial SBP (model 2) together with additional covariables (age, age^2, sex, body weight, body height [for IMT and eGFR], regular smoking, regular alcohol intake, diabetes mellitus or an HbA_{1c}>6.1%, pulse rate and type of antihypertensive drug treatment in hypertensives).

Table 4.17. Independent contribution (relationships) of brachial versus aortic haemodynamic factors to variations in left ventricular mass index (LVMI) in normotensives and hypertensives of a community sample.

LVMI versus		Normotensives		Hypertensives	
		Partial r* (95% CI)	p value	Partial r* (95% CI)	p value
Models					
1.	Aortic PP	0.05 (-0.05 to 0.14)	=0.33	0.06 (-0.03 to 0.15)	=0.19
	Brachial PP	0.06 (-0.03 to 0.16)	=0.18	-0.007 (-0.10 to 0.08)	=0.88
2.	Aortic PP	0.08 (-0.02 to 0.17)	=0.11	0.09 (-0.003 to 0.18)	=0.06
	Brachial SBP	0.10 (0.001 to 0.19)	<0.05	0.03 (-0.07 to 0.12)	=0.59
3.	Aortic PI	-0.05 (-0.14 to 0.05)	=0.34	0.05 (-0.04 to 0.14)	=0.29
	Brachial PP	0.15 (0.05 to 0.24)	<0.005	0.04 (-0.06 to 0.13)	=0.45
4.	Aortic PI	0.07 (-0.02 to 0.16)	=0.14	0.11 (0.02 to 0.20)	<0.05
	Brachial SBP	0.16 (0.07 to 0.25)	<0.001	0.08 (-0.01 to 0.17)	=0.08
5.	Aortic Pf	-0.04 (-0.13 to 0.06)	=0.45	-0.05 (-0.14 to 0.05)	=0.32
	Brachial PP	0.13 (0.04 to 0.22)	<0.01	0.15 (0.06 to 0.24)	=0.001
6.	Aortic Pf	0.04 (-0.05 to 0.14)	=0.37	-0.009 (-0.10 to 0.08)	=0.85
	Brachial SBP	0.14 (0.04 to 0.23)	<0.005	0.13 (0.04 to 0.22)	=0.005
7.	Aortic PWV	0.10 (0.001 to 0.20)	<0.05	0.08 (-0.02 to 0.18)	=0.12
	Brachial PP	0.23 (0.13 to 0.32)	<0.0001	0.14 (0.04 to 0.24)	<0.01
8.	Aortic PWV	0.08 (-0.02 to 0.18)	=0.13	0.07 (-0.03 to 0.17)	=0.19
	Brachial SBP	0.22 (0.12 to 0.31)	<0.0001	0.16 (0.07 to 0.26)	=0.001

See table 4.3 for additional abbreviations and tables 2-5 for sample sizes. Models are adjusted for age, age^2, sex, body weight, regular smoking, regular alcohol intake, diabetes mellitus or an HbA_{1c}>6.1%, pulse rate and type of antihypertensive drug treatment in hypertensives.

Table 4.18. Independent contribution (relationships) of brachial versus aortic haemodynamic factors to variations in carotid intima-media thickness (IMT) in normotensives and hypertensives of a community sample.

IMT versus		Normotensives		Hypertensives	
		Partial r* (95% CI)	p value	Partial r* (95% CI)	p value
Models					
1.	Aortic PP	0.14 (0.03 to 0.24)	=0.01	0.04 (-0.07 to 0.14)	=0.50
	Brachial PP	-0.06 (-0.17 to 0.05)	=0.25	-0.01 (-0.12 to 0.09)	=0.80
2.	Aortic PP	0.11 (0.006 to 0.22)	<0.05	0.006 (-0.10 to 0.11)	=0.91
	Brachial SBP	0.01 (-0.09 to 0.12)	=0.81	0.06 (-0.05 to 0.16)	=0.31
3.	Aortic PI	0.07 (-0.04 to 0.17)	=0.22	-0.04 (-0.14 to 0.07)	=0.46
	Brachial PP	0.005 (-0.10 to 0.11)	=0.93	0.07 (-0.04 to 0.17)	=0.21
4.	Aortic PI	0.09 (-0.02 to 0.19)	=0.10	-0.002 (-0.11 to 0.10)	=0.97
	Brachial SBP	0.08 (-0.03 to 0.19)	=0.14	0.08 (-0.02 to 0.19)	=0.12
5.	Aortic Pf	-0.03 (-0.14 to 0.07)	=0.55	0.08 (-0.02 to 0.19)	=0.11
	Brachial PP	0.09 (-0.02 to 0.19)	=0.11	-0.002 (-0.11 to 0.10)	=0.97
6.	Aortic Pf	0.01 (-0.10 to 0.12)	=0.86	0.07 (-0.04 to 0.19)	=0.19
	Brachial SBP	0.10 (-0.008 to 0.20)	=0.07	0.04 (-0.06 to 0.15)	=0.43
7.	Aortic PWV	0.11 (0.001 to 0.22)	<0.05	0.001 (-0.11 to 0.12)	=0.98
	Brachial PP	0.14 (0.03 to 0.25)	<0.02	0.06 (-0.06 to 0.17)	=0.34
8.	Aortic PWV	0.10 (-0.01 to 0.21)	=0.08	0.005 (-0.11 to 0.12)	=0.93
	Brachial SBP	0.15 (0.04 to 0.26)	<0.01	0.04 (-0.07 to 0.15)	=0.48

See table 4.3 for additional abbreviations and tables 2-5 for sample sizes. Models are adjusted for age, age^2, sex, body weight, body height, regular smoking, regular alcohol intake, diabetes mellitus or an HbA_{1c}>6.1%, pulse rate and type of antihypertensive drug treatment in hypertensives.

