

https://dspace.org/

Effects of blood pressure reduction on central arterial pressure waves in severe pre-eclampsia

Carreira, Nicol

2020
https://hdl.handle.net/10539/31637

Downloaded from a DSpace repository. https://dspace.org/

Effects of Blood Pressure Reduction on Central Arterial Pressure Waves in Severe Pre-eclampsia

Nicol Carreira

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in Anaesthesia

Supervisors: Gavin Norton

Oliver Smith

Angela Woodiwiss

DECLARATION

I, Nicol Marie Carreira declare that this Research Report is my own, unaided work. It is being submitted for the Degree of Master of Medicine in Anaesthesia at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

_____

Signature of candidate

_____23rd_____day of_____September_____20_____20_____in _____Johannesburg_____

ACKNOWLEDGEMENTS

Thank you to my husband for the countless hours of support and editing and input.

Thank you to Gavin Norton for your academic input and endless patience.

Thank you to Angela Woodiwiss for your academic input and kindness.

Thank you to Oliver Smith for your clinical input and support.

Thank you to the department of Obstetrics and Gynaecology for allowing us to collect data in their admissions and high care areas.

ABSTRACT

BACKGROUND

Hypertensive disorders of pregnancy are the second commonest cause of morbidity and mortality in pregnancy. Severe pre-eclampsia is a hypertensive emergency with a high mortality rate. Even in survivors of pre-eclampsia, the lifelong risk of cardiac events is increasedUntreated hypertension results in target organ damage in organs which are supplied by a pulsatile blood flow, such as the kidneys and the brain.

AIM

Although blood pressure (BP) reduction in severe pre-eclampsia is well recognised as preventing the complications thereof, the impact of BP reduction on central arterial pulsatile load mediated by wave reflection, which is not detected at the brachial pulse, is unknown.

METHODS

Using non-invasive tonometric approaches and wave separation analysis (SphygmoCor software) the impact of BP reduction using standard pharmacological approaches on central arterial pressure waves was determined in 19 women with a *de novo* diagnosis of severe pre-eclampsia.

RESULTS

Whilst brachial BP was markedly reduced ($p<0.0001$), brachial pulse pressure (PP) failed to show significant decreases ($p=0.10$) with therapy. In contrast, even after adjustments for steady component pressures (mean arterial pressure) central arterial PP (PPc) decreased ($p<0.01$) and this change was attributed to an attenuation of reflected (backward wave, Pb) ($p<0.05$), but not forward ($p=0.64$) wave pressures. Although pharmacological reduction in BP was strongly associated with decreases in arteriolar tone (as indexed by mean arterial pressure, MAP), the strong relations between decreases in Pb and PPc ($p<0.0001$) were unaffected by adjustments for MAP.

CONCLUSION

This study is the first to assess the effect of antihypertensive therapy on central aortic pressures in a hypertensive emergency. Central arterial pulsatile load is decreased by standard pharmacological approaches to managing hypertensive emergencies in pre-eclampsia. Importantly, this effect is through an impact of therapy on wave reflection independent of arteriolar function and no peripheral BP measure adequately indexes this beneficial effect.

TABLE OF CONTENTS

DECLARATION 2
ABSTRACT 4
LIST OF TABLES 7
LIST OF ABBREVIATIONS 8
INTRODUCTION 11
1.2 Pulse pressure in central and peripheral arterial pulses 13
1.3 Components of central aortic pulsatile load (forward and backward waves). 15
1.4. Why do changes in the peripheral pulse not adequately index central arterial pulsatile load? . 17
1.5 Determinants of the component waves of central arterial pulse pressure. Possible changes in pregnancy 18
1.5.2 Reflected waves 22
1.6. The haemodynamic consequences of pregnancy 22
1.7. Pre-eclampsia and associated cardiovascular risk 23
1.7.1 Pathogenesis of pre-eclampsia 23
1.7.2 Pre-eclampsia and the disrupted glycocalyx 24
1.7.3 Cerebrovascular changes in pre-eclampsia 25
1.7.4 Posterior Reversible Encephalopathy Syndrome (PRES) and Reversible Cerebral Vasoconstriction Syndrome (RCVS) 26
1.7.5 Renal consequences of pre-eclampsia 26
1.7.6 The haemodynamic changes in pre-eclampsia 27
1.7.7 Importance of the contribution of pulsatile load to cerebral and renal damage: Relevance to pre-eclampsia 28
1.8 Antihypertensive effects and central versus peripheral BP 28
1.9 Problem statement 31
1.10. Aims 31
METHODS 33
RESULTS 41
DISCUSSION 55
REFERENCES 61
APPENDIX 1 68
APPENDIX 2 69
APPENDIX 3 70
APPENDIX 4 71

LIST OF FIGURES

Figure **Page**

1.1 Arterial pressure waveforms determined from central to peripheral vessels……..……10

1.2 Central aortic and component pressure traces……..……12

1.3 Derived peripheral and central pressure traces……..15

1.4 Alterations in the aortic pressure-volume relationship ……..……17

2.1 SphygmoCor device employed to evaluate central arterial pressures.....……..……32

2.2 Derived non-invasive central arterial pulse wave……..……33

2.3 Approach used to determine the triangulation method of central aortic pressure assessment……34

3.1 The effect of antihypertensive therapy ……..……41

3.2 The effect of antihypertensive therapy on central arterial pulsatile wave components ……45

LIST OF TABLES

Table Page

3.1 Participant characteristics.....39

3.2 The effect of antihypertensive therapy on unadjusted brachial and central artery blood pressure in severe pre-eclamptics.....41

3.3 The effect of antihypertensive therapy on central arterial pulsatile wave components or aortic pulse wave velocity (PWV) in severe pre-eclamptics 44

3.4 Relationships between changes in central artery pulse pressure (PP) and changes in central artery pressure components in response to antihypertensive therapy.....46

3.5 Bivariate correlations between brachial or central artery blood pressure (BP) or pulse wave velocity and laboratory values in severe pre-eclamptics 47

3.6 Multivariate stepwise regression model to identify the primary determinants of changes in central artery pulse pressure (PP) with antihypertensive therapy.....49

LIST OF ABBREVIATIONS

ACEI angiotensin converting enzyme inhibitors

AIx Augmentation index

ALT alanine aminotransferase

AP Augmented pressure

AST aspartate aminotransferase

BBB Blood brain barrier

BH Body height

BMI Body mass index

BP Blood pressure

BW Body weight

CCB Calcium channel blocker

CO Cardiac output

cPP Central pulse pressure

DBP Diastolic blood pressure

DM Diabetes mellitus

GFB glomerular filtration barriers

IL Interleukin

ISH Isolated systolic hypertension

Hb Haemoglobin

HELLP Haemolysis. Elevated Liver Enzymes and Low Platelets

HR Heart rate

LV Left ventricle

MAP Mean arterial pressure

$MgSO_4$ Magnesium sulphate

Pa Augmentation pressure

Pb Backward wave pressure

Pf Forward wave pressure

Pi Incident wave

Plt Platelets

PP Pulse pressure

PPamp Pulse pressure amplification

PRES Posterior Reversible Encephalopathy Syndrome

PWV Pulse wave velocity

Q peak aortic flow

R Pearson's correlation coefficient

RAS renin-angiotensin system

RM Reflected magnitude

RCVS Reversible Cerebral Vasoconstriction Syndrome

SBP Systolic blood pressure

sFLT-1 soluble fms-like tyrosin kinase-1

SD Standard deviation

SEM Standard Error of the mean

SVR systemic vascular resistance

TNF-α Tumor necrosis factor alpha

U:Cr Urea-to-creatinine ratio

VEGF-A vascular endothelial growth type factor A

Zc characteristic impedance

INTRODUCTION

Globally, hypertension is a major cause of morbidity and mortality in pregnancy(Deaths, 2015 #30;Pattinson, 2006 #6;Say, 2014 #7;Theron, 2011 #31). As noted in the last four confidential enquiries into maternal deaths, hypertension is the second commonest cause of maternal death in South Africa (1, 4-6) and was identified as the cause of greatest concern in the last enquiry (6). Hypertensive disorders of pregnancy are diagnosed after 20 weeks' gestation and are classified according to changes in biochemistry, haematology and the presence or absence of proteinuria (7, 8). Pre-eclampsia is characterised by a blood pressure (BP) between 140-159mmHg systolic and/ or 90-109 mmHg diastolic BP and is associated with at least 1+ proteinuria on a midstream urine sample measured with a standard reagent strip or a urine protein: creatinine ratio greater than 30mg/mmol without target organ damage (7, 8). Pre-eclampsia is further classified in terms of its' onset during gestation, where early and late onset occur before, and after 34 weeks' gestation, respectively. Pre-eclampsia may progress to severe pre-eclampsia, which is defined as pre-eclampsia with a systolic BP greater than 160mmHg or a diastolic BP ≥ 110mmHg or with signs of organ dysfunction, such as renal, hepatic or central nervous system dysfunction. Pre-eclampsia may subsequently progress to become eclampsia, which is characterised by raised intracranial pressure, resulting in seizures. Pre-eclampsia may also be accompanied by a syndrome characterised by the presence of hypertension, elevated liver enzymes and low platelet counts (HELLP syndrome), the consequences of which are organ dysfunction and a higher risk of morbidity and mortality (7).Thus, several pathophysiological changes may occur in pregnancy-associated hypertension which ultimately lead to advanced clinical complications in pre-eclampsia.

Cerebrovascular changes are the major cause of death from pre-eclampsia, with intracranial haemorrhage accounting for most deaths(9-12). For a number of reasons women of African ancestry are three times more likely to die from intracerebral haemorrhage than any other group (13). Data to show the importance of intracranial haemorrhage as the major cause of death from pre-eclampsia came from the MAGPIE trial conducted prior to the worldwide acceptance of magnesium sulphate as a treatment for the prevention of target organ damage associated with pre-eclampsia (14). The MAGPIE trial marked a significant shift in treatment of eclampsia and subsequently the incidence of cerebrovascular haemorrhage decreased in economically developed countries(14). Other causes of death have subsequently emerged, with multi organ damage including renal and hepatic failure and pulmonary oedema (15) occurring more frequently than before. However, cerebrovascular haemorrhage remains the primary cause of death in pre-eclampsia in the developing world (12, 16).
As shall be discussed later in this chapter, the cause of organ failure in severe pre-eclampsia is recognised as being a consequence of several changes at a cellular level. However, these changes are

associated with an increased susceptibility to damage produced by a raised pressure load (hypertension) and an increase in blood pressure *per se*. Thus, treating BP levels to target is well recognised as preventing the complications of pre-eclampsia. Despite recent advances in guidelines regarding the treatment of pre-eclampsia (7, 17), the haemodynamic management of pre-eclampsia nevertheless remains a challenge for the obstetrician and the peri-operative physician. Importantly, what has not been given significant attention is the relative role of different components of central as opposed to peripheral arterial BP load in mediating the adverse effects of BP in pre-eclampsia; whether changes noted in the central arterial pulse are adequately managed by current approaches to treating pre-eclampsia; and from peripheral arterial BP measurements how best to identify whether these central arterial effects have indeed occurred. In the present chapter I will therefore describe the contemporary view of the haemodynamic components of BP that cause cardiovascular damage; explain how the peripheral arterial pulse is in-part limited in the ability to detect these central arterial loading conditions and in so doing, identify the importance of the question addressed in the present dissertation.

1.1 Steady-state versus pulsatile pressure load

The adverse effects of hypertension are currently viewed as being mediated by increases in a steady-state or a pulsatile pressure load. While steady-state pressure loads are best indexed by mean arterial pressure (MAP), for convenience, diastolic BP (DBP) is generally employed as a surrogate thereof. In contrast although pulsatile load is best indexed by pulse pressure (PP=Systolic BP-diastolic BP), for convenience systolic BP (SBP) is employed as a surrogate thereof. The argument as to the relative importance of steady-state and pulsatile loads as causes of cardiovascular damage has largely originated from debate over the last century as to the importance of SBP versus DBP. For many years DBP was considered the only BP component of hypertension that can be modified, and thus was considered as being the primary target for antihypertensive treatment. In this regard, isolated increases in SBP (isolated systolic hypertension, ISH) were initially thought to represent a benign adaptation to progressive arterial vessel stiffening associated with old age (18). The Framingham Heart Study, as well as other studies, nevertheless demonstrated that SBP was an important determinant of morbidity and mortality. Indeed, SBP has been shown to be a greater predictor of mortality than DBP (18) with SBP showing a predictive value independent of the effects of DBP after the age of 50 years (19). Further work has highlighted the importance of ISH as a key cause of cardiovascular events. Indeed, landmark trials such as the Systolic Hypertension in the Elderly Program (1) and the SYST-EUR and SYST-CHINA trials have demonstrated the importance of decreasing SBP and PP without necessarily modifying DBP in those with largely increases in SBP and PP in cardiovascular risk reduction (21, 22). The therapeutic

targets for antihypertensive therapy are therefore well accepted as including both systolic and diastolic BP components. As such, steady-state and pulsatile pressure loads are presently considered as modifiable and important targets for risk reduction in hypertension. However, as will be discussed the pulsatile components of BP that cause cardiovascular damage are often not detected with a brachial BP measurement.

1.2 Pulse pressure in central and peripheral arterial pulses

As highlighted in above discussion the deleterious effects of increases in SBP are largely accounted for by PP effects (23, 24). In this regard, PP increases from the central aorta to the peripheral arteries, an effect referred to as PP amplification. Pulse pressure amplification is the consequence of differences in the characteristics of arteries in the central aorta as compared to the periphery. Thus, a decrease in vessel diameter and in the elastin to collagen ratios characterise more peripheral as compared to more central (aorta) arteries. The decreased elastin-to-collagen ratio generates a greater stiffness (less compliance) in more peripheral vessels. In this regard, a fundamental functional role of the aorta is to store elastic energy during ventricular ejection so that recoil of this normally compliant vessel maintains forward flow in the diastolic period when the heart is relaxing. To generate elasticity, the aorta contains a high proportion of elastin and a low proportion of the stiff collagen molecule. In contrast, peripheral vessels do not contribute to the ability to maintain flow in diastole and hence contain far less elastin and far more collagen, the consequence being that they are stiffer and less compliant than the aorta. Thus, as a pulse wave generated in central arteries (proximal aorta) travels peripherally to the brachial artery it encounters decreased diameter and stiffer (less compliant) vessels and thus an increased resistance to forward flow in a pulsatile system (known as impedance) (25-27). The greater impedance to flow generated from central to peripheral arteries (often called an impedance mismatch) therefore amplifies the pulse as it travels outward resulting in a more pronounced peak of the pressure wave (Figure 1.1). The peak of the peripheral pulse wave is obviously SBP. In contrast, DBP (or the trough of the forward travelling pressure wave), which is not determined by the impedance to flow, but rather by arteriolar function which generates systemic vascular resistance (SVR), is unaffected by differences in central and peripheral arterial pressures (28). As the peripheral pulse is strikingly different from the aortic pulse, over the past several decades it has been questioned as to whether non-invasively determined central arterial

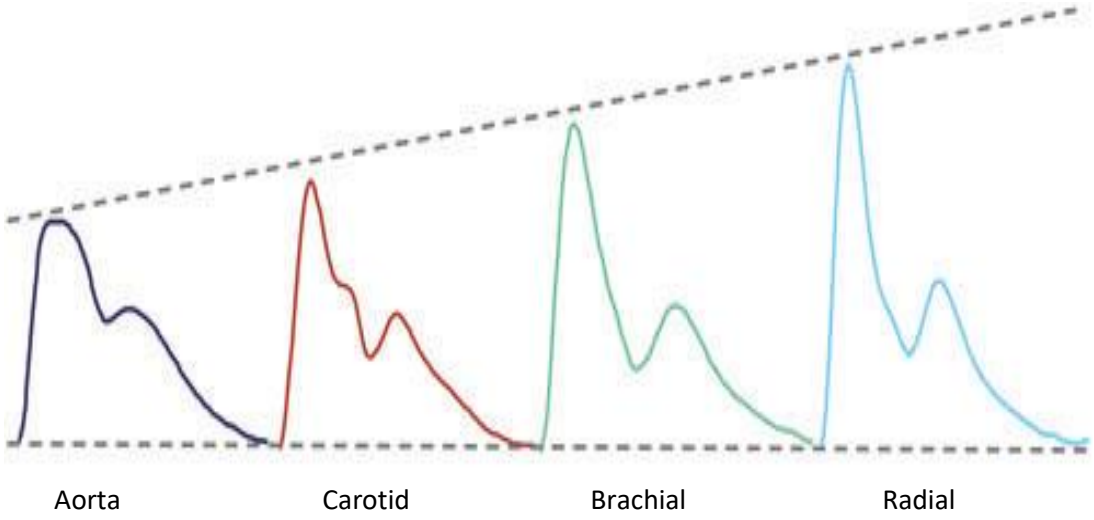


Figure 1.1 Arterial pressure waveforms determined from central to peripheral vessels, illustrating the increase in pulse pressure (pulse pressure amplification) which occurs from the central aorta to the peripheral pulse. (Adapted from McEniery, 2014).

pressures better index the adverse effects of BP than brachial BP measurements. In this regard, adverse effects produced by several factors that influence central arterial loads have been demonstrated to predict risk beyond brachial BP. What then are the factors which determine pulsatile load in central arteries that may not be adequately detected at the peripheral pulse?

