COMPARISON OF AORTIC HAEMODYNAMICS IN COMMUNITY PARTICIPANTS AND PATIENTS WITH SYSTOLIC HEART FAILURE AND THE IMPACT OF BLOOD PRESSURE CONTROL

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A Dissertation submitted to the Health Sciences Faculty, at the University of the
Witwatersrand, Johannesburg, for the degree of
Master of Science in Medicine (Physiology)

Johannesburg, 2024

Declaration

I, Ntapo Marcus Lebelo declare that this dissertation is my work. It is being submitted for the Degree of Masters of Science in Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

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(Signature of student)

20th day of March 2024

I certify that the studies contained in this dissertation have been approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, Johannesburg, under the ethics approval numbers (M02-04-72 and renewed as M07-04-69, M12-04-108, M17-04-01 and M22-03-93; and M18-05-07 renewed as M23-08-53).

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(Signature of student)

14th day of August 2024

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(Signature of supervisor)	(Signature of supervisor)
14th day of August 2024	14th day of August 2024

Dedication

I dedicate this work to my parents, Lesiba and Kabiwa Lebelo, and my foster mother Raisibe Lebelo I am well aware that it wasn't always easy for you. Your sacrifices, whether big or small, have not gone unnoticed. Your encouragement during challenging times gave me the strength to persevere. Your words of wisdom have been a guiding light, helping me navigate through the complexities of academics. To my siblings, Tobi, Morongoa, Seipati, Mankete, and Lesiba, I am proud to say that your efforts have borne fruit. Your support has not only helped me academically but has also instilled in me values that go beyond textbooks. Your unwavering support has taught me the importance of determination, resilience, and the value of family. Thank you all for the support.

Presentations (oral) Arising From This Study

Comparison of Aortic Haemodynamics in Community Participants and Patients with Systolic Heart Failure and the Impact of Blood Pressure Control. **Marcus N Lebelo**, Vernice R Peterson, Danelle Els, Jamie-Leigh Kinsey, Ferande Peters, Angela J Woodiwiss. South African Hypertension Society 2nd NextGen Virtual Spring School, University of the Witwatersrand Health Sciences Campus - 12 October 2023.

Comparison of Aortic Haemodynamics in Community Participants and Patients with Systolic Heart Failure and the Impact of Blood Pressure Control. **Marcus N Lebelo**, Vernice R Peterson, Danelle Els, Jamie-Leigh Kinsey, Ferande Peters, Angela J Woodiwiss. Molecular Biosciences Research Thrust Research Symposium, University of the Witwatersrand Health Sciences Campus - 07 December 2023.

Student role

The pressure wave data and the echocardiographic images had already been collected. I extracted the raw pressure wave data coordinates, and the aortic diameter and velocity images to determine Zc, Q, Pf, Pb, reflect and re-reflected pressure. As described in section 2.6, in my Masters degree I recreated 42 aortic velocity waves from echo images using Diacom viewer. I also extracted the raw pressure versus time coordinates from the SphygomoCor database for 42 systolic heart failure patients. These pressure versus time coordinates were paired with the recreated aortic velocity images according to time. This allowed me to calculate Zc, determine Q, and calculate QxZc. Furthermore, I performed wave separation analyses using these paired pressure-velocity time coordinates to determine Pf, Pb, reflect and re-reflected pressure. Using the echocardiographic images, as described in section 2.6, I also calculated SV (stroke volume), CO (cardiac output) and SVR (systemic vascular resistance). Moreover, I performed all of the statistical analyses described in section 2.8 in order to address my objectives and hence the aim of my MSc. Furthermore, during the course of my Masters degree I spent time learning how to measure central arterial pressure using the SphygmoCor device and observing the measurement of cardiac structure and function using echocardiography.

Abstract

In patients with systolic heart failure (HF), both decreases and increases in pulse pressure (PP) are associated with poor prognosis. If aortic PP in systolic HF is decreased due to systolic dysfunction, then improvements in stroke volume (SV) or forward wave pressure (Pf) would be beneficial. Alternatively, if hypertension is the primary cause of systolic HF, aortic PP may be increased as a consequence of high aortic characteristic impedance (Zc) and backward wave pressure (Pb), which would be detrimental. Accordingly, blood pressure (BP) lowering would be advantageous. However, the changes in central hemodynamics that accompany systolic HF are currently unclear. Hence, I aimed to assess central hemodynamics in systolic HF patients compared to community participants.

I therefore compared aortic haemodynamics (central pressures [SphygmoCor], aortic tract outflow [echocardiography]), and the impact of controlled BP (SBP/DBP<140/90 mm Hg or SBP/DBP<130/80 mm Hg) between stable systolic HF patients (n=42) and age and sex-matched community participants (n=298).

Systolic HF patients had lower central PP and Pb ($p<0.005$) and higher HR ($p<0.005$) than community participants. However, no other differences were noted. When assessing the impact of BP control (SBP/DBP<140/90 mm Hg), HF patients with uncontrolled BP had higher Zc ($p<0.005$), Pf ($p<0.05$), and systemic vascular resistance (SVR) ($p<0.05$) than both HF patients and community participants with controlled BP. Moreover, despite similar peripheral and central PP to community participants with uncontrolled BP, Zc ($p<0.005$) and SVR ($p<0.05$) were higher in HF patients with uncontrolled BP. However, when assessing more intense BP control (SBP/DBP<130/80 mm Hg), the differences in Zc, QxZc, and SVR between the systolic HF patients with uncontrolled BP and the community participants with uncontrolled BP were eliminated.

In conclusion, a lower aortic PP, which was not due to decreased SV, was observed in stable systolic HF patients. However, in the presence of uncontrolled BP (SBP/DBP≥140/90 mm Hg), but not SBP/DBP≥130/80 mm Hg, Zc, QxZc and SVR were increased in patients with systolic HF. Hence, BP control and its level of control are imperative in patients with systolic HF to protect the heart from the detrimental effects of increased afterloads.

Acknowledgements

I could not accomplish this project individually. It had the guidance and cooperation of esteemed people. I would like to take this opportunity to thank the late Professor Gavin Norton, Professor Angela Woodiwiss, Dr. Vernice Peterson, Dr. Nonhlanhla Mthembu, and Dr Suraj Yusuf for their supervision, patience, knowledge, understanding, leadership qualities, and dedication. To the head of the School of Physiology, Professor William Daniels, and the Oppenheimer Memorial Trust (OMT), thank you for the sponsorship you have granted me to complete my Masters degree.

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List of Abbreviations

Ao Diam	Aortic root diameter
BP	Blood pressure
CAD	Coronary artery disease
CVDs	Cardiovascular diseases
CO	Cardiac output
DBP	Diastolic blood pressure
ED	Ejection duration
EF	Ejection fraction
HF	Heart failure
LV	Left ventricle
LVEF	Left ventricular ejection fraction
LVH	Left ventricular hypertrophy
MAP	Mean arterial pressure
MI	Myocardial infarction
Pb	Peak backward wave pressure
Pf	Peak forward wave pressure
PP	Pulse pressure
PQxZc	Product of flow and characteristic impedance
PWV	Pulse wave velocity
Q	Aortic flow
SBP	Systolic blood pressure
sHF	Systolic heart failure
SPRINT	Systolic Blood Pressure Intervention Trial
SSA	Sub-Saharan Africa
SV	Stroke volume
SVR	Systemic vascular resistance
Zc	Characteristic impedance

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CHAPTER 1 INTRODUCTION

1.1 Heart Failure and Hypertension as Cardiovascular Risk Factors

Heart failure (HF) remains one of the world's greatest public health challenges. Heart failure is the most common type of cardiovascular diseases (CVDs), and it is associated with high morbidity and mortality, and affects about 6.4 million people worldwide (Chioncel *et al*., 2017). Due to the aging and growing population, there is an increase in the number of HF patients. In this regard, the older population (aged above 60 years) is at higher risk of developing HF as compared to the younger population (Adams *et al.*, 2005; Yancy *et al.*, 2013). However, in Sub-Saharan Africa (SSA) the mean age of patients with HF (58 years) is about 14 years younger than developed countries (72 years) (Damasceno *et al.*, 2012; Adams *et al*., 2005). Moreover, in SSA non-ischemic etiologies are the leading cause of HF, with most cases (80%) being due to hypertension (Damasceno *et al.*, 2012; Ogah *et al*., 2015; Irazola *et al.*, 2016), compared to developed countries where most cases are due to coronary artery disease (CAD) (Adams *et al.*, 2005).

South Africa (SA) has a high number of hypertensive people, with approximately 30-50% of adult South Africans being affected (Kandala *et al.*, 2021; Woodiwiss *et al.*, 2023). Furthermore, based on Statistics SA Mortality Report, hypertension contributes to four of the top ten natural causes of death, being cerebrovascular diseases (3rd), non-ischemic heart diseases (4th), hypertensive diseases (6th), and ischemic heart diseases (9th) (Stats SA, 2019). As hypertension is prevalent and identified as the major contributor to HF, in order to improve the prevention and management of HF in SA, the impact of hypertension on the heart needs to be explored.

Hypertension is characterised by increases in pulsatile pressure (pulse pressure, PP), which is a strong determinant of cardiovascular damage beyond steady pressure (mean arterial pressure, MAP) (Staessen *et al*., 1991). In hypertension, the increased central aortic PP together with increased aortic stiffness (Safar *et al.,* 2018), result in increases in cardiac afterload. In patients with HF, increases in cardiac afterload would place an additional burden on an already compromised heart, leading to worsened cardiac function (Weber and Chirinos, 2018; Ikonomidis *et al*., 2019). Hence, an understanding of the haemodynamic mechanisms of the changes in aortic PP in HF is essential to improve clinical outcomes in patients with HF. However, currently, there is limited data on the role of central aortic PP and its determinants in HF. Two previous studies have shown no differences in central PP between patients with systolic

HF and controls (Parragh *et al*., 2015; Steinberg *et al*., 2023), whereas in another study a lower central PP was observed in patients with severe systolic HF compared to controls (Denardo *et al*., 2010). Moreover, one study reported that increases in central PP were associated with increases in cardiovascular events (Sung *et al*., 2011). One study reported that increases in the speed of wave reflection (a determinant of central aortic PP) were associated with an increased risk of death (Steinberg *et al.*, 2023). In comparison, an alternative study reported a delayed return of wave reflection in patients with severe systolic HF (Denardo *et al*., 2010). These data which are all from studies in severe systolic HF are inconsistent. Furthermore, whether central aortic PP or its determinants are altered in patients with mild-to-moderate systolic HF associated with hypertension has not been assessed. In this chapter of my dissertation, I will first summarise the current literature on the role of peripheral PP and then central PP in HF. I will then introduce the components of central aortic PP and the haemodynamic determinants thereof. The potential impact on systolic HF of changes in these haemodynamic factors will then be discussed in the context of ventricular-arterial coupling. In addition, as hypertension is the primary cause of HF in SA, the potential impact of BP control and intense BP lowering in HF will be considered.

1.2 Pulse Pressure in HF

Pulse pressure (PP) is defined as the difference between SBP and DBP, during the cardiac cycle. High PP is associated with poor prognosis and the European Guidelines on Hypertension state that peripheral (brachial) PP ≥ 60 mm Hg in older people results in asymptomatic stiffening of large arteries (Williams *et al.*, 2018; Weber *et al*., 2019). Practically, it is common for clinicians to measure brachial BP for the diagnosis and management of hypertension. In addition, in patients with HF, brachial BP is used as an index of clinical improvement and to assess patients' response to medication. However, in patients with HF, despite an improvement in brachial BP with medical therapy (Ho., 2018; Kashihara *et al*., 2020), aortic PP may be increased relative to peripheral PP due to increased aortic stiffness (Zc). As already mentioned that an increased central aortic PP is a strong determinant of cardiovascular damage beyond steady pressure (Staessen *et al*., 1991), central aortic PP more closely reflects the impact of PP on the heart (Li *et al*., 2017). In this regard, increases in central aortic PP causes an increase in cardiac afterload, leading to a further worsened cardiac function (Weber and Chirinos, 2018; Ikonomidis *et al*., 2019). Hence, it is important to identify whether central PP is increased in systolic HF. Furthermore, the impact of the factors determining central PP needs to be considered. However, currently, there is limited data on the role of central aortic PP and its determinants in HF. Due to ease of measurement, most of the current literature pertains to peripheral PP. Hence in the subsequent two sections, I will first discuss the current literature on changes in peripheral PP in HF and then the current literature on changes in central PP in HF.

1.2.1 Peripheral PP in Systolic HF

Numerous studies have looked at peripheral PP and its association with HF, cardiovascular events and mortality (Petrie *et al*., 2012; Jackson *et al*., 2015). At present, the data is unclear, because both increases and decreases in peripheral PP are associated with increased mortality, as well as with reduced risks of cardiovascular events (see Table 1.1 for references). The discrepancies are unlikely to be due to differences in types of HF, because both systolic HF (HF with reduced ejection fraction [HFrEF]) and diastolic HF (HF with preserved ejection fraction [HFpEF]) are associated with increased or decreased peripheral PP (see Table 1.1 for references). In a study conducted on patients with asymptomatic LV dysfunction, after suffering from myocardial infarction (MI), an increased peripheral PP predicted CV mortalities (Domanski *et al*., 1999). In contrast, one study involving symptomatic HF patients with LV dysfunction has shown that a decreased rather than an increased peripheral PP was an independent predictor of mortality (Petrie *et al*., 2012). Similarly, a study by Yildiran *et al,* (2010) has shown that a decreased peripheral PP was the only predictor of death and it was associated with echocardiographic indices of poor systolic function. In addition, a community-based study has shown that there is a relationship between high peripheral PP and the risk of congestive HF (Haider *et al*., 2003). The relationship appears to be very complex. Indeed, two studies have shown that it is not a linear association and suggest that the association is more U-shaped, whereby both lower and higher peripheral PP are associated with increased cardiovascular risks, with the nadir of the U-shaped curve being around a peripheral PP of 50 mm Hg (Laskey *et al.,* 2016; Tokitsu *et al*., 2016; Teng *et al.*, 2018). This non-linear relationship is shown for both HFrEF (Laskey *et al.,* 2016; Teng *et al.*, 2018) and HFpEF (Tokitsu *et al*., 2016; Teng *et al.*, 2018). It is possible that the relationship between lower peripheral PP and higher risk for cardiovascular events when peripheral PP is ≤50 mm Hg reflects a worsening of LV function. Confirming this suggestion Regnault *et al,* (2014) have shown that improvements in LV function are associated with improvements in peripheral PP. In comparison,

Table 1.1 Comparison between studies showing decreased or increased peripheral pulse pressure (PP) in patients with heart failure with reduced ejection fraction (HFrEF, systolic HF) or heart failure with preserved ejection fraction (HFpEF) or community-based studies, and the impact on clinical outcomes.

Decreased peripheral PP			**Increased peripheral PP**		
Author	Study	Outcome	Author	Study	Outcome
Shah *et al*., 2019	HFrEF	↑ mortality	Domanski *et al*., 1999	HFrEF	↑ mortality
Aronson and Burger, 2004	HFrEF	↑ mortality	Haider *et al*., 2003	Community	↑ risk of HF
Jackson *et al*., 2015	HFrEF	↑ mortality	Regnault *et al*., 2014	HFrEF	↓ mortality
Ferreira *et al*., 2016	HFrEF	↑ mortality	Sung *et al*., 2011	HFrEF	↑ cardiac events
Schillaci *et al*., 2004	HFrEF & HFpEF	↑ mortality	Tokitsu *et al*., 2016	HFpEF	↑ mortality
Petrie *et al*., 2012	HFrEF	↑ mortality	Weiss *et al*., 2009	Community	↑ mortality
Voors *et al*., 2005	HFrEF	↑ mortality			
Yildiran *et al*., 2010	HFpEF	↑ mortality			
Laskey *et al*., 2016	HFrEF	↑ mortality	Laskey *et al*., 2016	HFrEF	↑ mortality
Teng *et al*., 2018	HFrEF & HFpEF	↑ mortality	Teng *et al*., 2018	HFrEF & HFpEF	↑ mortality
Tokitsu *et al*., 2016	HFpEF	↑ mortality	Tokitsu *et al*., 2016	HFpEF	↑ mortality

HF, heart failure; HFrEF, heart failure with reduced ejection fraction (systolic HF); HFpEF, heart failure with preserved ejection fraction; PP, pulse pressure; ↓ decreased; ↑ increased.

the association observed over peripheral PP ≥50 mm Hg implies that there is a high cardiac afterload (higher peripheral PP), putting more strain on the already compromised heart, consequently leading to severe HF and possible death. In support of this, Regnault *et al*, (2014) have shown that a high cardiac afterload [high PWV (Pulse wave velocity) and arterial stiffness] may worsen cardiovascular outcomes. Clearly, the relationship between HF and peripheral PP is complex and non-linear, and it appears to depend on LV function, cardiac loads and aortic stiffness. We therefore need to explore the impact of cardiac afterload, aortic stiffness, and other aortic haemodynamics in patients with HF. I will therefore discuss the current literature on central PP in HF.

1.2.2 Central PP in Systolic HF

There is limited data assessing central PP in patients with HF. Most of the studies have been done in patients with systolic HF (HFrEF). Importantly, these studies were all done in patients with severe systolic HF (NYHA FC III or IV) (Denardo *et al*., 2010; Parragh *et al*., 2015; Steinberg *et al*., 2023). Of note, data is unclear, because both decreases, and no differences in central PP between the cases and controls were observed in these studies (Denardo *et al*., 2010; Parragh *et al*., 2015; Steinberg *et al*., 2023). In one study, central PP was not different between patients with CAD and reduced EF compared to CAD patients with normal EF (Parragh *et al*., 2015). However, studies have shown that an increase in central PP is associated with a worse prognosis in individuals with increased cardiovascular risk (Weber *et al*., 2005; Williams, 2006), and with an increase in cardiovascular events in patients with systolic HF (Sung *et al*., 2011). Concerning arterial stiffness, data is also unclear. Studies have shown an increased PWV in patients with HFpEF compared to normal participants (Desai *et al*., 2009), and that increased PWV is associated with increased cardiovascular events (Sung *et al*., 2011) or an increased risk of hospitalization and cardiac death (Bonapace *et al*., 2013). Furthermore, a study showed that increased speed of Pb (as occurs with increased arterial stiffness) is associated with an increased risk of death (Steinberg *et al*., 2010). However, a study by Denardo *et al*, (2010) showed a greater delay in the return of Pb towards the heart, implying that there is a decreased aortic stiffness in HFrEF patients compared to normal participants. The data on arterial stiffness in HF are therefore also unclear. Clearly, further studies need to be done to assess central PP and its determinants in systolic HF patients. Of note, to my knowledge there is no data on mild-moderate systolic HF patients.

1.3 Determinants of Central Pulse Pressure

Central aortic PP is determined by cardiac components (LV ejection, stroke volume, heart rate) and arterial circulation properties such as peripheral vascular tone and aortic distensibility (Dart and Kingwell, 2001). In addition, aortic PP is determined by the summation of its components, the forward (Pf) and backward (Pb) pressure waves (Li *et al*., 2017) (Figure 1.1). The Pf wave is generated by the contraction of the left ventricle (LV) and hence the ejection of blood (stroke volume) into the highly elastic conduit, namely the aorta (Torjesen *et al*., 2014). This forward pulsatile pressure wave is transmitted in a forward direction, down the arterial tree, in all arterial beds to reach the peripheral arteries (Nichols *et al*., 2011). This forward pulsatile pressure wave is called the forward travelling pressure wave (Pf), and the peak of this pressure wave is termed peak forward wave pressure (Nichols *et al*., 2011) (Figure 1.1). Notably, the same pressure wave generated by LV contraction into the proximal part of the aorta is the same pressure wave seen in all arterial beds downstream (Nichols *et al*., 2011). Additionally, the energy stored in the aorta during systole drives blood flow down the aorta when it recoils during diastole (Nichols *et al*., 2011). Hence, the forward wave pressure is an index of central elastic mechanical properties and ventricular function (Nichols and Edwards, 2001).

In any conduit that transmits flow in a pulsatile system, where narrowing of blood vessels (changes in peripheral vascular tone) or bifurcation occurs in the arterial system, there will be a generation of local forward pressure waves by intermittent flow in the conduit, which will result in reflected pressure waves being generated and returning to the point of origin (Nichols *et al*., 2022). These reflected pressure waves are known as the backward pressure waves (Pb) (Figure 1.1). Similar to the speed of the forward pulsatile pressure wave, the backward pulsatile pressure waves travel at a speed of about 5-15m/sec in a healthy human aorta (Nichols *et al*., 2022). At sites distal to the heart and closer to reflection sites (peripheral pressure), the reflected pressure waves return to points in large arteries where the antinodes of these waves meet the antinodes of the forward pressure waves, resulting in maximal summation of the forward and backward pressure waves (Nichols *et al*., 2022) (Figure 1.2, lower left panel). In comparison, at sites proximal to the heart, such as the proximal aorta there is a greater chance that nodes and antinodes of the Pf and Pb overlap, and hence summation is reduced (Nichols *et al*., 2022).