Table 4.19. Independent contribution (relationships) of brachial versus aortic haemodynamic factors to variations in estimated glomerular filtration rate (eGFR) in normotensives and hypertensives of a community sample.

eGFR versus		Normotensives		Hypertensives	
		Partial r* (95% CI)	p value	Partial r* (95% CI)	p value
Models					
1.	Aortic PP	-0.06 (-0.14 to 0.02)	=0.14	0.10 (0.02 to 0.19)	<0.02
	Brachial PP	0.01 (-0.07 to 0.09)	=0.75	-0.11 (-0.19 to -0.02)	<0.02
2.	Aortic PP	-0.02 (-0.10 to 0.06)	=0.65	0.05 (-0.03 to 0.13)	=0.24
	Brachial SBP	-0.08 (-0.16 to 0.004)	=0.06	-0.05 (-0.14 to 0.03)	=0.21
3.	Aortic PI	-0.002 (-0.08 to 0.08)	=0.95	0.07 (-0.01 to 0.15)	=0.10
	Brachial PP	-0.04 (-0.12 to 0.04)	=0.32	-0.07 (-0.16 to 0.01)	=0.09
4.	Aortic PI	-0.02 (-0.10 to 0.06)	=0.56	0.03 (-0.05 to 0.12)	=0.46
	Brachial SBP	-0.11 (-0.19 to -0.03)	=0.01	-0.04 (-0.12 to 0.05)	=0.41
5.	Aortic Pf	-0.10 (-0.18 to -0.02)	<0.05	0.04 (-0.04 to 0.13)	=0.31
	Brachial PP	0.05 (-0.03 to 0.13)	=0.26	-0.05 (-0.13 to 0.04)	=0.28
6.	Aortic Pf	-0.05 (-0.13 to 0.03)	=0.20	0.04 (-0.05 to 0.12)	=0.40
	Brachial SBP	-0.07 (-0.15 to 0.01)	=0.10	-0.04 (-0.12 to 0.04)	=0.35
7.	Aortic Pb	-0.05 (-0.13 to 0.03)	=0.25	0.05 (-0.03 to 0.13)	=0.23
	Brachial PP	-0.02 (-0.10 to 0.06)	=0.59	-0.05 (-0.14 to 0.03)	=0.22
8.	Aortic Pb	-0.01 (-0.09 to 0.07)	=0.74	0.05 (-0.04 to 0.13)	=0.28
	Brachial SBP	-0.09 (-0.17 to -0.006)	<0.05	-0.05 (-0.13 to 0.04)	=0.25

See table 4.3 for additional abbreviations and tables 2-5 for sample sizes. Models are adjusted for age, age^2, sex, body weight, body height, regular smoking, regular alcohol intake, diabetes mellitus or an HbA_{1c}>6.1%, pulse rate and type of antihypertensive drug treatment in hypertensives.

eGFR) independent of steady-state pressures and additional confounders in the normotensive and hypertensive BP range, while in the same regression models, steady-state pressures contributed little to variations in end-organ assessments. Importantly, the impact of pulsatile haemodynamics on end-organ measures was often stronger in the normotensive than the hypertensive BP range (brachial PP, PPc, Pf and Pb for LVH); present in normotensives, but not hypertensives (brachial PP, PPc and Pb for IMT); and associated with end-organ changes independent of brachial BP in normotensives but not hypertensives (Pb for IMT). Moreover, to best identify all end-organ effects of pulsatile haemodynamics required measures of aortic function (Pb for LVMI or IMT and PWV for eGFR) in the normotensive BP range.

It is well-recognized that increases in BP within the normotensive BP range are associated with cardiovascular outcomes (Lewington et al. 2002; Vasan et al. 2001; Hsia et al. 2007; Butler et al. 2011), and in several studies this has translated into benefits of BP reduction for outcomes within this BP range (Wright et al. 2015; Tumbull et al. 2003; Law et al. 2009; Thompson et al. 2011; Thomopoulos et al. 2016; Ettehad et al. 2016; Xie et al. 2016). However, the results of BP lowering within the normotensive BP range have been inconsistent (Schrier et al. 2002; Patel et al. 2007; Yusuf et al. 2008a; Yusuf et al 2008b; Yusuf et al 2008c; Cushman et al. 2010; Cooper-DeHoff et al. 2010; McMurray et al. 2010; Brunstrom et al 2016; The SP3 Investigators 2013) and hence approaches that refine the ability to identify those at risk of an event within the normotensive BP range are required. Whether the benefits of BP lowering within the normotensive BP range in some studies (Wright et al. 2015; Tumbull et al. 2003; Law et al. 2009; Thompson et al. 2011; Thomopoulos et al. 2016; Ettehad et al. 2016; Xie et al. 2016) are mediated by reductions in largely steady-state pressures or pulsatile haemodynamic changes, is uncertain. In this regard antihypertensive therapy can reduce PP through several mechanisms including a decrease in aortic distending pressure (MAP) and thus stiffness, with a consequent decrement in forward wave pressures as well as through vasodilator-mediated reductions in aortic wave reflection. Moreover, antihypertensive therapy, through a decrease in aortic distending pressure and thus stiffness, may reduce the impedance mismatch between the aorta and more distal vessels resulting in a decreased pulsatile flow and an attenuated microvascular damage. To the best of our knowledge there is only some evidence that selective determinants of aortic PP (aortic pulse wave velocity) may predict risk in normotensives (Ben-Shlomo et al. 2014) and only one small study suggests that LV function may be determined by aortic haemodynamic factors in pre-hypertensives (Celik et al. 2013). Furthermore, an alternative study conducted in the present community suggests that aortic SBP is more closely associated with end-organ measures than brachial SBP in pre-hypertensives (Booysen et al. 2013). However, the latter study (Booysen et al. 2013) failed to identify the extent to which this was determined by pulsatile haemodynamic changes. The present study therefore provides the first strong evidence obtained in a large community-based sample that pulsatile haemodynamic factors rather than steady-state pressures account for cardiovascular end-organ changes in the