1.3 Components of central aortic pulsatile load (forward and backward waves).

The central arterial pulse wave which determines PP and hence SBP centrally, is comprised of both forward and reflected (backward) travelling pressure waves (29) (Figure 1.2). During ventricular ejection, the contracting left ventricle generates a forward travelling pressure wave that as with any oscillating wave (such as a sound wave) is then transmitted throughout the systemic arterial tree. When oscillating pressure waves reach areas of bifurcation, the impedance mismatch (change from a very compliant aorta to less compliant peripheral artery) results in wave reflection and the oscillating reflected pressure wave travels back up the arterial tree to the proximal aorta. Several points of impedance mismatch occur along the arterial tree resulting in the generation of multiple oscillating reflected waves. These oscillating reflected pressure waves travel sufficiently rapidly that they meet the oscillating forward travelling pressure wave at various points along the arterial tree. As with any oscillating wave, the forward and reflected waves are often timed so that at points where antinodes overlap, summation of the two waves will occur . Although innumerable reflected pressure waves are generated at multiple points in the arterial tree, many will return to the aorta and summate together to generate what appears to be a single reflected wave (backward wave, the peak of which is designated Pb) in the proximal aorta (Figure 1.2)(23).

Importantly, at a peripheral level, as reflected waves do not have far to travel before encountering forward waves, reflected wave antinodes will occur close to forward wave antinodes, producing maximal summation and generating a pressure wave which appears as a single pulsatile wave (30). In contrast, closer to the proximal aorta reflected waves will have had further to travel before encountering forward waves. Thus, the chances of reflected wave antinodes being synchronised with forward wave antinodes decreases with significantly less summation occurring, generating a pressure wave which appears as two pulsatile waves with a first and second systolic shoulder (Figure 1.2). In children and adolescents, the reflected wave travels sufficiently slowly that it only summates with the forward wave in diastole, an effect that enhances diastolic BP and thus coronary perfusion

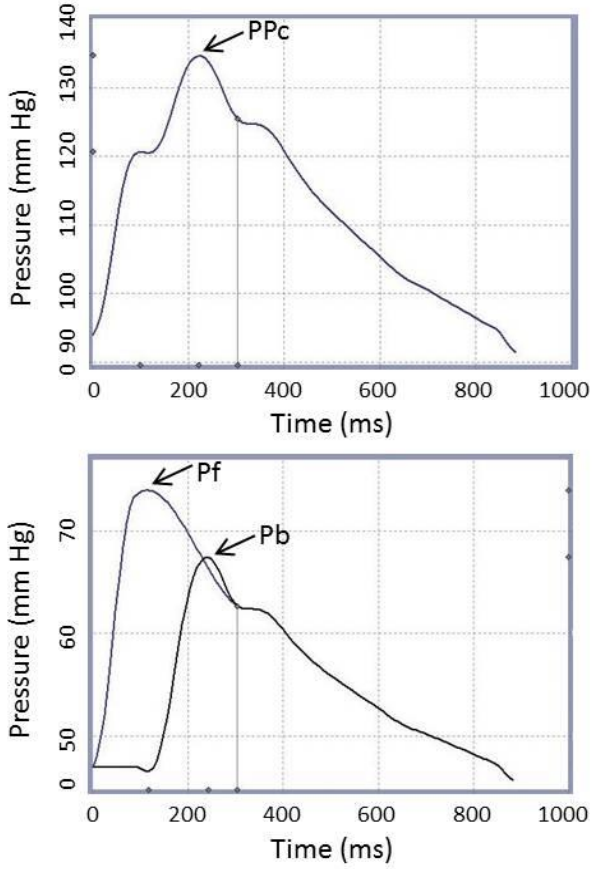


Figure 1.2 Aortic pressure wave (upper panel) and forward and backward travelling pressure waves (lower panel) showing (arrows) peak aortic pulse pressure (PPc), peak forward (Pf) and peak backward (2) pressures. Note that the forward and backward waves summate centrally to produce an aortic pressure wave with a first and a second systolic shoulder (upper panel) where the second systolic shoulder is the peak of aortic PP.

pressures, contributing to increases in coronary flow during exercise (30). As the reflected wave occurs in diastole at this age, it does not contribute to central arterial PP and SBP. However, from early adulthood, reflected waves arrive sufficiently early in the central aorta that summation with the forward wave markedly augments central arterial PP and SBP (Figure 1.2) (30). It is now recognised that wave reflection is a major determinant of central arterial PP and SBP (30). As peripherally reflected wave antinodes closely correspond with forward wave antinodes, one would expect that the impact of wave reflection that occurs centrally is closely indexed by BP at the brachial pulse. However, as will be discussed, this is indeed not the case.

1.4. Why do changes in the peripheral pulse not adequately index central arterial pulsatile load?

In the aforementioned section I provide an important reason as to why brachial PP and SBP markedly overestimate central arterial PP and SBP. To reiterate, while central arteries have a low stiffness and high diameter, peripheral arteries have a low diameter and high stiffness, the consequence being an impedance mismatch between central and peripheral arteries. However, the question is whether this is a systematic error that can simply be corrected for and hence that changes rather than absolute values of brachial PP and SBP closely index central arterial PP and SBP? In this regard, there are two reasons why changes in brachial PP and SBP do not appropriately index changes in central arterial PP and SBP.

Increases in forward travelling wave pressures are generated by the product of peak aortic flow (Q) and the impedance to flow in the proximal aorta (in the absence of wave reflection this is called characteristic impedance, and is designated as Zc). Importantly, aortic Zc is determined by aortic diameter and stiffness in the proximal aorta. As aortic stiffness increases (and hence forward wave pressures increases), the stiffness of more distal arteries may remain unchanged. The impedance mismatch between the aorta and more distal vessels decreases and while aortic forward wave pressures and hence aortic PP and SBP increase when stiffness of the aorta increases, brachial PP and SBP increase to a lesser extent. Thus, increases in forward wave pressures and hence central arterial PP do not faithfully translate into increases in brachial PP and brachial PP changes do not closely index aortic stiffness induced increases in central arterial PP and SBP.

The second reason why brachial PP and SBP do not adequately index changes in central arterial PP and SBP is through the impact of reflection phenomena. As indicated in the aforementioned discussion, peripherally reflected waves have a greater impact on PP and SBP than centrally reflected waves and

hence one may infer that peripheral BP should closely index changes in wave reflection. However, it is now recognised that variations in central arterial Pb are determined largely by variations in wave reflection from the lower part of the body (30). In contrast, the impact of wave reflection of the brachial pulse is derived from waves generated in the upper limb which contribute little to variations in central Pb (30). As variations in wave reflection centrally are more closely related to central arterial than peripheral PP and SBP, an assumption is that variations in wave reflection from the lower half of the body differ markedly from those generated in the upper limb. Reflected waves generated from the lower half of the body are transmitted outward, forming a second systolic shoulder on the peripheral pulse, unlike the central arterial pulse where these reflected waves augment PP producing a second systolic shoulder that is higher than the first. In the peripheral pulse they do not augment PP and thus produce a second systolic shoulder that is lower than the first (31). Thus, increases in backward wave pressures and central arterial PP do not faithfully translate into increases in brachial PP, similarly brachial PP changes do not closely index reflected wave pressure-induced increases in central arterial PP and SBP.

1.5 Determinants of the component waves of central arterial pulse pressure. Possible changes in pregnancy

As indicated in the aforementioned sections, two pressure waves contribute to central arterial PP and hence SBP, the forward travelling pressure wave and the backward or reflected pressure wave. What are the determinants of the above pressure waves and how may these factors change in pregnancy-associated hypertension?

1.5.1 Forward wave pressures

The forward travelling pressure wave is determined by the product of peak aortic Q and proximal aortic Zc (26). Therefore, the forward wave is driven by the factors that determine stroke volume including left ventricle (32) contractility and increases in blood volume which influence LV filling volumes (Frank-Starling effects). Several additional factors determine peak aortic Q other than stroke volume including ejection duration (stroke volume may increase without increasing peak aortic Q through a prolonged ejection duration and hence a longer period for ejecting a higher volume of blood). However, the major determinant of peak aortic Q is stroke volume and as shall be discussed, a major determinant of stroke volume (33)(and thus possibly peak aortic Q) in

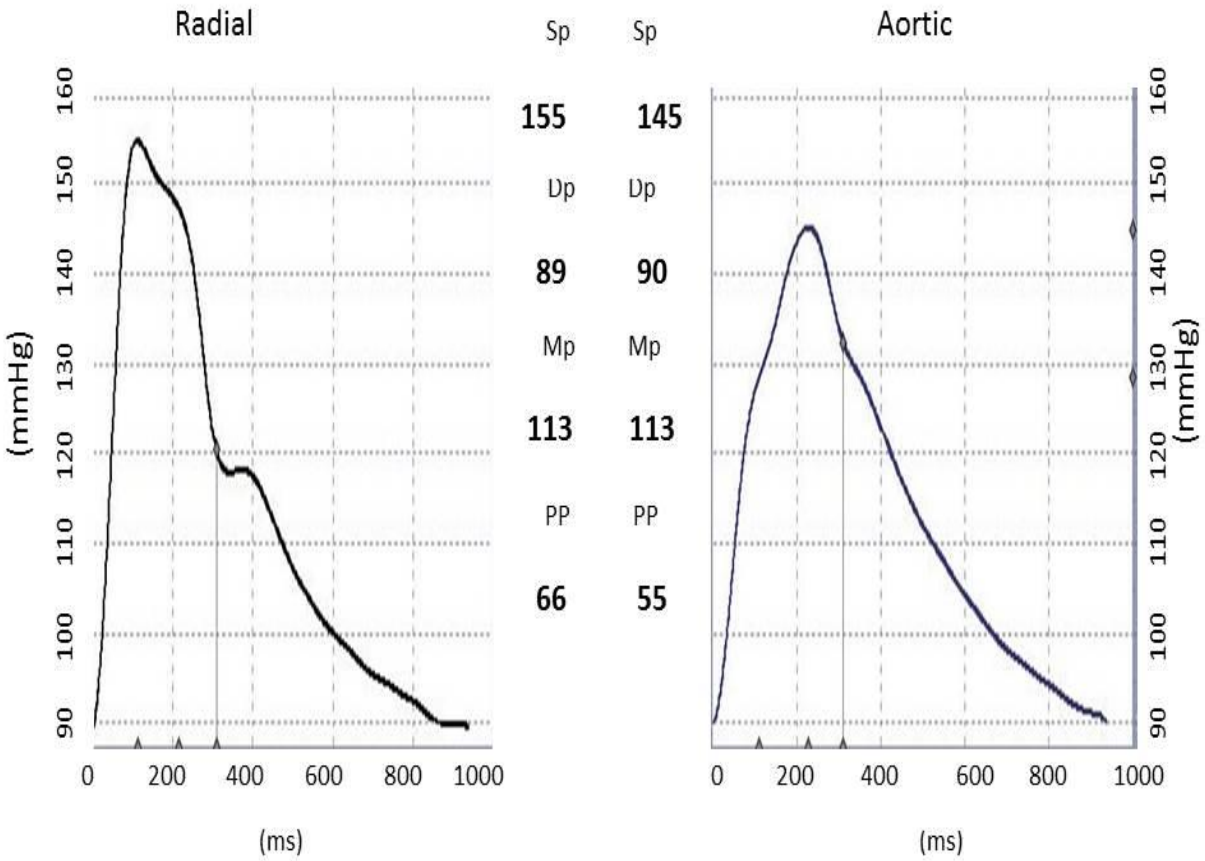


Figure 1.3 Peripheral (radial) pressure trace (left panel) and central (aortic) pressure trace (right panel) derived from a generalised transfer function incorporated in SphygmoCor software. Sp, systolic blood pressure; Dp, diastolic blood pressure; MP, mean arterial pressure; PP, pulse pressure. Note that while centrally the second systolic shoulder is higher than the first and hence adds to PP, peripherally the second systolic shoulder is lower than the first and hence is not a determinant of PP.

pregnancy is an increased blood volume and the Frank-Starling effect. Therefore, pregnancy-associated hypertension is likely to be related to an increased central arterial PP and SBP mainly through the impact of an enhanced blood volume and hence peak aortic Q. What of changes in proximal aortic Zc?

As indicated above, proximal aortic Zc is determined by two factors: aortic diameter (a decreased diameter will increase resistance to flow and hence Zc) and aortic stiffness. In this regard, aortic diameter increases with aging (30), a change thought to occur as compensation for increases in aortic stiffness, but a lesser degree of aortic dilatation may contribute to ISH (30). In contrast, through the impact of risk factors (mainly constant pulsatile load produced by BP effects) aortic stiffness increases with age. As a result, constant pulsatile load produces fragmentation and destruction of the aortic elastic lamina and replacement with collagen fibres, diabetes mellitus (through advanced glycosylation products) and oxidative stress (another risk factor) enhance collagen cross-linking and increase the tensile strength of collagen, and calcification of the aorta produced by a variety of factors decreases tissue elasticity (34). Although none of the aforementioned changes are likely to account for pregnancy-associated increases in PP and SBP, an important factor often ignored is the impact of distending pressures on aortic stiffness and hence on Zc and the forward travelling wave pressures.

Aortic stiffness is defined as the change in pressure that occurs for a given change in volume and the relationship is exponential in nature (Figure 1.4). As indicated in figure 1.4, an increased aortic stiffness produces a left shift in the pressure-volume relationship so that for a given change in volume, a greater increase in pressure occurs. Increasing volume in the aorta will shift the point up the pressure-volume curve so that it generates a similarly high pressure as that noted at a lower volume in an aorta that is much stiffer (Figure 1.4). This effect is often referred to as a passive change in aortic stiffness, where although the properties of the aortic wall are unchanged, stiffness is modified. What then determines aortic volume? In this regard, distention of the aorta is driven entirely by mean arterial pressure (MAP) and hence MAP is not only referred to as steady-state pressure, but also to distending pressures. As MAP is determined by the product of systemic vascular resistance (SVR) and cardiac output (CO) assuming right atrial pressure is 0 mm Hg, and CO is determined by SV and heart rate, through increases in blood volume and hence SV (Frank-Starling effect), an increased forward wave pressure and hence central aortic PP and SBP in pregnancy-associated hypertension may be increased not only by an enhanced peak aortic Q, but also by distending pressure effects on aortic stiffness and hence Zc. Moreover, as SVR may be increased in pregnancy associated hypertension (see later), further

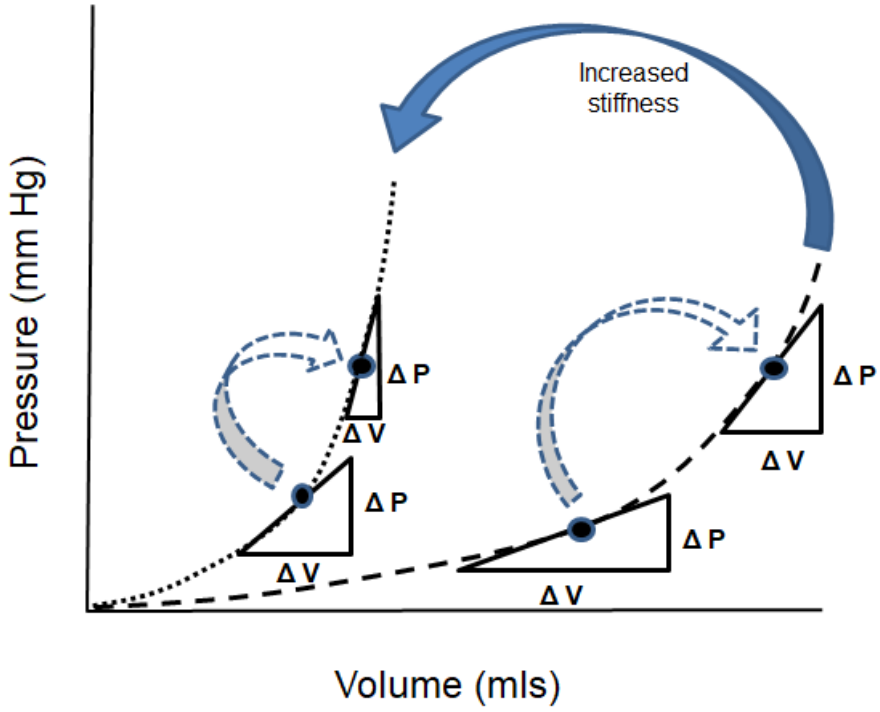


Figure 1.4 Alterations in the aortic pressure-volume relationship. Increases in aortic stiffness shift the relationship to the left so that for a given volume in the aorta, pressures are higher (arrow with closed lines). However, changes in volume will also shift the point of the relationship so that even if stiffness is low (right curve) pressures will be high if volume is high (arrows with dashed lines). Thus, decreases in volume, caused by reductions in distending pressures (mean arterial pressure, MAP) will reduce the pressure in the aorta.

increases in distending pressures and hence aortic stiffness and forward wave pressures may occur further magnifying the impact on PP and SBP.

1.5.2 Reflected waves

For several years, the impact of wave reflection was seen more as a curiosity than an important clinical concept. This was in part because reflected waves were so strongly driven by the impact of forward wave pressures and also because through dampening effects as pressure waves travel through the arterial tree, reflected wave pressures are always smaller than forward wave pressures (Figure 1.2). With respect to the dependence of reflected waves on forward waves, through Newton's Laws of Motion (inertial effects and for every action there is an equal and opposite reaction), increases in forward wave pressures usually result in increases in backward wave pressures. However, several lines of evidence now show that wave reflection is driven by factors beyond forward wave pressures and that the impact of wave reflection on end organs is often well beyond forward wave pressures. Indeed, age-related increases in wave reflection are marked before and after 50 years of age while forward wave pressures only begin to increase after 50 years of age(35, 36) (37, 38). Moreover, the impact of reflected wave pressures on cardiovascular end organ damage and events is often well beyond that of forward wave pressures (37, 39-43). Increases in wave reflection are attributed to alterations in the vasculature, with increases in arteriolar tone and more proximal arterial vessel tone producing marked effects on wave reflection. Through harmonic effects on oscillating waves, decreases in heart rate and the effects of a lower frequency increase the amplitude of the reflected wave (44-47). Could pregnancy-associated hypertension alter the magnitude of wave reflection? First, through Newton's Laws of Motion pregnancy-associated increases in forward wave pressures (associated with increases in Zc and peak aortic Q) may enhance the magnitude of backward wave pressures and thus central arterial PP and SBP. Second, as shall be discussed, SVR (arteriolar tone) may increase in pre-eclampsia and through arteriolar effects wave reflection may thus also increase. Thus, there are several potential changes that may occur in pregnancy-associated hypertension that cause an increase in central arterial pulsatile load.