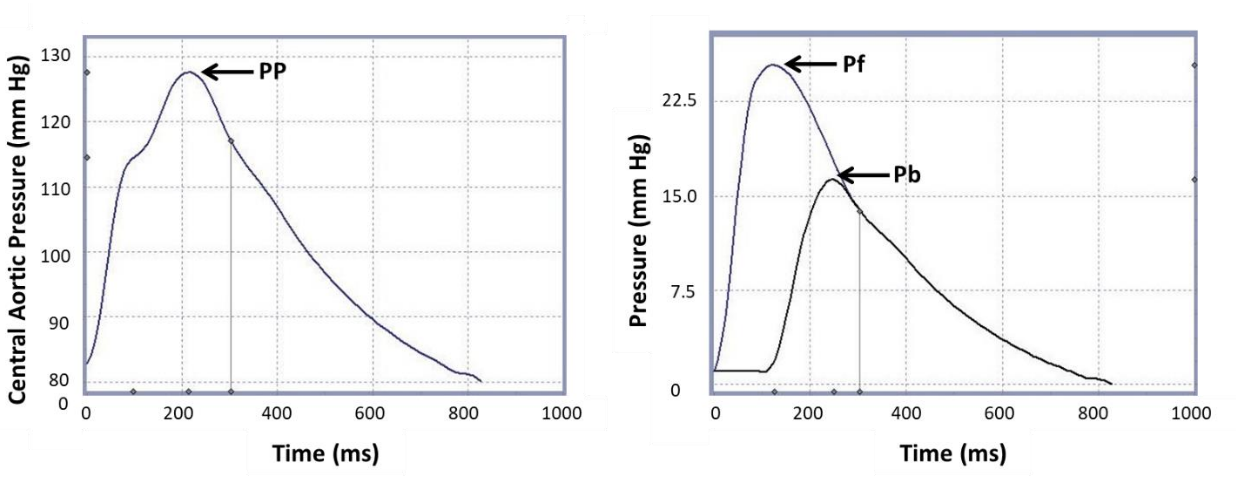


Figure 1.1 Central aortic pressure wave (left panel) and its component forward (Pf) and backward (Pb) travelling pressure waves (right panel). The arrow on the left panel shows peak aortic pulse pressure (PP), and the arrows on the right panel show peak forward wave pressure (Pf), and peak backward wave pressure (Pb).

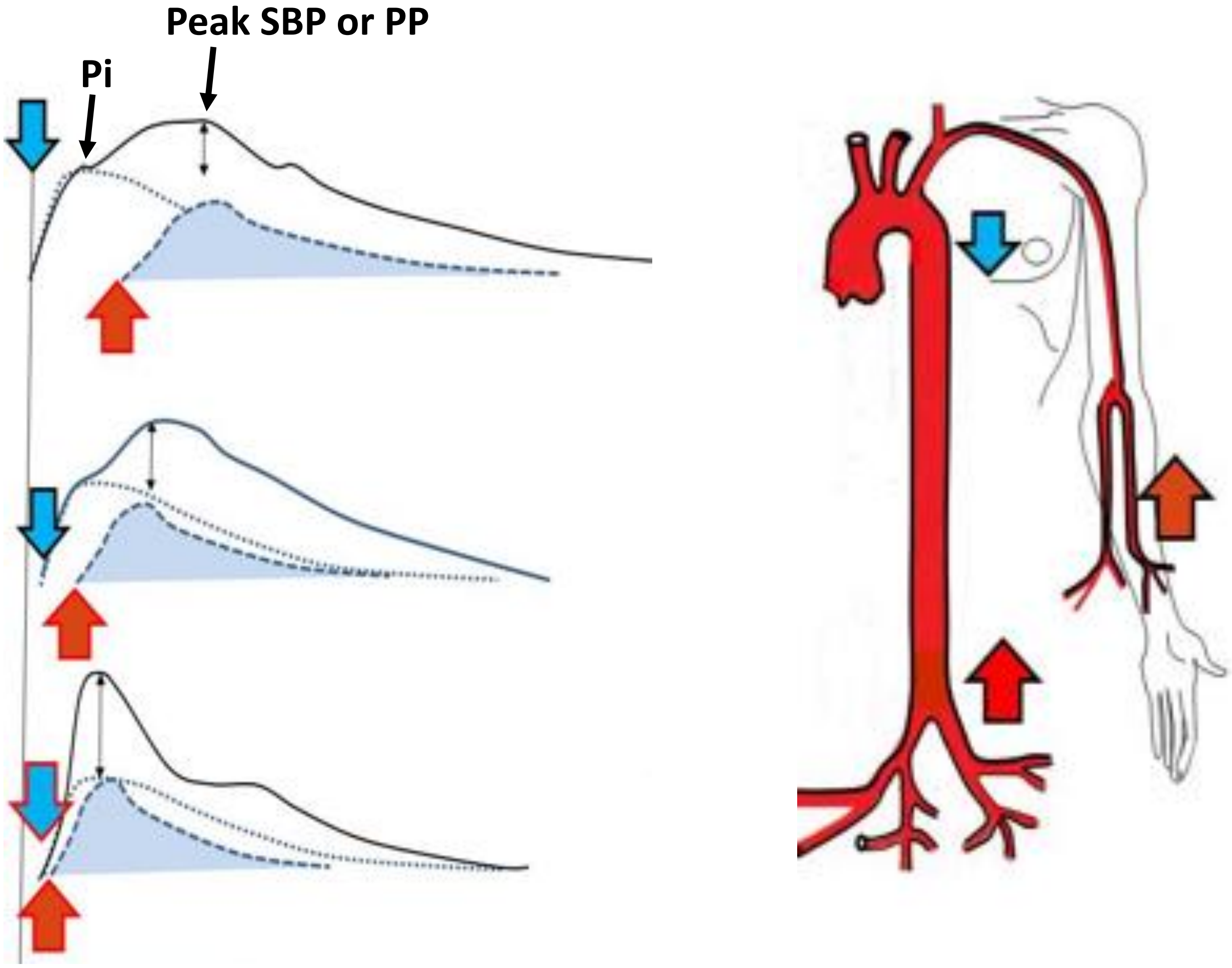


Figure 1.2 The impact of the backward pressure wave (dashed line with light blue shading underneath) generated by the reflection of waves from the points of vascular tapering (red arrows in the right panel) on the summed pressure wave (continuous line). The pressure produced by the forward pressure wave (dotted line with no shading underneath) (blue arrows) adds to the pressure generated by the backward pressure wave in order to generate the summed pressure wave. At the distal vascular sites (red arrows in right panel), there is a greater chance of pressure waves summating (thin doubled headed black arrows) due to antinodes of the oscillating waves overlapping (bottom panel on the left), whilst at the site of the proximal aorta there is a greater chance that nodes and antinodes overlap and hence summation is reduced (top panel on the left). Pi, inflection point; peak SBP, peak aortic systolic blood pressure; peak PP, peak aortic PP.

(Figure 1.2, upper left panel). In essence, a single pulse pressure wave appears from the summation of the forward and backward pressure waves (Avolio *et al*., 2009; Phan *et al.,* 2016). The magnitude of this single pulse pressure wave depends on the extent of summation of the forward and backward pressure waves. Consequently, central aortic PP is lower than peripheral PP.

The single pulse pressure wave in the aorta is characterised by two points of curvature termed the first and second systolic shoulder (Figure 1.2, left panels). The first systolic shoulder is termed the inflection point (Pi) and the second systolic shoulder coincides with peak aortic SBP and PP. Importantly, the first systolic shoulder (inflection point, Pi) is the point where the peak of aortic flow velocity occurs and after this point, the forward pressure wave starts to generate less pressure over time. The opposite happens to the backward pressure wave, as there is an increase in pressure change over time at the inflection point. Thus, the speed of reflected pressure waves is important. The slower the wave reflection, the more likelihood that the backward pressure wave will arrive well after the forward pressure wave in the aorta and augment the diastolic more than systolic BP. This happens in childhood in the presence of a very elastic aorta (Nichols *et al*., 2011), and is advantageous as it promotes coronary blood flow, which mainly occurs during a diastolic period of the cardiac cycle. However, with increases in age (starting from 16 years onwards), there is stiffening of the aorta resulting in faster travel of the pulsatile waves (Nichols *et al.,* 2011). Consequently, the backward pressure waves arrive at the heart during mid-to-late systole and summate with the forward pressure waves, causing unfavourable effects. These unfavourable effects include an increase in aortic SBP, and a decrease in DBP, and consequently an elevation in aortic pulse pressure (Weber and Chirinos, 2018; Avolio *et al*., 2009; Nichols *et al*., 2011). In addition, mid-to-late systolic cardiac load is increased (Avolio *et al*., 2009; Weber and Chirinos, 2018), and reflected waves cause an increase in the amplitude of the forward pressure wave, by re-reflecting at the heart (Nichols, 2005; Townsend *et al*., 2015; Weber *et al*., 2016; Chirinos and Sweitzer, 2017). Hence, in a stiff aorta (which occurs with aging and in the presence of high BP), aortic PP is augmented in association with changes in the forward and backward pressure waves (Mitchell *et al.,* 2010; Hodson *et al*., 2017). Hence, the factors that determine forward and backward pressure waves need to be discussed further.

The forward pressure wave is determined by ventricular ejection and hence LV function and ejection duration (Nichols *et al*., 2011). Decreases in ventricular ejection, such as would occur in systolic HF, result in decreases in aortic blood flow (Q) and hence forward wave pressure. In addition, a decrease in aortic elastance (as occurs with aging), produces resistance to aortic blood flow. The resistance to flow in a pulsatile system is termed characteristic impedance (Zc) (Nichols *et al*., 2011). Importantly, as the aorta is an elastic artery, it normally has a very low characteristic impedance. Thus, in the aorta of a young healthy individual, most of the pressure generated during left ventricular ejection (forward wave pressure) is dependent on flow, and not on characteristic impedance (Nichols *et al*., 2011). Conversely, in a stiff aorta, forward wave pressure is heavily influenced by characteristic impedance (Nichols *et al*., 2011). In addition, as discussed above, the amplitude of Pf is increased by reflected pressure waves when they are re-reflected at the heart (Nichols, 2005; Townsend *et al*., 2015; Chirinos and Sweitzer, 2017). The determinants of the reflected pressure wave are primarily vascular tone (systemic vascular resistance) and heart rate (inverse relationship) (Xiao *et al.*, 2018).

Aortic flow (Q) is determined by factors that influence left ventricular contraction, whereas Zc is determined by the diameter of the aorta and the stiffness of the aorta (Nichols *et al*., 2011). Although, both aortic stiffness and diameter increase with age (Mitchell *et al*., 2003), increments in stiffness increase Zc, whereas increases in aortic diameter decrease Zc (Mitchell *et al*., 2003). An important determinant of Zc is arteriosclerosis, which involves the degradation and degeneration of elastin, cross-linking of elastic fibers and increases in collagen. These structural changes which increase intima-media thickness, are enzymatically and mechanically driven (Nichols *et al*., 2011). However, there are cardiovascular risk factors that can accelerate normal arterial stiffening, including diabetes, hypertension, and dyslipidemia (Saeed *et al.*, 2020). In summary, risk factors related to arteriosclerotic changes are thought to be the main determinants of Zc and hence forward wave pressure. In addition, a reduced aortic compliance results in a faster travelling forward pressure wave, a faster return of the reflected pressure wave to the proximal aorta, a higher amplitude of the reflected and re-reflected pressure waves and consequently an amplified central PP (Saeed *et al*., 2020).

In patients with systolic HF, one of the main determinants of forward wave pressure, namely LV ejection and hence stroke volume is often reduced. Hence, forward wave pressure and consequently central aortic PP may be decreased. If the predominant determinant of aortic PP in systolic HF is LV ejection, then improvements in systolic function with medical therapies would be beneficial. However, as the majority of patients with systolic HF in SSA have hypertension as the etiology, Zc may be increased in these patients. Additionally, as the arteriolar constrictor tone may be increased (a sympathetic compensatory response to a decreased stroke volume), backward wave (Pb) may also be increased. If this is the case, then intense blood pressure (BP) control may be required to manage patients with hypertension-induced systolic HF. A better understanding of the haemodynamic mechanisms of changes in central aortic PP and the determinants thereof in patients with systolic HF is imperative to more effective management of systolic HF. Hence, the impact of stroke volume and blood flow, as well as aortic stiffness and arteriolar tone on central aortic PP in patients with systolic HF warrants discussion.

1.4 Pulse Pressure Caused by Aortic Flow and Stroke Volume in Systolic HF

During systolic HF, the heart's ability to pump blood effectively is impaired or significantly reduced during the contraction phase (systole) (Fukuta and Little, 2008). A decrease in the overall pumping efficiency of the heart results in a reduced ejection fraction (EF), stroke volume (SV), and cardiac output (CO) (Borlaug *et al.*, 2011; Fukuta and Little, 2008). The reduced SV and consequently aortic blood flow (Q) would result in a reduced Pf and hence could lead to a decrease in aortic PP. Indeed, in systolic HF, stroke volume (SV) ventricular ejection and blood flow are reduced, consequently decreasing peripheral BP (Mak *et al*., 2008). However, due to autonomic nervous system activation (adrenergic-induced increases in cardiac contractility), the heart attempts to compensate for its reduced pumping efficiency by pumping out more blood into the aorta with each contraction during the cardiac cycle (Fukuta and Little, 2008). The increased SV contributes to a higher systolic BP, which could potentially lead to an increased PP (Bighamian and Hahn, 2014). The potential benefits of a high PP in systolic HF include, increased perfusion of tissues and organs, and maintenance of adequate blood flow to vital tissues and organs. In addition, coronary arteries that supply blood to the heart muscles may benefit from the higher pressure during systole, improving nutrients and O_2 delivery to the heart (McEniery *et al*., 2005). This is important because organs such as the kidneys, brain, and other tissues require a continuous supply of nutrients and O_2. Indeed, in a study investigating the relationship between PP and outcomes in patients with systolic HF, it was observed that patients with higher PP had better exercise tolerance and a reduced risk of adverse cardiovascular events (Mentz *et al*., 2013). Of note, these findings imply that the compensatory increase in PP may have a protective effect on systolic HF patients. However, it is important to note that while a high PP may have some compensatory benefits in systolic HF, it does not address the underlying issue of impaired cardiac function. Moreover, this compensation may come at the cost of an increased afterload on the heart (increased systemic vascular resistance [SVR]), potentially worsening the HF over time (Fukuta and Little, 2008). Of note, data on the impact of SV on central aortic PP and its determinants in systolic HF patients is limited. In a study by Parragh *et al*, (2015) there were no differences in Pf between patients with reduced EF (systolic HF) compared to patients with normal EF, but on analysis of bivariate data EF, SV and CO were associated with central PP, Pf and Pb. However, no adjustments for potential confounders were made in these association analyses. Hence, whether SV, and Q determine central aortic PP and its component waves in HF is unclear. Furthermore, despite high PP caused by high SV and Q being potentially beneficial in systolic HF patients, how does high PP caused by high Zc and SVR affect patients with systolic HF?

1.5 Pulse Pressure Caused by Aortic Stiffness and Systemic Vascular Resistance in Systolic HF

High aortic stiffness and SVR are common features in systolic HF. In response to the reduced cardiac contractile function and decreased CO in systolic HF (Borlaug *et al*., 2011), the sympathetic nervous system is activated. Consequently, SVR is increased, contributing to a high BP and PP (Weber *et al*., 2004). Moreover, in patients with systolic HF associated with hypertension, SVR and aortic stiffness are likely to be increased. Increases in SVR and aortic stiffness cause an increase in cardiac afterload which would be detrimental in systolic HF, because the heart already struggles to pump blood effectively. Moreover, the increased afterload caused by high PP places an additional burden on the left ventricle, leading to increased myocardial O_2 demand and worsening left ventricular dysfunction (Hoffman and Buckberg, 2014). This creates a vicious cycle where the heart's already compromised function is further compromised by increased workload. Of note, several studies have shown that an increased proximal aortic stiffness is related to both LV systolic and diastolic function indices (Patrianakos *et al*., 2009). An increased PWV leads to an increase in wave reflection on the aorta during systole, rather than diastole, and consequently an increased systolic pressure and PP. Consequently, LV afterload (related to increased arterial resistance [SVR] and wave reflection) is likely to be increased. To confirm this, a study by Said *et al*, (2018) has shown that increased arterial stiffness and PP were associated with increased risks of HF and mortality. Similarly, another study by Tsao *et al*, (2015) has shown that HFrEF patients have increased arterial stiffness. It is therefore important to understand the relationship between the heart and the vasculature and the impact of this interaction (ventricular-arterial coupling) on patients with systolic HF.

1.6 Ventricular-Arterial Coupling

Ventricular-Arterial Coupling refers to the interaction and balance between the ventricular contractility (the ability of the heart to pump blood) and the arterial load (the resistance and compliance of the arteries) (Antonini-Canterin *et al*., 2013). Ventricular contraction influences arterial compliance, however increased arterial stiffness can compromise ventricular contraction and lead to cardiac systolic dysfunction (Pagoulatou *et al*., 2021). Notably, there is a strong relationship between the heart and the vasculature. Indeed, the important role of ventricular-arterial coupling in the physiology of cardiac and aortic mechanics, as well as in the pathophysiology of cardiac disease has long been recognized (Ikonomidis *et al.*, 2019). As discussed above, the ejection of blood from the heart generates blood flow and consequently forward wave pressures. The forward pressure waves are transmitted down the arterial tree, giving rise to wave reflections. In a stiffened aorta (as would occur with hypertension and aging), the reflected waves arrive earlier in systole, thus increasing central SBP and reducing DBP. Consequently, central PP is increased and the coronary perfusion gradient is reduced (Patrianakos *et al*., 2009). The high central PP and stiff aorta result in an increase in cardiac afterload (Weber and Chirinos, 2018) which increases myocardial oxygen demand. The increase in myocardial oxygen demand together with the reduction in coronary perfusion pressure and subsequent decrease in oxygen delivery, create conditions of relative myocardial ischaemia (Patrianakos *et al*., 2009). The consequence in patients with systolic HF, is a further deterioration in LV systolic function (Mitchell *et al*., 1997).

In addition, ventricular-arterial coupling is influenced by the arterial load. The steady component of afterload (SVR) depends largely on the properties of the microvasculature and is therefore influenced by the degree of vasoconstriction and the use of vasodilator agents. In contrast, pulsatile LV afterload is predominantly influenced by the properties of the conduit vessels (aorta). Key determinants of pulsatile LV load therefore include the Zc of the proximal aorta, and the magnitude and timing of wave reflections (Ikonomidis *et al.*, 2019). Indeed, increases in Zc and the magnitude and timing of Pb during systole summate to produce an impact of arterial load on LV function

(Chirinos *et al.*, 2012). Increases in arterial load trigger the onset of clinical symptoms in patients with systolic HF, and contribute to incident cardiovascular events and HF (Chirinos *et al.*, 2012). Furthermore, haemodynamic and structural changes of large conduit arteries resulting in increased arterial stiffness, which occur with aging and hypertension (Laurent *et al*., 2006; Mitchell *et al*., 2010), have been associated with cardiac mortalities (Vlachopoulos *et al*., 2010). In this regard, there is a powerful cushioning function exerted by the systemic conduit arteries, which results in a nearly steady flow in the microvasculature (Kaess *et al*., 2015). However, the cushioning function gets impaired due to large artery stiffening (including the aorta) in systolic HF patients, consequently leading to a major impact on cardiovascular health (Kaess *et al*., 2015).

Wave reflection and central pressure are also related to ventricular function (Weber and Chirinos, 2018). In a population-based analysis the contribution of pulsatile haemodynamics (Pf and Pb) and SVR on geometry and LV mass was investigated (Zamani *et al*., 2015). Of note, although both SVR and Pb were directly associated with LV mass, reflected wave (Pb) showed a stronger relationship compared to SVR (Weber *et al*., 2004). Importantly, LV pump function is reduced in systolic HF, which together with increases in wave reflection (high afterload) may lead to further decreases in flow (Parragh *et al*., 2015). Indeed, in patients with severe LV systolic dysfunction wave reflection reduces SV, truncates flow, and induces a shortening of ejection duration (Paglia *et al*., 2014; Parragh *et al*., 2015).

Notably, high PP due to an increased SV and peak Q, is beneficial for the perfusion of the tissues including the heart. However, high PP due to increased aortic stiffness and SVR is detrimental to the heart, because it causes high cardiac afterload. However, several drug therapies can assist in reducing the increased cardiac afterload (by vasodilation) in systolic HF patients and hence improve their cardiac function (Schwartzenberg *et al*., 2012).

1.7 Vasodilator Treatment in Patients with Systolic HF

In systolic HF, an increase in impedance to left ventricular ejection is an important factor in impairing the performance of the LV. Furthermore, decreased arterial compliance and arteriolar narrowing decrease left ventricular EF, consequently leading to decreased cardiac filling (Cohn, 1981). The above-mentioned vascular events are the result of activation of the sympathetic nervous and renin-angiotensin systems in HF (Cohn, 1981). Thus, the mechanism of vasodilator drugs is to relax the increased vascular tone, consequently reducing cardiac afterload and increasing SV (Cohn, 1981). This improves the patient's myocardial metabolic state and haemodynamics (Cohn, 1981). Hence, vasodilators are highly recommended during the onset of systolic HF with high BP at presentation (Teerlink, 2007). To further intervene and reduce the high cardiac afterload (high aortic stiffness and SVR) experienced by systolic HF patients, there is a need to control BP (Upadhya *et al*., 2017), as studies have shown that BP control and the level of its control has an impact on central and cardiac haemodynamics in HF patients (Upadhya *et al*., 2021).

1.8 Blood Pressure Control

Several observational studies have shown graded associations between higher SBP/DBP and increased incidence of cardiovascular diseases (Tajeu *et al*., 2017). Of note, hypertension or uncontrolled BP for a prolonged time is known to trigger incident HF (Tajeu *et al*., 2017). The majority of incidents of HF occur among adults with SBP/DBP ≥140/90 mm Hg (Tajeu *et al*., 2017). Hence, to prevent cardiovascular incidents, patients need to be managed at BP thresholds lower than 140/90 mm Hg and 130/80 mm Hg based on the ISH (International Society of Hypertension) and AHA (American Heart Association) guidelines respectively. Importantly, even with guidelines that suggest BP control at <140/90 mm Hg, if there are people who are at high risk of CVDs, such as those with diabetes or chronic kidney disease, then lower thresholds should be used (Tajeu *et al*., 2017). Importantly, in the SPRINT study, intensive BP lowering (≤130/80 mm Hg) resulted in reductions in incident HF (Wright *et al.*, 2015).