normotensive BP range and that this effect is more consistent than in the hypertensive range. It is therefore likely that antihypertensive effects on pulsatile haemodynamics account for the benefits of BP reduction within the normotensive BP range (Nissen et al. 2004; Remme et al. 2009; PROGRESS Collaborative Group 2001; Wright et al. 2015; Tumbull et al. 2003; Law et al. 2009; Thompson et al. 2011; Thomopoulos et al. 2016; Ettehad et al. 2016; Xie et al. 2016). Hence, measures of pulsatile haemodynamics may better identify those at risk of a cardiovascular event in the normotensive BP range. Moreover, targeting these pulsatile haemodynamic changes rather than brachial BP may produce data that show more consistent benefits to clinical outcomes when antihypertensive therapy is given to those traditionally considered to be normotensives, than data that has been reported on to-date (Nissen et al. 2004; Remme et al. 2009; PROGRESS Collaborative Group 2001; Wright et al. 2015; Tumbull et al. 2003; Law et al. 2009; Thompson et al. 2011; Thomopoulos et al. 2016; Ettehad et al. 2016; Xie et al. 2016; Schrier et al. 2002; Patel et al. 2007; Yusuf et al. 2008a; Yusuf et al 2008b; Yusuf et al 2008c; Cushman et al. 2010; Cooper-DeHoff et al. 2010; McMurray et al. 2010; Brunstrom et al 2016; The SP3 Investigators 2013).

Although current antihypertensive therapy reduces aortic PP and the determinants thereof, brachial SBP or PP are employed as a surrogate of these effects. However, in the present study aortic backward wave pressures showed a greater slope of the relationship with both LVMI and IMT than the slope of the relationships between brachial SBP or PP and LVMI or IMT in normotensives. Moreover, in normotensives the relationship between backward wave pressures and LVH was stronger than that between brachial SBP or PP and LVH. Furthermore in normotensives PWV, but neither brachial SBP nor PP showed independent relations with eGFR when assessed in the same multivariate models. Hence, aortic backward wave pressures and PWV may be better markers to guide therapy in normotensives. Targeting brachial SBP or PP rather than these aortic pulsatile haemodynamic changes (backward wave pressures and PWV) with antihypertensive therapy may be one possible reason why several intervention studies have failed to show benefits of BP lowering within the normotensive range (Schrier et al. 2002; Patel et al. 2007; Yusuf et al. 2008a; Yusuf et al 2008b; Yusuf et al 2008c; Cushman et al. 2010; Cooper-DeHoff et al. 2010; McMurray et al. 2010; Brunstrom et al 2016; The SP3 Investigators 2013).

Although several studies suggest that aortic PP or the determinants thereof better index the impact of pulsatile changes on cardiovascular damage than brachial PP or SBP (Wang et al. 2010; Chirinos et al. 2012; Weber et al. 2012; Zamani et al. 2014), not all studies support this notion. Indeed, the Framingham Heart Study failed to show a relationship between aortic PP or augmentation index, an index of backward wave function, and cardiovascular outcomes (Mitchell et al. 2010). However, in that study (Mitchell et al. 2010) 32% of participants were receiving antihypertensive medication, and as suggested by the present study the impact of aortic haemodynamic effects beyond brachial BP may not be as robust in the hypertensive as it

is in the normotensive BP range. Hence, the present study suggests that the use of backward wave pressures to risk predict beyond brachial BP may be more useful in normotensives than it is in hypertensives.

The limitations of the present study include the cross-sectional design which prevents us from drawing conclusions on cause and effect. Hence, it is possible that the steady-state pressure-independent relations between aortic pulsatile haemodynamic factors and end-organ measures represent residual confounding. Intervention studies are therefore required to assess whether on-treatment decreases in pulsatile haemodynamic factors best account for regression of end-organ changes in normotensives. Second, the assumptions intrinsic to the use of the 'triangulation method' of aortic wave separation (to derive aortic forward and backward wave pressures) may not be ideal (Kips et al. 2009). However, in 392 participants with aortic velocity measurements (normotensives and hypertensives), we have shown a correlation (r2) between backward wave pressure derived from the 'triangulation method' versus 'actual aortic flow' methods of wave separation of 0.82. Hence, at least in the present study, the use of the 'triangulation method' is unlikely to have significantly affected our results. Third, in the present study, calibration of the radial waveform from brachial BP measurements ignores amplification of BP from brachial to radial arteries (Picone et al. 2015). Therefore, aortic pressures are likely to have been underestimated using the current approach. Fourth, the present study was conducted in one ethnic group and more women than men participated. Our findings may therefore be sex-specific and may not apply to other ethnic groups.