1.6. The haemodynamic consequences of pregnancy

To understand the pulsatile pressure effects of pregnancy-associated hypertension, an understanding of the haemodynamic changes which occur in a normal pregnancy and in hypertensive disorders of pregnancy is required. Pregnancy is associated with a progressive increase in nutrient supply following a greater demand as the body works to support a developing foetus (48, 49). Echocardiographic findings

at gestational term include a greater SV, CO, as well as an increase in left and right ventricular chamber sizes consistent with increases in filling volumes and a Frank-Starling effect (49, 50). These changes are reversed after pregnancy (48). However, SVR is reduced in pregnancy (an impact of hormonal changes such as progesterone), thus resulting in a progressive reduction in BP in pregnancy despite marked increases in SV and CO and hence presumably peak aortic Q (49, 50). Consequently, decreases in SVR will reduce MAP and hence aortic distending pressures, opposing the impact of increases in aortic Q on forward wave pressures and PP or SBP or the effect of forward wave pressures on the magnitude of reflected waves and hence central arterial PP and SBP. Inconsistent changes in indices of aortic stiffness have been reported with no significant change throughout pregnancy or between pregnant and non-pregnant controls in some studies (50, 51) whilst others report a reduction in aortic stiffness until the third trimester(52, 53). Reductions in aortic stiffness would be through passive effects of aortic distention mediated by decreases in MAP and would further contribute to reductions in Zc and hence forward wave pressures and PP or SBP.

1.7. Pre-eclampsia and associated cardiovascular risk

Several changes occur in pre-eclampsia that enhance the risk of a cerebrovascular events. These include changes at a cellular level and in several haemodynamic factors beyond what is noted during a normal pregnancy. In the following section I will discuss the pathogenesis of pre-eclampsia highlighting the factors which may ultimately lead to cerebrovascular events. In so doing I will indicate how pathophysiological changes in pre-eclampsia may translate into adverse effects in central arteries that may not be detected at the peripheral pulse.

1.7.1 Pathogenesis of pre-eclampsia

Although the pathogenesis of pre-eclampsia is poorly understood, many theories have emerged, including poor embryological trophoblast invasion, oxidative stress, endothelial cell dysfunction and immunological dysfunction (54, 55). A two-stage model of pre-eclampsia has been proposed, with the first stage resulting from an ischaemic placental condition and the second stage associated with a pathological maternal condition, where placental ischaemia results in angiogenesis and the release of multiple soluble substances into the bloodstream (56). In occurrence with the second stage, widespread endothelial damage, as evidenced by a disrupted glycocalyx is believed to be a contributor to the outcomes observed in pre-eclampsia (55). Despite the fact that a consensus regarding the pathogenesis still needs to be reached, it is agreed that pre-eclampsia is associated with diseases where microvascular

pathology occurs (for example, hypertension and diabetes mellitus) and in maternal conditions where the placenta is enlarged (for example, multiple gestations and hydatidiform moles) (54).

The first of the two-stage model is supported by evidence from animal models. In this regard, during normal embryological development, until 10 weeks of gestation, the implanted embryo exists in a relative state of hypoxaemia until embryological trophoblast invasion occurs (57). The trophoblastic invasion results in dilatation of the spiral arteries in the uterus which coalesce with the developing placental bed. Incomplete remodelling of the uterine spinal arteries results in a narrower diameter of these arteries, and hence a state of relative placental ischaemia. Therefore, placental perfusion and oxygenation is impaired, resulting in apoptosis (54). The second stage is characterised by a poorly understood maternal condition where soluble components of the placenta, syncytiotrophoblast molecules (STBM), amongst others, are released into the bloodstream, resulting in a systemic inflammatory response and endothelial dysfunction. The release of STBM is proposed to result from apoptosis within the placenta. However, oxidative stress may also play a role. The evidence for the role of oxidative stress is controversial, as lipid peroxidases (which are markers for oxidative stress) are known to be modified independently of the effect of oxidative stress. Further, the administration of anti-oxidants showed a significant reduction in the incidence of pre-eclampsia in only one study where the sample size was small (58). Importantly, thrombin activation occurs consequent either to endothelial dysfunction or the release of inflammatory cytokines such as TNF-α and IL-1β (59). Thrombin activation results in fibrin deposition in multiple organs such as the liver, kidneys and brain, which is linked pathogenetically to the progression of pre-eclampsia (59).

Endothelial dysfunction, noted to occur in the second stage of the two-stage model, results in widespread physiological changes in multiple organ systems. The glycocalyx is the component of the endothelium which is damaged. Evidence for glycocalyx destruction is found in target organs associated with hypertension, such as the brain and the kidneys. Glomerular endothelial swelling consequent to glycocalyx destruction results in capillary lumen occlusion, a finding which is not found in other forms of hypertension (55). Few studies have attempted to link the endothelial dysfunction seen in pre-eclampsia to mortality outcomes (60, 61).

1.7.2 Pre-eclampsia and the disrupted glycocalyx

The glycocalyx is a layer of proteoglycans lining the endothelium of all blood vessels. In the cerebrovascular and renal (glomerular) systems, the glycocalyx forms a selective permeable barrier,

controlling the movement of substances entering the blood brain barrier (BBB) and the glomerular filtration barriers (GFB), respectively (62). Evidence supporting glycocalyx destruction is found in non-invasive measurements of glycocalyx permeability and high levels of circulating components of the glycocalyx in women with pre-eclampsia (63). Glycocalyx destruction at the level of the placenta is evidenced by the presence in the bloodstream of components of the placenta as well as circulating inflammatory markers, such as TNF-α, IL-1, IL-17 and IL-6 and intracellular cell surface adhesion molecules (64). Using non-invasive measurements of glycocalyx permeability to red blood cells (a known marker for glycocalyx destruction), it was noted that pre-eclampsia is indeed associated with glycocalyx destruction (63). Consequent to glycocalyx destruction, oedema, inflammation, loss of vascular responsiveness and hypercoagulability occurs (65). Indeed, 100% of subjects who later developed pre-eclampsia were found to have early evidence of abnormal endothelial function, as evidenced by platelet aggregation to endothelial collagen (66),(63). The disrupted glycocalyx therefore has important implications for further clinical management in terms of fluid choice and consideration of altered rheology in women with pre-eclampsia. (61).

1.7.3 Cerebrovascular changes in pre-eclampsia

How does pre-eclampsia cause intracranial haemorrhage? The extent of the BP change associated with intracranial haemorrhage in pre-eclampsia and the duration over which the BP is elevated to cause intracranial haemorrhage is often not as remarkable as one would expect. Thus, the cerebral vasculature is likely to be predisposed to the adverse effects of increases in BP. How may this occur? Pre-eclampsia is associated with a dysregulated cerebrovascular system and hence an elevated lifelong risk of stroke (60, 61). Although it is accepted that the disruption of the glycocalyx and BBB are involved in the pathogenesis, the exact mechanism by which cerebrovascular dysregulation occurs is still under debate. It is proposed that cerebral perfusion pressure, cerebral blood flow or cerebral resistance are compromised, but the evidence is mixed (60). Nevertheless, pre-eclamptic women have increased baseline cerebral perfusion pressures and impaired vasodilatory function (as assessed by transcranial doppler) compared to pregnant women without hypertension (67),(68),(69). Moreover, in an animal model of pre-eclampsia, mechanically induced placental ischaemia resulted in impaired cerebral perfusion (70) and cerebral oedema persisting for 2 months into the postpartum period (71). Importantly, infusions of magnesium, a treatment known for neuroprotective effects that prevent the progression from pre-eclampsia to eclampsia, into rat models of placental ischaemia, resulted in a reduction in cerebral oedema (72).

Disruption of cerebral autoregulation has been demonstrated in pre-eclampsia (73, 74), a change that may result in an increased cerebral flow at lower perfusion pressures, thus contributing toward vascular damage (75). The combination of a raised cerebral perfusion at BP values that although elevated would not normally be considered to require immediate attention, with consequent increases in pulsatile pressures in the microcirculation and a disrupted BBB and endothelial integrity may thus result in a higher propensity for an intracranial bleed (61). Indeed, in a case report of 28 women who died from intracranial haemorrhage consequent either to pre-eclampsia or eclampsia, the vast majority (75%) of subjects had mean systolic blood pressures reaching 175mmHg, which in isolation is unlikely to be sufficient to exceed the limits of autoregulation (76). Therefore, it is possible that the combination of a disrupted glycocalyx and a higher blood pressure associated with an impaired cerebral autoregulatory capacity, results in a greater propensity for intracranial haemorrhage (61).

1.7.4 Posterior Reversible Encephalopathy Syndrome (PRES) and Reversible Cerebral Vasoconstriction Syndrome (RCVS)

In addition to an increased propensity for intracranial bleeding, the disrupted glycocalyx may result in oedema. Posterior Reversible Encephalopathy Syndrome (PRES) and Reversible Cerebral Vasoconstriction Syndrome (RCVS) are cerebrovascular complications of pre-eclampsia. PRES is a syndrome occurring as a consequence of an increased capillary permeability, combined with impaired cerebral autoregulation, resulting in oedema affecting mostly occipital and parietal regions of the brain and may occur in patients with pre-eclampsia or other conditions, such as renal failure. The location of the oedema accounts for the symptoms associated with severe pre-eclampsia, including visual disturbances, seizures and coma. A significantly high proportion (as high as 98%) of women with eclampsia have radiological evidence of PRES (16, 77). RCVS is a vasospastic condition of the cerebral arteries resulting in stroke, cerebral oedema, haemorrhage and seizures. RCVS shares many radiological and clinical features with PRES, leading some to believe that the two pathologies are possibly linked (77).

1.7.5 Renal consequences of pre-eclampsia

The association between pre-eclampsia and renal dysfunction, including a lifelong risk of renal failure is well established (78). The endothelial damage found in pre-eclampsia is not only isolated to the cerebrovascular system. Indeed, as indicated in the aforementioned sections, the disrupted glycocalyx results in a dysregulated glomerular filtration barrier (GFB). The GFB is composed of the glomerular

endothelium, podocytes and the glomerular basement membrane. It is believed that a component of the placenta, soluble fms-like tyrosin kinase-1 (sFLT-1) binds to circulating vascular endothelial growth type factor A (VEGF-A), resulting in endothelial dysfunction (79),(80),(81). In the glomeruli, VEGF-A is responsible for podocyte function and therefore alterations in VEGF-A results in structural changes to the endothelium and podocyte, causing a disruption of the GFB (82),(83). The endothelial cells of the podocytes swell and the fenestrations are lost, resulting in proteinuria (83) as well as loss of podoyctes in the urine (podoycturia) (84). Podocyturia is found to predate the onset of pre-eclampsia after 20 weeks of gestation (84) and is found in pre-eclampsia where subjects have not met the haemodynamic criteria for severe pre-eclampsia (81). Thus, similar to the changes noted in the cerebrovascular architecture, it is possible that a disrupted glycocalyx combined with higher pulsatile pressures delivered to the kidney may result in endotheliosis, or endothelial scarring.

1.7.6 The haemodynamic changes in pre-eclampsia

Although the placental cellular alterations that account for pre-eclampsia have been reasonably well defined, the mechanisms responsible for increases in BP are less well described. Indeed, the exact reasons for the haemodynamic changes that accompany increases in BP in pre-eclampsia are uncertain. Pre-eclampsia is an abnormal response to pregnancy, with a high CO in response to greater cardiovascular demands, but paradoxically accompanied by a higher SVR (85) and debatable changes in central aortic stiffness. The classification of pre-eclampsia according to its' onset is associated with different cardiovascular changes. For example early-onset pre-eclampsia is associated with endothelial glycocalyx destruction (63) and greater MAP and CO, and possibly also an increased SVR (86, 87). The echocardiographic findings of late-onset pre-eclampsia are still the subject of debate, where some have reported a normal cardiac index with high SVR and others reporting a high cardiac index and low SVR (87). Importantly, if SVR is increased this will add to the impact of an increased CO on MAP and hence in contrast to normal pregnancy where SVR and hence MAP is decreased despite a high SV. In pre-eclampsia an increased MAP will increase distending pressure effect on aortic stiffness and Zc and hence forward and backward wave pressures and PP and SBP will markedly increase. In addition, through arteriolar effects, an increased SVR may enhance wave reflection independent of forward wave pressure effects and thus further increase PP and SBP centrally. Indeed, pre-eclampsia is associated with an increased central arterial PP as compared to uncomplicated pregnancies (88) and this is in-part attributed to an enhanced central aortic stiffness (52, 89, 90). Moreover, two studies have demonstrated increases in central aortic pressures and indices of wave reflection (augmentation index) in pre-eclamptic subjects of African ancestry (90, 91). No study thus far has attempted to elucidate the

changes in central arterial pulsatile load with antihypertensive therapy in pre-eclamptics with a hypertensive emergency.

1.7.7 Importance of the contribution of pulsatile load to cerebral and renal damage: Relevance to pre-eclampsia

An important concept that has emerged over the past two decades is that the cerebral and renal microvasculature are particularly vulnerable to damage produced by increases in pulsatile load. Unlike other vascular beds, these two organs have pulsatile rather than steady-state flow (92). Consequently, at a microvascular level, pulsatile pressures may cause vascular damage in the brain and kidney. Thus, pulsatile load may be a particularly important determinant of cerebrovascular haemorrhage or cerebral oedema in patients with pre-eclampsia. As indicated, increases in central arterial PP may accompany hypertension in pre-eclampsia through several effects. Therefore, an important target for antihypertensive therapy in pre-eclampsia may be an enhanced central arterial PP and the factors determining PP in central arteries. Current antihypertensive agents, including those employed in the management of severe pre-eclampsia, have variable effects on central arterial function. What then are the possible haemodynamic effects, particularly on central arterial PP, of antihypertensive agents that may be employed to target increases in BP in pre-eclampsia?

1.8 Antihypertensive effects and central versus peripheral BP

The exact mechanisms by which antihypertensives act on BP have not been well delineated. Indeed, it is only more recently that therapeutic targets for BP have been defined with a greater understanding of the haemodynamic determinants of hypertension. To briefly recapitulate, in the early years DBP was the principal target for antihypertensive administration (18). With emerging evidence however, PP was later identified as a critical target in relation to SBP (23, 24). The role of reflected waves as determinants of PP and hence SBP have nevertheless received little attention despite the significance of these waves in mediating the adverse effects of BP. Importantly, these waves are not measured at the brachial pulse. Furthermore, the impact of forward wave pressures may not be adequately detected at the brachial pulse. As they often are associated with increases in aortic stiffness and impedance to flow centrally, whilst through alterations in impedance mismatches between central and peripheral vessels, the same changes are not necessarily detected at the peripheral pulse. What then are the possible mechanisms of agents employed to decrease BP in pre-eclampsia and is there a possibility that central arterial effects may differ from peripheral arterial effects? In this regard, several classes of agents are employed to

treat hypertensive emergencies in pre-eclampsia.

With a few exceptions, the fundamental haemodynamic effect that explains decreases in BP of most antihypertensives employed today is through arteriolar vasodilation with a decrease in SVR. Calcium channel blockers (CCBs), renin-angiotensin system (RAS) blockers, and α-adrenergic receptor blockers (or other vasodilators such as hydralazine, minoxidil, centrally acting agents, etc) all decrease SVR (93). Although diuretic agents are often suggested as agents to reduce plasma volume (hence blood volume, ventricular preload, stroke volume and CO), decreasing BP through a different mechanism than vasodilators, there is no evidence that these agents produce sustained reductions in plasma volume, stroke volume and CO. Rather, through autoregulatory effects, systemic blood flow (CO) is maintained and SVR decreases. In contrast, β-adrenergic receptor blockers reduce BP through decreases in heart rate (CO=SV x HR) and hence CO. Although decreases in DBP are easy to understand (MAP [and the its surrogate, DBP]=SVR x CO), the more difficult question to answer is how may decreases in SVR or CO reduce PP and hence SBP with antihypertensive agents?

The fundamental mechanism responsible for decreases in SBP with agents that reduce CO or SVR is through a reduction in MAP and aortic distending pressures. As discussed, aortic stiffness and hence characteristic impedance (94) of the aorta is determined in-part by passive effects. Therefore, shifts along the aortic pressure-volume relationship may occur simply by decreasing aortic distension, the fundamental determinant of aortic pressure being MAP. Thus, any agent that reduces SVR or CO will reduce aortic stiffness (passive effect), characteristic impedance to flow, forward wave pressures and hence PP and SBP. Indeed, antihypertensive agents with well-recognised specific effects on vasodilation, such as calcium channel blockers (CCBs) or angiotensin converting enzyme inhibitors (ACEI), reduce aortic stiffness and forward wave pressure amplitude (23, 95, 96). Moreover, arteriolar vasodilation may reduce the magnitude of reflected (backward) wave pressures produced in central arteries. Any agent that reduces SVR may also reduce wave reflection and hence PP and SBP in central arteries. Despite these possible effects of antihypertensive agents centrally, through impedance mismatches between central and peripheral vessels, and through reflection phenomena, central BP effects may not be appropriately reflected in brachial BP measurements. Indeed, antihypertensive agents may increase PP amplification (23, 29). What is the evidence that antihypertensives which reduce MAP decrease central arterial PP and SBP in hypertension in the general population or in pregnancy-associated hypertension or pre-eclampsia and exactly how do these effects occur? Moreover, is there significant evidence to show that these effects are not adequately detected at the brachial pulse?