1.9 What is Known About Central Pulse Pressure, Aortic Stiffness, and Cardiac Haemodynamics in Systolic Heart Failure?

Concerning central PP and its determinants (Pb and Pf) in systolic HF, the data is controversial and limited. As discussed above, both increases and decreases in central PP have been reported, and there is very limited data on Pf and Pb in systolic HF. Furthermore, the data on PWV (a measure of aortic stiffness) in systolic HF is contradictory. As discussed above, both increases and decreases in PWV have been reported in patients with systolic HF. Furthermore, whether Zc (resistance to flow in a pulsatile system) and hence cardiac afterload, rather than PWV which is an index of the stiffness of the full length of the aorta, is altered in systolic HF is unknown. In addition, the majority of the studies to date on central aortic PP in systolic HF have been conducted in patients with severe HF, and most of the patients with systolic HF have coronary artery disease as the primary etiology. However, the impact of mild-to-moderate HF associated with hypertension on central aortic PP and its hemodynamic determinants is currently unknown.

As in SSA the majority of patients with HF have hypertension as the etiology, it is important to understand the role of central aortic PP and its hemodynamic determinants. In the presence of hypertension, Zc may be increased in patients with mild-to-moderate systolic HF in SA. In addition, as arteriolar constrictor tone is increased in hypertension and HF (a sympathetic compensatory response to a decreased stroke volume), backward pressure wave (Pb) may also be increased. If this is the case, then intense blood pressure (BP) control may be required in the management of patients with hypertension-associated systolic HF. Indeed, increases in SVR, Zc, and Pb in systolic HF, cause an increase in cardiac afterload and hence further LV dysfunction (Roman *et al*., 2010). Alternatively, if the predominant determinant of aortic PP in systolic HF is stroke volume, then improvements in systolic function with medical therapies would be beneficial. In this regard, increases in central BP caused by increases in aortic blood flow (Q) and hence forward pressure wave (Pf), have been reported to be beneficial in systolic HF (Phan *et al*., 2016).

However, whether patients with mild-to-moderate systolic HF have increased Zc is not known. Furthermore, whether central aortic PP in patients with systolic HF is primarily determined by SV and aortic blood flow (Q), or Zc and Pb is unknown. A better understanding of the changes in central hemodynamics that accompany systolic HF are important for better management of systolic HF. I aimed to assess central hemodynamic changes in systolic HF patients compared to community participants.

1.10 Aim

To compare central aortic and cardiac hemodynamics, and the impact of controlled BP (SBP/DBP<140/90 mm Hg or SBP/DBP<130/80 mm Hg) between stable systolic heart failure patients and community participants, adjusting for potential confounders that may differ between these two groups.

1.11 Objectives

To achieve my aim, my objectives are:

1. To compare central blood pressure (central systolic pressure, central pulse pressure, forward wave pressure, backward wave pressure) and peripheral blood pressure, between patients with systolic heart failure and community participants.
2. To compare aortic blood flow (stroke volume [SV] and aortic flow [Q]), between patients with systolic heart failure and community participants.
3. To compare aortic stiffness in terms of Zc and arterial stiffness in terms of SVR (systemic vascular resistance) between patients with systolic heart failure and community participants.
4. To assess the impact of blood pressure control on central and cardiac haemodynamics between patients with systolic heart failure and community participants.

CHAPTER 2 METHODS

2.1 Ethical Approval

The present studies were conducted based on the guidelines outlined in the Helsinki Declaration. The University of the Witwatersrand Human Research Ethics Committee approved and reviewed the protocol (ethics approval numbers: M02-04-72 and renewed as M07-04-69, M12-04-108, M17-04-01 and M22-03-93; and M18-05-07 renewed as M23-08-53). All participants gave informed, written consent to participate in the study.

2.2 Study Design and Participants

Consecutive consenting heart failure patients (n=42), diagnosed with HF of systolic origin, males and females across the full adult age range (≥18 years of age), in different ethnic groups from the hypertension clinic at Life Flora Hospital, Johannesburg, South Africa, were randomly recruited. Data collected from 42 stable heart failure patients on a single visit as outpatients at a doctor's room, was compared to data collected from 298 age- and sex-matched participants from a community-based study. Stable heart failure patients and community participants were recruited from similar geographical area, but measured at different health care facilities by different health care professionals. The community-based study consisted of 824 participants of African ancestry, living in a similar geographical area, but not all have similar socio-economic backgrounds, with non-invasive measurements of central arterial pressure recorded at the same healthcare facility, using SphygmoCor, version 9.0 software (AtCor Medical Pty, Ltd, West Ryde, New South Wales, Australia), as well as non-invasive assessments of aortic diameter and velocity using echocardiography. Our community participants were not tested for HIV/AIDS, hence it was not an inclusion or exclusion criteria. All patients with stable systolic heart failure were included in the study, and patients with valve dysfunction were excluded from participating.

2.3 Sample Size Calculations

We have previously shown (Motau *et al*., 2020 and 2021) differences in central pressure waveform between a sample size of 287 cases (stroke and critical limb ischemia) and a sample size of 390 age- and sex-matched healthy controls at p values of <0.005 to <0.0001. Based on a difference of 4.8 mm Hg in aortic pulse pressure between cases and controls (Motau *et al*., 2020 and 2021) and a ratio of 1:3 for case to controls, sample sizes of 34 cases (patients with stable heart failure) and

102 controls (age-and sex-matched community participants) would be required to achieve a p-value <0.05 at 80% power.

2.4 Clinical, Demographic, and Anthropometric Measurements

A standardised questionnaire was used to obtain demographic and clinical information from each participant. The data was collected based on the health attributes of the participants. The questionnaire contained questions i.e., presence of diabetes mellitus, presence of hypertension, regular alcohol intake, regular smoking, gender, and treatment for hypertension. The questions in the questionnaire required a simple response of either "YES" or "NO" answers, coded as (YES=1) and (NO=0).

Standard approaches were used to calculate body mass index (BMI) from the measured weight and height (BMI=weight [kg]/height [m^2]) (Motau *et al.*, 2020 and 2021). Participants with BMI ≥25 kg/m^2 or BMI ≥30 kg/m^2 were classified as overweight or obese respectively. Blood tests of percentage glycated hemoglobin (HbA1c) and blood glucose were performed in an accredited laboratory. Diabetes mellitus (DM) was defined as the use of glucose-lowering agents or insulin or an HbA1c value >6.5%. Office brachial (peripheral) BP measurements were obtained after 5 minutes of rest in a seated position, by a trained nurse technician using a mercury sphygmomanometer. The mean of 5 measurements obtained 30 seconds apart, were taken as the office brachial BP. The use of antihypertensive medication or a mean office systolic BP≥140 mm Hg or a mean diastolic BP≥90 mmHg was used to define the presence of hypertension. Furthermore, uncontrolled hypertension was defined as clinical BP ≥140/90 mm Hg (according to International Society of Hypertension [ISH] guidelines) or ≥130/80 mm Hg (according to American Heart Association [AHA] guidelines).

2.5 Haemodynamics

Pulse wave analysis was conducted to measure central arterial pressure. After 15 minutes of rest in the supine position, the arterial waveform at the radial artery was obtained using applanation tonometry (Figure 2.1). The radial arterial waveform was recorded over 8 seconds, with the use of a high-fidelity SPC-301 micromanometer (Millar Instrument, Inc, Houston, TX) interfaced with SphygmoCor, version 9.0 software (AtCor Medical Pty, Ltd, West Ryde, New South Wales, Australia). The pulse wave was calibrated by manual measurement (auscultation) of brachial BP taken immediately before the recordings. A validated generalized transfer function incorporated in the SphygmoCor software was used to convert the radial arterial (peripheral) pressure waveform into a central aortic pressure waveform (Figure 2.2).

2.6 Assessment of Determinants of Central Haemodynamics

Immediately after central arterial pressure waveforms were obtained, the aortic diameter was assessed using an Acuson SC2000 (Siemens Medical Solutions, United States, Inc) (Figure 2.3) ultrasound in the long axis parasternal view with the participants lying in the left lateral decubitus position. Aortic diameter measurements were obtained, proximal to the aortic leaflets, and the largest aortic diameter was recorded in early systole and used to construct the aortic flow waveform (Figure 2.4).

Aortic velocity was assessed using Acuson SC2000 (Siemens Medical Solutions, United States, Inc) ultrasound in the 5-chamber view with the participants lying in the left lateral decubitus position (Figure 2.5). High-quality assessments were identified as those with a smooth curved velocity waveform with a dense leading (outer) edge and a clear maximum velocity. The maximum aortic velocity and velocity time integral were measured and used together with the aortic velocity images to construct the aortic flow waveform, where flow (Q) is velocity x aortic cross-sectional area.

2.7 Central Arterial Function

Dicom Viewer software was used to recreate the aortic velocity waveform from the aortic velocity waveforms that were obtained in the 5-chamber view of the heart. Taking care to avoid any overshoot of the image, the leading (outer) edge or the densest or brightest portion of the spectral image of the aortic velocity waveform was outlined using the Dicom viewer software (Figure 2.6). The maximum aortic velocity was measured. Using images of the aortic root taken in the parasternal long-axis view, the aortic diameter was measured. Aortic flow (Q) was then calculated as maximum aortic velocity multiplied by aortic root area (calculated from aortic diameter). Zc was calculated in the time domain as a change in aortic pressure divided by a change in aortic flow from the start (foot) of the flow wave, until 95% of peak flow (Mitchell *et al*., 2010; Segers *et al*., 2017; Tramunt *et al*., 2020). Using the flow, pressure waveforms, and Zc values, wave separation analysis (separation of the aortic pressure waveform into its 2 component waves) was performed

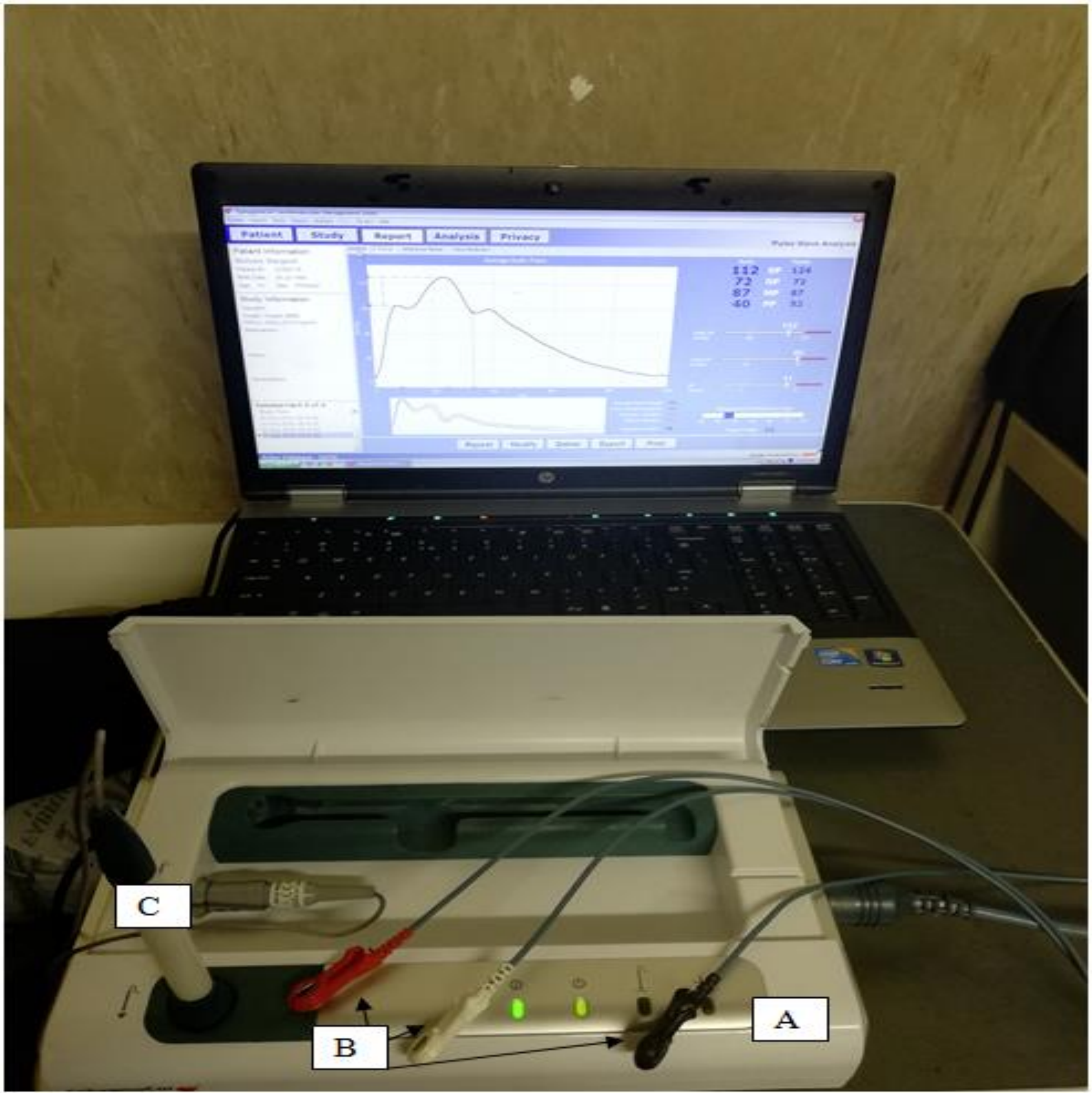


Figure 2.1 SphygmoCor device used to determine aortic haemodynamics through applanation tonometry. A, = SphygmoCor device, B, = Electrocardiogram leads, and C, = Tonometer pen.

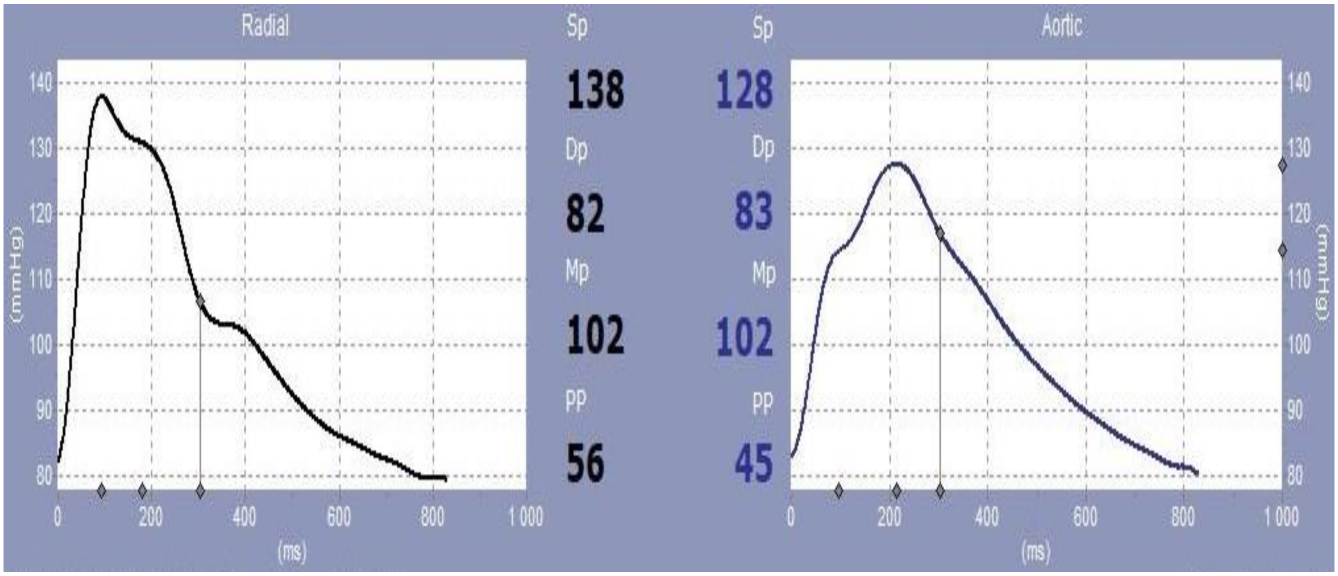


Figure 2.2 Radial pressure trace shown on the left panel and aortic pressure trace shown on the right panel, as derived from SphygmoCor software which incorporates a validated generalised transfer function. Sp, systolic blood pressure; Dp, diastolic blood pressure; Mp, mean arterial pressure; pp, pulse pressure.

with the use of the following formulae: Forward wave pressure (Pf)=[Aortic P+(QxZc)]/2 and backward wave pressure (Pb)=[Aortic P-(QxZc)]/2. Peak compression pressure waves were calculated by multiplying peak Q by peak Zc (Peak PQxZc). Peak PQxZc was used instead of Pf because PQxZc is the component of Pf generated by aortic stiffness, and thus Zc rather than wave re-reflection (Figure 2.7). The velocity-time integral of the aorta velocity wave and the aortic root diameter were used to calculate SV (aortic root area x velocity-time integral) using established methods.

2.8 Data Analysis

SAS version 9.4 was used for statistical analysis. Continuous data were expressed as (mean±SD). Unpaired students t-test and chi-squared analysis were used to compare unadjusted data between patients with systolic heart failure and community participants. Multivariate adjusted ANOVA was used to compare the haemodynamic variables between the patients with systolic heart failure and the community participants. Adjustments were made for age, sex, and heart rate, as well as for age, sex, heart rate, and MAP in separate analyses. Heart rate was included as an adjustor as there is a strong inverse relationship between central PP and heart rate. Further adjustments were made for MAP to eliminate the impact of steady pressure components. To assess the impact of BP control (either ≤140/90 mm Hg or ≤130/80 mm Hg), on haemodynamic variables between patients with systolic heart failure and community participants, multivariate-adjusted ANOVA was used to compare the four groups (systolic heart failure patients with controlled BP; systolic heart failure patients with uncontrolled BP; community participants with controlled BP; community participants with uncontrolled BP). Adjustments were made for age, sex, and heart rate, as well as for age, sex, heart rate, and MAP in separate analyses. $p<0.05$ was considered significant.

Figure 2.3 Echocardiograph machine used to obtain aortic root diameter from the long axis parasternal view of the heart and aortic velocity waveforms in the apical 5-chamber view of the heart. A= electrocardiography cables, B= 1-4 MHz probe.

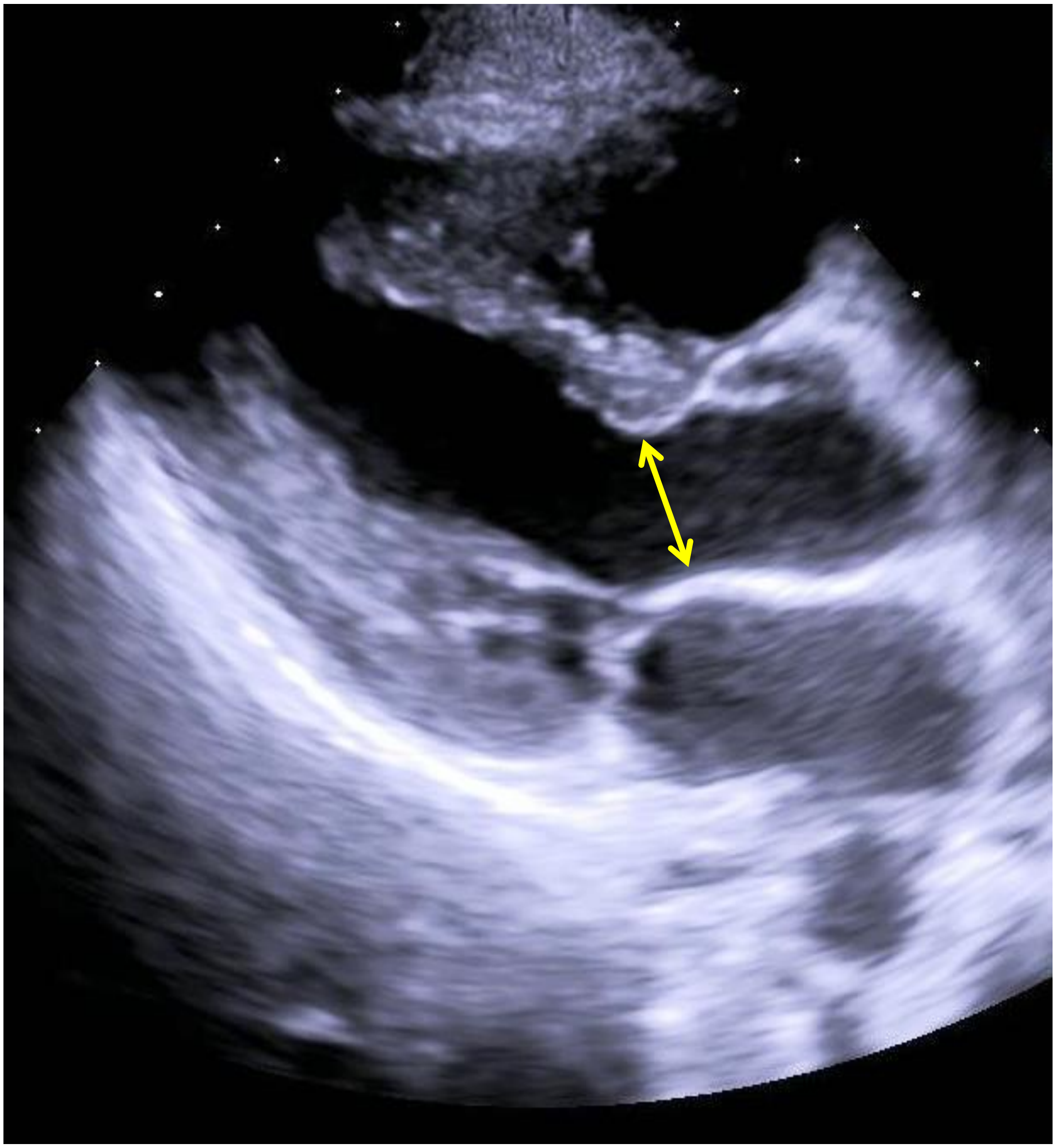


Figure 2.4 Aortic root diameter (arrow) obtained during systole in the long axis parasternal view of the heart.