4.5 Conclusions

In the present study conducted in a large, randomly selected community sample, we show that pulsatile haemodynamics and the determinants thereof rather than steady-state pressures account for end-organ changes in the normotensive BP range and that measures of brachial PP are inadequate at detecting these effects. In this regard, aortic backward wave pressures showed a greater impact on LVMI, LVH and IMT than brachial SBP or PP in the normotensive range and PWV showed an effect on eGFR beyond brachial SBP or PP. The impact of aortic pulsatile changes beyond brachial BP and steady-state pressures was often noted to be more consistent in normotensives than in hypertensives. These data suggest that the benefits of BP lowering in the normotensive range demonstrated in some studies (Nissen et al. 2004; Remme et al. 2009; PROGRESS Collaborative Group 2001; Wright et al. 2015; Tumbull et al. 2003; Law et al. 2009; Thompson et al. 2011; Thomopoulos et al. 2016; Ettehad et al. 2016; Xie et al. 2016) may be attributed to the effect of these agents on pulsatile haemodynamics. Moreover, the contrasting results of alternative studies which failed to show benefits of BP lowering within the normotensive range (Schrier et al. 2002; Patel et al. 2007; Yusuf et al. 2008a; Yusuf et al 2008b; Yusuf et al 2008c; Cushman et al. 2010; Cooper-DeHoff

et al. 2010; McMurray et al. 2010; Brunstrom et al 2016; The SP3 Investigators 2013) could be accounted for by failure to effectively achieve adequate pulsatile haemodynamic targets (backward wave pressures and PWV). Further studies are required to determine whether measures of pulsatile haemodynamic changes (backward wave pressures and PWV) refine the ability to identify those at risk of a cardiovascular event in the normotensive BP range and whether targeting pulsatile changes in these individuals rather than brachial BP with BP lowering therapy produces benefits.

CHAPTER 5

Contextual Narrative and Conclusions.

5.1 Introduction.

Sub-Saharan Africa is presently facing a health-related epidemiological transition with a shift from infectious diseases and diseases of poverty to non-communicable diseases (Bradshaw et al 2010; Dhalal et al 2011; Kapiga, 2011). In this regard, cardiovascular disease is the most common non-communicable disease accounting for death in Africa and the risk factor that explains the highest proportion of cardiovascular events in Africa is hypertension. Out of necessity, the diagnosis of hypertension and the decision to lower blood pressure (BP) is currently made according to thresholds of BP. In most countries today guidelines committees recognise a BP threshold of 140 mm Hg for systolic BP and 90 mm Hg for diastolic BP. This is despite a linear association between BP and cardiovascular events occurring from a systolic BP of as low a value as 115 mm Hg and a well-recognised relationship between BP values ranging from 120 to 140 mm Hg systolic BP (normal and high-normal BP) and end organ changes or events as compared to those with optimal systolic BP values (<120 mm Hg). Moreover, this is despite the data to substantiate a role for a possible better effect on events when lowering BP to values well below the currently accepted thresholds. The evidence for and against lower thresholds than those currently employed by most countries today has been extensively reviewed in chapter I of the present thesis. Moreover, the recent clinical trial (SPRINT) providing the evidence for BP lowering to much lower thresholds than 140/90 mm Hg is discussed in chapter 1 (Wright et al 2015). However, as also underscored in chapter 1 of the present thesis, this has not translated into lower BP thresholds for most countries and this is not only due to limitations in the interpretation of the SPRINT results, but also because of the cost implications to healthcare systems, particularly in low or middle-income countries. However, our group have contemplated the probability that the measurement of aortic function may enhance risk stratification in normotensive individuals. In chapters 2 - 4 of the present thesis I have described and discussed my findings in detail. In the present chapter, I will nonetheless discuss the importance of these findings from a more general context.

5.2 Aortic pressure better identifies those normotensives with end organ changes

As I have underscored in the introductory chapter and in chapter 4 of my thesis, our group have previously demonstrated that aortic systolic BP is better than brachial systolic BP at identifying those with a normal or a high-normal BP with cardiovascular end organ changes (Booysen et al 2013). These data (Booysen et al 2013) therefore offer an approach that may enhance risk prediction in those with a normal or a high-normal BP. However, as also highlighted in several sections throughout the present thesis, there is a great deal of uncertainty as to the value of measuring central arterial BP *per se* in enhancing risk prediction. These data have been discussed at length in chapter 1 of the present thesis. Hence, pending

outcome driven data assessing the ability of central arterial BP *per se* to enhance risk prediction in individuals with BP in the normotensive range, it is possible that central arterial BP *per se* will have a limited ability to detect those with a normal or high-normal BP who are at risk of a cardiovascular event. Consequently, in the present thesis I focussed my attention on those factors that determine the differences between central arterial and peripheral systolic BP. In this regard, it is well recognised that the main difference in central BP as compared to peripheral arterial BP is in pulsatile haemodynamics and that two factors explain the amplification of pulse pressure (PP) from the central to the peripheral arteries. As explained in chapter 1, an increased impedance to blood flow from the aorta to peripheral arteries and a greater pressure augmentation of the peripheral as compared to the central arterial pulse produced by reflected wave effects explain central-to-peripheral PP amplification. Reductions in PP amplification are in-turn determined by an increase in central arterial impedance produced by an increased aortic stiffness and enhanced central arterial reflected wave effects produced by an increased wave reflection. Thus, in the present thesis I focussed my attention on the possibility that measures of aortic stiffness and wave reflection may increase the capacity to identify those individuals with a normal or a high-normal brachial BP (controlled BP) who may have an increased risk of a cardiovascular event. In this regard, I evaluated the extent to which age-related alterations in aortic function occur in those with a normal or high-normal BP and then the extent to which these aortic functional changes could explain the effects of a normal or high-normal BP on end organ changes. However, before I assessed these questions I attempted to provide further clarity on age-related changes in aortic function at a general community level. Why was this study necessary and how has this study added to our understanding of the field?