A number of studies have demonstrated the efficacy of current antihypertensive therapy in reducing central arterial PP (96, 97) and these studies have been summarised in meta-analyses (98, 99). Importantly however, with the exception of β-adrenergic receptor blockers, the effects of which will be discussed, the impact of most of these agents on central arterial PP is no greater than that at the peripheral pulse and there is therefore little evidence of changes in PP amplification. Although indices of wave reflection such as augmented pressures (Pa, which is the pressure generated from the first to the second systolic shoulder) may decrease with standard therapy, meta-analyses (93) indicate that this decrease is in keeping with a similar reduction in forward travelling pressure waves. In this regard, meta-analyses suggest that indices of wave reflection beyond forward waves such as augmentation index (AIx=Pa/PP x 100) are not reduced by standard therapy, and if they are, that this is through effects other than wave reflection (see discussion). Hence, decreases in Pa with antihypertensive therapy are thought to be consequent to an impact of Newton's Laws of Motion secondary to reductions in forward wave pressures. These findings are no different for the treatment of pre-eclampsia or pregnancy-associated hypertension, with several studies demonstrating decreases in central arterial PP and Pa, but with similar reductions in brachial PP and hence no obvious effects on PP amplification (30, 100), (101). Importantly, there are currently no studies that have evaluated the impact of antihypertensive therapy on central arterial BP in hypertensive emergencies when BP values are in the severe range. Presently there is no evidence to show whether current approaches to therapy produce effective decreases in PP centrally (when BP values are in the severe range) and if so, what the mechanisms involved are and whether these effects can be adequately detected at the brachial pulse. Although standard antihypertensive agents have generally been demonstrated to decrease central arterial PP in mild-to-moderate forms of hypertension, β-adrenergic receptor blockers are considered to be the exception. What is the impact of β-adrenergic receptor blockers on central arterial PP?

For the same decrease in brachial BP, β-adrenergic receptor blockers (which are sometimes employed to manage hypertensive emergencies) are now well-recognised as being less effective than alternative antihypertensive agents at reducing central PP and SBP and hence preventing mortality outcomes (102). The exact mechanism responsible for this effect has not been well described, but is associated with increases in indices of wave reflection (specifically augmentation index) (102, 103),(95),(104). There are several potential mechanisms that may explain this effect including a heart rate-related increase in backward wave pressures produced by lower frequency oscillating waves (harmonic effects on oscillating waves) (a β-adrenergic receptor blocker class effect); a lack of vasodilator effect on wave reflection (specific to some vasodilators such as atenolol); an extended ejection duration increasing the overlap of forward with backward waves in central arteries (a class effect); or an increased forward wave

pressure (which through Newton's Laws will increase Pb) generated by an increased peak aortic flow following compensatory increase in stroke volume (force-frequency relationship)(a class effect)(46, 97). In comparison to atenolol, agents with vasodilator properties such as carvedilol and labetalol (combined α and β-adrenergic blocking agents) reduce central PP and augmentation index more effectively (105). This suggests atenolol's adverse effect on central arterial PP and SBP is through a lack of vasodilator properties. However, any β-adrenergic receptor blocker mediated increased in central PP and reflected wave pressures for a given forward wave pressure, irrespective of whether vasodilator properties exist, has not been identified. Therefore, if MAP effects on forward waves are held constant, it is likely that through lower frequency oscillating waves, central arterial PP and SBP will remain elevated. Irrespective of the mechanism that explains central arterial PP and hence SBP effects of β-adrenergic blocking agents, the possibility that the effect of these agents centrally may not be appropriately detected at the peripheral pulse raises the question of whether monitoring BP peripherally adequately indexes the impact of antihypertensive agents in hypertensive emergencies.

1.9 Problem statement

Severe pre-eclampsia is a hypertensive emergency which when untreated carries a high mortality rate. Mortality in severe pre-eclampsia is mainly secondary to cerebrovascular haemorrhage and cerebral oedema. These cerebrovascular effects are mediated by two major changes. First, placental products cause endothelial dysfunction and hence increase the susceptibility of the microvasculature to hypertensive damage. Second, pre-eclampsia is associated with increases in BP levels *per se*. Thus, decreasing BP with standard antihypertensives is well recognised as preventing events in severe pre-eclampsia. However, the brain is particularly susceptible to pulsatile damage and these effects, driven by PP in central arteries, may not be detected at the brachial pulse. Whether current approaches to the management of hypertensive emergencies in general and specifically in severe pre-eclampsia are able to appropriately decrease central arterial pulsatile load, is presently unknown. Moreover, whether reductions in central arterial PP in pre-eclampsia are adequately detected at the peripheral pulse is also unknown.

1.10. Aims

In the present study I therefore aimed to determine whether current approaches to the management of severe pre-eclampsia are able to appropriately decrease pulsatile load and the determinants thereof

and whether these effects can be detected at the peripheral pulse.

METHODS

Study participants

The present study was cross-sectional in design involving 19 of 21 women diagnosed with severe pre-eclampsia recruited in the Obstetrics and Gynaecology Department at Chris Hani Baragwanath Academic Hospital. All subjects gave informed, written consent. The study was approved by the Human Research Ethics Committee of the University of the Witwatersrand (clearance number: M170671) and was conducted according to the Declaration of Helsinki (Appendix 2) (106).

Clinical, anthropometric and laboratory assessments

A clinical history was obtained by the attending physician assigned to manage the hypertensive emergency. This included information on demographic features, the obstetric history (gravidity, singleton or multiple pregnancy), gestational age, pre-existing hypertension or gestational hypertension, diabetes mellitus and the treatment thereof, symptoms of imminent eclampsia and additional co-morbidities. A clinical examination was conducted to assess whether the patient was in heart failure at the time of data collection and whether signs of imminent eclampsia were present. Anthropometric measurements (weight and height) were taken by a single, trained observer and rounded up to a whole number. Body mass index (BMI) was calculated for each subject using standard approaches and obesity was defined as a BMI≥ 35kg.m^{-2}. Laboratory blood tests, such as a full blood count (including platelets), liver function tests (aspartate aminotransferase (AST) and alanine aminotransferase (ALT)) and renal function tests (urea and creatinine) were measured to screen for renal dysfunction and HELLP syndrome. Urine was tested with a standard reagent strip and a laboratory measured urine protein: creatinine ratio. Clinically significant proteinuria was defined as 3+ on a standard reagent strip or a protein: creatinine ratio of greater than 0.3mg/dL. Late onset of severe pre-eclampsia was defined as a diagnosis of pre-eclampsia at a gestational age of greater than 34 weeks. Patients diagnosed with HELLP syndrome at the time of recruitment were excluded from the study.

Management

Once the criteria for severe pre-eclampsia were met (either a systolic blood pressure greater than 170 mmHg or a diastolic blood pressure greater than 110 mmHg), an intravenous fluid bolus of 200 ml crystalloid solution was given and antihypertensive agents (either MgS04, CCB or labetalol) were

administered in a stepwise fashion until a target non-invasive blood pressure of 140/90 mmHg was obtained. The choice of antihypertensive depended on what treatment was provided earlier and whether the subject had signs of imminent eclampsia or not. If signs of imminent eclampsia were displayed at any point, the subject was admitted to a high dependency area and MgS04 administered. An initial dose of CCB was given and blood pressure was measured thereafter. If the blood pressure still exceeded 140/90 mmHg, a second and then a third dose of CCB was administered if target blood pressure had not been achieved. Thereafter, if the blood pressure remained above target, and the subject had not received MgS04, they were admitted to a high dependency area and MgS04 administered. If blood pressure still exceeded 140/90mmHg, a labetalol infusion was initiated. All antihypertensives were administered and prescribed according to the published guidelines of the University of Witwatersrand Department of Obstetrics and Gynaecology (Appendix 1) and the current national guidelines (107). The treating obstetrician was responsible for all antihypertensives administered.

Blood pressure measurements

Blood pressure was measured in a supine, left lateral position after 10 minute's rest by a single, trained observer. A blood pressure cuff measuring two thirds' the diameter of the subjects' upper arm was used. A calibrated, aneroid sphygmomanometer (Welch Allyn, Durashock DS54, NYC) was used to measure blood pressure. An average of three measurements, taken at one-minute intervals apart, were used. Korotkov phases I and V were used to identify systolic and diastolic blood pressures, respectively.

Central aortic pressure

All measurements were conducted in a supine, left lateral position by a trained observer following a 10-minute period of rest. The measurements were conducted before and 30 minutes following antihypertensive administration. Only data obtained after maximal decreases in BP achieved were employed for analysis of changes after therapy. Central aortic pressures were determined using pulse wave analysis of the radial artery pressure derived during applanation tonometry performed with a high fidelity SPC-301 micromanometer (Millar Instrument, Houghston, TX) with a piezoelectric strain gauge located at the tip of a transducer (Figure 2.1). The micromanometer was interfaced with a computer employing version 9.0 Sphygmocor software (AtCor Medical, West Ryde, Australia) (Figure 2.1). The peripheral pressure waveform was converted into a central aortic waveform using a validated generalized transfer function incorporated in SphygmoCor software. Measurements where the

variability of the systolic or diastolic blood pressure showed a greater variability than 5% or where the signal strength was less than 80mv were discarded. The recordings were calibrated with an auscultatory blood pressure reading (as described above) immediately prior to measurement. Central PP was defined as central DBP subtracted from central SBP. Mean arterial pressure (MAP) was determined from an electronic mean of the pressure wave using SphygmoCor software. Central arterial augmented pressure (Pa) was determined from the difference between peak aortic PP and the pressure at the first systolic shoulder (Figure 2.2). Augmentation index (AIx) was determined as augmented pressure (Pa)/aortic PP x 100). The pressure from the foot of the central arterial pulse wave to the first systolic shoulder (incident wave pressure (Pi) was employed as an index of that component of the central arterial pulse derived from the product of aortic flow and characteristic impedance to flow (Figure 2.2).

Wave separation analysis

Wave separation software was employed to determine the peak of the forward (Pf) and backward (2) wave pressures. In this regard, SphygmoCor software uses the triangulation method of wave separation analysis.(108, 109) (Figure 2.3). The original method described employed simultaneous measurements of flow (with echocardiography) and pressure (using implanted micromanometers) of the ascending aorta. Characteristic impedance (94) was calculated using the 4^{th} to 7^{th} harmonic with applanation tonometry (109). As shall be described below, the central aortic waveform is assumed to be triangular in shape during ejection. Therefore, a triangle hypothesised by the software is aligned with the beginning and end of systole (dicrotic notch) of the central aortic pressure wave. The peak of the triangle is aligned with the first systolic shoulder of the central aortic pressure waveform at 30% of the ejection time.

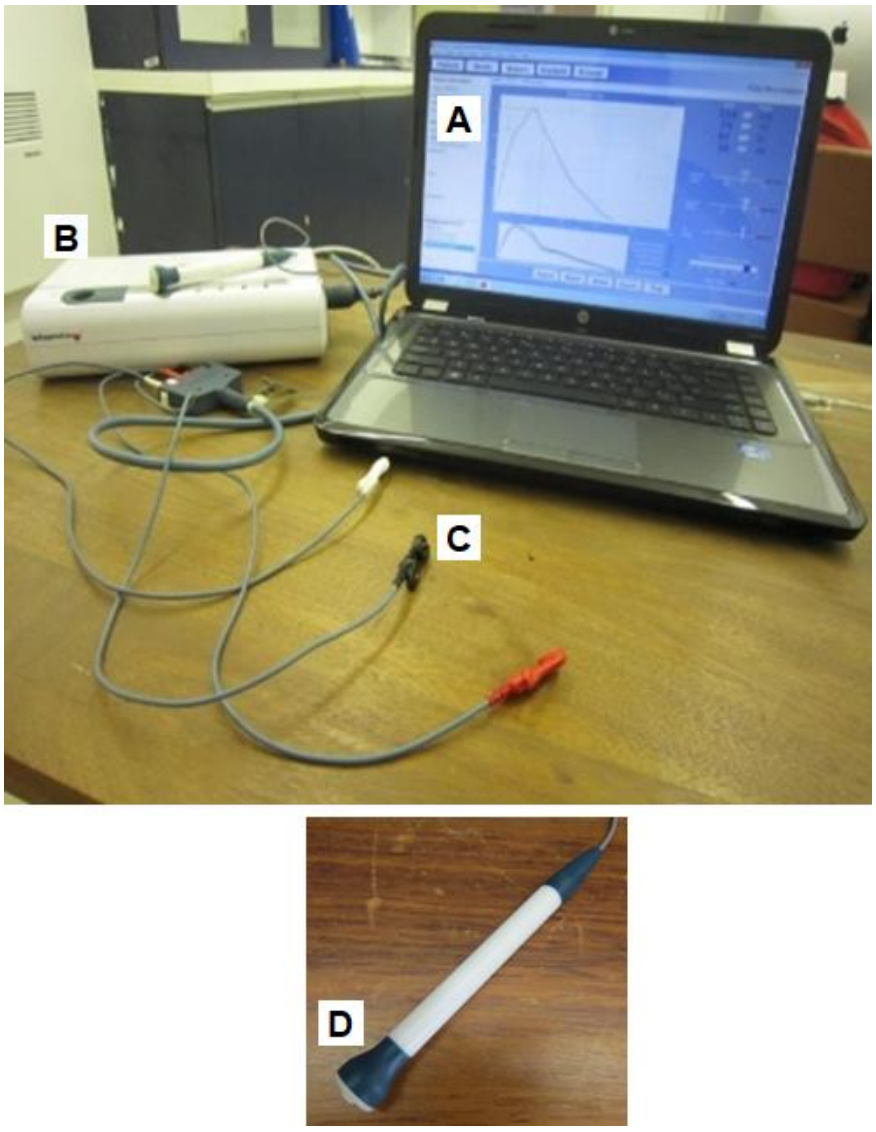


Figure 2.1. SphygmoCor device employed to evaluate central arterial pressures. A, Software display demonstrating pressure recordings, B, SphygmoCor hardware, C. Electrocardiographic leads to determine fiducial points, D, High fidelity tonometer employed to assess radial pulse non-invasively.

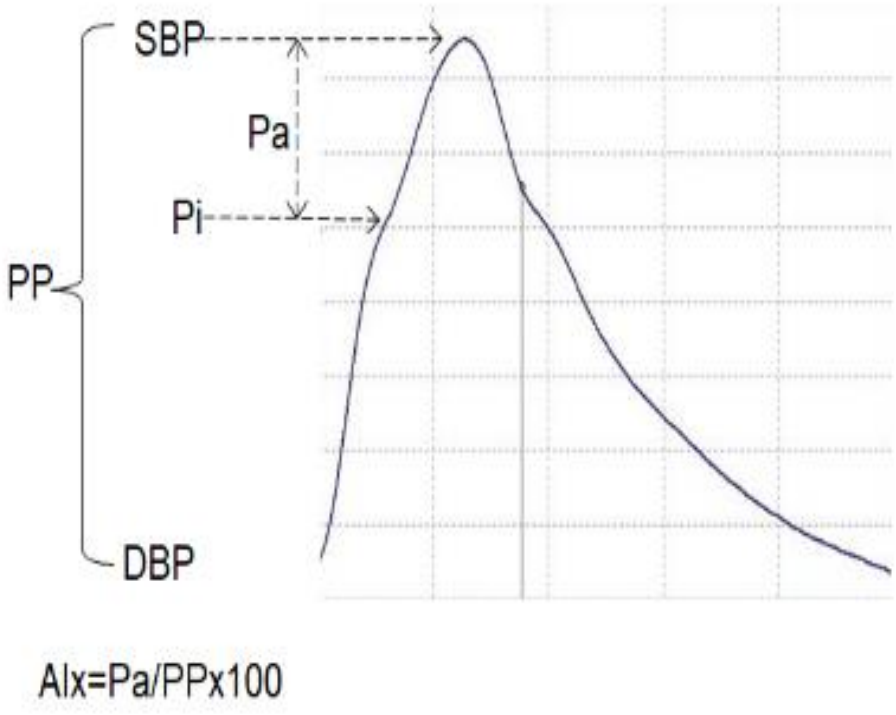


Figure 2.2 Central arterial pulse wave derived non-invasively using SphygmoCor software showing the identification of central arterial systolic blood pressures (SBP), diastolic blood pressure (DBP), pulse pressure (PP), augmentation pressure (Pa), and the calculation of augmentation index (AIx).

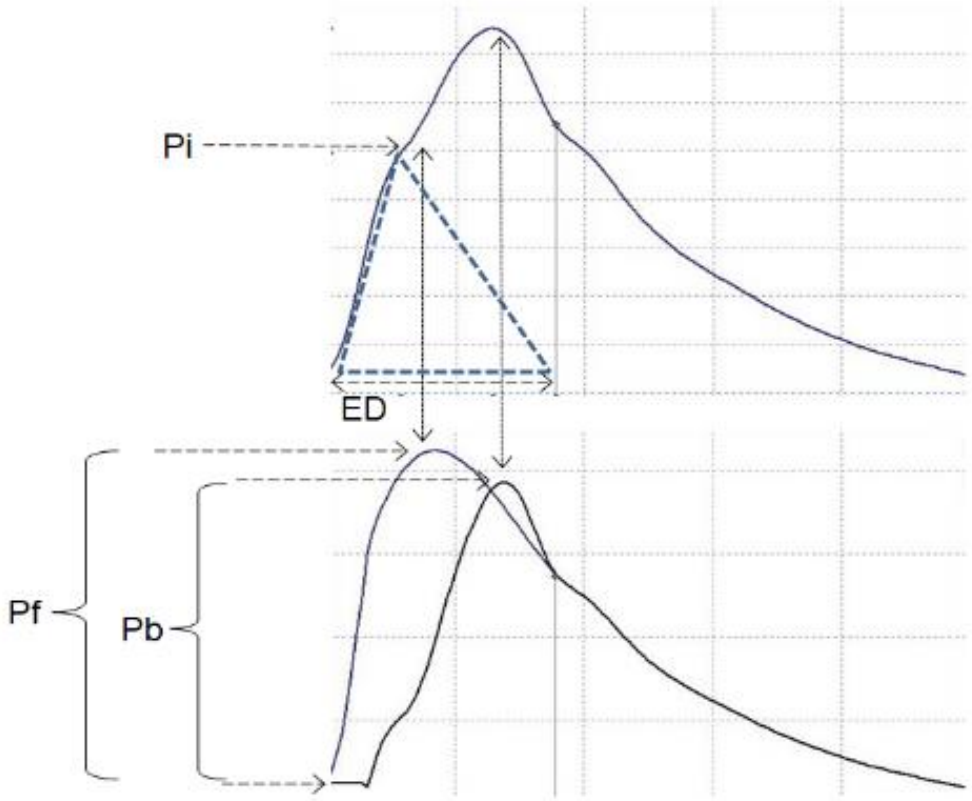


Figure 2.3. Approach employed to perform wave separation analysis assuming a triangular flow waveform. The base of the triangle (dashed line) is aligned with the foot of the pressure waveform (left tip of triangle) and with end systole (dicrotic notch) (right tip of the triangle). That is, the base of the triangle is the period of the cardiac cycle which represents ejection duration (ED). The top of the triangle (peak flow) is aligned with incident wave pressures (first systolic shoulder) (Pi). Wave separation analysis separates the forward from the backward waves, the peak of which are designated Pf and Pb respectively.