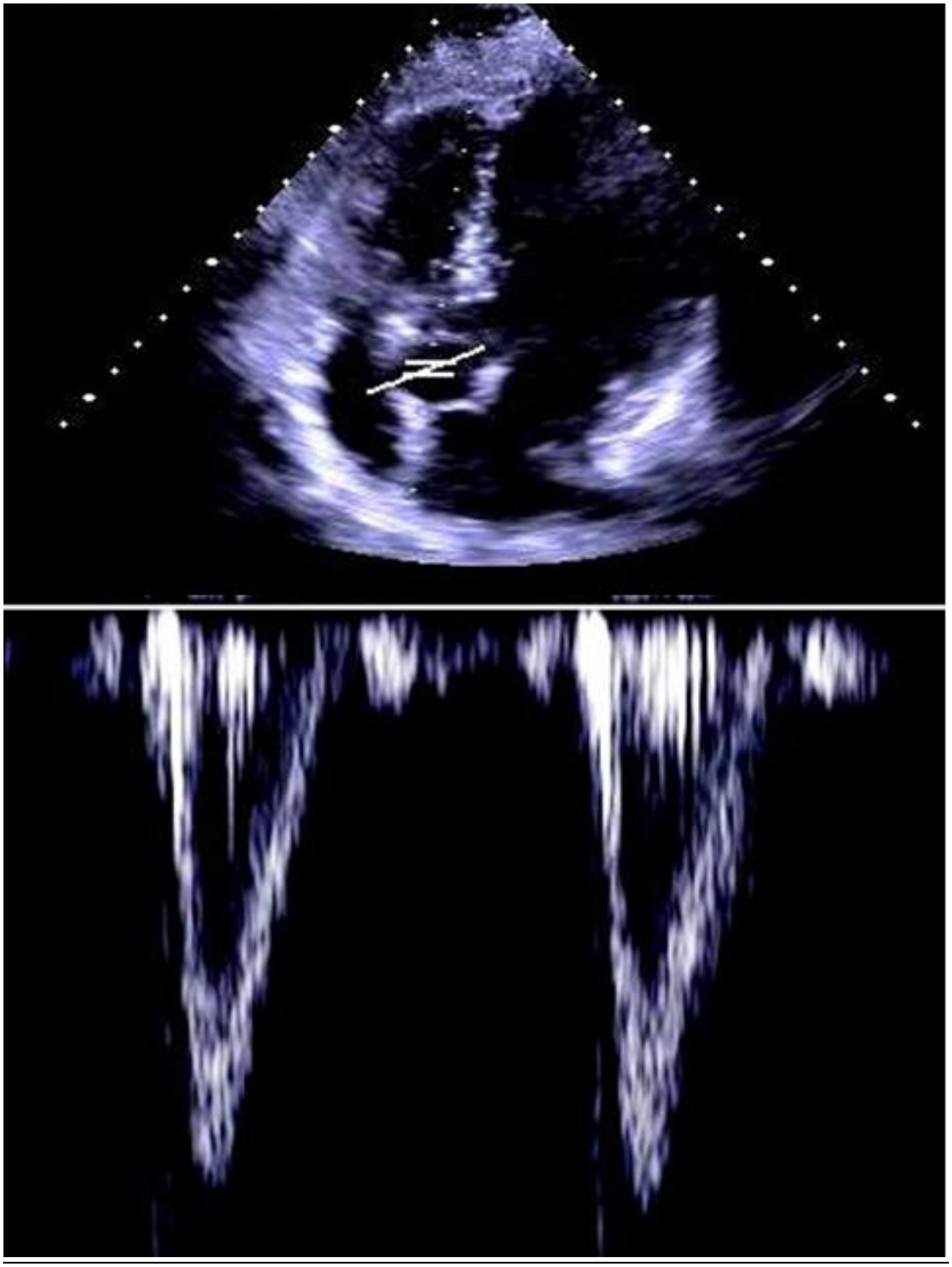
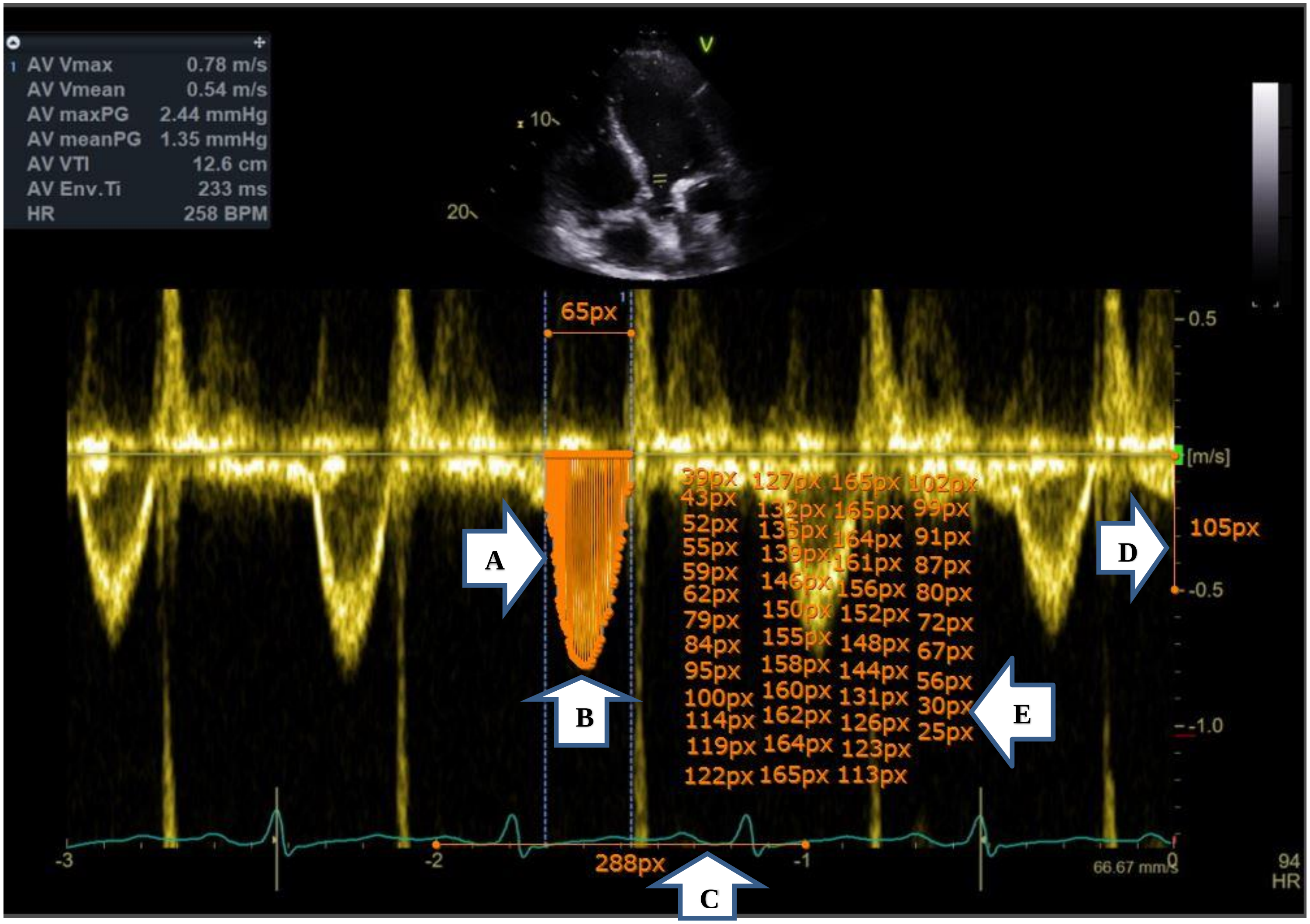


Figure 2.5 Aortic velocity waveforms attained in the apical 5-chamber view of the heart. The apical 5 chamber view of the heart is shown in the upper panel and the aortic root velocity waveforms are shown in the lower panel.



AV Vmax	0.78 m/s
AV Vmean	0.54 m/s
AV maxPG	2.44 mmHg
AV meanPG	1.35 mmHg
AV VTI	12.6 cm
AV Env.Ti	233 ms
HR	258 BPM

Figure 2.6 A, Aortic velocity waveform traced using Dicom viewer software. B, Velocity wave maximum point. C, X-scale in (mm/s), D, Y-scale in (m/s). E, Tracing points in pixels.

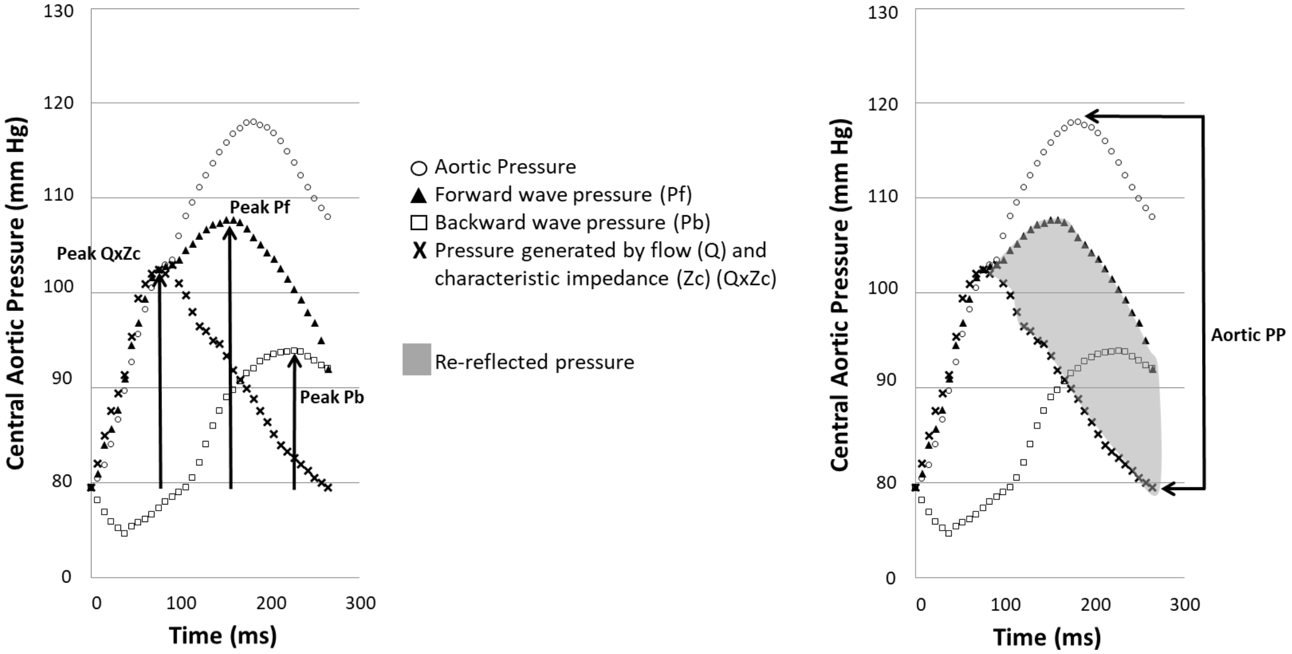


Figure 2.7 Central aortic pressure waveform and the determinants of central aortic pulse pressure (PP). Pf, forward pressure wave; Pb, backward pressure wave; QxZc, the pressure generated by the product of aortic flow (Q) and characteristic impedance (Zc); shaded area, re-reflected pressure.

CHAPTER 3 RESULTS

3.1. General Characteristics

Table 3.1 shows the general characteristics of community participants and patients with systolic heart failure (sHF). As per the methodology, the patients with systolic HF were age- and sex-matched to the community participants. The community participants and patients were predominantly middle-aged (approximate mean age of 60 years) and about 60% were men. The New York Heart Association (NYHA) functional class shows that most (94.1%) of the patients with systolic HF had mild to moderate symptoms of heart failure. Table 3.1 also shows two classifications of BP control with their threshold values. Based on the International Society of Hypertension (ISH) guidelines uncontrolled BP was defined as SBP/DBP≥140/90 mm Hg. In addition, based on the American Heart Association (AHA) guidelines, uncontrolled BP was defined as SBP/DBP≥130/80 mm Hg. Compared to the community participants, a lower proportion of patients with systolic HF had hypertension and uncontrolled BP. The community participants and systolic HF patients were being treated with diuretics, however, the percentage was much greater in the systolic HF patients. The only type of medication being received by the community participants was diuretics. Whereas in addition to diuretics, about 70% of the systolic HF patients were also receiving vasodilator therapy (angiotensin-converting enzyme inhibitors [ACEi], Hydralazine, and/or Ismo), about a quarter were receiving lipid-lowering agents, and the vast majority were receiving beta-blocker therapy.

3.2. Peripheral and Central Haemodynamic Parameters

Table 3.2 shows the comparison of the unadjusted peripheral and central blood pressures between the systolic HF patients and the community participants. Importantly, peripheral (systolic and diastolic) BP and MAP were lower in the systolic HF patients compared to the community participants. However, the systolic HF patients had a similar peripheral PP compared to the community participants. Central (systolic and diastolic) BP and MAP were also lower in the systolic HF patients compared to the community participants. In addition, central PP was lower in the systolic HF patients compared to the community participants.

Table 3.3 shows the comparison of the unadjusted central haemodynamic parameters obtained by wave separation analyses and the cardiac haemodynamic parameters between the patients with

Table 3.1. Comparison of general characteristics between community participants (community) and patients with systolic HF (sHF).

	Community	**sHF**	**p-value**
Sample size (n)	298	42	
Age (years)	57.4±11.8	60.5±13.3	0.11
Sex (% women)	44.6	40.5	0.61
Body mass index (kg/m^2)	30.3±7.6	30.6±8.6	0.80
% Overweight/obese	27.9/46.6	37.8/37.8	0.43
NYHA FC I/II/III	-	41.2/52.9/5.9	-
% Diabetes mellitus (DM)	29.9	18.0	0.12
% Hypertension	65.8	55.3	**0.020**
<u>% Uncontrolled BP</u>			
ISH (≥140/90 mm Hg)	46.0	31.0	**0.061**
AHA (≥130/80 mm Hg)*	74.5	57.1	**0.019**
<u>% Medication</u>			
Diuretics	37.3	84.9	**<0.0001**
ACEi	0	60.6	**<0.0001**
Beta Blockers	0	87.9	**<0.0001**
Vasodilators (Hydralazine)	0	3.0	**<0.0001**
Positive inotropes (Digoxin)	0	6.1	**<0.0001**
ARNi (Entresto)	0	21.2	**<0.0001**
Nitrate vasodilator (Ismo)	0	21.2	**<0.0001**
Lipid lowering (Simvastatin)	0	27.3	**<0.0001**

Data are expressed as mean±SD; n, sample size; NYHA, New York Heart Association functional class: I, no symptoms and no limitation in ordinary physical activity; II, mild symptoms and slight limitation during ordinary activity; III, marked limitation in activity due to symptoms, even during less than ordinary activity; ACEi, angiotensin-converting enzyme inhibitor; ARNi, Angiotensin receptor-neprilysin inhibitor; ISH, International Society of Hypertension; *, BP thresholds based on American Heart Association guidelines. p<0.05 is in bold font.

Table 3.2. Comparison of unadjusted peripheral and central blood pressures between community participants (community) and patients with systolic HF (sHF).

	Community	**sHF**	**p-value**
Sample size (n)	298	42	
Peripheral			
SBP (mm Hg)	133±18	124±22	**0.007**
DBP (mm Hg)	85±11	79±11	**0.0011**
MAP (mm Hg)	101.0±13.0	94.0±13.0	**0.001**
PP (mm Hg)	47.0±14.0	45.0±17.0	0.30
Central			
SBP (mm Hg)	125±18	112±18	**<0.0001**
DBP (mm Hg)	86±11	80±11	**0.0007**
MAP (mm Hg)	99.0±13.0	91.0±12.0	**<0.0001**
PP (mm Hg)	39.0±13.0	33.0±14.0	**0.0042**

Data are expressed as mean±SD. SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure. p<0.05 is in bold font.

Table 3.3. Comparison of unadjusted central haemodynamic parameters obtained by wave separation analysis and cardiac haemodynamic parameters between community participants (community) and patients with systolic HF (sHF).

	Community	**sHF**	**p-value**
Sample size (n)	298	42	
Central			
Pf (mm Hg)	28.6±8.3	26.4±9.9	0.11
Pb (mm Hg)	14.4±5.3	11.7±5.6	**0.0024**
Zc (dynes/cm^5)	80.8±40.1	82.4±52.5	0.82
Q (mls/s)	388.0±177.0	383±197	0.85
QxZc (mm Hg)	26.7±7.6	25.4±9.4	0.32
Ao Diam (cm)	2.7±0.5	2.5±0.4	0.34
Cardiac			
SV (ml/beat)	80.4±32.7	81.9±32.7	0.77
HR (beats/min)	66±12	72±13	**0.0023**
CO (L/min)	5.3±2.3	5.9±2.7	0.12
SVR (mm Hg/min.l^{-1})	21.1±10.0	19.4±9.2	0.30

Data are expressed as mean±SD. Pf, peak forward wave pressure; Pb, peak backward wave pressure; Zc, characteristic impedance; Q, peak aortic flow; QxZc, product of flow and characteristic impedance; Ao Diam, aortic root diameter; SV, stroke volume; HR, heart rate; CO, cardiac output; SVR, systemic vascular resistance. p<0.05 is in bold font.

systolic HF and the community participants. Peak backward wave pressure (Pb) was lower and HR was higher in the systolic HF patients. No differences in Zc, Q, QxZc, Ao Diam, SV, CO, or SVR were noted between the systolic HF patients and the community participants before adjustments for confounders (Table 3.3).

After adjusting for age, sex, and HR, central SBP, PP, and Pb remained lower in the systolic HF patients compared to the community participants (Figure 3.1). There were no differences in Pf, Zc, Q, QxZc, or Ao Diam between the systolic HF patients and the community participants after adjusting for age, sex, and HR (Figures 3.1 and 3.2). Heart rate remained higher in the systolic HF patients compared to the community participants after adjusting for age and sex (Figure 3.3), and there were no differences in SV, SVR, or CO between the systolic HF patients and the community participants after adjusting for age, sex and HR (Figure 3.3). However, after further adjusting for MAP, although central SBP remained lower in the systolic HF patients compared to the community participants (Table 3.4), the lower Pb and central PP in the systolic HF patients compared to the community participants were eliminated (Table 3.4). Similar to before adjustments for MAP, after further adjusting for MAP, no differences in peripheral SBP and PP, Zc, Q, QxZc, Ao Diam, SV, SVR, or CO were noted between the systolic HF patients and the community participants (Table 3.4).

3.3. Impact of BP control (threshold = 140/90 mm Hg, based on ISH guidelines) on comparisons between patients with systolic HF and community participants.

Table 3.5 shows the impact of BP control (controlled BP [<140/90 mm Hg] and uncontrolled BP [≥140/90 mm Hg]) on the comparison of general characteristics and unadjusted peripheral and central blood pressures between patients with systolic HF and the community participants. Within the community participants, those with uncontrolled BP were older than those with controlled BP, however, no differences in age were noted between the systolic HF patients with controlled versus uncontrolled BP. Before adjusting for any confounders, as expected when BP was uncontrolled, community participants and systolic HF patients had higher peripheral and central BP (systolic and diastolic), MAP, and PP than those with controlled BP. However, systolic HF patients with controlled BP had lower SBP and MAP (peripheral and central), and lower central PP compared to community participants with controlled BP.

Adjusted for age, sex and HR

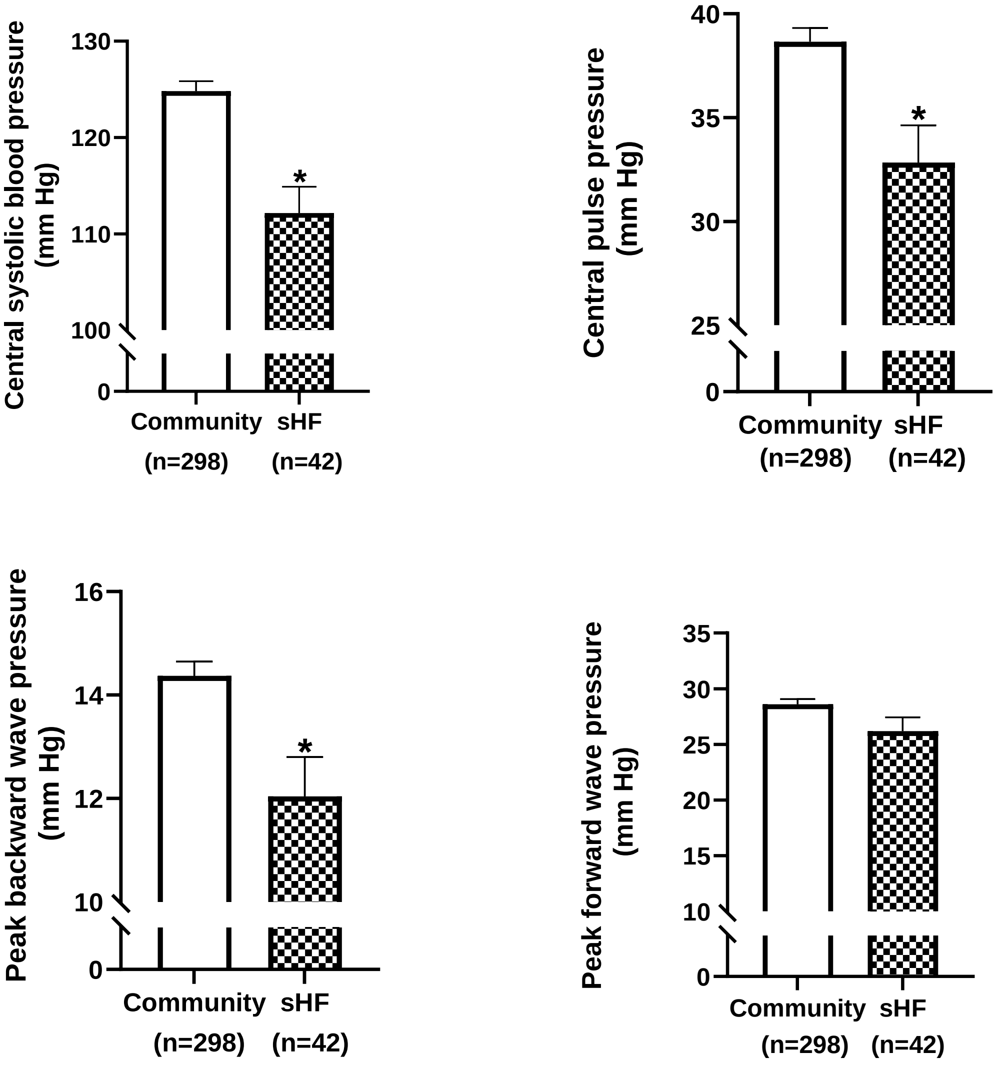


Figure 3.1. Comparison of central systolic blood pressure, central pulse pressure, backward wave pressure, and forward wave pressure between patients with systolic heart failure (sHF) and community participants (community). Data are adjusted for age, sex, and heart rate (HR). *p<0.05.