5.3 Age-related increase in aortic pulse pressure: The role of forward or backward pressure waves

The most important factor that accounts for aortic dysfunction is an increasing age. As discussed in chapter 1 of the current thesis, age-related increases in aortic PP are determined by summation of two pressure waveforms, a forward travelling pressure wave which is largely influenced by characteristic impedance (Zc) and hence aortic stiffness and a backward travelling pressure wave that is reflected off sites of vascular tapering. As also highlighted in the introduction to the present thesis, it is therefore possible that central arterial BP identifies those at risk of events better than peripheral BP, because central arterial PP indexes the haemodynamic impact of aortic stiffness or wave reflection. However, as also underscored in the introduction to the current thesis and again in chapter 2, studies assessing the relative roles of age-related increases in forward versus backward wave pressures to age-related increases in PP had produced conflicting data (Cecelja et al 2009; Namasivayam et al 2009;

Namasivayam et al 2016; Mitchell et al 2010; Segers et al 2007; Torjesen et al 2014). Importantly, in these studies (Cecelja et al 2009; Namasivayam et al 2009; Namasivayam et al 2016; Mitchell et al 2010; Segers et al 2007; Torjesen et al 2014) a high percentage of the participants were hypertensives who were receiving antihypertensive therapy. In this regard, reflected waves are markedly influenced by vascular tone and hence some of the controversy (Cecelja et al 2009; Namasivayam et al 2009; Namasivayam et al 2016; Mitchell et al 2010; Segers et al 2007; Torjesen et al 2014) may have been related to the confounding effects of antihypertensive therapy. At this time there were no studies that had compared the contribution of aortic forward and backward wave pressures to age-related increases in aortic PP in individuals who were not receiving antihypertensive treatment, hence in the current thesis I conducted such a study. In this regard, at the time of conducting this study, populations of African ancestry in Africa tended to obey the “rule of halves” where only half of all hypertensives were receiving therapy and only half of these were treated to target BP. The outcomes of this study were a necessary prelude to better understanding the role of aortic function in contributing to increases in central arterial BP in those with a normal or high-normal BP. The results of that study were published in *J Am Soc Hypertens* (Hodson et al 2017) and are discussed and explained in chapter 2 of the current thesis. What were the essential findings of that study and how does this assist in better understanding aortic dysfunction in those with a normal or high-normal BP?

The main findings of that study (Hodson et al 2017) was that in a community sample with a high prevalence of hypertension, but in which only half of the hypertensives were receiving antihypertensive therapy, in all of the participants who were not receiving treatment although peak aortic backward wave pressures (Pb) contributed to age-related increases in aortic PP throughout the adult lifespan, peak aortic forward wave pressures (Pf) only contributed in individuals over 50 years of age. However, in product of coefficient mediation analysis, the contribution of Pb to age-related increases in aortic PP in those over 50 years of age was markedly attenuated by adjustments for Pf. Thus, although there are arguments for and against a more important role of either Pf over Pb or Pb over Pf, arguments extensively outlined in the discussion of chapter 1 and in the publication (Hodson et al 2017), there should be no question that both forward and backward wave pressures are important determinants of age-related increases in aortic PP.

An important issue not addressed in chapter 2 and worthy of emphasis at this point is the potential impact of wave re-reflection on the role of forward wave pressures in age-related increases in aortic PP. In this regard, none of the aforementioned studies (Cecelja et al 2009; Mitchell et al 2010; Namasivayam et al 2009; Namasivayam et al 2016; Segers et al 2007; Torjesen et al 2014) including our own study (Hodson et al 2017) evaluated the extent to which age-related increases in aortic Pf could be explained by excess pressure generated by backward wave pressures causing wave re-reflection (Phan et al 2016). It is only once data on

the contribution of wave re-reflection to age-related increases in aortic PP (Phan et al 2016) has been published, that conclusions on the relative contribution of forward versus backward wave pressures to age-related increased in aortic PP can be drawn. At this point however, credence must be given to an important role of both forward and backward wave pressures and their determinants as important contributors to age-related alterations in aortic PP.

As both forward and backward wave pressures are likely to be important in contributing to age-related increases in aortic PP, the possibility that the determinants of both forward and backward wave pressures contribute to increases in aortic systolic BP in the normal and the high-normal brachial BP ranges must be considered. In this regard, as extensively discussed in chapter 1 of the current thesis, and indicated again above, forward wave pressures are influenced largely by Zc and Zc is largely driven by aortic stiffness. In contrast, independent of forward wave and steady-state pressures, reflected waves are driven by the tone of distal arteries. Thus, as part of the present thesis I examined the age-related aortic functional changes that characterize those with a peripheral BP in the normotensive BP range. Indeed, a high peripheral BP is one of the strongest determinants of an abnormal aortic function and consequently, age-related changes in aortic function may be normal in the normotensive BP range. In other words, I examined whether peripheral BP control accounts for most age-related alterations in aortic function and hence whether within the normotensive peripheral BP range little residual aortic dysfunction exists. If this is indeed the case, then using aortic functional assessments to identify normotensives at risk of cardiovascular events is a redundant exercise.