The forward and backward waves, respectively, were calculated using the following equations:

$Pf(t) = [P(t) + Zc .F(t)]/2$
$Pb(t) = [P(t) – Zc .F(t)]/2.$

Where P(t) is the measured pressure wave and F(t) is the measured or constructed flow wave. As impedence represents the quotient of pressure and flow (P/F), Zc could also be represented as Zc = Pf/Ff = -Pb/Fb. The consequence of such a relationship is that if Zc was multiplied by F, then the influence of the flow wave is no longer significant. It is also noteworthy that the product of Zc and F remains unaltered as it will always be accounted for by reciprocal changes in one of the variables. Therefore, the need for invasive pressure measurements is eliminated and the pressure waveform is all that is required to perform such a measurement (109, 110) (Figure 2.4).

To determine reflected wave effects beyond forward waves, (beyond Newtons Laws of Motion), reflected wave magnitude (RM) was determined as Pb/Pf and expressed as a percentage. Therefore, as a ratio is employed to calculate this relationship, it provides further justification that flow does not need to be calibrated (109). These assertions therefore lead to the justification used to calculate the forward and backward waves, that is to use the peak-trough of both pressure waveforms.

Pulse wave velocity

Carotid-femoral (aortic) pulse wave velocity (PWV) was determined 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 wave velocity was calculated as the quotient of the time taken for the pulse wave to travel between the carotid and femoral sites and the distance between these sites. The distance travelled was determined from the difference between the distance from the sternal notch to femoral pulse and from the sternal notch to carotid pulse.

Data analysis

All statistical analyses were performed with SAS software version 9.1 (SAS Institute, Cary NC) and Graphpad Prism (Graphpad Software, USA). Data were expressed as means ± SD or SEM. A paired Student's t test was used to determine unadjusted changes in variables with antihypertensive therapy.

An analysis of co-variance was performed to determine changes in variables with antihypertensive therapy with adjustments for baseline differences in haemodynamic variables, the type of therapy employed and changes in heart rate (for PP and indices of wave reflection including Pa, AIx, Pb and RM). Pearson's correlations or multivariate linear regression analysis were employed to determine the factors that accounted for changes in central arterial PP with therapy. Multivariate adjusted logistic regression analysis was employed to determine relationships between BP and symptoms of imminent eclampsia.

RESULTS

General clinical features

Two participants who originally agreed to participate were excluded from the study immediately after recruitment as they required emergency caesarean sections. All participants were diagnosed with *de novo* severe pre-eclampsia or pre-existing gestational hypertension with superimposed severe pre-eclampsia and therefore required management for a pre-eclamptic hypertensive emergency. Most of the subjects were either overweight (10.5%) or obese (84.6%) and had late-onset severe pre-eclampsia (Table 3.1). All participants had singleton pregnancies and had attended antenatal bookings with either their local clinic or with Chris Hani Baragwanath Academic Hospital prior to arrival. Therefore, none had refused antenatal care in the past. 95% of the participants had proteinuria on either a standard reagent urine dipstick or on a laboratory analysed urine protein: creatinine ratio. One of the participants had had eclamptic seizures from the time of referral from a local clinic. 36% (7 subjects) had symptoms of imminent eclampsia or had documented seizures and therefore were treated with $MgSO_4$ prior to arrival. Whilst being treated at the referral hospital all participants received a CCB, 4 received a CCB and $MgSO_4$ and 4 received a CCB, $MgSO_4$ and labetalol, but post-treatment central arterial function was assessed prior to initiating labetalol therapy. Laboratory results showed no marked alteration in end organ function or in haematological parameters (Table 3.1). None of the participants had evidence of congestive heart failure.

Brachial artery blood pressure

Table 3.2 and Figure 3.1 show the effect of antihypertensive therapy on brachial artery BP and PP values in severe pre-eclampsia. Without adjustments, marked decreases in all components of brachial BP except for brachial artery PP were noted (Table 3.2). After adjustments for changes in HR and MAP in response to antihypertensive therapy, no significant decreases in brachial artery BP were noted in response to antihypertensive therapy (Figure 3.1).

Central arterial pressures

Table 3.2 and Figure 3.1 show the effect of antihypertensive therapy on central arterial SBP and PP values in severe pre-eclampsia. Without adjustments, marked decreases in all components of central arterial BP including central arterial PP were noted. Importantly, the limited decrease in brachial PP ($p=0.095$) whilst a significant decrease in central arterial PP ($p=0.0125$) was noted, translated into

increases in PP amplification with therapy (Table 3.2). After adjustments for changes in HR and MAP in response to antihypertensive therapy, central aortic PP still showed a decrease in response to antihypertensive therapy (Figure 3.1).

Table 3.1 Participant characteristics.

Characteristic	
Sample size	19
Age (years)	32.6±6.8
Gestational age (weeks)	34.2±4.6
Height (m)	162.3±5.1
Weight (kg)	91.1±14.9
Body mass index (kg/m^2)	34.7±6.4
% Overweight/obese (n)	10.5(34)/84.2(16)
% Chronic Antihypertensive treatment given (n)	42.1 (8)
% Antihypertensives given at referral centre (n)	73.7 (14)
% Pre-existing hypertension (n)	36.8 (7)
% Gestational hypertension (n)	36.8 (7)
% Diabetes mellitus	0
% Early onset: pre-eclampsia (n)	36.8 (7)
% Eclamptic seizures (n)	5.3 (34)
% Signs of imminent eclampsia: (present or absent) (n)	26.3 (5)
% Signs of raised intracranial pressure (headache and/or blurred vision)(n)	21.1 (4)
% Signs of imminent eclampsia: headache (n)	21.1(4)
% Signs of imminent eclampsia: blurred vision (n)	10.5 (34)
% Signs of imminent eclampsia: epigastric pain (n)	10.5 (34)
% Signs of imminent eclampsia: hyperreflexia	0
% History of tobacco use	0
Urinalysis	
% Proteinuria (n)	94.7 (18)
Blood results	
ALT(U/L)	39.8±50.8 (median=16.5, range=5.0 to 165.0)
AST(U/L)	56.4±91.4 (median=21.0, range=12.0 to 385.0)
Creatinine(µmol/L)	59.8±18.5 (median=63.0, range=7.2 to 90.0)
Urea (mmol/L)	2.73±1.21 (median=2.6, range=1.3 to 5.8)
Urea: Creatinine	0.32±0.58 (median=0.07, range=0.03 to 1.91)
Hb(g/dL)	12.2±1.8 (median=12.1, range=10.0 to 16.9)

Plt($x10^9$/L)	228.7±92.1 (median=193.0, range=105.0 to 467.0)

Data are shown as mean±SD or proportions. Signs of raised intracranial pressure suggested by headache or blurred vision.

Table 3.2 The effect of antihypertensive therapy on unadjusted brachial and central artery blood pressure (BP) and pulse pressure (PP) in severe pre-eclamptics.

Blood Pressure	Before	After	Change	p-value
Brachial systolic (mm Hg)	179±17	160±17	-19±14	<0.0001
Brachial diastolic (mm Hg)	106±13	95±16	-11±14	=0.0036
Brachial PP (mm Hg)	73±22	65±23	-8±20	=0.095
Mean arterial pressure (mm Hg)	133±13	117±13	-16±13	<0.0001
Heart rate (beats/min)	96±15	105±22	-9±20	=0.069
Central systolic (mm Hg)	159±15	138±14	-21±15	<0.0001
Central PP (mm Hg)	50±16	41±14	-9±15	=0.0125
PP amplification	1.47±0.17	1.60±0.21	0.13±0.23	=0.0224

Data are shown as mean±SD. Negative change indicates a decrease in response to therapy.

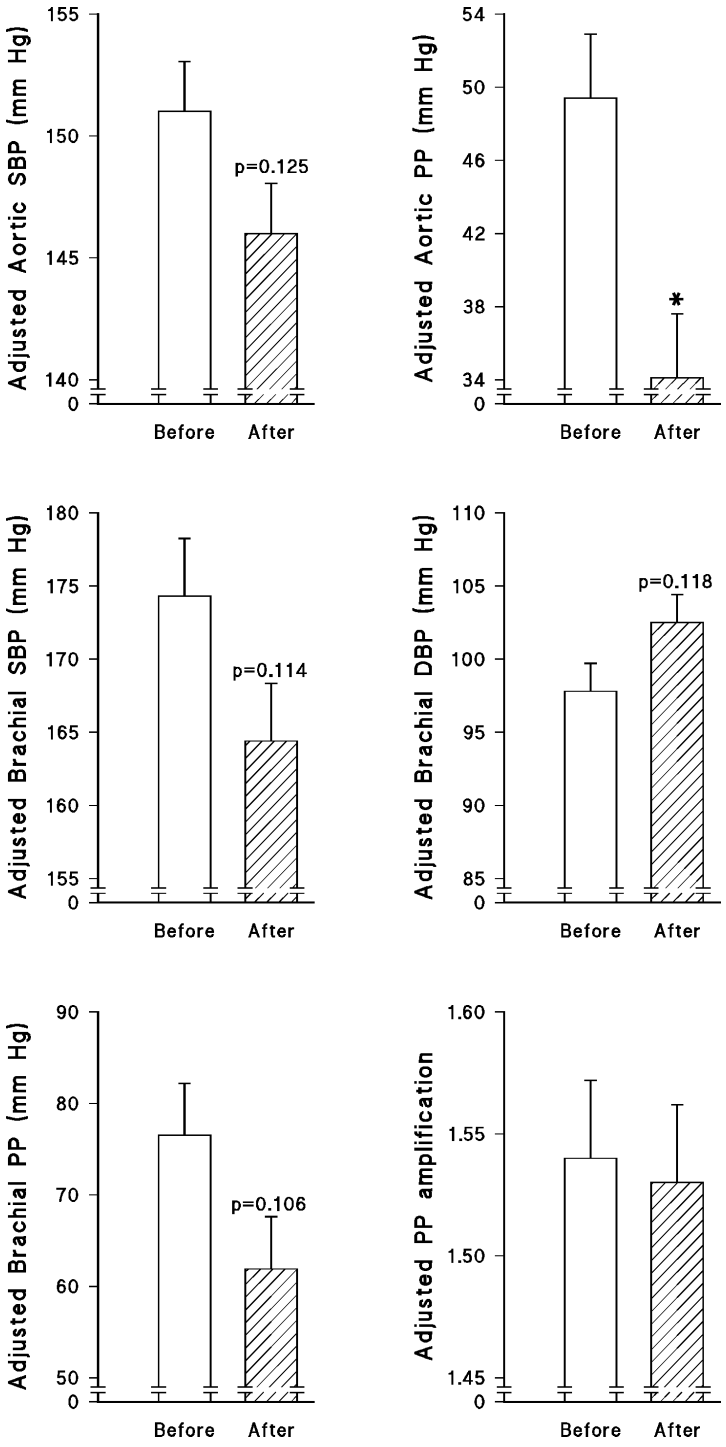


Figure 3.1 The effect of antihypertensive therapy on brachial systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse pressure (PP), and central arterial SBP (aortic SBP), and PP (aortic PP) and aortic-to-brachial PP amplification after adjustments for antihypertensive therapy-induced changes in heart rate and mean arterial pressure in severe pre-eclamptics. *p<0.01 versus before antihypertensive therapy.

Central arterial pressure wave components

Table 3.3 and Figure 3.2 show the effect of antihypertensive therapy on central arterial pulsatile wave components or aortic PWV in severe pre-eclamptics. Without adjustments for changes in heart rate and MAP in response to antihypertensive therapy, marked decreases in augmented pressures (Pa) ($p=0.0039$), central augmentation index (AIx) ($p=0.0022$), backward wave pressures (2) ($p=0.0125$), reflected wave magnitude (RM) ($p=0.066$) and carotid-radial PWV ($p=0.032$) were noted (Table 3.3). In contrast, antihypertensive effects were not associated with decreases in incident and forward wave pressures or with aortic (carotid-femoral) PWV (Table 3.3). After adjustments for changes in heart rate and MAP in response to antihypertensive therapy, only backward wave pressures were noted to decrease ($p<0.05$) (Figure 3.2). Adjustments for mean arterial pressure (MAP) are a standard approach used when assessing the impacts of pulsatile components (pulse pressure, forward wave pressure [Pf], backward wave pressure [Pb]) of pressures independent of the impact of the steady components (MAP) of pressures. In this regard, the steady components (MAP) influence the pulsatile components through an impact of distending pressures (MAP) on aortic stiffness and hence on Pf and Pb.

Haemodynamic determinants of antihypertensive effects on central arterial SBP and PP

Table 3.4 shows relationships between decreases in central arterial pressure wave components and PP. With and without adjustments for changes in HR and MAP, decreases in augmented pressures (Pa), backward wave pressures (2), forward wave pressures (Pf) and incident wave pressures were significantly correlated with decreases in central arterial PP (Table 3.4). No relationships between decreases in central augmentation index (AIx) and the reflected wave magnitude (RM) and central arterial PP were noted ($p>0.05$) (Table 3.4).

Brachial and central arterial pressures and laboratory values or clinical features

Some laboratory values (ALT, urea, and creatinine concentrations, urea:creatinine ratio, and proteinuria) showed relationships with brachial or central aortic pressures or pulse wave velocity (Table 3.5). ALT and urea concentrations and Urea:Creatinine ratio were associated with an attenuated decrease in MAP in response to antihypertensive therapy ($p>0.05$) (Table 3.5). The presence of proteinuria was associated with MAP before antihypertensive therapy. In addition, urea concentrations were positively associated with an increased change in aortic PP in response to antihypertensive therapy, and a lower carotid-radial PWV before antihypertensive therapy. Creatinine concentrations

were positively associated with a higher PP amplification ratio before antihypertensive therapy (Table 3.5). No associations between gestational age, platelet count, haemoglobin concentration, signs of raised intracranial pressure, age, BMI, pre-existing hypertension, or late onset pre-eclampsia, or gestational hypertension were associated with brachial or central aortic pressures or PWV.

Table 3.3 The effect of antihypertensive therapy on unadjusted central arterial pulsatile wave components or aortic pulse wave velocity (PWV) in severe pre-eclamptics.

	Before	After	Change	p-value
Augmented pressure (Pa) (mm Hg)	11.2±6.9	3.9±6.2	-7.4±9.4	=0.0039
Augmentation index (%)	129.9±18.2	112.6±16.1	-17.9±21.0	=0.0022
Backward wave pressure (2) (mm Hg)	21.0±5.8	16.4±5.5	-4.6±6.5	=0.0125
Forward wave pressure (Pf) (mm Hg)	39.4±11.5	35.5±13.1	-3.9±14.1	=0.283
Incident wave pressure (Pi) (mm Hg)	39.7±12.3	35.8±12.4	-3.9±11.4	=0.150
Reflected wave magnitude (RM) (%)	55.1±13.9	46.5±7.4	-8.6±17.4	=0.066
Pb/Pi (%)	56.8±14.8	46.8±7.4	-9.9±16.8	=0.0316
PWV carotid-femoral (m/s)	8.1±1.9	8.9±2.7	0.8±1.7	=0.110
PWV carotid-radial (m/s)	8.3±2.8	6.8±1.7	-1.5±2.5	=0.032

Data are shown as mean ± SD. Negative change indicates a decrease in response to therapy.