Adjusted for age, sex and HR

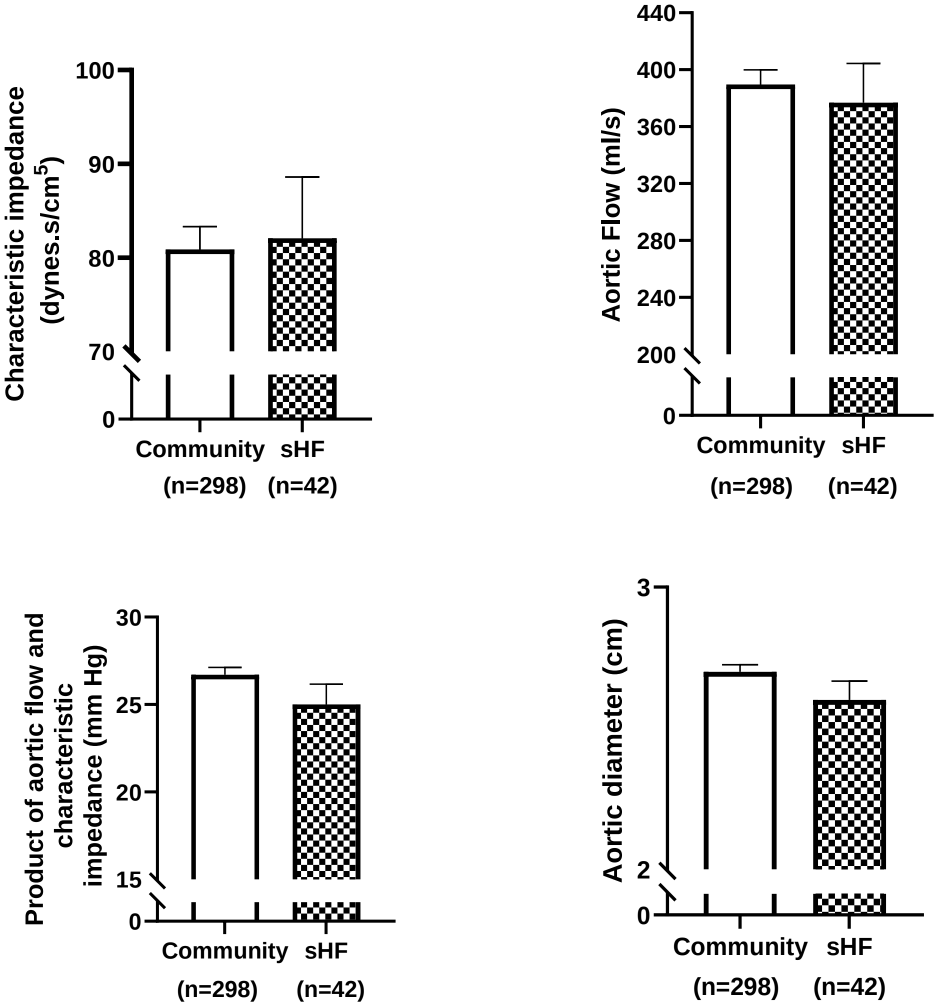


Figure 3.2. Comparison of characteristic impedance, aortic blood flow, the product of aortic flow and characteristic impedance, and aortic diameter between patients with systolic heart failure (sHF) and community participants (community). Data are adjusted for age, sex, and heart rate (HR).

Adjusted for age, sex and HR

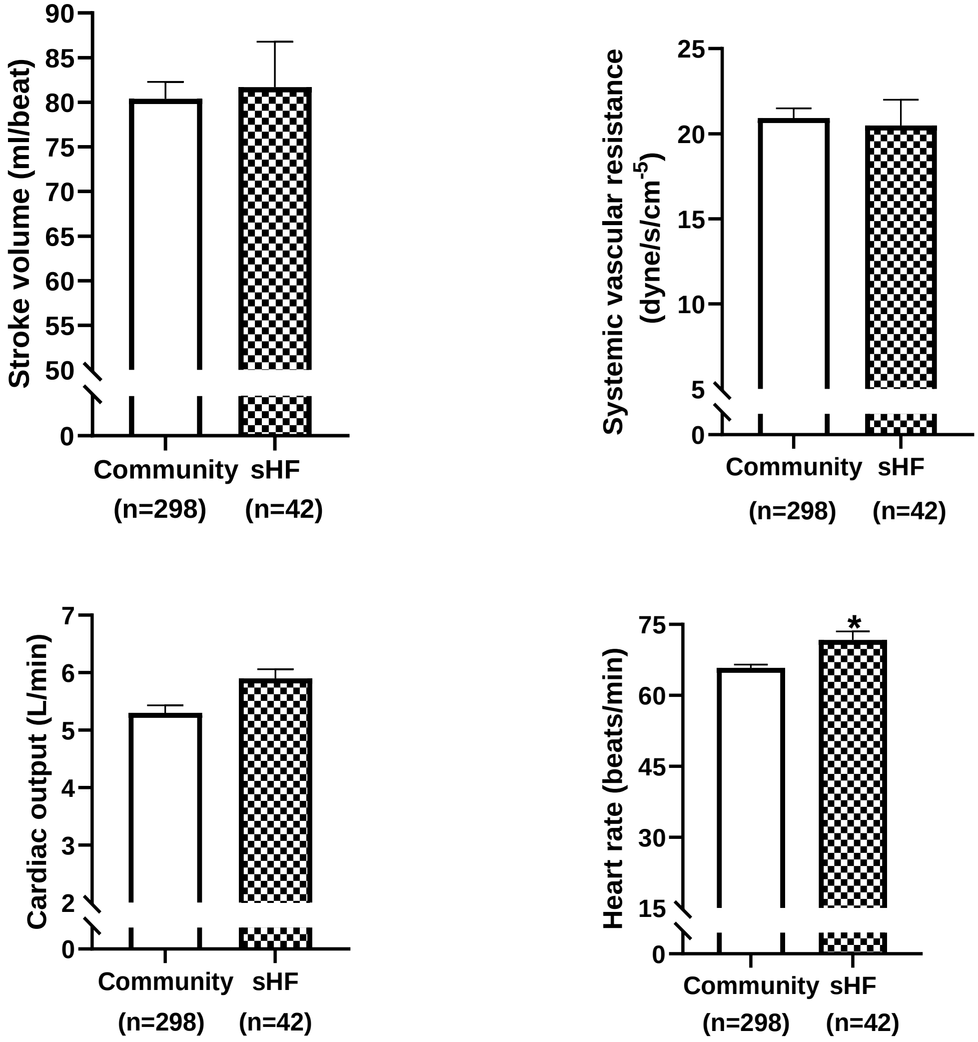


Figure 3.3. Comparison of cardiac haemodynamic parameters (stroke volume, systemic vascular resistance, cardiac output, and heart rate) between patients with systolic heart failure (sHF) and community participants (community). Data are adjusted for age, sex, and heart rate (HR), except for heart rate which was only adjusted for age and sex. *$p<0.05$.

Table 3.4. Comparison of central and peripheral blood pressures, central haemodynamic parameters, and cardiac haemodynamics between community participants (community) and patients with systolic HF (sHF), after adjustments for age, sex, HR, and MAP.

	Community	**sHF**	**p-value**
Sample size (n)	298	42	
Peripheral			
SBP (mm Hg)	132±8	132±8	0.63
PP (mm Hg)	47.0±12.0	47.6±12.0	0.77
Central			
SBP (mm Hg)	124±119	121±1	**0.013**
PP (mm Hg)	38.0±10.3	36.0±6.0	0.143
Pf (mm Hg)	28.4±6.9	27.9±7.7	0.70
Pb (mm Hg)	14.2±5.1	13.1±4.5	0.15
Zc (dynes.s/cm^5)	80.2±41.4	87.2±41.6	0.31
Q (ml/s)	389.7±177.5	376.9±179.9	0.67
QxZc (mm Hg)	26.6±6.9	26.5±7.0	0.96
Ao Diam (cm/s)	2.7±1.7	2.6±0.6	0.27
Cardiac			
SV (ml/beat)	80.2±32.7	83.0±33.3	0.61
SVR (mm Hg/min/l^{-1})	20.8±10.3	21.2±9.6	0.81
CO (L/min)	5.3±2.2	5.5±2.2	0.56

Data are expressed as mean±SD. SBP, systolic blood pressure; PP, pulse pressure; Pf, peak forward wave pressure; Pb, peak backward wave pressure; Zc, characteristic impedance; Q, peak aortic flow; QxZc, product of aortic flow and characteristic impedance; Ao diam, aortic root diameter; SBP; systolic blood pressure; SV, stroke volume; CO, cardiac output; SVR, systemic vascular resistance. $p<0.05$ is in bold font.

Table 3.5. Comparison of general characteristics and unadjusted peripheral and central blood pressures between community participants (community) and patients with systolic HF (sHF) with either controlled BP (<140/90 mm Hg) or uncontrolled BP (≥140/90 mm Hg) based on ISH guidelines.

	Community		**sHF**	
	Controlled BP	Uncontrolled BP	Controlled BP	Uncontrolled BP
Sample size (n)	160	138	29	13
Age (years)	55.6±11.6	59.3±11.2**	60.1±11.6	61.4±11.4
Sex (% Women)	43.1	46.4	51.7	15.4
BMI (kg/m^2)	29.7±7.7	31.0±7.7	31.1±8.5	29.8±7.8
% Medication				
Diuretics	34.4	40.6	68.9	46.2
ACEi	0	0	55.2	23.1
Beta Blockers	0	0	62.1	53.8
Vasodilators (Hydralazine)	0	0	0	8.0
Positive inotropes (Digoxin)	0	0	6.9	0
ARNi (Entresto)	0	0	20.6	8.0
Nitrate vasodilator (Ismo)	0	0	17.2	15.4
Lipid lowering (Simvastatin)	0	0	20.6	30.8
Peripheral				
SBP (mm Hg)	120±13	147±13***	114±13*††	146±12***‡
DBP (mm Hg)	78±8	94±8***	75±19††	88±8***†‡

MAP (mm Hg)	92.0±8.0	111.0±8.0***	88.0±8.0*††	107.0±8.0**‡
PP (mm Hg)	42.0±13.0	53.0±13.0***	39.0±8.0††	59.0±12.0***‡
Central				
SBP (mm Hg)	112±12	139±12***	105±12**††	130±12***‡
DBP (mm Hg)	79±8	95±8***	76±8††	88±8***†‡
MAP (mm Hg)	90.0±8.0	110.0±8.0***	86.0±8.0**††	102.0±8.0***†‡
PP (mm Hg)	34.0±12.0	45.0±12.0***	29.0±11.0*††	42.0±11.0*‡

Data are expressed as mean±SD. BMI, body mass index; ACEi, angiotensin-converting enzyme inhibitor; ARNi, Angiotensin receptor-neprilysin inhibitor; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure. *p<0.05, **p<0.001, ***p<0.0001 versus community participants with controlled BP; †p<0.001, ††p<0.0001 versus community participants with uncontrolled BP; ‡p<0.0001 versus sHF patients with controlled BP.

Table 3.6 shows the impact of BP control (controlled BP [<140/90 mm Hg] and uncontrolled BP [≥140/90 mm Hg]) on the comparison of unadjusted central haemodynamics obtained by wave separation analysis and cardiac haemodynamics between community participants and patients with systolic HF. Before adjusting for any confounders, in both community participants and systolic HF patients, Pf, Pb, Zc and QxZc were higher in those with uncontrolled BP compared to controlled BP. Importantly, systolic HF patients with uncontrolled BP had higher Zc than the other three groups. However, there were no differences in either Q or Ao Diam between the four groups. Systolic HF patients with controlled BP had a lower Pb and SVR, but higher HR and CO compared to the community participants with controlled BP. HR and SVR were higher and SV was lower in systolic HF patients with uncontrolled BP compared to systolic HF patients with controlled BP.

After adjusting for age, sex, and HR, the differences in peripheral and central BP (systolic and diastolic), MAP, and PP noted between the four groups remained (Figure 3.4 and Table 3.7). Similarly, both Pb and Pf were higher in those with uncontrolled BP compared to those with controlled BP (Figure 3.4). Both Pb and Pf were lower in systolic HF patients with controlled BP compared to community participants with controlled BP (Figure 3.4**).** Importantly, the high Zc in systolic HF patients with uncontrolled BP compared to the other three groups remained after adjustments for age, sex, and HR (Figure 3.5), and QxZc was higher in the systolic HF patients with uncontrolled BP compared to the other three groups. After adjustments for age, sex, and HR, SVR was higher in systolic HF patients with uncontrolled BP compared to the other three groups (Figure 3.6). After adjustment for age, sex, and HR, stroke volume remained lower and CO was lower in systolic HF patients with uncontrolled compared to controlled BP (Figure 3.6).

Table 3.8 shows the impact of further adjustments for MAP on the comparisons of peripheral and central BP, central haemodynamics, and cardiac haemodynamics between community participants and patients with systolic HF, with controlled BP (<140/90 mm Hg) and uncontrolled BP (≥140/90 mm Hg). Although peripheral SBP and PP were higher in the systolic HF patients with uncontrolled BP compared to the other three groups, central SBP was not different, and central PP was only higher than that in the systolic HF patients with controlled BP. After further adjustments for MAP, Pf but not Pb was higher in systolic HF patients with uncontrolled BP compared to

Table 3.6. Comparison of unadjusted central haemodynamic parameters obtained by wave separation analysis and cardiac haemodynamics between community participants (community) and patients with systolic HF (sHF), with either controlled BP (<140/90 mm Hg) or uncontrolled BP (≥140/90 mm Hg) based on ISH guidelines.

	Community		**sHF**	
	Controlled BP	Uncontrolled BP	Controlled BP	Uncontrolled BP
Sample size (n)	160	138	29	13
Pf (mm Hg)	26.0±7.8	32.0±7.8***	23.0±7.7†††	34.0±7.6**‡‡‡
Pb (mm Hg)	13.0±4.9	17.0±4.9***	10.0±4.8*†††	16.0±4.7*‡‡
Zc (dynes.s/cm^5)	74.0±40.2	89.0±40.2**	65.0±39.7††	120.0±38.8***††‡‡‡
Q (mls/s)	390.0±179.1	387.0±179.1	398.0±176.2	351.0±172.5
QxZc (mm Hg)	25.0±7.3	29.0±7.4***	22.0±7.2†††	33.0±7.1***‡‡‡
Ao Diam (cm)	2.6±0.5	2.7±0.4	2.6±0.4	2.6±0.4
Cardiac				
HR (beats/min)	65±12	66±12	71±12*	74±12*‡
SV (ml/beat)	80.0±32.4	83.0±31.6	88.0±32.0	68.0±9.1‡
SVR (mm Hg/min/l^{-1})	20.7±10.1	21.5±9.4	16.8±9.5*†	25.2±9.4‡
CO (L/min)	5.1±2.5	5.5±2.3	6.2±2.1*	5.0±2.1

Data expressed as mean±SD. Pf, forward pressure wave; Pb, backward pressure wave; Zc, characteristic impedance; Q, peak aortic flow; QxZc, product of aortic flow and characteristic impedance; Ao Diam, aortic root diameter; HR, heart rate; SV, stroke volume; SVR, systemic vascular resistance; CO, cardiac output. *p<0.05, **p<0.001, ***p<0.0001 versus community participants with controlled BP; †p<0.05, ††p<0.001, †††p<0.0001 versus community participants with uncontrolled BP; ‡p<0.05, ‡‡p<0.001, ‡‡‡p<0.0001 versus sHF with controlled BP.

Adjusted for age, sex and HR

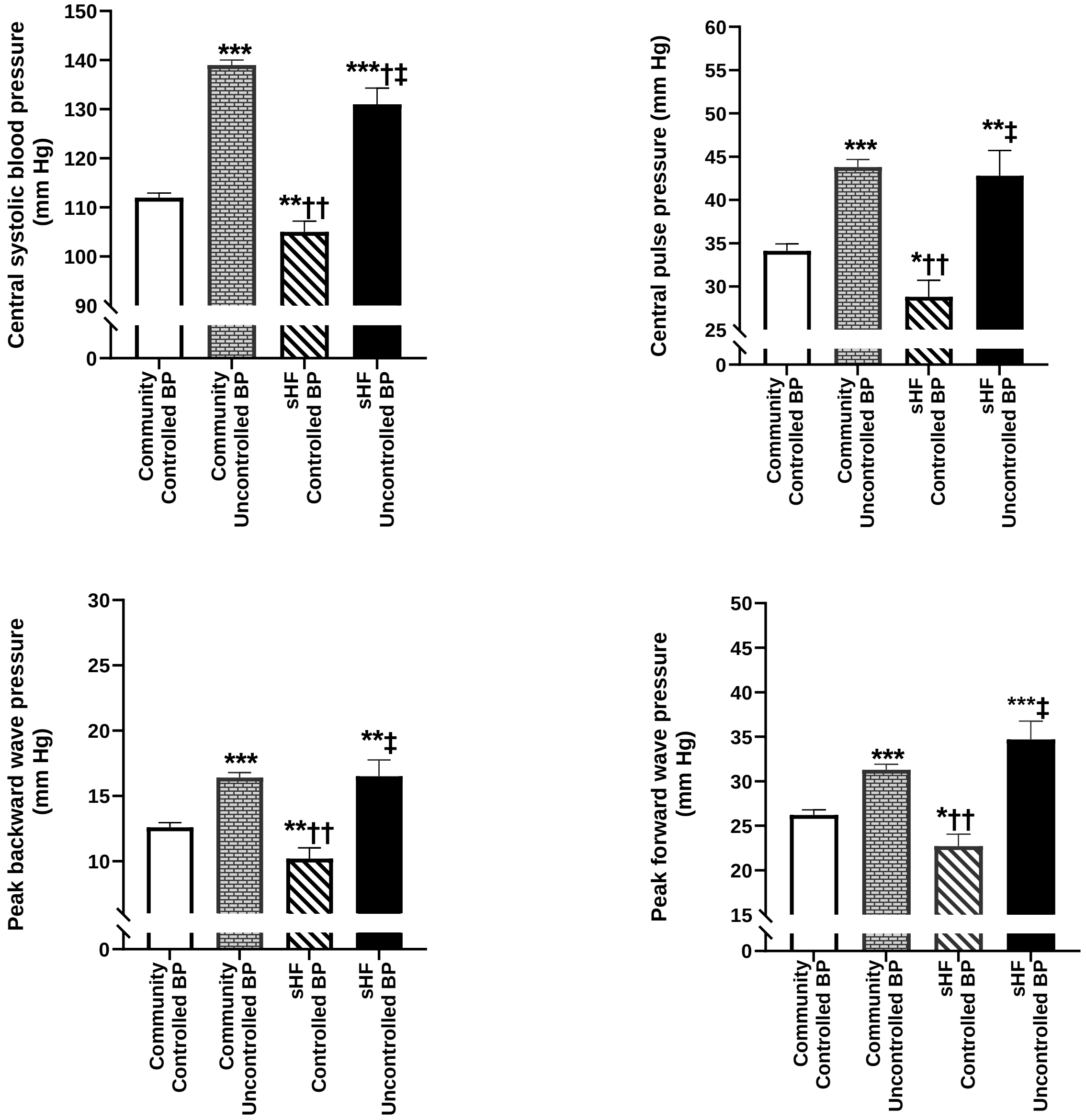


Figure 3.4. Comparison of central systolic blood pressure, central pulse pressure, backward wave pressure, and forward wave pressure between community participants (community) and patients with systolic HF (sHF), with either controlled BP (<140/90 mm Hg) or uncontrolled BP (≥140/90 mm Hg) based on ISH guidelines, after adjustments for age, sex and heart rate (HR). *p<0.05, **p<0.001, ***p<0.0001 versus community participants with controlled BP; †p<0.05, ††p<0.0001 versus community participants with uncontrolled BP; ‡p<0.0001 versus sHF with controlled BP.

Table 3.7. Comparison of peripheral and central blood pressures between community participants (community) and patients with systolic HF (sHF), with either controlled BP (<140/90 mm Hg) or uncontrolled BP (≥140/90 mm Hg) based on the ISH guidelines, after adjustments for age, sex and HR.