5.4 Age-related changes in aortic function in the normotensive peripheral BP range.

As discussed in chapter 3 of the current thesis and in the paper published in the *Am J Hypertens* (Hodson et al 2016) I demonstrated that across the adult lifespan in a community sample of African descent with a high prevalence of uncontrolled BP, brachial BP control fails to account for most MAP-independent, age-related changes in aortic function, including increases in aortic PP, Pb, reflected wave magnitude, and aortic stiffness as indexed by carotid-femoral PWV, and decreases in PP amplification. Indeed, only modest MAP-adjusted increases in aortic PP, Pf and Pb were noted in those with an uncontrolled versus a controlled BP older than 50 years of age. In other words, marked age-related alterations in aortic functional parameters were noted in those with brachial BP values within the normal or high-normal BP range and these age-related alterations were similar to those noted in participants with a hypertensive peripheral BP. There are several implications to these data that require consideration.

Although not highlighted in the discussion of chapter 3, these findings underscore the importance of considering aortic functional changes as the possible haemodynamic disturbances that may account for cardiovascular risk in individuals with brachial BP in the normal or high-normal ranges. In this regard, we have already identified that aortic BP may

better identify those individuals with a normal or a high-normal brachial BP with end organ changes (Booysen et al 2013). However, as described in the introduction to the current thesis, the role of aortic PP or systolic BP in the prediction of risk independent of peripheral BP may be limited and hence the determinants of differences between aortic and peripheral PP or PP amplification itself may need to be considered as possible measures that may enhance risk prediction in the normotensive BP range. In this regard, as highlighted in chapter 1 and again briefly outlined above, differences between central and peripheral arterial BP are determined by two major factors and that is the extent of the impedance mismatch between the aorta and more peripheral vessels which is in-turn determined by aortic stiffness and differences in the impact of wave reflection on peripheral as opposed to central arteries. As several indexes of aortic stiffness (PWV) and reflected wave function (Pb and RM or RI) were markedly altered by age irrespective of BP control, it is possible that these age-related alterations in aortic function explain cardiovascular damage even n individuals with brachial BP within the normal or high-normal ranges and that these effects occur independent of aortic PP. Indeed, RM predicts cardiovascular events beyond brachial BP whilst aortic PP does not (Chirinos et al 2012; Zamani et al 2015) and aortic PWV predicts events beyond brachial BP (Ben-Shlomo et al 2014; Vlachopoulos et al 2010) whilst aortic PP fails to achieve significance (Vlachopoulos et al 2010). In this regard, as discussed at length in the introductory chapter to the current thesis, aortic stiffness may produce several haemodynamic changes that account for cardiovascular events beyond pulsatile load as indexed by aortic PP, and reflected waves may mediate pulsatile damage through an impact that is confounded by the effects of forward wave pressure on aortic PP (Sibiya et al 2015).

The results of the data described in chapter 3 have several additional implications that have been extensively discussed in that chapter and in the publication originating from that study (Hodson et al 2017). In this regard, as discussed although it is well-accepted that targeting brachial BP with BP lowering therapy modifies several aspects of age-related aortic functional changes, including increases in aortic PP; indexes of wave reflection and decreases in PP amplification (Agabiti-Rosei et al 2007), the study described in chapter 3 suggests that most age-related aortic haemodynamic changes remain unaccounted for when brachial BP is controlled. The study described in the present thesis (Hodson et al 2017) therefore supports the views that the identification of thresholds for reflected wave function, aortic PWV, and PP amplification may increased the prediction of risk independent of brachial BP (Townsend et al 2015) and that targeting aging-induced aortic haemodynamic changes in either normotensives or hypertensives may result in further reductions in cardiovascular events.

As I was able to show that age-related alterations in indexes of aortic reflected wave function and stiffness were as distinct in the normotensive as in the hypertensive peripheral BP range, I subsequently assessed whether these indexes could increase the ability to identify end organ changes and whether this ability was similar in the normotensive as compared to in the

hypertensive brachial BP range. What were the results of this study and the implications thereof?

5.5. Aortic function and end organ changes in the normotensive BP range

As discussed in chapter 4 of the current thesis and in the paper published in *J Hypertens* (Hodson et al 2017) I demonstrated that in a randomly selected community sample, across a wide range of brachial BP values within the normotensive range (SBP<140 mm Hg), stepwise increases in aortic PP and the major determinants thereof (backward and forward wave pressures and pulse wave velocity) were noted. This translated into significant associations between several pulsatile haemodynamic changes and end-organ measures (left ventricular mass index, left ventricular hypertrophy, carotid intima-media thickness and estimated glomerular filtration rate) beyond steady-state pressures and additional confounders in the normotensive and hypertensive BP range. In the same regression models, steady-state pressures contributed little to variations in end-organ measures. Importantly, the impact of pulsatile haemodynamics on end-organ measures was often stronger in the normotensive BP range than it was in the hypertensive BP range (brachial PP, aortic PP, Pf and Pb for left ventricular hypertrophy); present in normotensives, but not hypertensives (brachial PP, aortic PP and Pb for carotid intima-media thickness); and related to end organ changes beyond brachial BP in normotensives but not in hypertensives (Pb for carotid intima-media thickness). Moreover, to best identify all of the end organ effects of pulsatile haemodynamics required aortic function measurements (Pb for left ventricular mass index or carotid intima-media thickness and PWV for estimated glomerular filtration rate) in the normotensive BP range.