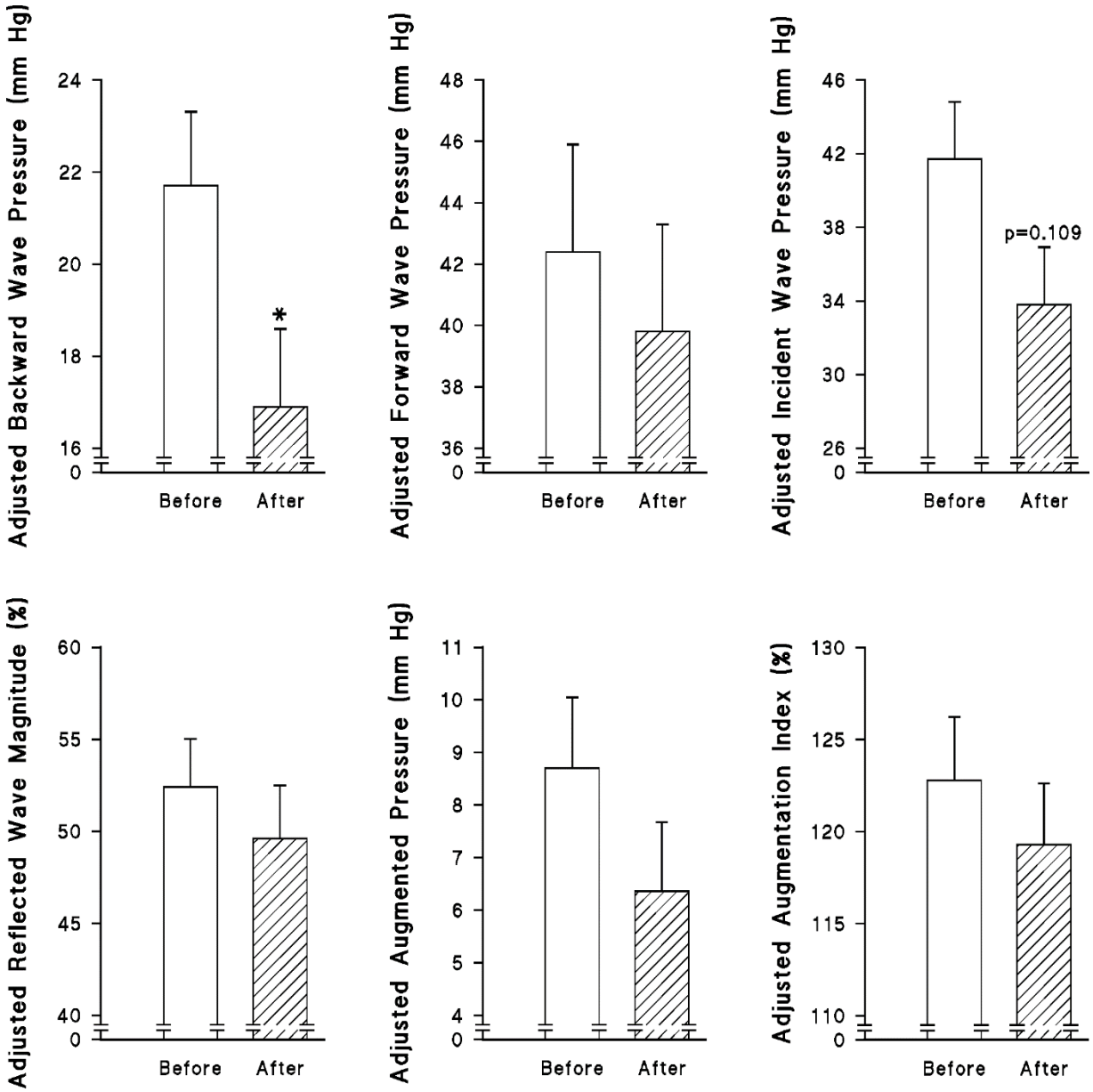


Figure 3.2 The effect of antihypertensive therapy on central arterial pulsatile wave components after adjustments for antihypertensive therapy-induced changes in heart rate and mean arterial pressure in severe pre-eclamptics. *p<0.05 versus before antihypertensive therapy.

Table 3.4 Relationships between changes in central artery pulse pressure (PP) and changes in central artery pressure components in response to antihypertensive therapy in severe pre-eclamptics.

Change in aortic PP vs	Unadjusted			Adjusted for changes in HR and MAP		
	r	95% CI	p value	partial r	95% CI	p value
Change in						
Augmented P (Pa)	**0.580**	**(0.138 to 0.818)**	**=0.012**	**0.693**	**(0.279 to 0.879)**	**=0.0021**
Augmentation index (AIx)	0.345	(-0.155 to 0.694)	=0.16	0.458	(-0.064 to 0.771)	=0.074
Backward wave P (2)	**0.903**	**(0.733 to 0.963)**	**<0.0001**	**0.909**	**(0.728 to 0.968)**	**<0.0001**
Forward wave P (Pf)	**0.826**	**(0.555 to 0.932)**	**<0.0001**	**0.850**	**(0.578 to 0.946)**	**<0.0001**
Incident wave P (Pi)	**0.828**	**(0.584 to 0.929)**	**<0.0001**	**0.885**	**(0.690 to 0.956)**	**<0.0001**
Reflection magnitude (RM)	0.103	(-0.417 to 0.567)	=0.71	0.067	(-0.483 to 0.575)	=0.82
Pb/Pi	0.181	(-0.351 to 0.617)	=0.50	0.190	(-0.385 to 0.650)	=0.52

P, pressure; R, Pearson's correlation coefficient. Significant correlations are shown in bold.

Table 3.5 Bivariate correlations between brachial or central artery blood pressure (BP) or pulse wave velocity and laboratory values in severe pre-eclamptics.

Blood Pressure	Log ALT		Log Urea		Log U:Cr		Creatinine		Proteinuria	
	r	p value	r	p value	r	p value	r	p value	r	p value
Brachial PP	0.29	0.26	-0.23	0.34	0.20	0.56	-0.02	=0.95	-0.30	=0.22
Aortic PP	0.26	0.30	-0.19	0.45	0.09	0.80	-0.20	=0.41	-0.20	=0.43
Mean arterial pressure	0.22	0.38	0.18	0.48	0.05	0.88	-0.16	=0.51	**0.66**	**=0.0015**
PP amplification	0.08	0.76	-0.15	0.56	0.23	0.50	**0.58**	**=0.008**	-0.17	=0.48
PWV carotid-femoral	0.05	0.87	-0.39	0.12	-0.35	0.37	-0.03	=0.90	-0.05	=0.84
PWV carotid-radial	0.09	0.74	**-0.50**	**0.035**	-0.31	0.39	-0.23	=0.37	-0.12	=0.63
Change in aortic PP	-0.39	0.11	**0.50**	**0.029**	0.26	0.45	0.33	=0.18	0.30	=0.21
Change in MAP	**-0.55**	**0.017**	**-0.58**	**0.0076**	**-0.89**	**<0.0001**	-0.17	=0.49	-0.26	=0.30

ALT, alanine transaminase; U:Cr, urea-to-creatinine ratio. r, Pearson's correlation coefficient. Data were logarithmically transformed to improve distribution. Significant correlations are shown in bold

Primary determinants of antihypertensive effects on central arterial SBP and PP

Table 3.6 shows the multivariate relationships between decreases in central arterial PP and pressure wave components as well as signs of or risk factors for imminent eclampsia. The model explained 99% of the variation in change in central arterial PP in response to antihypertensive therapy, with the main determinant being a decrease in backward wave pressures (r^2=0.8124; p<0.0001). Decreases in forward wave pressures (r2=0.1284; p=0.0001) as well as body mass index (r^2=0.0198; p=0.0142) and ALT (r^2=0.0093; p=0.0232) played a more minor role.

Table 3.6 Multivariate stepwise regression model to identify the primary determinants of changes in central artery pulse pressure (PP) with antihypertensive therapy in severe pre-eclamptics.

Change in aortic PP vs	partial r^2	p value
Change in backward wave pressure	**0.8124**	**<0.0001**
Change in forward wave pressure	**0.1284**	**=0.0001**
Body mass index	**0.0198**	**=0.0142**
Proteinuria	**0.0095**	**=0.036**
Log Urea	0.0137	=0.082
Log ALT	**0.0093**	**=0.0232**
Change in heart rate	0.0040	=0.205
Change in mean arterial pressure	0.0029	=0.268
Gestational age	0.0001	=0.776
Age	0.0000	=0.859
Model r^2	0.9907	

r, Pearson's correlation coefficient; ALT, alanine transaminase. Data were logarithmically transformed to improve distribution. Significant correlations are shown in bold. Determinants are listed in order of contribution.

DISCUSSION

The main findings of the present study are as follows. In the treatment of severe pre-eclampsia (hypertensive emergency) I show that in association with marked decreases in peripheral SBP and DBP, no significant changes in brachial artery PP were noted with therapy. In contrast, even with adjustments for steady component pressures, (MAP), central arterial PP was significantly decreased by conventional therapy, an effect that was accounted for by reductions in backward, but not incident or forward wave pressures. While, with adjustments for MAP, neither Pi (incident wave pressure) nor Pf (forward wave pressure) were reduced by conventional therapy, Pb (backward wave pressure) was decreased, and reductions in Pb were closely correlated with decreases in central arterial PP. These effects on backward wave pressures were therefore accounted for by an impact of therapy on wave reflection and are likely to have occurred beyond arteriolar function (as indexed by MAP).

The present study is the first to evaluate the impact of antihypertensive therapy on central aortic PP and the wave components of central aortic PP, including forward and backward wave effects (wave separation analysis) in a hypertensive emergency (severe pre-eclampsia). In this regard, central aortic PP has previously been demonstrated to decrease with antihypertensive treatment in Caucasian pre-eclamptics with more modest increases in BP (30, 100) and in chronic hypertension in pregnancy in Afro-Caribbeans also with mild-to-moderate increases in BP (101). These findings are consistent with several studies that have evaluated the impact of antihypertensive therapy on mild-to-moderate increases in BP in hypertension in the general population (20, 30, 111, 112). However, no study has assessed the effect of therapy on central arterial function in the presence of marked initial increases in BP or in an emergency situation. Indeed, previous studies report on pre-treatment mean BP values ranging from 135 to 160 mm Hg SBP and 80 to 94 mm Hg DBP (112, 113) (93, 97, 114, 115), while in the present study the initial mean BP values prior to initiating therapy in the referral centre were 178/105 mm Hg SBP/DBP. Whilst prior studies report on marked decreases in PP in both the aorta and brachial artery with antihypertensive therapy (99), the present study shows decreases in PP in only central arteries. This effect in the present study is accounted for by the impact of therapy on PP attributed to reductions in wave reflection, changes which are not detected at the brachial artery. In contrast, in a meta-analysis of studies in the general population with mild-to-moderate hypertension, decreases in PP could not be accounted for by consistent decreases in augmentation index (AIx), an index of wave reflection beyond the impact of forward wave pressures on the amplitude of backward waves (97, 99). Thus, it is likely that as noted in alternative studies conducted in hypertensives from the general population, reductions in PP are largely accounted for by MAP effects (distending pressure effects) on aortic stiffness, Zc and consequently aortic incident and forward wave pressures. As the

forward wave drives variations in brachial PP, changes in Pf produced by distending pressure changes will translate into as much of a decrease in brachial as in central arterial PP. Nevertheless, as with studies conducted in the general hypertensive population, despite the MAP-adjusted reduction in Pb and hence PPc noted in the present study, this failed to translate into significant MAP-adjusted decreases in augmented pressure (Pa) or AIx. Thus, it is possible that previous results demonstrating inconsistencies in the ability of antihypertensive therapy to show decreases in wave reflection in hypertensives from the general population, simply highlights the limitations of assessing wave reflection effects using Pa and AIx rather than wave separation analysis (37, 40). These limitations will be discussed in the subsequent paragraph.

Although previous studies have assessed the impact of antihypertensive therapy on indices of wave reflection in pregnancy-associated hypertension or pre-eclampsia with mild-to-moderate increases in BP (30, 100)), as with most studies conducted in hypertensives from the general population, the investigators of these studies employed Pa or AIx to determine these effects, rather than reflection wave indices derived from wave separation analysis. Importantly, these pulse wave analysis acquired indices (Pa and AIx) are affected not only by the extent of wave reflection, but also by cardiac function and hence aortic flow and forward wave pressures (116, 117)as well as the speed of wave reflection and hence the extent to which the reflected wave summates with the forward wave (an earlier return of the reflected wave increases the chances that forward and backward wave pressure antinodes coincide)(34). In this regard, several studies have demonstrated that Pa and AIx underestimate the impact of alterations in backward wave effects on aortic PP (37, 40). Thus, changes in Pa or AIx with therapy in prior studies may have been determined by the impact of therapy on forward wave pressures or the speed of wave reflection rather than on wave reflection itself. The present study is therefore the first to show that the impact of antihypertensive therapy in severe pre-eclampsia at least, on aortic PP is determined by effects on wave reflection *per se* (2). Whether similar effects of therapy are noted in less severe forms of pre-eclampsia or hypertension in pregnancy requires further study.

Assuming that further studies show limited effects of antihypertensive therapy on Pb, are there possible reasons for the striking differences of the impact of therapy on wave reflection in severe pre-eclamptics in the present study versus mild to moderate hypertensives from the general population or in alternative studies conducted in pre-eclamptics or those with pregnancy-associated hypertension (20, 30, 90, 111, 112)? One possible reason is that the impact of therapy on wave reflection may only occur when BP values are in the severely hypertensive range. Indeed, reflected wave effects are

generally acknowledged to have a major impact on BP at higher pressures (118) and CCBs and MgSO4 may reduce wave reflection through vasodilator effects (29), (119). The second reason for the distinct effect of therapy on wave reflection in the present study is that pre-eclampsia may be a condition where wave reflection is markedly elevated beyond the effects of Newton's Laws of Motion and hence forward wave pressures. Increases in SVR, which may enhance wave reflection, are indeed associated with pre-eclampsia (86, 87). However, in the present study mean reflected wave magnitudes (Pb/Pf x 100) before therapy were not particularly striking (mean value=56 %) in severe pre-eclamptics as compared to age and sex-matched participants from the general population of the same ethnic group (120). Thus, it is unlikely that pre-eclampsia represents a condition where marked wave reflection occurs. Alternatively, as the present study was conducted in an ethnic group (black Africa ancestry) where wave reflection is notably higher than alternative populations (120), the possibility that reflected wave effects are specific to the group studied (black African) rather than the condition (pre-eclampsia) requires consideration. Further studies in alternative forms of severe hypertension in groups of African ancestry are required to evaluate the hypothesis that antihypertensives are able to reduce wave reflection when BP values begin at high levels or that reflected wave effects represent effects distinct to groups of African ancestry.

An important observation in the present study is the inability of antihypertensive therapy to significantly reduce incident and forward wave pressures despite an ability to decrease backward wave pressures. The participants studied had low PWV values, an index of aortic stiffness. As a consequence, Zc, which depends on aortic stiffness, is likely to have been relatively low as well. Nevertheless, Pi and Pf values before therapy in the present study were striking (Pi mean value= 147.7; Pf mean value = 40.8) in severe pre-eclamptics as compared to age and sex-matched participants from the general population (39) (121). These high values of Pi and Pf are more likely to reflect marked increases in aortic flow (SV and CO are increased in pregnancy (122), and in pre-eclamptic subjects (123), (124)) rather than an enhanced aortic stiffness and hence Zc. In this circumstance, even large decreases in MAP produced by vasodilation are unlikely to modify Pi and Pf through distending pressure effects, as these values are largely driven by flow and not Zc.

An important consideration of the present study is whether the small study sample (n=19) has produced population stratification and hence whether the data are representative of severe pre-eclampsia in general. In this regard, the characteristics of the study sample is indeed in keeping with risk factors for the development of pre-eclampsia, namely a high BMI and advanced maternal age (125, 126). Moreover, central aortic pulse pressures were increased to a similar extent in the present study

as compared to those pressures found in previous studies (30, 100, 101). However. most of the subjects in this study were diagnosed with late-onset pre-eclampsia and hence whether similar data would be obtained in those with early onset pre-eclampsia is unknown.

Although speculative, the clinical implications of the present study require consideration. The present study suggests that decreases in pulsatile load may in-part contribute to the beneficial effects of antihypertensive therapy in severe pre-eclampsia. Moreover, the present study suggests that these beneficial effects are mediated by an impact of therapy on wave reflection, changes which are not detected at the brachial pulse. Whether decreases in wave reflection are indeed essential for benefits in pre-eclampsia nevertheless requires further study. There is therefore no question that decreases in perfusion pressures (MAP), which are readily detected at the brachial pulse are essential for mediating the benefits of antihypertensive therapy in pre-eclampsia. Indeed, in organs which have pulsatile flow (brain and kidney) (92, 127), perfusion pressures will determine flow: and hence reducing MAP is likely to markedly limit microvascular damage in these organs, preventing haemorrhagic cerebrovascular events or the development of renal failure, the key causes of mortality in severe pre-eclampsia (1, 4-6, 8, 10, 15, 16, 107)). Nevertheless, transmission of pulsatile pressures into microvascular beds in organs with pulsatile flow may contribute to microvascular damage in pre-eclampsia. Decreasing central arterial PP through reductions in wave reflection may be essential for producing the therapeutic benefits of antihypertensive agents in severe pre-eclampsia. Whether monitoring the impact of agents on wave reflection and targeting reflected wave effects as well as MAP enhances outcomes in severe pre-eclampsia, therefore requires further study.

The strikingly higher baseline Pi and Pf in pre-eclamptics as compared to age and sex-matched controls from a community sample (see previous paragraphs) may have important clinical implications. As indicated in the aforementioned, these changes may have been accounted for by increases in aortic flow rather than Zc and hence did not respond to reductions in MAP produced by antihypertensive therapy. As previously indicated, the brain is an organ which has pulsatile flow. The high systemic flow values in pre-eclampsia may therefore contribute to pulsatile damage in the susceptible microvasculature (produced by placental products that cause glycocalyx changes in the endothelium) of pre-eclamptics. Thus, it is possible that an essential cause of microvascular damage in pre-eclampsia is indeed pulsatile damage (rather than steady-state damage) and that any approach to decreasing pulsatile pressures (such as reductions in wave reflection) may be critical to preventing cerebral events.

As the impact of antihypertensive therapy in the present study on central arterial PP was mediated by decreases in wave reflection, consideration should be given to the possibility that agents which have a limited benefit on wave reflection should be avoided. In this regard, β-adrenergic receptor blockers may not decrease central arterial PP as well as alternative agents, an effect accounted for by a limited ability to decrease wave reflection (46, 97, 99, 105). Thus, whether labetalol should be employed with more caution in severe pre-eclampsia requires careful thought. The adverse effects of β-adrenergic receptor blockers on wave reflection are thought to be through several mechanisms which have not been clearly elucidated and hence may involve class effects or effects related to non-vasodilator agents. In the present study only 4 participants required labetalol administration and hence I could not assess whether labetalol therapy produced limited benefits to central arterial PP despite similar reductions in brachial PP. Further studies are therefore required to evaluate this question.