	Community		**sHF**	
	Controlled BP	Uncontrolled BP	Controlled BP	Uncontrolled BP
Sample size (n)	160	138	29	13
Peripheral				
SBP (mm Hg)	121±13	147±13**	114±12*††	147±12**‡
DBP (mm Hg)	78±8	94±8**	75±8††	87±8**†‡
MAP (mm Hg)	92.1±8.2	111.3±8.2**	88.2±8.1*††	107±8.0**‡
PP (mm Hg)	43.0±12.0	52.4±11.9**	38.7±11.8††	58.6±11.7**‡
Central				
DBP (mm Hg)	79±8	95±8**	76±8††	88±8*‡
MAP (mm Hg)	90.0±8.3	109.5±8.2**	85.4±8.1*†	102.4±8.1*†‡

Data are expressed as mean±SD. SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure. *p<0.05, **p<0.0001 versus community participants with controlled BP; †p<0.001, ††p<0.0001 versus community participants with uncontrolled BP; ‡p<0.0001 versus sHF patients with controlled BP.

Adjusted for sex, age and HR

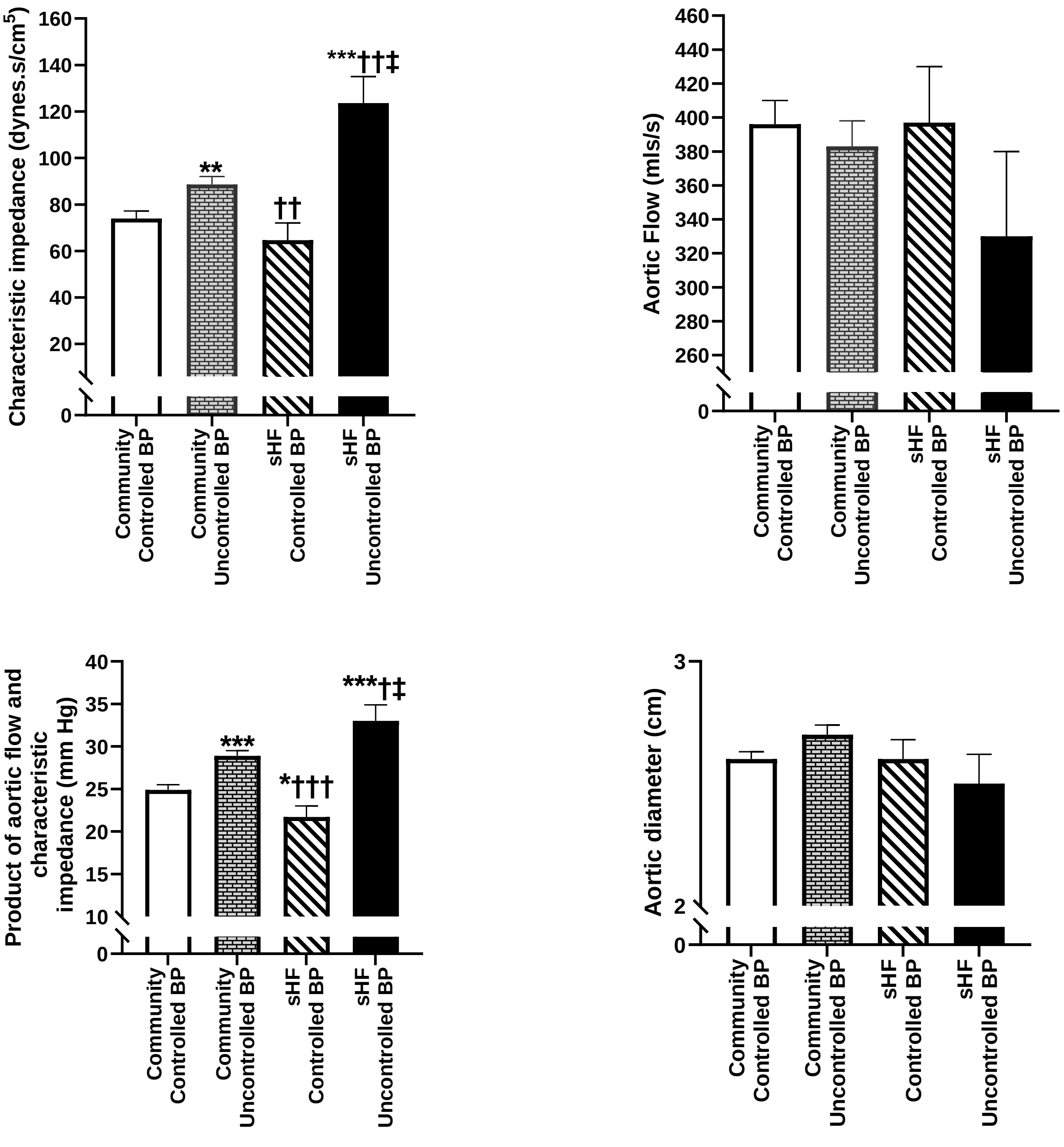


Figure 3.5. Comparison of characteristic impedance, aortic blood flow, the product of aortic flow and characteristic impedance, and aortic diameter between systolic HF (sHF) patients and community participants (community), with either controlled BP (<140/90 mm Hg) or uncontrolled BP (≥140/90 mm Hg) based on ISH guidelines, after adjustments for age, sex and heart rate (HR). *p<0.05, **p<0.001, ***p<0.0001 versus community participants with controlled BP; †p<0.05, ††p<0.001, †††p<0.0001 versus community participants with uncontrolled BP; ‡p<0.0001 versus sHF with controlled BP.

Adjusted for sex, age and HR

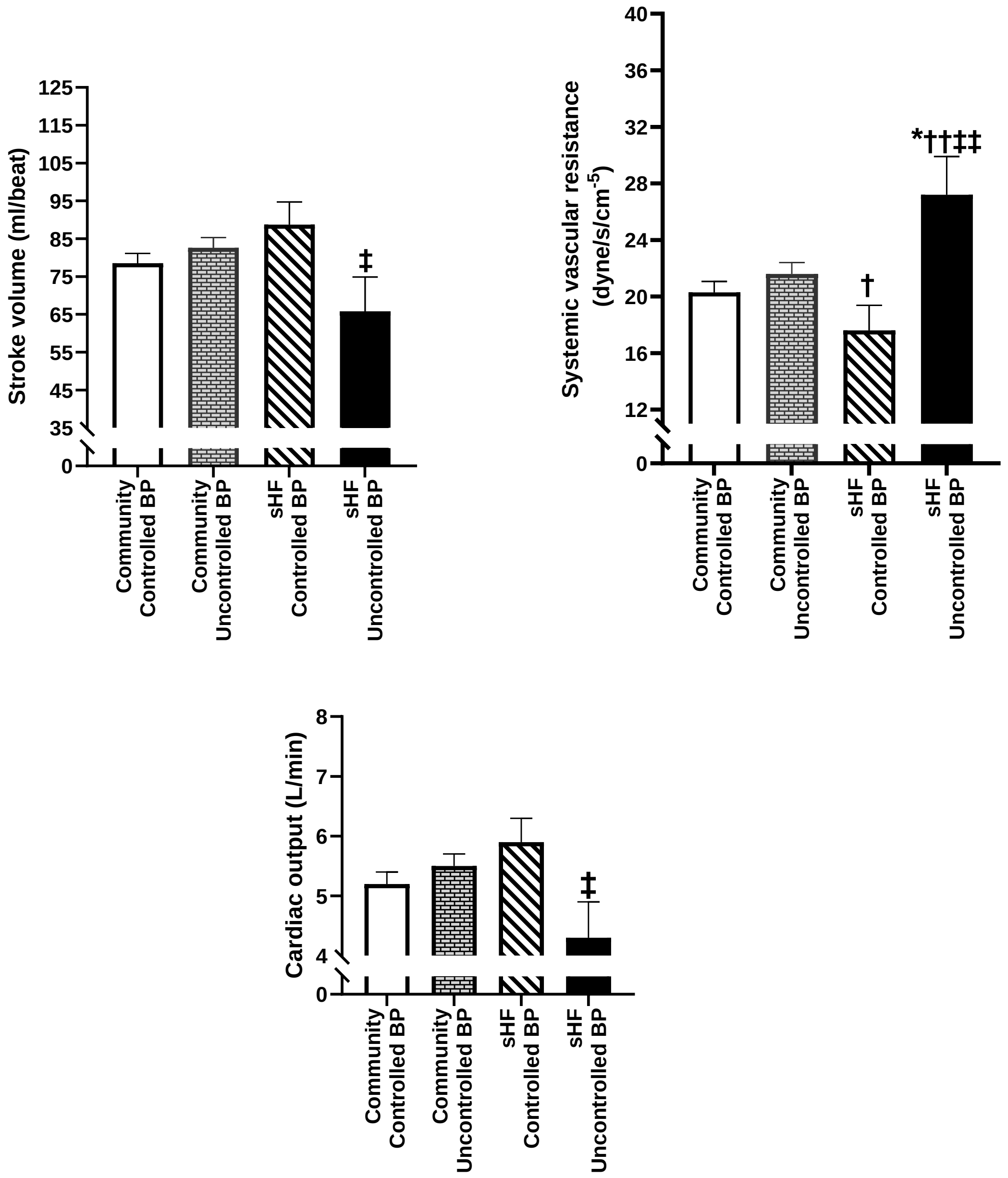


Figure 3.6. Comparison of cardiac haemodynamics between systolic HF (sHF) patients and community participants (community), with either controlled BP (<140/90 mm Hg) or uncontrolled BP (≥140/90 mm Hg) based on ISH guidelines, after adjustments for age, sex, and heart rate (HR). *$p<0.05$ versus community participants with controlled BP; †$p<0.05$, ††$p<0.001$ versus community participants with uncontrolled BP; ‡$p<0.05$, ‡‡$p<0.001$ versus sHF with controlled BP.

Table 3.8. Comparison of peripheral and central blood pressures, central haemodynamic parameters, and cardiac haemodynamics between community participants (community) and patients with systolic HF (sHF), with either controlled BP (<140/90 mm Hg) or uncontrolled BP (≥140/90 mm Hg), based on the ISH guidelines, after adjustments for age, sex, HR and MAP.

	Community		**sHF**	
	Controlled BP	Uncontrolled BP	Controlled BP	Uncontrolled BP
Sample size (n)	160	138	29	13
<u>Peripheral</u>				
SBP (mm Hg)	131±9	133±10	129±8†	138±7***†‡‡‡
PP (mm Hg)	45.7±14.0	48.7±15.0	42.8±12.0	56.3±12.0**†‡‡
<u>Central</u>				
SBP (mm Hg)	122±8	126±8**	119±7*†††	123±6
PP (mm Hg)	36.5±12.1	40.5±13.2*	32.4±10.7*††	40.7±9.9‡
Pf (mm Hg)	27.6±8.7	29.3±9.5	24.9±7.7†	33.4±7.1**†
Pb (mm Hg)	13.4±5.3	15.2±5.7*	11.5±4.7*†††	15.8±4.3‡‡
Zc (dynes.s/cm^5)	77.8±48.5	83.4±53.1	70.2±43.1	120.4±39.8**††‡
Q (mls/s)	405.9±213.1	368.8±232.9	412.1±189.4	320.8±174.9
QxZc (mm Hg)	26.3±8.3	27.0±9.0	23.8±7.4	31.8±6.8*†‡‡
<u>Cardiac</u>				
SV (ml/beat)	81.5±38.8	78.4±12.6	93.2±34.4	63.1±31.9‡
SVR (mm Hg/min/l^{-1})	21.2±11.3	20.4±12.6	18.9±10.2	26.4±9.5†‡
CO (L/min)	5.4±2.5	5.2±2.3	6.3±2.1	4.1±2.1*†‡‡

Data are expressed as mean±SD. SBP, systolic blood pressure; PP, pulse pressure; Pf, peak forward wave pressure; Pb, peak backward wave pressure; Zc, characteristic impedance; Q, peak aortic flow; QxZc, product of aortic flow and characteristic impedance; SV, stroke volume; SVR, systemic vascular resistance; CO, cardiac output. *$p<0.05$, **$p<0.001$, ***$p<0.0001$ versus community participants with controlled BP; †$p<0.05$, ††$p<0.001$, †††$p<0.0001$ versus community participants with uncontrolled BP; ‡$p<0.05$, ‡‡$p<0.001$, ‡‡‡$p<0.0001$ versus CCF with controlled BP.

community participants with uncontrolled BP (Table 3.8). However, after further adjustments for MAP, Zc and QxZc remained higher and CO was lower in systolic HF patients with uncontrolled BP compared to the other three groups (Table 3.8).

3.4. Impact of BP control (threshold = 130/80 mm Hg, based on AHA guidelines) on comparisons between community participants and patients with systolic HF.

Table 3.9 shows the impact of more intense BP control (controlled BP [<130/80 mm Hg] and uncontrolled BP [≥130/80 mm Hg]) on the comparison of participant general characteristic and unadjusted peripheral and central blood pressures between community participants and patients with systolic HF. Community participants and systolic HF patients with uncontrolled BP were older and had a higher BMI than community participants with controlled BP. Before adjustments for any confounders, as expected when BP was uncontrolled community participants and systolic HF patients had higher peripheral and central (systolic and diastolic) BP, MAP, and PP than those with controlled BP. Systolic HF patients with controlled BP had a lower central SBP compared to community participants with controlled BP. Importantly, systolic HF patients with uncontrolled BP had lower central SBP, DBP, and MAP than community participants with uncontrolled BP.

Table 3.10 shows the impact of more intense BP control (controlled BP [<130/80 mm Hg] and uncontrolled BP [≥130/80 mm Hg]) on the comparison of unadjusted central haemodynamic parameters between community participants and patients with systolic HF. Before adjustments for confounders, in both community participants and systolic HF patients, Pf, Pb, and QxZc were higher in those with uncontrolled BP compared to controlled BP. Importantly, only systolic HF patients with uncontrolled BP had higher Zc than community participants and systolic HF patients with controlled BP. Community participants with uncontrolled BP had an increased Ao diam and SV compared to community participants with controlled BP. There were no differences in Q and SVR between the four groups. Systolic HF patients with uncontrolled BP had an increased HR compared to both groups of community participants. Compared to community participants with controlled BP, CO was higher in those with uncontrolled BP.

Figure 3.7 and Table 3.11 show that after adjustments for age, sex, and HR, the differences in peripheral and central BP and PP between systolic HF patients and community participants

Table 3.9. Comparison of general characteristics and unadjusted peripheral and central blood pressures between community participants (community) and patients with systolic HF (sHF), with either controlled BP (<130/80 mm Hg) or uncontrolled BP (≥130/80 mm Hg) based on the AHA guidelines.

	Community		**sHF**	
	Controlled BP	Uncontrolled BP	Controlled BP	Uncontrolled BP
Sample size (n)	76	222	18	24
Age (years)	55.1±12.1	58.1±11.9*	60.0±11.5	60.8±11.5*
Sex (%Women)	40.8	46.0	55.6	29.2
BMI (kg/m^2)	28.3±7.8	31.0±7.4**	28.4±7.8	32.3±8.1*
% Medication				
Diuretics	34.2	38.3	83.3	54.2‡
ACEi	0	0	61.1	37.5
Beta Blockers	0	0	55.6	62.5
Vasodilators (Hydralazine)	0	0	0	4.2
Positive inotropes (Digoxin)	0	0	0	8.3
ARNi (Entresto)	0	0	22.2	12.5
Nitrate vasodilator (Ismo)	0	0	16.7	16.7
Lipid lowering (Simvastatin)	0	0	22.2	16.7
Peripheral				
SBP (mm Hg)	114±17	139±15***	108±12†††	137±14***‡‡
DBP (mm Hg)	74±9	89±15***	71±8†††	85±10***†‡‡

MAP (mm Hg)	87.0±9.0	106.0±15.0***	83.0±8.0†††	102.0±10.0***‡‡
PP (mm Hg)	41.0±13.0	50.0±13.0***	37.0±13.0†††	52.0±13.0**‡
Central				
SBP (mm Hg)	107±17	131±15***	98±12*†††	123±14***†‡‡
DBP (mm Hg)	74±9	90±15***	71±8†††	86±10***†‡‡
MAP (mm Hg)	85.0±9.0	104.0±15.0***	80.0±8.0†††	98.0±10.0***††‡‡
PP (mm Hg)	32.6±10.0	41.0±13.0***	26.8±8.0†††	37.0±16.0‡

Data are expressed as mean±SD. BMI, body mass index; ACEi, angiotensin-converting enzyme inhibitor; ARNi, Angiotensin receptor-neprilysin inhibitor; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure. *p<0.05, **p<0.001, ***p<0.0001 versus community participants with controlled BP; †p<0.05, ††p<0.001, †††p<0.0001 versus community participants with uncontrolled BP; ‡p<0.001, ‡‡p<0.0001 versus sHF with controlled BP.

Table 3.10. Comparison of unadjusted central haemodynamic parameters obtained by wave separation analysis and cardiac haemodynamics between community participants (community) and patients with systolic HF (sHF), with either controlled BP (<130/80 mm Hg) or uncontrolled BP (≥130/80 mm Hg) based on the AHA guidelines.

	Community		**sHF**	
	Controlled BP	Uncontrolled BP	Controlled BP	Uncontrolled BP
Sample size (n)	76	222	18	24
Central				
Pf (mm Hg)	24.9±7.8	29.8±7.4***	21.5±7.8††	30.0±8.2**‡‡
Pb (mm Hg)	12.5±5.2	15.1±4.6***	9.6±4.9*††	13.3±5.3‡
Zc (dynes.s/cm^5)	74.2±41.5	83.1±41.6	68.3±40.4	92.9±40.7*‡
Q (mls/s)	374.8±177.5	393.6±178.3	339.5±174.0	416.0±175.0
QxZc (mm Hg)	23.5±7.7	27.8±7.4***	20.9±7.4††	28.8±7.2**‡‡
Ao Diam (cm)	2.6±0.4	2.7±0.4*	2.6±0.4	2.6±0.4
Cardiac				
HR (beats/min)	64.4±12.1	66.4±11.9	69.6±11.5	73.8±12.0***†
SV (mm Hg)	74.3±32.0	82.4±32.7*	84.5±31.7	80.0±31.7
SVR (mm Hg/min/l^{-1})	20.9±9.5	21.1±10.4	17.1±9.5	21.1±9.6
CO (L/min)	4.7±2.6	5.5±3.0*	5.8±2.8	5.9±2.9*

Data are expressed as mean±SD. Pf, peak forward wave pressure; Pb, peak backward wave pressure; Zc, characteristic impedance; Q, peak aortic flow; QxZc, product of aortic flow and characteristic impedance; Ao Diam, aortic root diameter; HR, heart rate; SV, stroke volume; SVR, systemic vascular resistance; CO, cardiac output. *$p<0.05$, **$p<0.001$, ***$p<0.0001$ versus community participants with controlled BP; †$p<0.001$, ††$p<0.0001$ versus community participants with uncontrolled BP; ‡$p<0.05$, ‡‡$p<0.0001$ versus sHF with controlled BP.

Adjusted for age, sex and HR

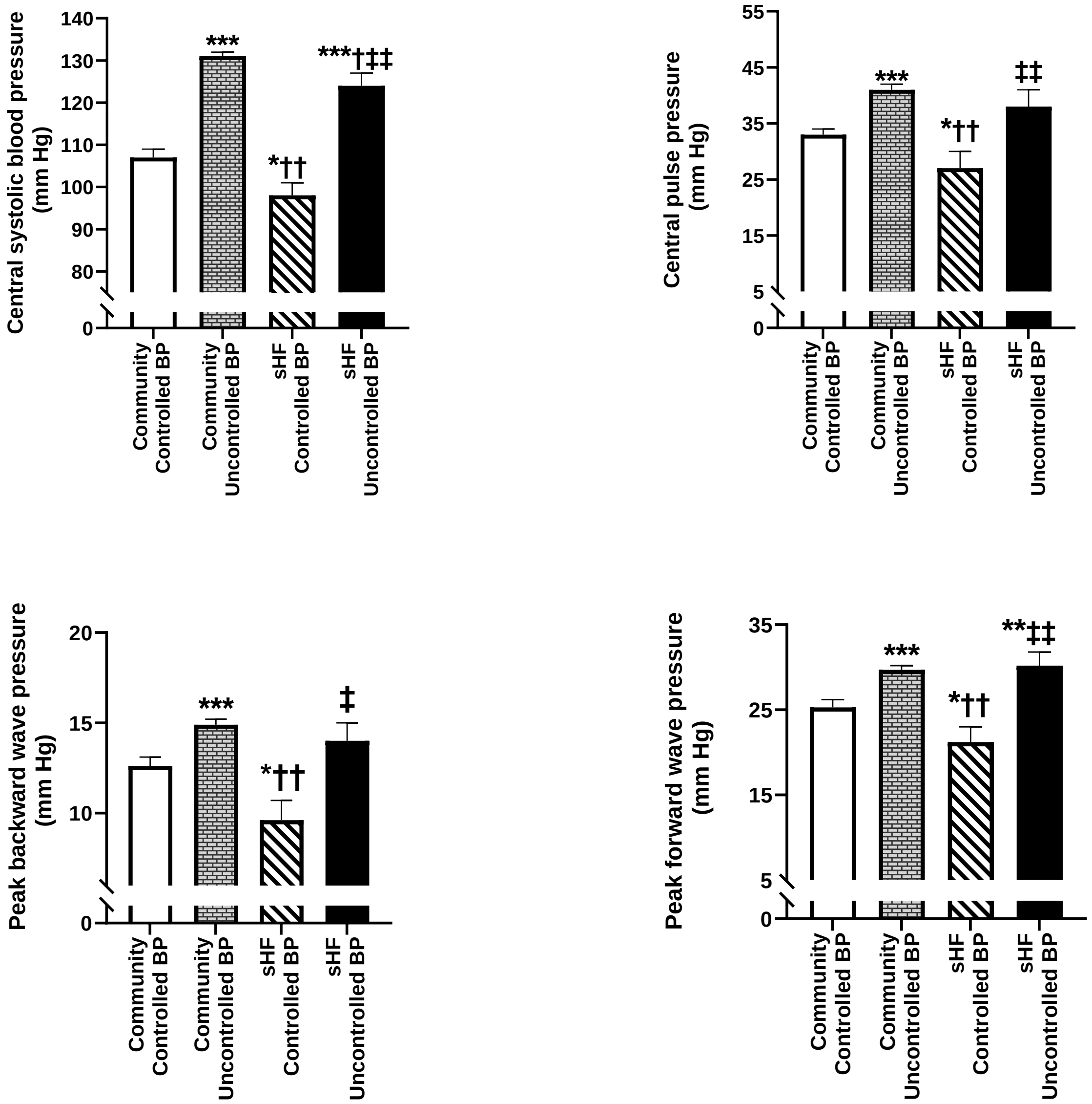


Figure 3.7. Comparison of central systolic blood pressure, central pulse pressure, backward wave pressure, and forward wave pressure between community participants (community) and systolic HF (sHF) patients, with either controlled BP (<130/80 mm Hg) or uncontrolled BP (≥130/80 mm Hg) based on AHA guidelines, after adjustments for age, sex and heart rate (HR). *$p<0.05$, **$p<0.01$, ***$p<0.0001$ versus community participants with controlled BP; †$p<0.05$, ††$p<0.0001$ versus community participants with uncontrolled BP; ‡$p<0.001$, ‡‡$p<0.0001$ versus sHF with controlled BP.