As underscored in the introductory chapter and also in chapter 4 of the current thesis, it is well-recognized that increases in BP within the normotensive BP range are related to cardiovascular outcomes (Butler et al 2011; Hsia et al 2007; Lewington et al 2002; Vasan et al 2001). In a number of studies this has translated into beneficial effects of BP reduction on cardiovascular outcomes within the normotensive BP range (Ettehad et al 2016; Law et al 2009; Thompson et al 2011; Thomopoulos et al 2016; Tumbull et al 2003; Wright et al 2015; Xie et al 2016). However, the results of BP lowering within the normotensive BP range have not been consistent (Brunstrom et al 2016; Cooper-DeHoff et al 2010; Cushman et al 2010; McMurray et al 2010; Patel et al 2007; Schrier et al 2002; Yusuf et al 2008a; Yusuf et al 2008b; Yusuf et al 2008c; The SP3 Investigators 2013). Hence approaches that refine the ability to detect individuals at risk of a cardiovascular event within the normotensive BP range are required. Whether the benefits of decreasing BP within the normotensive BP range in some studies (Ettehad et al 2016; Law et al 2009; Thompson et al 2011; Thomopoulos et al 2016; Tumbull et al 2003; Wright et al 2015; Xie et al 2016) are mediated by decreases in largely steady-state pressures or pulsatile haemodynamic changes, is unclear. In this regard antihypertensive

treatment can reduce PP through a number of mechanisms including a reduction in aortic distending pressure (MAP) and hence stiffness, with a consequent decrease in forward wave pressures as well as through vasodilator-mediated reductions in aortic wave reflection. Moreover, antihypertensive treatment, through a reduction in aortic distending pressure and hence stiffness, may decrease the impedance mismatch between the aorta and more distal vessels resulting in a reduced pulsatile flow and an attenuation in damage to the microvasculature. To the best of our knowledge there is only some evidence that selective determinants of aortic PP (aortic pulse wave velocity) may predict risk in normotensives (Ben-Shlomo et al 2014) and only one small study suggests that left ventricular function may be determined by aortic haemodynamic factors in pre-hypertensives (Celik et al 2013). Furthermore, an alternative study conducted in the present community suggests that aortic systolic BP is more closely related to end organ measures than brachial systolic BP in pre-hypertensives (Booysen et al 2013). However, the latter study (Booysen et al 2013) failed to identify the extent to which this relationship was determined by pulsatile haemodynamic changes. The results of our recent study (Hodson et al 2017) therefore provide the first strong evidence obtained in a large community-based sample that pulsatile haemodynamic factors rather than steady-state pressures account for cardiovascular end organ changes in the normotensive BP range and that this effect is more consistent than in the hypertensive BP range. It is therefore likely that the antihypertensive effects on pulsatile haemodynamics are responsible for the benefits of BP reduction within the normotensive BP range (Ettehad et al 2016; Law et al 2009; Nissen et al 2004; Remme et al 2009; PROGRESS Collaborative Group 2001; Thompson et al 2011; Thomopoulos et al 2016; Tumbull et al 2003; Wright et al 2015; Xie et al 2016). Hence, measures of pulsatile haemodynamics may better detect those individuals with brachial BP in the normotensive range who are at risk of a cardiovascular event. Moreover, targeting these pulsatile haemodynamic changes rather than brachial BP may produce data that show more consistent benefits to clinical outcomes when antihypertensive therapy is given to those individuals traditionally considered to be normotensives, than the data that has been reported on to-date (Brunstrom et al 2016; Cooper-DeHoff et al 2010; Cushman et al 2010; Ettehad et al 2016; Law et al 2009; McMurray et al 2010; Nissen et al 2004; Patel et al 2007; PROGRESS Collaborative Group 2001; Remme et al 2009; Schrier et al 2002; The SP3 Investigators 2013; Tumbull et al 2003; Thompson et al 2011; Thomopoulos et al 2016; Wright et al 2015; Xie et al 2016; Yusuf et al 2008a; Yusuf et al 2008b; Yusuf et al 2008c).

Although current antihypertensive therapy decreases aortic PP and the determinants thereof, brachial systolic BP or PP are used as a surrogate of these effects. However, in the study described in chapter 4, aortic backward wave pressures showed a greater slope of the relationship with both left ventricular mass index and carotid intima-media thickness than the slope of the relationships between brachial SBP or PP and left ventricular mass index or carotid intima-media thickness in normotensives. Moreover, in normotensives the association between

backward wave pressures and left ventricular hypertrophy was stronger than that between brachial systolic BP or PP and left ventricular hypertrophy. Furthermore in normotensives PWV, but neither brachial systolic BP nor PP showed independent relations with estimated glomerular filtration rate when assessed in the same multivariate models. Hence, it is possible that aortic backward wave pressures and PWV are better markers to guide therapy in normotensives. Targeting brachial systolic BP or PP rather than these aortic pulsatile haemodynamic changes (backward wave pressures and PWV) with antihypertensive therapy may be one possible reason why several intervention studies have failed to show benefits of BP lowering within the normotensive range (Brunstrom et al 2016; Cooper-DeHoff et al 2010; Cushman et al 2010; McMurray et al. 2010; Patel et al 2007; Schrier et al 2002; The SP3 Investigators 2013; Yusuf et al 2008a; Yusuf et al 2008b; Yusuf et al 2008c).