Importantly, as indicated in above discussion, there is no convincing evidence that vasodilators decrease wave reflection beyond changes in forward wave pressures. Indeed, meta-analyses (99, 104) and more recent large studies(128) show no effect of most antihypertensive agents on AIx (Pa/PP x 100). Although it is well accepted that augmented pressures (Pa) decrease with therapy, the most likely explanation for this effect is that forward wave pressures are reduced and that through Newton's Laws of Motion, backward wave pressures are then also reduced. The impact of antihypertensive therapy on forward wave pressures as previously described through distending pressure effects on proximal aortic stiffness and hence Zc. Thus, the present study provides the first clear evidence that independent of distending pressure effects, Pa and hence central aortic PP may be reduced by vasodilator therapy through effects associated with decreases in backward wave pressures (2). These effects are likely to be explained by alterations in vascular tone resulting in a decrease in wave reflection. The ability of vasodilator therapy to produce effects on Pb in the present study, conducted in more severe hypertension (while similar effects have not previously been described in alternative studies conducted in largely mild-to-moderate hypertension) may be explained by the relative contribution of reflected waves to PP at higher BP values.

Other than the small study sample there are several additional limitations to the present study. First, I did not assess flow and diameter in the left ventricular outflow tract and hence I was unable to determine SV, Q or Zc. Moreover, the use of an assumed triangular flow wave to perform wave separation analysis in the present study has limitations. Indeed, as previously described, the original method was based on a relatively small sample size of 19 middle aged patients with medical conditions requiring direct (invasive) cardiac cannulation (109) and the approach showed several limitations

when applied to a larger sample (129). Furthermore, I calibrated the arterial pressure wave forms from the brachial and not the radial artery pulse, thus not accounting for brachial to radial pressure amplification with a consequent underestimation of central aortic pressures (130, 131). Moreover, as pre-eclampsia is prevalent in those of African ancestry and the mortality is much higher (13), the results may not be readily extrapolated to other ethnic groups.

Various clinical applications are emerging with regards to the use of central aortic pressure measurements beyond an outpatient setting. Indeed, the relatively low cost of the Sphygmocor device, combined with its' ease of use makes it an attractive option for clinical applications. Importantly, the rapid processing ability of the software lends it to timeous assessments of central pressures which may be used to guide therapy in an emergency setting.

In conclusion, in the present study I show for the first time that in the treatment of the hypertensive emergency, severe pre-eclampsia, central aortic and not peripheral pulse pressures are reduced significantly following antihypertensive treatment. The reduction in central aortic pulse pressure is accounted for primarily by the effects of wave reflection, and these changes are not attributed to arteriolar effects.

REFERENCES

1. Moodley J. Saving Mothers 2011-2013: Sixth report on confidential enquiries into maternal deaths in South Africa: Fact sheet. Pretoria: National Department of Health; 2015: 1-79.
2. Pattinson B, Moodley J. Saving Mothers: Third Report on Confidential Enquiries Into Maternal Deaths in South Africa, 2002-2004: Department of Health; 2006.
3. Say L, Chou D, Gemmill A, Tunçalp Ö, Moller A, Daniels J et al. Global causes of maternal death: a WHO systematic analysis. *The Lancet Global Health.* 2014;2(6):e323-e33.
4. Theron G. Saving mothers: Report on the confidential enquiries into maternal deaths in South Africa. *South African Family Practice*. 2011;22(7).
5. Moodley J. Saving Mothers 2014-2016: Seventh triennial report on confidential enquiries into maternal deaths in South Africa: Short report. Republic of South Africa2016. p. 1-139.
6. Moodley J. Saving Mothers 2017: Annual Report on Confidential inquiries into maternal death in South Africa. Department of Health: Republic of South Africa; 2017. p. 1-97.
7. Brown M, Magee L, Kenny L, Karumanchi S, McCarthy F, Saito S, Hall D, Warren C, Adoyi G, Ishaku S. The hypertensive disorders of pregnancy: ISSHP classification, diagnosis & management recommendations for international practice. *Pregnancy Hypertension*. 2018;13:291-310.
8. Buchmann, Walt Vd, Geldenhuys, Moshabela, Mafura, Schoon, et al. Guidelines for Maternity Care in South Africa: A manual for clinics, community health centres and district hospitals In: National Department of Health, 4 ed. South Africa 2015. p. 83-90.
9. Moodley J. Maternal deaths due to hypertensive disorders in pregnancy. *Best Pract Res Cl Ob.* 2008;22(3):559-67.
10. Foo L, Bewley S, Rudd A. Maternal death from stroke: a thirty year national retrospective review. *Eur J Obstet Gynecol Reprod Biol*. 2013;171(1):266-70.
11. Khan KS. WD, Say L, Gülmezoglu AM , Van Look PFA WHO analysis of causes of maternal death: a systematic review. The Lancet Global Health. 2006;367(9516):1066-74.
12. Nyflot LT, Ellingsen L, Yli BM, Oian P, Vangen S. Maternal deaths from hypertensive disorders: lessons learnt. *Acta Obstet Gynecol Scand.* 2018; 97: 976-987.
13. MacKay AP, Berg CJ, Atrash HK. Pregnancy-related mortality from preeclampsia and eclampsia. Obstetrics and gynecology. 2001;97(4):533-8.
14. Lewis G, Drife J, Chatton-Broch T, Cooper G, Hall M, Harper A, Hepburn M, et al. Confidential Enquiry into Maternal and Child Health: Why Mothers Die 2000–2002. Sussex: *RCOG*; 2004.
15. Hecht JL, Ordi J, Carrilho C, Ismail MR, Zsengeller ZK, Karumanchi SA, et al. The pathology of eclampsia: An autopsy series. *Hypertension in pregnancy*. 2017;36(3):259-68.
16. Swartz RH, Cayley ML, Foley N, Ladhani NNN, Leffert L, Bushnell C, et al. The incidence of pregnancy-related stroke: A systematic review and meta-analysis. *International journal of stroke : official journal of the International Stroke Society*. 2017;12(7):687-97.
17. Altman D, Carroli G, Duley L, Farrell B, Moodley J, Neilson J, et al. Do women with pre-eclampsia and their babies benifit from management sulphate? The Magpie Trial: a randomised placebo controlled trial. *Lancet*. 2002 ; 359(9321):1877-90
18. Kannel WB. Fifty years of Framingham Study contributions to understanding hypertension. *J Hum Hypertens.* 2000;14(1):83.
19. Franklin SS, Wong ND. Hypertension and cardiovascular disease: contributions of the framingham heart study. *Global heart*. 2013;8(1):49-57.
20. Asmar R, Gosse P, Topouchian J, N'Tela G, Dudley A, Shepherd GL. Effects of telmisartan on arterial stiffness in Type 2 diabetes patients with essential hypertension. *Journal of the renin-angiotensin-aldosterone system : JRAAS. 2002;3(3):176-80*.
21. Amery A, Birkenhager W, Bulpitt CJ, Clement D, De Leeuw P, Dollery CT, et al. Syst-Eur. A multicentre trial on the treatment of isolated systolic hypertension in the elderly: objectives, protocol, and organization. *Aging*. 1991;3(3):287-302.

22. Wang JG, Staessen JA, Gong L, Liu L. Chinese trial on isolated systolic hypertension in the elderly. Systolic Hypertension in China (Syst-China) Collaborative Group. *Archives of internal medicine.* 2000;160(1):211-20.
23. Avolio AP, Bortel LMV, Boutouyrie P, Cockcroft JR, McEniery CM, Protogerou AD, et al. Role of Pulse Pressure Amplification in Arterial Hypertension. *Hypertension*. 2009;54(1):375-83.
24. Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, et al. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension.* 2001;37(5):1236-41.
25. Pierce GL, Casey DP, Fiedorowicz JG, Seals DR, Curry TB, Barnes JN, et al. Aortic pulse wave velocity and reflecting distance estimation from peripheral waveforms in humans: detection of age- and exercise training-related differences. *American Journal of Physiology-Heart and Circulatory Physiology.* 2013;305(1):H135-H42.
26. Sweitzer NK, Shenoy M, Stein JH, Keles S, Palta M, LeCaire T, et al. Increases in Central Aortic Impedance Precede Alterations in Arterial Stiffness Measures in Type 1 Diabetes Mellitus. *Diabetes Care*. 2007.
27. Hashimoto J, Ito S. Pulse Pressure Amplification, Arterial Stiffness, and Peripheral Wave Reflection Determine Pulsatile Flow Waveform of the Femoral Artery. *Hypertension.* 2010;56(5):926-33.
28. McEniery CM, Cockcroft, J. R., Roman, M. J., Franklin, S. S., & Wilkinson, I. B. Central blood pressure: current evidence and clinical importance. *European heart journal.* 2014;35(26):1719–25.
29. Nichols WW. Clinical measurement of arterial stiffness obtained from noninvasive pressure waveforms. *Am J Hypertens.* 2005;18(1 Pt 2):3s-10s.
30. Morgan T, Lauri J, Bertram D, Anderson A. Effect of different antihypertensive drug classes on central aortic pressure. *Am J hypertens.* 2004;17(1):118-23.
32. MB F, M B, A N, Zeisle H, R S, M G-W, et al. Augmentation index and pulse wave velocity in normotensive and pre-eclamptic pregnancies. *Acta Obstetricia et Gynecologica Scandinavica.* 2013;92(8):960-6.
33. van Veen TR, Panerai RB, Haeri S, Singh J, Adusumalli JA, Zeeman GG, et al. Cerebral autoregulation in different hypertensive disorders of pregnancy. *American Journal of Obstetrics & Gynecology.* 2015;212(4):513.e1-.e7.
34. Nichols WW, O'Rourke, M.F., Vlachopoulos, C., 2011. *McDonald's blood flow in arteries: Theoretical, experimental and clinical principles.* 6th ed 2011; p148.
35. 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. *Journal of the American Society of Hypertension : JASH.* 2017;11(10):616-26.e2.
36. Namasivayam M, McDonnell BJ, McEniery CM, O'Rourke MF. Does wave reflection dominate age-related change in aortic blood pressure across the human life span? *Hypertension.* 2009;53(6):979-85.
37. Booysen HL, Woodiwiss AJ, Sibiya MJ, Hodson B, Raymond A, Libhaber E, et al. Indexes of Aortic Pressure Augmentation Markedly Underestimate the Contribution of Reflected Waves Toward Variations in Aortic Pressure and Left Ventricular Mass Novelty and Significance. *Hypertension.* 2015;65(3):540-6.
38. Namasivayam M, Adji A, O'Rourke MF. Evaluating the Hemodynamic Basis of Age-Related Central Blood Pressure Change Using Aortic Flow Triangulation. *Am J Hypertens.* 2015;29(1):178-84.
39. Sibiya MJ, Woodiwiss AJ, Booysen HL, Raymond A, Millen AM, Maseko MJ, et al. Reflected rather than forward wave pressures account for brachial pressure-independent relations between aortic pressure and end-organ changes in an African community. *Journal of hypertension.* 2015;33(10):2083-90.

40. Chirinos JA, Kips JG, Jacobs DR, Jr., Brumback L, Duprez DA, Kronmal R, et al. Arterial wave reflections and incident cardiovascular events and heart failure: MESA (Multiethnic Study of Atherosclerosis). *J Am Coll Cardiol.* 2012;60(21):2170-7.
41. Wang KL, Cheng HM, Sung SH, Chuang SY, Li CH, Spurgeon HA, et al. Wave reflection and arterial stiffness in the prediction of 15-year all-cause and cardiovascular mortalities: a community-based study. *Hypertension.* 2010;55(3):799-805.
42. Weber T, Wassertheurer S, Rammer M, Haiden A, Hametner B, Eber B. Wave reflections, assessed with a novel method for pulse wave separation, are associated with end-organ damage and clinical outcomes. *Hypertension.* 2012;60(1):534-41.
43. Zamani P, Jacobs DR, Jr., Segers P, Duprez DA, Brumback L, Kronmal RA, et al. Reflection magnitude as a predictor of mortality: the Multi-Ethnic Study of Atherosclerosis. *Hypertension.* 2014;64(5):958-64.
44. Xiao H, Tan I, Butlin M, Li D, Avolio AP. Mechanism underlying the heart rate dependency of wave reflection in the aorta: a numerical simulation. *Am J Physiol-Heart C.* 2018;314(3):H443-h51.
45. Liao CF, Cheng HM, Sung SH, Yu WC, Chen CH. Determinants of pressure wave reflection: characterization by the transit time-independent reflected wave amplitude. *J Hum Hypertens.* 2011;25(1):665-71.
46. Williams B, Lacy PS. Impact of heart rate on central aortic pressures and hemodynamics: analysis from the CAFE (Conduit Artery Function Evaluation) study: CAFE-Heart Rate. *J Am Coll Cardiol.* 2009;54(8):705-13.
47. Laurent P, Albaladejo P, Blacher J, Rudnichi A, Smulyan H, Safar ME. Heart rate and pulse pressure amplification in hypertensive subjects. *Am J Hypertens.* 2003;16(5):363-70.
48. Naqvi TZ, Elkayam U. Serial Echocardiographic Assessment of the Human Heart in Normal Pregnancy. *Circulation: Cardiovascular Imaging.* 2012;5(3):283-5.
49. Smith SA, Morris JM, Gallery ED. Methods of assessment of the arterial pulse wave in normal human pregnancy. *Am J Obstet Gynecol.* 2004;190(1):472-6.
50. Macedo ML, Luminoso D, Savvidou MD, McEniery CM, Nicolaides KH. Maternal wave reflections and arterial stiffness in normal pregnancy as assessed by applanation tonometry. *Hypertension.* 2008;51(4):1047-51.
51. Delachaux A, Waeber B, Liaudet L, Hohlfeld P, Feihl F. Profound impact of uncomplicated pregnancy on diastolic, but not systolic pulse contour of aortic pressure. *Journal of hypertension.* 2006;24(8):1641-8.
52. Robb AO, Mills NL, Din JN, Smith IB, Paterson F, Newby DE, et al. Influence of the menstrual cycle, pregnancy, and preeclampsia on arterial stiffness. *Hypertension.* 2009;53(6):952-8.
53. Oyama-Kato M, Ohmichi M, Takahashi K, Suzuki S, Henmi N, Yokoyama Y, et al. Change in pulse wave velocity throughout normal pregnancy and its value in predicting pregnancy-induced hypertension: A longitudinal study. *Am J Obstet Gynecol.* 2006;195(1):464-9.
54. Roberts JM, Escudero C. The placenta in preeclampsia. *Pregnancy hypertension.* 2012;2(1):72-83.
55. Roberts JM, Hubel CA. The two stage model of preeclampsia: variations on the theme. *Placenta.* 2009;30 Suppl A(Suppl A):S32-7.
56. Roberts JM, Gammill HS. Preeclampsia: recent insights. *Hypertension.* 2005;46(6):1243-9.
57. Roberts JM, Escudero C. The placenta in preeclampsia. *Pregnancy Hypertens*. 2012;2(1):72-83.
58. Chappell LC, Seed PT, Briley AL, Kelly FJ, Lee R, Hunt BJ, et al. Effect of antioxidants on the occurrence of pre-eclampsia in women at increased risk: a randomised trial. *Lancet*. 1999;354(9181):810-6.
59. Chaiworapongsa T, Chaemsaithong P, Yeo L, Romero R. Pre-eclampsia part 1: current understanding of its pathophysiology. *Nature reviews Nephrology.* 2014;10(8):466-80.
60. McDermott M, Miller EC, Rundek T, Hurn PD, Bushnell CD. Preeclampsia: Association With Posterior Reversible Encephalopathy Syndrome and Stroke. *Stroke.* 2018;49(3):524-30.

61. Miller EC. Preeclampsia and Cerebrovascular Disease. *Hypertension.* 2019;74(1):5-13.
62. Alphonsus CS, Rodseth RN. The endothelial glycocalyx: a review of the vascular barrier. *Anaesthesia.* 2014;69(7):777-84.
63. Weissgerber TL, Garcia-Valencia O, Milic NM, Codsi E, Cubro H, Nath MC, et al. Early Onset Preeclampsia Is Associated With Glycocalyx Degradation and Reduced Microvascular Perfusion. *J Am Heart Assoc.* 2019;8(4):e010647.
64. Lau SY, Guild SJ, Barrett CJ, Chen Q, McCowan L, Jordan V, et al. Tumor necrosis factor-alpha, interleukin-6, and interleukin-10 levels are altered in preeclampsia: a systematic review and meta-analysis. *American journal of reproductive immunology.* 2013;70(5):412-27.
65. Becker BF, Chappell D, Bruegger D, Annecke T, Jacob M. Therapeutic strategies targeting the endothelial glycocalyx: acute deficits, but great potential. *Cardiovasc. res.* 2010;87(1):300-10.
66. Felfernig-Boehm D, Salat A, Vogl SE, Murabito M, Felfernig M, Schmidt D, et al. Early detection of preeclampsia by determination of platelet aggregability. *Thrombosis research.* 2000;98(1):139-46.
67. Riskin-Mashiah S, Belfort MA, Saade GR, Herd JA. Cerebrovascular reactivity in normal pregnancy and preeclampsia. *Obstetrics and gynecology*. 2001;98(5 Pt 1):827-32.
68. Riskin-Mashiah S, Belfort MA. Preeclampsia Is Associated With Global Cerebral Hemodynamic Changes. *The Journal of the Society for Gynecologic Investigation: JSGI.* 2005;12(4):253-6.
69. Belfort MA, Saade GR, Grunewald C, Dildy GA, Abedejos P, Herd JA, et al. Association of cerebral perfusion pressure with headache in women with pre-eclampsia. *BJOG*. 1999;106(8):814-21.
70. Warrington JP, Fan F, Murphy SR, Roman RJ, Drummond HA, Granger JP, et al. Placental ischemia in pregnant rats impairs cerebral blood flow autoregulation and increases blood-brain barrier permeability. *Physiol rep.* 2014;2(8).
71. Clayton AM, Shao Q, Paauw ND, Giambrone AB, Granger JP, Warrington JP. Postpartum increases in cerebral edema and inflammation in response to placental ischemia during pregnancy. *Brain, behavior, and immunity.* 2018;70:376-89.
72. Li X, Han X, Yang J, Bao J, Di X, Zhang G, et al. Magnesium Sulfate Provides Neuroprotection in Eclampsia-Like Seizure Model by Ameliorating Neuroinflammation and Brain Edema. *Molecular neurobiology.* 2017;54(10):7938-48.
73. van Veen TR, Panerai RB, Haeri S, Singh J, Adusumalli JA, Zeeman GG, et al. Cerebral autoregulation in different hypertensive disorders of pregnancy. *Am J Obstet Gynecol.* 2015;212(4):513.e1-7.
74. Oehm E, Hetzel A, Els T, Berlis A, Keck C, Will HG, et al. Cerebral hemodynamics and autoregulation in reversible posterior leukoencephalopathy syndrome caused by pre-/eclampsia. *Cerebrovascular diseases*. 2006;22(2-3):204-8.
75. Zeeman GG, Hatab MR, Twickler DM. Increased cerebral blood flow in preeclampsia with magnetic resonance imaging. *Am J Obstet Gynecol.* 2004;191(4):1425-9.
76. Martin JN, Jr., Thigpen BD, Moore RC, Rose CH, Cushman J, May W. Stroke and severe preeclampsia and eclampsia: a paradigm shift focusing on systolic blood pressure. *Obstetrics and gynecology.* 2005;105(1):246-54.
77. Brewer J, Owens MY, Wallace K, Reeves AA, Morris R, Khan M, et al. Posterior reversible encephalopathy syndrome in 46 of 47 patients with eclampsia. *Am J Obstet Gynecol.* 2013;208(6):468.e1-6.
78. Kristensen J, Basit S, Wohlfahrt J, Damholt M, Boyd H. Pre-eclampsia and risk of later kidney disease: nationwide cohort study. *BMJ.* 2019;365:l1516.
79. Powe CE, Levine RJ, Karumanchi SA. Preeclampsia, a disease of the maternal endothelium: the role of antiangiogenic factors and implications for later cardiovascular disease. *Circulation.* 2011;123(24):2856-69.