Table 3.11. Comparison of peripheral and central blood pressures between community participants (community) and patients with systolic HF (sHF), with either controlled BP (<130/80 mm Hg) or uncontrolled BP (≥130/80 mm Hg), based on the AHA guidelines, adjusted for age, sex, and HR.

	Community		**sHF**	
	Controlled BP	Uncontrolled BP	Controlled BP	Uncontrolled BP
Sample size (n)	76	222	18	24
Peripheral				
SBP (mm Hg)	115±17	139±15***	107±12*††	137±14***‡
DBP (mm Hg)	74±9	89±15***	71±8††	85±10***†‡
MAP (mm Hg)	87.0±8.7	106.0±14.9***	83.0±8.2††	102.0±9.6***‡
PP (mm Hg)	41.5±12.1	49.4±11.9***	36.2±12.0††	51.2±2.6**‡
Central				
DBP (mm Hg)	74±9	90±15***	71±8††	85±10***†‡
MAP (mm Hg)	85.0±8.7	104.0±14.9***	80.0±8.2*††	98.0±9.6***†‡

Data are expressed as mean±SD. SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; QxZc, product of flow and characteristic impedance; Ao Diam, aortic diameter; HR, heart rate; CO, cardiac output. *p<0.05, **p<0.001, ***p<0.0001 versus community participants with controlled BP; †p<0.05, ††p<0.0001 versus control with uncontrolled BP; ‡p<0.0001 versus sHF with controlled BP.

remained. Furthermore, after adjustments for age, sex, and HR, the differences in Pb and Pf (Figure 3.7), in Zc, QxZc, and Ao Diam (Figure 3.8), and SV (Figure 3.9) between systolic HF patients and community participants largely remained. However, CO was no longer higher in the systolic HF patients with uncontrolled BP compared to the community participants with controlled BP (Figure 3.9 and Table 3.10). As with the unadjusted data (Table 3.10), no differences in Q (Figure 3.8**)** and SVR (Figure 3.9) were noted between the four groups.

Table 3.12 shows the impact of further adjustments for MAP on the comparisons of peripheral and central BP, central hemodynamic parameters, and cardiac hemodynamics between community participants and systolic HF patients with either controlled BP (<130/80 mm Hg) or uncontrolled BP (≥130/80 mm Hg). Importantly, the differences in peripheral and central BP were eliminated (Table 3.12). Moreover, Pf, Zc, and QxZc were no longer different between the four groups (Table 3.12). Systolic HF patients with controlled BP had lower central SBP and Pb compared to community participants with controlled BP.

Adjusted for age, sex and HR

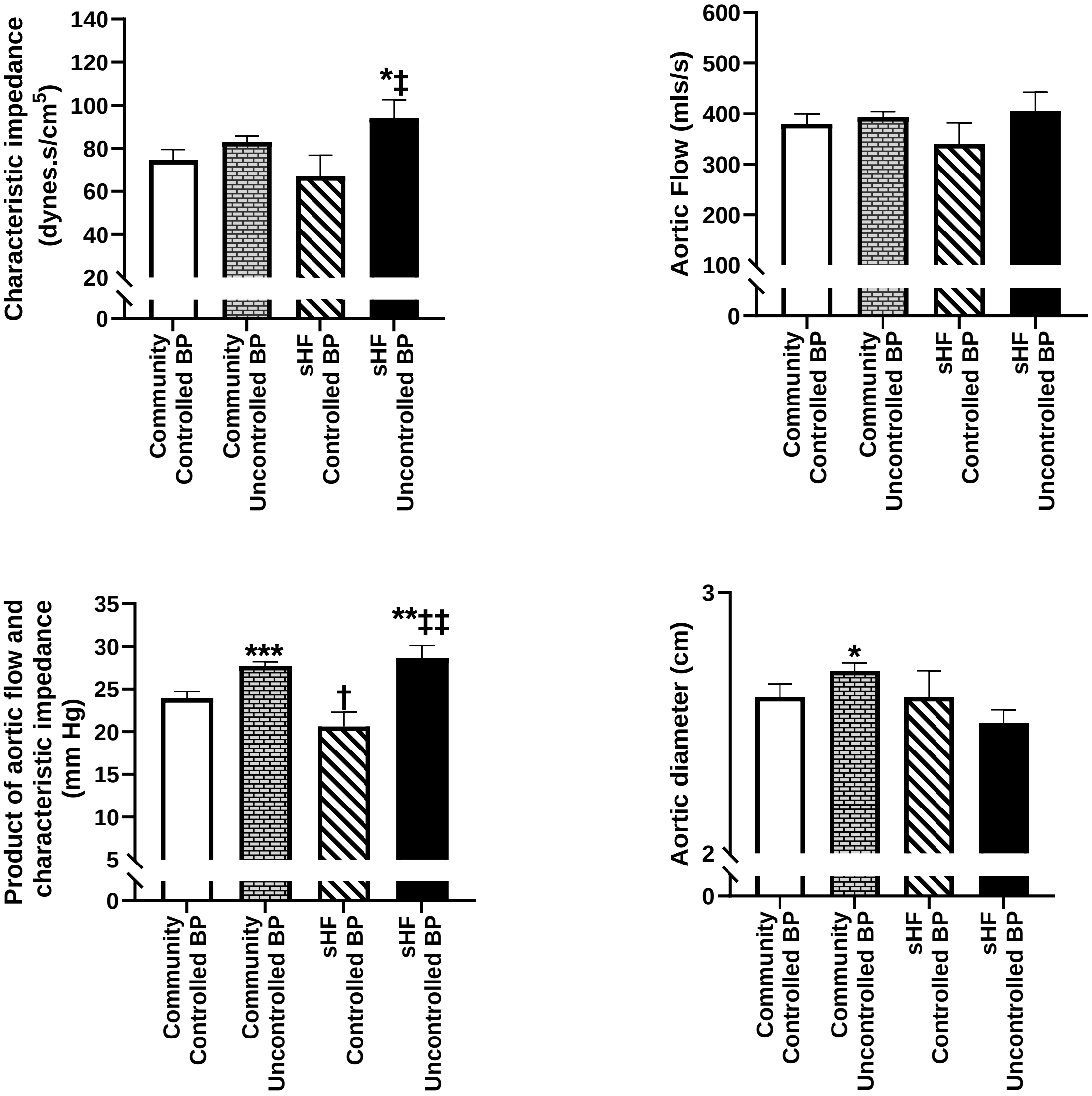


Figure 3.8. Comparison of aortic characteristic impedance, aortic blood flow, the product of aortic flow and characteristic impedance, and aortic diameter berween community participants (community) and systolic HF (sHF) patients, with either controlled BP (<130/80 mm Hg) or uncontrolled BP (≥130/80 mm Hg) based on AHA guidelines, after adjustments for age, sex and heart rate (HR). *$p<0.05$, **$p<0.001$, ***$p<0.0001$ versus community participants with controlled BP; †$p<0.0001$ versus community participants with uncontrolled BP; ‡$p<0.05$, ‡‡$p<0.0001$ versus sHF with controlled BP.

Adjusted for age, sex and HR

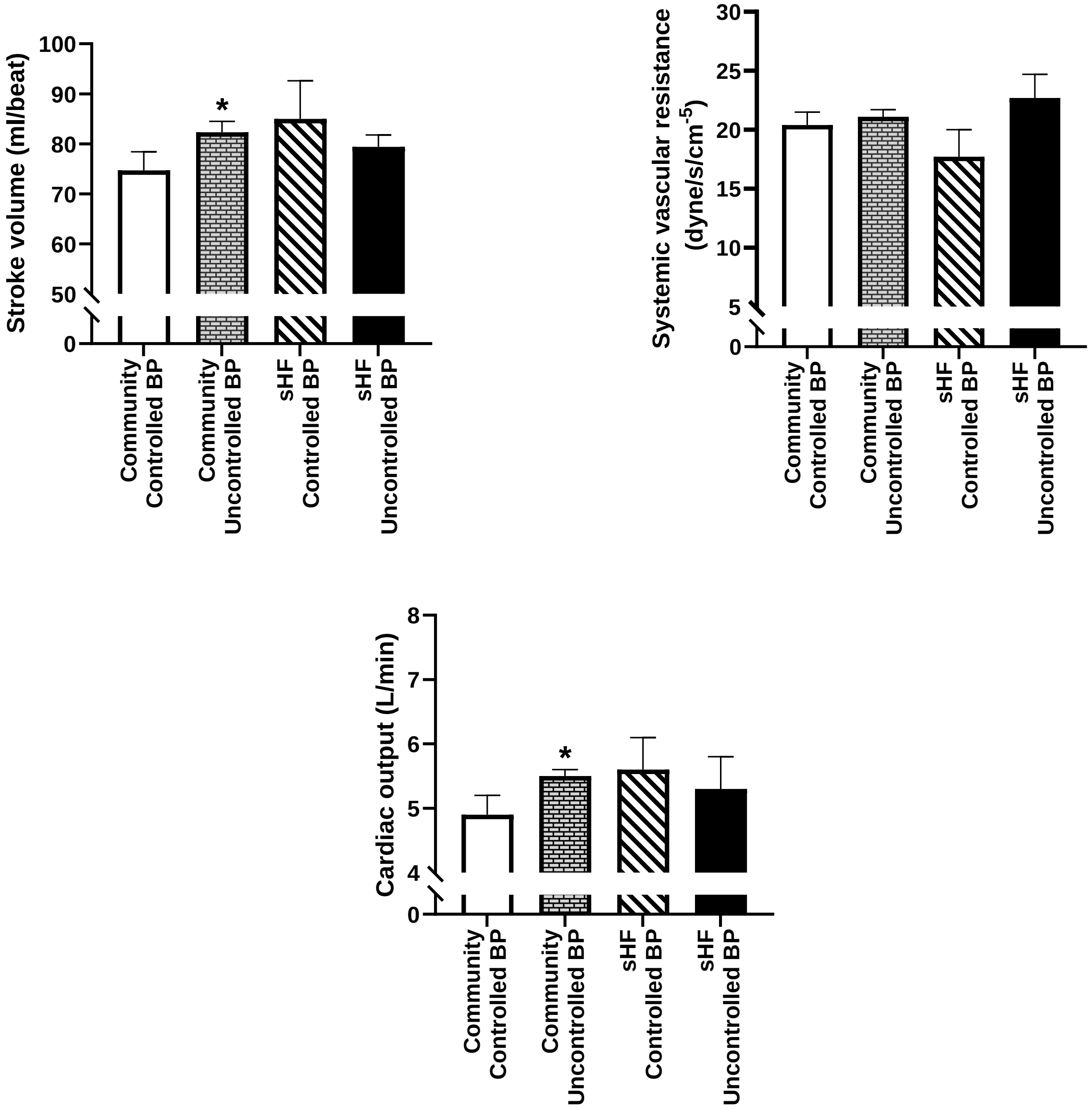


Figure 3.9. Comparison of cardiac haemodynamics (stroke volume, systemic vascular resistance and cardiac output) between systolic HF (sHF) patients and community participants (community), with either controlled BP (<130/80 mm Hg) or uncontrolled BP (≥130/80 mm Hg) based on AHA guidelines, after adjustments for age, sex, and heart rate (HR). *p<0.05 versus community participants with controlled BP.

Table 3.12. Comparison of central and cardiac haemodynamics obtained by wave separation between community participants (community) and patients with systolic HF (sHF), with controlled BP (<130/80 mm Hg) and uncontrolled BP (≥130/80 mm Hg), based on the AHA guidelines, adjusted for age, sex, HR, and MAP.

	Community		**sHF**	
	Controlled BP	Uncontrolled BP	Controlled BP	Uncontrolled BP
Sample size (n)	76	222	18	24
Peripheral				
SBP (mm Hg)	132±9	132±3	130±8	134±8
PP (mm Hg)	47.1±14.0	46.9±4.0	43.7±12.4	50.4±11.8
Central				
SBP (mm Hg)	124±8	124±2	120±7*	121±6.4
Pf (mm Hg)	28.3±8.7	28.4±7.4	25.2±7.8	29.7±7.2
Pb (mm Hg)	14.9±5.2	14.0±4.6	12.6±4.5*	13.7±4.3
PP (mm Hg)	38.6±12.1	38.1±11.9	33.9±10.7	37.1±10.1
Zc (dynes.s/cm^5)	86.3±48.5	77.9±44.6	82.5±42.9	92.2±40.8
Q (mls/s)	368.4±209.6	397.8±194.7	325.0±186.4	407.7±176.5
QxZc (mm Hg)	26.5±1.0	26.6±0.5	24.1±1.8	28.2±1.4
Ao diam (cm)	2.6±0.5	2.7±0.1	2.6±0.4	2.5±0.4
Cardiac				
SV (ml/beat)	76.3±38.5	81.6±11.0	87.1±34.2	79.1±32.6
SVR (mm Hg/min.l^{-1})	22.1±11.4	20.4±3.3	20.0±10.1	22.4±9.6
CO (L/min)	5.0±2.6	5.4±2.8	5.7±2.3	5.5±2.2

Data are expressed as mean±SD. SBP, systolic blood pressure; PP, pulse pressure; Pf, peak forward wave pressure; Pb, peak backward wave pressure; Zc, characteristic impedance; Q, peak aortic flow; QxZc, product of aortic flow and characteristic impedance; SV, stroke volume; SVR, systemic vascular resistance; CO, cardiac output. *p<0.05 versus community participants with controlled BP.

CHAPTER 4 DISCUSSION

4.1 Summary of the Main Findings

The main findings of the present study are as follows: In a cohort of patients with systolic HF (94.1% with mild-to-moderate systolic HF [NYHA FC I or II] and 69.7% receiving vasodilator therapy), as compared to age- and sex-matched community participants, unadjusted central PP, but not peripheral PP, was lower and HR was greater. After adjustments for confounders including HR, central PP, and Pb remained lower in patients with systolic HF, but no differences in Zc, Q, SV, Pf, SVR, or aortic diameter were noted between the patients with systolic HF and the community participants. However, after further adjusting for MAP, no differences except for a lower central SBP in the patients with systolic HF, were noted between the two groups. When assessing the impact of BP control, based on the ISH guideline threshold of <140/90 mm Hg, it was noted that after adjusting for confounders (age, sex, and HR), systolic HF patients with uncontrolled BP had higher Zc, QxZc, Pf and SVR than systolic HF patients with controlled BP as well as community participants with controlled BP. Moreover, despite similar peripheral and central PP to community participants with uncontrolled BP, Zc, QxZc and SVR were higher in systolic HF patients with uncontrolled BP. However, when uncontrolled BP was based on the AHA guideline threshold of ≥130/80 mm Hg (more intense BP control), the differences in Zc, QxZc, and SVR between the systolic HF patients with uncontrolled BP and the community participants with uncontrolled BP were eliminated.

4.2 Is PP Increased or Decreased in Systolic HF?

4.2.1 Peripheral PP in Systolic HF

The lack of differences in peripheral PP between patients with mild-to-moderate systolic HF and community participants in the present study, is similar to that observed in patients with severe systolic HF compared to controls (Parragh *et al*., 2015; Steinberg *et al*., 2023). These data differ from those observed by Denardo *et al*, (2010) who showed a lower peripheral PP in patients with severe systolic HF compared to normal participants. It is possible that the severity of HF may explain the differences observed in peripheral PP between these studies. In studies where no differences in peripheral PP were observed between cases and controls, only 51% of patients had NYHA FC III or IV HF (Steinberg *et al*., 2023) or only 5.9% of patients had NYHA FC III HF (none had NYHA FC IV HF) (present study). In comparison, in the study reporting decreases in peripheral PP between cases and controls, 92% of patients with systolic HF had NYHA FC III or IV HF (Denardo *et al*., 2010). In this regard, peripheral PP is reported to be an indicator of cardiac output in patients with severe systolic HF (Stevenson and Perloff, 1989), and there is a positive association between peripheral PP and LV function (Regnault *et al*., 2014). Hence, more severe HF is more likely to be associated with lower peripheral PP.

However, the relationship between peripheral PP and mortality or risk of cardiac events in patients with systolic HF is complex, with both decreases and increases in peripheral PP being associated with increased mortality or risk of cardiac events (Table 1.1 in the introduction section). Indeed, it has been shown that in patients with systolic HF, the relationship between peripheral PP and mortality is non-linear (Laskey *et al*., 2016). This relationship is U-shaped with a nadir at a peripheral PP of 50 mm Hg (Laskey *et al*., 2016). In patients with systolic HF, mortality rates increase with decreases in peripheral PP below 50 mm Hg, and increase with increases in peripheral PP above 50 mm Hg (Laskey *et al*., 2016). The increased mortality observed at lower peripheral PP is thought to be related to the worsening of LV function. In this regard, as the systolic function of the heart declines, the ability to generate pressure is reduced and hence the low peripheral PP is a consequence of the worsening systolic HF. In comparison, the increased mortality at peripheral PP above 50 mm Hg possibly reflects increases in cardiac afterload, which would impair systolic function and cause systolic HF to deteriorate further. Indeed, studies have reported associations between increases in aortic stiffness (PWV), a marker of increased cardiac afterload, and increases in cardiovascular events in patients with systolic HF (Sung *et al*., 2011; Regnault *et al*., 2014).

4.2.2 Central PP in Systolic HF

The lower central PP observed in the patients with mild-to-moderate systolic HF compared to the community participants in the present study, is similar to that observed in patients with severe systolic HF compared to controls (Denardo *et al*., 2010). However, these data differ from two previous studies showing no differences in central PP between patients with systolic HF and controls (Parragh *et al*., 2015; Steinberg *et al*., 2023). Moreover, one study reported increases in cardiovascular events in association with increases in central PP (Sung *et al*., 2011). It is unlikely that the differences between these studies are related to the severity of HF. Lower central PP has been observed in patients with mild-to-moderate systolic HF. Furthermore, no differences in central PP between patients with systolic HF and controls have been reported in patients with severe HF (51% NYHA FC II or IV) (Parragh *et al*., 2015; Steinberg *et al*., 2023). Hence, reasons for the discrepancies in the data between these studies are at present unclear. Furthermore, whether the relationship between central PP and mortality is non-linear and shows a U-shaped curve similar to peripheral PP is not known. Hence, outcomes studies examining the relationship between central PP and mortality need to be conducted.

4.3 Are Determinants of Central PP Increased or Decreased in Systolic HF?

Despite no differences in central PP in patients with systolic HF compared to controls, two studies have reported differences in the determinants of central PP. Steinberg *et al*, (2023) reported that increases in the speed of wave reflection (increased stiffness) were associated with an increased risk of death in patients with severe systolic HF. In comparison, Denardo *et al*, (2010) reported that Pb was decreased in patients with severe systolic HF compared to controls and that there was a delayed return of Pb (implying decreased arterial stiffness). Furthermore, in a study comparing patients with CAD and reduced EF to patients with CAD but normal EF, decreases in Pb but not Pf were noted (Parragh *et al*., 2015). However, the lower Pb was explained by differences in HR between the groups (Parragh *et al*., 2015). Despite assessing the magnitude of Pf and Pb in patients with severe systolic HF, no comparisons were made with the control group in another study (Steinberg *et al*., 2023). Hence, data on the determinants of central PP in systolic HF are very limited. Other than the present study, to my knowledge there are no previous data on Zc, wave reflection and re-reflection, Q or P_{QxZc} in systolic HF. Hence, future studies are required to assess all the determinants of central PP in systolic HF.

4.4 Arterial Stiffness in Systolic HF

Similar to the data on central PP in systolic HF, the data on changes in arterial stiffness in systolic HF are limited and contradictory. Pulse wave velocity (PWV, an index of arterial stiffness) is reported to not differ between patients with systolic HF and controls (Steinberg *et al*., 2023) or between CAD patients with reduced EF compared to CAD patients with normal EF (Parragh *et al*., 2015). In contrast, the return of Pb is delayed in patients with systolic HF compared to controls, implying a decreased arterial stiffness in patients with systolic HF (Denardo *et al*., 2010). However, these discrepant data may be explained by the differences in ejection duration between the patients and the controls. Despite no apparent differences in indices of arterial stiffness between patients and controls, two studies have reported an association of increased arterial stiffness (PWV, or speed of wave reflection) with increased risk of cardiac events (Sung *et al*., 2011) or death (Steinberg *et al*., 2013). Furthermore, in a community-based study, an increased aortic stiffness as measured using pulse wave velocity (PWV) was associated with decreased systolic function and increased risk of HF (Tsao *et al*., 2015). However, PWV is an index of the stiffness of the full length of the aorta, rather than an index of proximal aortic characteristic impedance (Zc, resistance to flow in a pulsatile system). To my knowledge, only one previous study has assessed aortic stiffness in patients with systolic HF (Pepine *et al*., 1978). Similar to previous studies reporting no differences in arterial stiffness between patients with systolic HF and controls (Parragh *et al*., 2015; Steinberg *et al*., 2023), the present study showed no differences in Zc between patients with systolic HF and controls. However, in the present study, Zc was increased in patients with systolic HF with uncontrolled BP. These data are supported by data in a small study (10 patients and 10 controls), reporting elevated Zc in the proximal aorta of HF patients compared to non-HF patients (Pepine *et al*., 1978). Importantly, these data were collected during cardiac catheterisation and hence under anaesthetic which may have influenced the results. Furthermore, no adjustments were made for HR which differed between the two groups. Hence, further studies are required to assess the impact of systolic HF on Zc.