Although a number of studies suggest that aortic PP or the determinants thereof better index the impact of pulsatile changes on cardiovascular damage than do brachial PP or systolic BP (Chirinos et al 2012; Wang et al 2010; Weber et al 2012; Zamani et al 2014), not all studies support this idea. Indeed, the Framingham Heart Study failed to show an association between aortic PP or augmentation index, an index of backward wave function, and cardiovascular outcomes (Mitchell et al 2010). However, in that study (Mitchell et al 2010) 32% of participants were receiving antihypertensive treatment, and as suggested by the present study the impact of aortic haemodynamic effects beyond brachial BP may not be as robust in the hypertensive BP range as it is in the normotensive BP range. Hence, the present study suggests that the use of backward wave pressures to risk predict beyond brachial BP may be more useful in normotensive individuals than it is in hypertensive individuals.

5.6 Limitations

The limitations to the current thesis have primarily been addressed in the relevant chapters. However, it is important to highlight several additional points. First, as pointed out throughout the current thesis relationships do not mean causality and hence longitudinal studies are required to assess the changes in aortic function with age and the ability of aortic functional changes to determine cardiovascular damage. These studies will require the evaluation over the entire adult human lifespan and hence are only feasible if planned to continue for decades to come. End organ changes are not events and hence outcome-based studies are required to determine whether aortic functional changes or the changes produced by antihypertensive therapy predict events. Because of poor follow-up in African populations, these studies are not feasible in our country (we predict only a 40% follow-up rate). Third, as also highlighted throughout the present thesis I employed SphygmoCor software in the majority of studies described to wave separate forward and backward pressure waves. Although for some of the studies I showed in sensitivity analysis that these findings could be reproduced using data

obtained from wave separation analysis using actual aortic flow waves, further studies are underway in our laboratory to wave separate in a much larger study sample using actual aortic flow waves. Importantly, using this approach we are also identifying the contribution of that component of forward wave pressures determined by the product of Q and Zc (Figure 1.2) and that component which is determined by wave re-reflection.

5.7 Conclusions

In the present thesis study conducted in a large, randomly selected community sample, I show first that independent of the effects of antihypertensive therapy, aortic backward waves contribute to age-related increases in aortic PP across the adult lifespan, but at an older age, this effect may be attributed in-part to the impact of forward on backward wave pressures. Second I show that brachial BP control in the general population fails to account for most distending pressure-independent, age-related changes in aortic haemodynamics, including changes in backward wave pressures, across the adult lifespan. In other words, age-related aortic dysfunction including increases in aortic stiffness and wave reflection characterize those individuals with a normal or high-normal peripheral BP as much as those with a hypertensive peripheral BP. Third, I show that pulsatile haemodynamics and the determinants thereof rather than steady-state pressures account for end organ changes in the normotensive BP range and that measures of brachial PP are inadequate at detecting these effects. In this regard, indexes of aortic stiffness and wave reflection best identify normotensives with end organ changes. The data described in the present thesis therefore highlight the importance of age-related changes in aortic function beyond brachial BP, even in the normotensive peripheral BP range. The present thesis therefore highlights the possibility that indexes of aortic function may enhance risk prediction across a wide range of peripheral BP values, including those in the normal or high-normal BP range.

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Appendix I: Ethics Clearances Certificates

R14/49 Mr Bryan Hodson et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M170769

NAME: (Principal Investigator)	Mr Bryan Hodson et al
DEPARTMENT:	School of Physiology University of Witwaterand, Faculty of Health Sciences School of Physiology
PROJECT TITLE:	The Impact of Brachial Blood Pressure Control and Antihypertensive Therapy on Aortic Function
DATE CONSIDERED:	Adhoc
DECISION:	Approved unconditionally
CONDITIONS:	Sub-study under Primary Study M1604106
SUPERVISOR:	Prof Gavin Norton and Prof Angela Woodiwiss
APPROVED BY:	Professor CB. Penny Co-Chairperson, HREC (Medical)
DATE OF APPROVAL:	18/08/2017

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

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004,10th floor, Senate House/3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/We fully understand the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. in this case, the study was initially review July and will therefore be due in the month of July each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

R14/49 Prof Angela Woodiwiss and Prof Gavin Norton

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M170401

NAME: (Principal Investigator)	Prof Angela Woodiwiss and Prof Gavin Norton
DEPARTMENT:	School of Physiology
PROJECT TITLE:	Gene Candidates as Determinants of Blood Pressure and Intermediary Phenotypes in the Pathogenesis of Hypertension in Black South Africans
DATE CONSIDERED:	26/04/2002 (Initial Approval)
DECISION:	Approved unconditionally
CONDITIONS:	Renewal for 5 Years Valid for the Period 01 April 2017 - 30 April 2022 Previously M1204108, M070469 and M020472
SUPERVISOR:	Prof Angela Woodiwiss
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	07/04/2017

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

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in April and will therefore be due in the month of April each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature _____ Date _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix II: Turn-it-in Report