80. Hertig A, Berkane N, Lefevre G, Toumi K, Marti H-P, Capeau J, et al. Maternal Serum sFlt1 Concentration Is an Early and Reliable Predictive Marker of Preeclampsia. *Clinical Chemistry.* 2020;50(9):1702-3.
81. Craici IM, Wagner SJ, Weissgerber TL, Grande JP, Garovic VD. Advances in the pathophysiology of pre-eclampsia and related podocyte injury. *Kidney International*. 2014;86(1):275-85.
82. Maynard SE, Min JY, Merchan J, Lim KH, Li J, Mondal S, et al. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. *The Journal of clinical investigation.* 2003;111(5):649-58.
83. Stillman IE, Karumanchi SA. The Glomerular Injury of Preeclampsia. *Journal of the American Society of Nephrology. 2007*;18(8):2281-4.
84. Garovic VD, Wagner SJ, Turner ST, Achenabach MS, Schiffer M, Grande JP. Podocyturia is a marker of preeclampsia. American Journal of Obstetrics and Gynaecology. 2007;3(8):e1-320.e7.
85. Visser W, Wallenburg H. A comparison between the haemodynamic effects of oral nifedipine and intravenous dihydralazine in patients with severe pre-eclampsia. *Journal of hypertension.* 1995;13(7):791-5.
86. Melchiorre K, Sutherland G, Sharma R, Nanni M, Thilaganathan B. Mid-gestational maternal cardiovascular profile in preterm and term pre-eclampsia: a prospective study. *BJOG:* An International Journal of Obstetrics & Gynaecology. 2013;120(4):496-504.
87. Valensise H, Vasapollo B, Gagliardi G, Novelli GP. Early and Late Preeclampsia. *Hypertension.* 2008;52(5):873-80.
88. Elvan-Tas¸pinar A, Franx A, Bots M, Bruinse H, Koomans H. Central Hemodynamics of Hypertensive Disorders in Pregnancy. *American journal of hypertension*. 2004;17(10):941-6.
89. Kaihura C, Savvidou MD, Anderson JM, McEniery CM, Nicolaides KH. Maternal arterial stiffness in pregnancies affected by preeclampsia. *American journal of physiology Heart and circulatory physiology*. 2009;297(1):H759-64.
90. Namugowa A, Iputo J, Wandabwa J, Meeme A, Buga GAB. Comparison of arterial stiffness in preeclamptic and normotensive pregnant women from a semi-rural region of South Africa. *Clinical and Experimental Hypertension.* 2017;39(3):277-83.
91. Namugowa A, Iputo J, Wandabwa J, Meeme A, Buga GAB, Abura S, et al. Arterial stiffness in women previously with preeclampsia from a semi-rural region of South Africa. Clinical and *Experimental Hypertension.* 2019;41(1):36-43.
92. O'Rourke MF, Pauca A, Jiang XJ. Pulse wave analysis. *Br J Clin Pharmacol.* 2001;51(6):507-22.
93. Manisty CH, Hughes AD. Meta-analysis of the comparative effects of different classes of antihypertensive agents on brachial and central systolic blood pressure, and augmentation index. *Br J Clin Pharmacol.* 2013;75(1):79-92.
94. Jankowski P, Kawecka-Jaszcz K, Czarnecka D, Brzozowska-Kiszka M, Styczkiewicz K, Loster M, et al. Pulsatile but not steady component of blood pressure predicts cardiovascular events in coronary patients. *Hypertension.* 2008;51(4):848-55.
95. Manisty CH, Hughes AD. Meta-analysis of the comparative effects of different classes of antihypertensive agents on brachial and central systolic blood pressure, and augmentation index. *Br J Clin Pharmacol.* 2013;75(1):79-92.
96. Boutouyrie P, Achouba A, Trunet P, Laurent S. Amlodipine-valsartan combination decreases central systolic blood pressure more effectively than the amlodipine-atenolol combination: the EXPLOR study. *Hypertension.* 2010;55(6):1314-22.
97. Williams B, Lacy PS, Thom SM, Cruickshank K, Stanton A, Collier D, et al. Differential Impact of Blood Pressure Lowering Drugs on Central Aortic Pressure and Clinical Outcomes. *Circulation.* 2006;113(9):1213-25.
98. Pucci G, Ranalli MG, Battista F, Schillaci G. Effects of B-Blockers With and Without Vasodilating Properties on Central Blood Pressure. *Hypertension.* 2016;67(1):316-24.

99. McGaughey TJ, Fletcher EA, Shah SA. Impact of Antihypertensive Agents on Central Systolic Blood Pressure and Augmentation Index: A Meta-Analysis. *Am J Hypertens.* 2016;29(4):448-57.
100. Manisty CH, Zambanini A, Parker KH, Davies JE, Francis DP, Mayet J, et al. Differences in the magnitude of wave reflection account for differential effects of amlodipine- versus atenolol-based regimens on central blood pressure: an Anglo-Scandinavian Cardiac Outcome Trial substudy. *Hypertension.* 2009;54(4):724-30.
101. Webster LM, Myers JE, Nelson-Piercy C, Harding K, Cruickshank JK, Watt-Coote I, et al. Labetalol Versus Nifedipine as Antihypertensive Treatment for Chronic Hypertension in Pregnancy: A Randomized Controlled Trial. *Hypertension.* 2017;70(5):915-22.
102. Olafiranye O, Qureshi G, Salciccioli L, Weber M, Lazar JM. Association of beta-blocker use with increased aortic wave reflection. *Journal of the American Society of Hypertension : JASH*. 2008;2(1):64-9.
103. Weber T, Auer J, O'Rourke MF, Punzengruber C, Kvas E, Eber B. Prolonged mechanical systole and increased arterial wave reflections in diastolic dysfunction. *Heart* (British Cardiac Society). 2006;92(1):1616-22.
104. Liu M, Li G-L, Li Y, Wang J-G. Effects of Various Antihypertensive Drugs on Arterial Stiffness and Wave Reflections. *Pulse* (Basel). 2013;1(1):97-107.
105. Shah NK, Smith SM, Nichols WW, Lo MC, Ashfaq U, Satish P, et al. Carvedilol reduces aortic wave reflection and improves left ventricular/vascular coupling: a comparison with atenolol (CENTRAL Study). *Journal of clinical hypertension* (Greenwich, Conn). 2011;13(12):917-24.
106. Association WM. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA.* 2013;310(1):2191.
107. Moodley J, Soma-Pillay P, Buchmann E, Pattinson RC. Hypertensive disorders in pregnancy: 2019 National guideline. *SAMJ.* 2019;109(9):12723.
108. Chirinos JA, Kips JG, Jacobs DR, Brumback L, Duprez DA, Kronmal R, et al. Arterial Wave Reflections and Incident Cardiovascular Events and Heart Failure. MESA (Multiethnic Study of Atherosclerosis). *J Am Col Cardiol.* 2012;60(21):2170-7.
109. Westerhof BE, Guelen I, Westerhof N, Karemaker JM, Avolio A. Quantification of Wave Reflection in the Human Aorta From Pressure Alone. *Hypertension.* 2006;48(4):595-601.
110. Mitchell GF. Triangulating the Peaks of Arterial Pressure. *Hypertension.* 2006;48:543-5.
111. Rajagopalan S, Kariisa M, Dellegrottaglie S, Bard RL, Kehrer C, Matlow S, et al. Angiotensin receptor blockade improves vascular compliance in healthy normotensive elderly individuals: results from a randomized double-blind placebo-controlled trial. *Journal of clinical hypertension. 2*006;8(1):783-90.
112. Deary AJ, Schumann AL, Murfet H, Haydock S, Foo RS, Brown MJ. Influence of drugs and gender on the arterial pulse wave and natriuretic peptide secretion in untreated patients with essential hypertension. *Clinical science.* 2002;103(5):493-9.
113. Eguchi K, Hoshide S, Kario K. Effects of Celiprolol and Bisoprolol on Blood Pressure, Vascular Stiffness, and Baroreflex Sensitivity. *Am J Hypertens*. 2015;28(7):858-67.
114. Ong KT, Delerme S, Pannier B, Safar ME, Benetos A, Laurent S, et al. Aortic stiffness is reduced beyond blood pressure lowering by short-term and long-term antihypertensive treatment: a meta-analysis of individual data in 294 patients. J Hypertens. 2011;29(6):1034-42.
115. Dhakam Z, McEniery CM, Yasmin, Cockcroft JR, Brown MJ, Wilkinson IB. Atenolol and Eprosartan: Differential Effects on Central Blood Pressure and Aortic Pulse Wave Velocity. *Am J Hypertens.* 2006;19(1):214-9.
116. Fok H, Guilcher A, Li Y, Brett S, Shah A, Clapp B, et al. Augmentation Pressure Is Influenced by Ventricular Contractility/Relaxation Dynamics. *Hypertension.* 2014;63(5):1050-5.
117. Torjesen AA, Wang N, Larson MG, Hamburg NM, Vita JA, Levy D, et al. Forward and Backward Wave Morphology and Central Pressure Augmentation in Men and Women in the Framingham Heart Study. *Hypertension.* 2014;64(1):259-65.

118. Li Y, Gu H, Fok H, Alastruey J, Chowienczyk P. Forward and Backward Pressure Waveform Morphology in Hypertension. *Hypertension.* 2017;69(1):375-81.
119. Scardo JA, Hogg BB, Newman RB. Favorable hemodynamic effects of magnesium sulfate in preeclampsia. *American Journal of Obstetrics & Gynecology.* 1995;173(4):1249-53.
120. Tade G, Norton GR, Booysen HL, Sibiya MJ, Ballim I, Sareli P, et al. Enhanced Aortic Reflected Wave Magnitude Accounts for the Impact of Female Gender on Aortic Pressure Augmentation in a Group of African Ancestry. *Am J Hypertens.* 2017;30(8):781-90.
121. Kamran H, Lazar JM, Patel R, Maraj I, Berman H, Salciccioli L. The Age-Dependent Contribution of Aortic Incident and Reflected Pressure Waves to Central Blood Pressure in African-Americans. *International journal of hypertension.* 2011;2011:585703.
122. Tay J, Foo L, Masini G, Bennett PR, McEniery CM, Wilkinson IB, et al. Early and late preeclampsia are characterized by high cardiac output, but in the presence of fetal growth restriction, cardiac output is low: insights from a prospective study. *AJOG.* 2018;218(5):517.e1-.e12.
123. Dennis AT, Castro J, Carr C, Simmons S, Permezel M, Royse C. Haemodynamics in women with untreated pre-eclampsia. *Anaesthesia.* 2012;67(10):1105-18.
124. Melchiorre K, Sharma R, Thilaganathan B. Cardiovascular Implications in Preeclampsia. *Circulation.* 2014;130(8):703-14.
125. Roos N, Kieler H, Sahlin L, Ekman-Ordeberg G, Falconer H, Stephansson O. Risk of adverse pregnancy outcomes in women with polycystic ovary syndrome: population based cohort study. *BMJ.* 2011;343:d6309.
126. Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. *BMJ.* 2005;330(7491):565.
127. Mitchell GF, Lacourcière Y, Arnold JMO, Dunlap ME, Conlin PR, Izzo JL. Changes in Aortic Stiffness and Augmentation Index After Acute Converting Enzyme or Vasopeptidase Inhibition. *Hypertension.* 2005;46(5):1111-7.
128. Mackenzie IS, McEniery CM, Dhakam Z, Brown MJ, Cockcroft JR, Wilkinson IB. Comparison of the Effects of Antihypertensive Agents on Central Blood Pressure and Arterial Stiffness in Isolated Systolic Hypertension. *Hypertension.* 2009;54(1):409-13.
129. Kips JG, Rietzschel ER, Buyzere MLD, Westerhof BE, Gillebert TC, Bortel LMV, et al. Evaluation of Noninvasive Methods to Assess Wave Reflection and Pulse Transit Time From the Pressure Waveform Alone. *Hypertension.* 2009;53(1):142-9.
130. Verbeke F, Segers P, Heireman S, Vanholder R, Verdonck P, Van Bortel LM. Noninvasive assessment of local pulse pressure: importance of brachial-to-radial pressure amplification. Hypertension. 2005;46(1):244-8.
131. Picone DS, Climie RE, Ahuja KD, Keske MA, Sharman JE. Brachial-to-radial SBP amplification: implications of age and estimated central blood pressure from radial tonometry. *J Hypertens.* 2015;33(9):1876-83; discussion 83.

APPENDIX 1

Guidelines for the antihypertensive management of severe pre-eclampsia

1. Admit to high care area
2. Preload with 200ml Ringer-Lactate solution over 20 minutes
3. Give Nifedipine 10mg orally as single dose unless heart rate ≥120bpm
4. Consider adding magnesium sulphate – 4g loading dose in 200ml ringers lactate or normal saline intravenously over 20 minutes or 10g intramuscularly (5g each buttock)
5. Measure the BP every 30 minutes at first, then hourly
6. Repeat Nifedipine ½ hourly if necessary (BP still ≥160/110mmHg)
7. Aim for a BP if 140/90mmHg
8. Add maintenance treatment – omitted for this study, as maintenance treatment is used once blood pressure is controlled.

For unconscious or tachycardic patients, infuse labetalol 200mg in 200ml normal saline at 20ml/hour (i.e. 20mg/hr, to a maximum of 300mg in 24 hours). Give 300ml preload just before starting the infusion. A 20mg starting bolus may be given (8, 107).

APPENDIX 2

R14/49 Dr Nicol Janse van Rensburg

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M170671

NAME: (Principal Investigator)	Dr Nicol Janse van Rensburg
DEPARTMENT:	Anaesthesia Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	The Effect of Antihypertensive Therapy on Central Aortic Pressures of Severe Pre-eclamptic Patients Receiving Antihypertensives
DATE CONSIDERED:	30/06/2017
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof G. Norton, Dr O. Smith and Prof A. Woodiwiss
APPROVED BY:	Professor P. Cleaton-Jones Chairperson, HREC (Medical)
DATE OF APPROVAL:	23/08/2017

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 June and will therefore be due in the month of June each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date 01/11/2017

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX 3

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 19th June 2017

TITLE OF PROJECT:

Central Aortic Pressures in Severe Pre-Eclamptic Patients receiving Antihypertensives.

UNIVERSITY: Witwatersrand

Principal Investigator: Dr N Janse van Rensburg

Department: Anaesthesiology

Supervisor : Prof Gavin Norton

Permission Head Department (where research conducted): Yes

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Academic Hospital. The CEO / management of Chris Hani Baragwanath Academic Hospital is accordingly informed and the study is subject to:-

- **Permission having been granted by the Committee for Research on Human Subjects of the University of the Witwatersrand.**
- The Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- The MAC will be informed of any serious adverse events as soon as they occur
- Permission is granted for the duration of the Ethics Committee Approval.

.....
Recommended
(On behalf of the MAC)
Date: 19/06/2017

.....
Approved/Not Approved
Hospital Management
Date: 29/6/17

APPENDIX 4

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

OBSTETRICS AND GYNAECOLOGY
School of Clinical Medicine

9th June 2017

To whom it may concern

Re: Confirmation of study approval in the Department of Obstetrics & Gynaecology, Chris Hani Baragwanath Academic Hospital

Title of Study: Central aortic pressures in severe pre-eclamptic patients receiving antihypertensives

This letter serves to confirm that Dr N Janse van Rensburg has approval to conduct this study in this Department. This approval is subject to unconditional approval from the Human research ethics committee and the CEO of Chris Hani Baragwanath Academic Hospital.

Thank you

Thank you
Yasmin Adam
Chief Specialist and Adjunct Professor
Department of Obstetrics & Gynaecology
The University of the Witwatersrand

Faculty of Health Sciences
Johannesburg Hospital I Private Bag X39, Johannesburg, South Africa I **T** +27 11 488 3179 I **F** +27 11 643 2522 I www.wits.ac.za