4.5 Ventricular-Arterial Coupling in Systolic HF - Implications of Alterations in Central PP and its Determinants in Systolic HF

Knowledge of central PP and its determinants in patients with systolic HF is not trivial as there is an intimate relationship between cardiac and arterial function, termed ventricular-arterial coupling (as discussed in section 1.6 of the introduction). Throughout the cardiac cycle, the heart-vessel coupling is constantly changing to match ventricular end-systolic and arterial elastances (García and Santos, 2020). Central PP is determined by the episodic nature of cardiac contraction and the elastic properties of the arteries. Central PP in turn determines LV systolic afterload (Weber and Chirinos, 2018). Consequently, changes in LV function and arterial stiffness influence central PP, and changes in central PP impact on LV function (Ikonomidis *et al*., 2019). As patients with systolic heart failure have compromised cardiac function, the normal balance in the relationship between the heart and the vessels is offset. Moreover, should arterial stiffness and cardiac afterload be altered in patients with systolic HF, this would further unbalance this relationship. Importantly, increases in arterial stiffness and cardiac afterload would further decrease LV function in patients with systolic HF. Hence, an understanding of the determinants of central PP in systolic HF is paramount.

As discussed in section 1.3 of my introduction, in patients with systolic HF, if central PP is primarily determined by aortic blood flow (Q), then improvements in Q and consequently central aortic BP would be beneficial. However, increases in Zc would increase central PP which would be detrimental to the heart, due to increases in cardiac afterload. In a previous study in patients with CAD, those patients with reduced EF had lower SV and CO than the patients with normal EF (Parragh *et al*., 2015), however central PP and PWV (an index of arterial stiffness) did not differ after adjustments for heart rate. Hence, the relationships between central PP, EF, SV and CO on bivariate analyses, were possibly due to the confounding effects of heart rate (Parragh *et al.*, 2015). Other previous studies comparing central PP in patients with systolic HF to controls have not included data on SV (Denardo *et al*., 2010; Steinberg *et al*., 2023). My data showing no differences in SV or Q between patients with systolic HF and controls, suggest that the lower central PP observed in the patients with systolic HF was not due to decreases in systolic function. It is possible that the lower central PP in the systolic HF patients in my present study could be attributed to the preponderance of vasodilator therapy (70%) in the systolic HF patients. Indeed, SVR which may be increased in HF, did not differ from that of the community participants. However, as my study was cross-sectional in design, the cause can only be inferred. Hence, future intervention studies need to be conducted to determine the cause of the low central aortic PP in stable systolic HF patients with mild-to-moderate systolic HF.

Although in my present study, central PP was not associated with changes in systolic function, increases in Zc were noted in patients with systolic HF and uncontrolled BP. Similar to the high Zc noted in the systolic HF patients with uncontrolled BP in my present study, Pepine *et al*, (1978), reported elevated Zc in the proximal aorta of HF patients compared to non-HF patients. As with my present study, Pepine *et al*, (1978) also reported no differences in aortic cross-sectional area between the HF patients and the non-HF group. In the absence of differences in aortic cross-sectional area, the increased Zc is likely to be due to structural changes in the arterial wall (decreased elastic tissue and more collagen, resulting in a less compliant aorta). Notably, the elastic properties of an aorta are important for optimal ventricular-arterial coupling. A decreased aortic distensibility (increased aortic stiffness) alters the buffering capacity of the aorta, which causes an early return of the reflected wave from the distal vascular arterial sites and consequently an increased cardiac afterload (Weber and Chirinos, 2018; Ikonomidis *et al*., 2019). Importantly, patients with systolic HF have an increased aortic PWV (an index of aortic stiffness), which is strongly associated with an increased risk of hospitalization and cardiac death (Bonapace *et al*., 2013). Furthermore, arterial stiffness and wave reflection parameters are strong prognostic indicators and are correlated with the development of CVDs in systolic HF patients after discharge (Anastasio *et al*., 2022).

Importantly, increments in aortic stiffness would increase cardiac afterload, which would further decrease LV function in patients with systolic HF. Indeed, in the present study in association with the increase in Zc, patients with systolic HF and uncontrolled BP had reduced SV. Increases in LV afterload are a major haemodynamic cause of left ventricular dysfunction (LVD), and the association of increased afterload with decreased arterial compliance, can explain the increased risk of HF in patients with high central PP (Lancellotti *et al*., 2010). The increased LV afterload associated with decreased arterial compliance is thought to be caused by the reflected wave arriving early at the aortic root (Nichols *et al*., 2011). Although, in the present study, the patients with uncontrolled BP (which had increased Zc and SVR) had increased Pb, this did not differ from the community participants with uncontrolled BP. Nevertheless, in a previous study, increased speed of wave reflection (as occurs with increased arterial stiffness) was associated with an increased risk of death in patients with systolic HF (Steinberg *et al*., 2023).

In support of the role of ventricular-arterial coupling in HF, in the presence of reduced LV pump function in systolic HF, increases in Pb and hence central PP lead to further decreases in SV and blood flow (Weber *et al*., 2020). Similarly, in my present study, in association with a higher Zc, SVR, and Pb in the systolic HF patients with uncontrolled BP, central PP was increased and SV was decreased. Notably, high central PP due to an increased SV and peak Q, is beneficial for the perfusion of the tissues including the heart. Consequently, increases in central PP associated with increases in SV would be advantageous to patients with systolic HF. However, high PP due to increases in aortic stiffness and SVR would be detrimental to patients with systolic HF, because of the high cardiac afterloads and consequent reductions in SV. As the high central PP, Zc, SVR, and low SV were only observed in the systolic HF patients with uncontrolled BP in my study, it is important to discuss the benefits of BP control.

4.6 Benefits of Intense BP Control

BP control of <140/90 mm Hg is recommended by the current international guidelines (ISH, as well as in South Africa) to prolong life and reduce CVDs (Mancia *et al*., 2013). However, the SPRINT study challenged this and reported that a further intense reduction of SBP control to a target of <120 mm Hg is mandatory in patients with increased cardiovascular risk (Mancia *et al*., 2013). In this regard, the SPRINT study demonstrated that an intensive SBP control target of <120 mm Hg in patients with increased cardiovascular risk, had health benefits compared to a standard SBP control target of <140 mm Hg. A 33% and 32% reduction in incident CVDs and mortalities were reported in response to intensive (SBP<120 mm Hg) as compared to standard BP control (SBP<140 mm Hg) (Wright and Williamson, 2015). In my present study, in addition to the 140/90 mm Hg threshold, data were also analysed according to the more intense BP control target of <130/80 mm Hg. Of note, when BP control was defined as <130/80 mm Hg, central SBP, PP, Pb, and Pf in systolic HF patients with uncontrolled BP, were no longer different from values in the community participants with uncontrolled BP. Furthermore, Zc, Q, SV, and SVR were no longer higher in systolic HF patients with uncontrolled BP compared to community participants with uncontrolled BP. Similar to the present study, the SPRINT study has shown that intensive BP control (<120/80 mm Hg) has an impact on reducing Pf and Pb compared to standard BP control (<140/90 mm Hg) (Todd and Clegg, 2016). In the SPRINT study, it was suggested that intensive BP control decreased central PP and arterial stiffness, which potentially led to reductions in Pb and Pf (Todd and Clegg, 2016). Furthermore, intensive BP control has been associated with better arterial compliance and reduced arterial stiffness (PWV) (Upadhya *et al*., 2021), which can influence Pf and Pb (Bangalore *et al*., 2016).

Importantly, in my present study when data were analysed according to the BP control target of <140/90 mm Hg, systolic HF patients with uncontrolled BP had increased Zc compared to the systolic HF patients with controlled BP as well as both groups of community participants. However, when BP was controlled at a target <130/80 mm Hg, the differences in Zc between systolic HF patients with uncontrolled BP and community participants with uncontrolled BP were eliminated. This data suggests that intense BP lowering may be beneficial in reducing the increased Zc in patients with systolic HF.

High BP impacts on the vasculature, consequently affecting arterial stiffness (PWV). Of note, increased BP increases PWV through several mechanisms (Chirinos, 2013). Prolonged BP elevation induces structural and arterial wall changes, leading to reduced compliance and arterial stiffening (Chirinos, 2013). Furthermore, arterial stiffening causes a loss of blood vessel elasticity, hence increasing the transmission of pressure waves along the arterial tree (Chirinos, 2013). Due to consistently high or uncontrolled BP, the arterial walls experience an exerted force during every cardiac cycle. These prolonged pressures cause structural modification in the arteries, inducing arterial stiffening and remodeling (Nichols, 2005). The continuous exposure of arterial walls to high-pressure pulsatile flow triggers cellular and molecular changes within the arterial walls (Nichols, 2005). Chronic uncontrolled BP induces collagen accumulation, elastin fragmentation, vascular smooth muscle cell hyperplasia, hypertrophy, and increased deposition of extracellular matrix proteins within the arterial walls, leading to severe increased aortic stiffness (Mitchell, 2008). The increased arterial stiffness changes the characteristic impedance throughout the arterial root. Importantly, when the LV contracts it generates pressure waves and ejects blood into an aorta, the pressure generated encounters impedance mismatch at different arterial network sites, more especially at the bifurcation of small and large arteries along the arterial tree (Baksi *et al*., 2016). Impedance mismatch causes wave reflection towards the heart, augmenting with the incident (Pf) waves during systole and contributing to an elevated central PP (Torjesen *et al*, 2014). Hence, with uncontrolled BP the increased Zc caused by arterial stiffness increases wave reflection, leading to central PP augmentation (Torjesen *et al*, 2014). The increased central PP has detrimental effects on the heart and leads to other CVDs associated with hypertension (Nichols, 2005). In essence, higher BP is associated with increased stiffness, hence intense BP control is necessary to protect the already compromised heart in systolic HF patients and reduce cardiac afterload. Lowering BP through intensive control (<130/80 mm Hg) could potentially reduce the afterload on the heart, leading to decreased myocardial workload and improved CO in some patients (Bangalore *et al*., 2016). Additionally, intensive BP control can influence SVR by reducing arterial stiffness and improving vascular compliance (Upadhya *et al*., 2021). Therefore, intensive BP control, by reducing cardiac afterload is likely to have a beneficial influence on SV (Bangalore *et al*., 2016). Of note, compared to the community participants with uncontrolled BP, the high Zc and reduced

SV that were noted in systolic HF patients when BP was uncontrolled at ≥140/90 mm Hg threshold, were no longer present when BP was uncontrolled at ≥130/80 mm Hg.

4.5 Clinical Implications

The high central PP in the patients with systolic HF when BP was uncontrolled at ≥140/90 mm Hg (based on the ISH guidelines) was not associated with SV, in fact, SV was low in patients with systolic HF with uncontrolled BP (≥140/90 mm Hg). If the increased central PP in the patients with systolic HF and uncontrolled BP was due to an increased SV then this would have been beneficial for perfusion of peripheral tissues and the heart itself. However, in my present study, the increased central PP in systolic HF patients with uncontrolled BP (≥140/90 mm Hg) was related to increases in Zc, and SVR, and not to increases in SV. The increased Zc and SVR result in an increased afterload to the heart and hence are detrimental in systolic HF patients as they already have a compromised heart. Indeed, the high Zc and SVR were associated with a low SV in these patients. Consequently, systolic HF patients need to be treated with BP lowering to decrease the impact of an increased afterload on the already compromised heart. The elimination of the differences in Zc, SVR and SV between systolic HF patients and community participants when BP was controlled at <130/80 mm Hg, based on the AHA guidelines, suggests that intense BP lowering is advisable. Decreases in Zc and SVR with intense BP lowering are likely to reduce cardiac afterload and hence prevent decreases in SV, which would be beneficial in systolic HF patients. Indeed, in the SPRINT study, reductions in incident HF were the most pronounced benefit of intensive BP lowering (Wright *et al.*, 2015).

4.6 Study Limitations

My study has several potential limitations. Firstly, the present study aimed to assess central haemodynamics in patients with mild-to-moderate systolic dysfunction. Hence, the data cannot be translated to all types of HF or different severities of HF. Therefore, future studies need to be conducted to determine the impact of different types of HF and the severity of HF on central aortic haemodynamics. Secondly, for ethical and practical reasons, patients could not have their central aortic haemodynamics measured while they were in an acute state of HF. Hence, only stable systolic HF patients were used in the present study which may have affected the outcomes. It is possible that the data could have been different if unstable systolic HF patients had been analysed.

Consequently, the results cannot be generalised to all patients with systolic HF. Another potential limitation to the present study is the use of applanation tonometry to estimate the central aortic pressures. This technique uses brachial BP (SBP and DBP) measurements to calibrate the radial waveform. Although a few researchers have criticized this approach as it ignores the possible amplification of BP from brachial to radial arteries (Hope *et al.*, 2004), there is still debate and lack of consensus on whether such amplification even occurs (Mahieu, *et al.*, 2010). Importantly, applanation tonometry and its calibration are internationally recognized and SphygmoCor is the only device approved by the Food and Drug Administration for assessing central aortic pressures (Butlin and Qassim, 2017). Of note, applanation tonometry depends on analysing arterial pulse waves to derive central BP. However, factors such as irregular heart rhythms introduce errors in pulse wave analysis, and hence a contraindication to the use of applanation tonometry and the acquisition of arterial pulse waves (SphygmoCor. Operator manual, AtCor Medical Pty, Ltd, West Ryde, New South Wales, Australia). Consequently, the present study excluded patients with arrhythmia, hence the data cannot be translated to systolic HF patients with arrhythmias. Importantly, HIV/AIDS status of systolic HF patients was not known, and research has shown that HF and ventricular dysfunction are quite prevalent in people with HIV/AIDS (Hsue *et al*., 2010). Systolic HF and community participants data were collected by different professionals at different times and sites, which could introduce an inter-observer error. A potential limitation is that all the community participants are of an African ancestry and the systolic heart failure patients consists of a mixure of ancestries. In addition, PWV and Zc are increased in people of African ancestry (Goel *et al*., 2017) compared to other ancestries and this could have impacted the data, however, it is likely to dilute the differences in data. Hence, if data was only collected on systolic HF patients of African ancestry, we could have found bigger differences. Another limitation is that the present study is a cross sectional study, hence it cannot establish causality. Lastly, interpretations of the data is subject to a small sample size.

4.7 Future Studies

As my study was conducted on systolic HF patients, future studies should be conducted to assess the role of aortic haemodynamics in patients with diastolic dysfunction and patients with HFpEF. Furthermore, as the present study assessed patients with mild-to-moderate stable systolic HF, future studies should be performed to assess the role of aortic haemodynamics in unstable patients as well as in patients with more severe systolic HF. In addition, as studies on central PP and its determinants in patients with systolic HF are very limited, and to my knowledge no other studies have assessed Zc, Q or P_{QxZc} in systolic HF, future studies are required to assess all the determinants of central PP in systolic HF. Furthermore, outcomes studies examining the nature of the relationship between central PP and mortality need to be conducted. My study was cross-sectional in design, hence to confirm the impact of intense BP control on aortic haemodynamics in patients with systolic HF, intervention and prospective studies should be done. Furthermore, studies should be done to determine the mechanisms of the changes in Zc in patients with systolic HF. An understanding of these mechanisms is important to guide future therapies designed to reduce Zc and hence afterload in patients with HF.

4.8 Conclusion

In conclusion, in stable patients with mild-to-moderate systolic HF a lower central aortic PP, but not peripheral PP was observed in comparison to an age-and sex-matched control group. The low central aortic PP was not associated with reductions in stroke volume (SV) or aortic blood flow (Q). However, in patients with mild-to-moderate systolic HF in the presence of uncontrolled BP (SBP/DBP≥140/90 mm Hg), Zc and SVR were increased and SV was decreased. When more intense BP control (SBP/DBP<130/80 mm Hg) was assessed, the differences in Zc, QxZc, and SVR between the patients with mild-to-moderate systolic HF patients with uncontrolled BP and the community participants with uncontrolled BP were eliminated. In essence, the present study has shown that in patients with hypertension-induced mild-to-moderate systolic HF in the absence of BP control, aortic stiffness is increased which would result in further impediments to the already compromised cardiac function. These data suggest that BP control is imperative in the management of patients with mild-to-moderate systolic HF to protect the heart from the detrimental effects of increased afterloads (high Zc and SVR). Furthermore, as the increased Zc and SVR, and decreased SV were no longer apparent when the groups were defined according to intense BP control thresholds (130/80 mm Hg), my data suggest that in systolic HF patients, BP should be managed to thresholds lower than 140/90 mm Hg. Hence, BP control and the level of its control have an impact on central and cardiac haemodynamics in patients with mild-to-moderate systolic HF.

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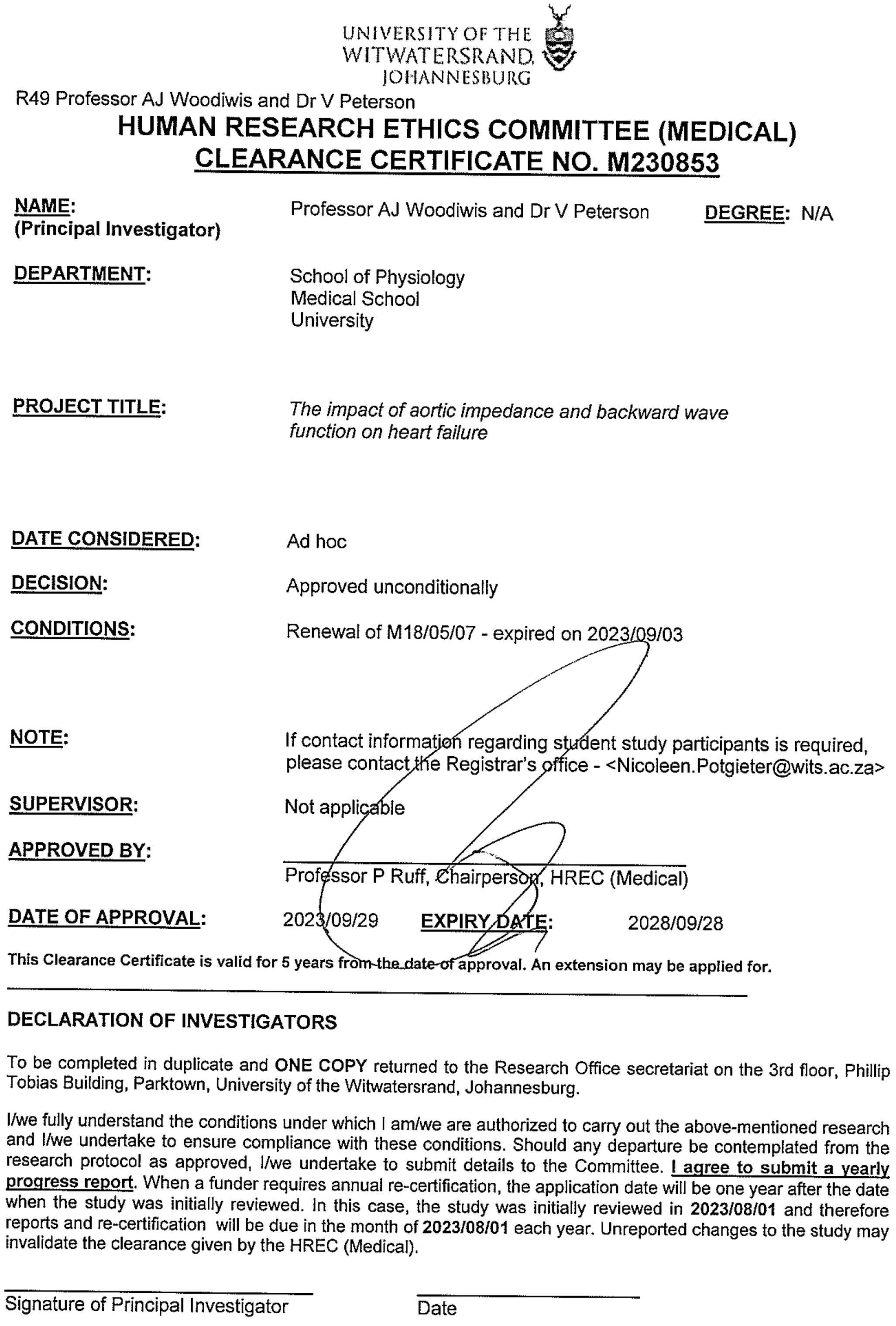
Appendix I: Ethical Clearance Certificate



UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

R49 Professor AJ Woodiwis and Dr V Peterson

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M230853

NAME:
(Principal Investigator) Professor AJ Woodiwis and Dr V Peterson **DEGREE:** N/A

DEPARTMENT: School of Physiology
Medical School
University

PROJECT TITLE: *The impact of aortic impedance and backward wave function on heart failure*

DATE CONSIDERED: Ad hoc

DECISION: Approved unconditionally

CONDITIONS: Renewal of M18/05/07 - expired on 2023/09/03

NOTE: If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>

SUPERVISOR: Not applicable

APPROVED BY: Professor P Ruff, Chairperson, HREC (Medical)

DATE OF APPROVAL: 2023/09/29 **EXPIRY DATE:** 2028/09/28

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

DECLARATION OF INVESTIGATORS

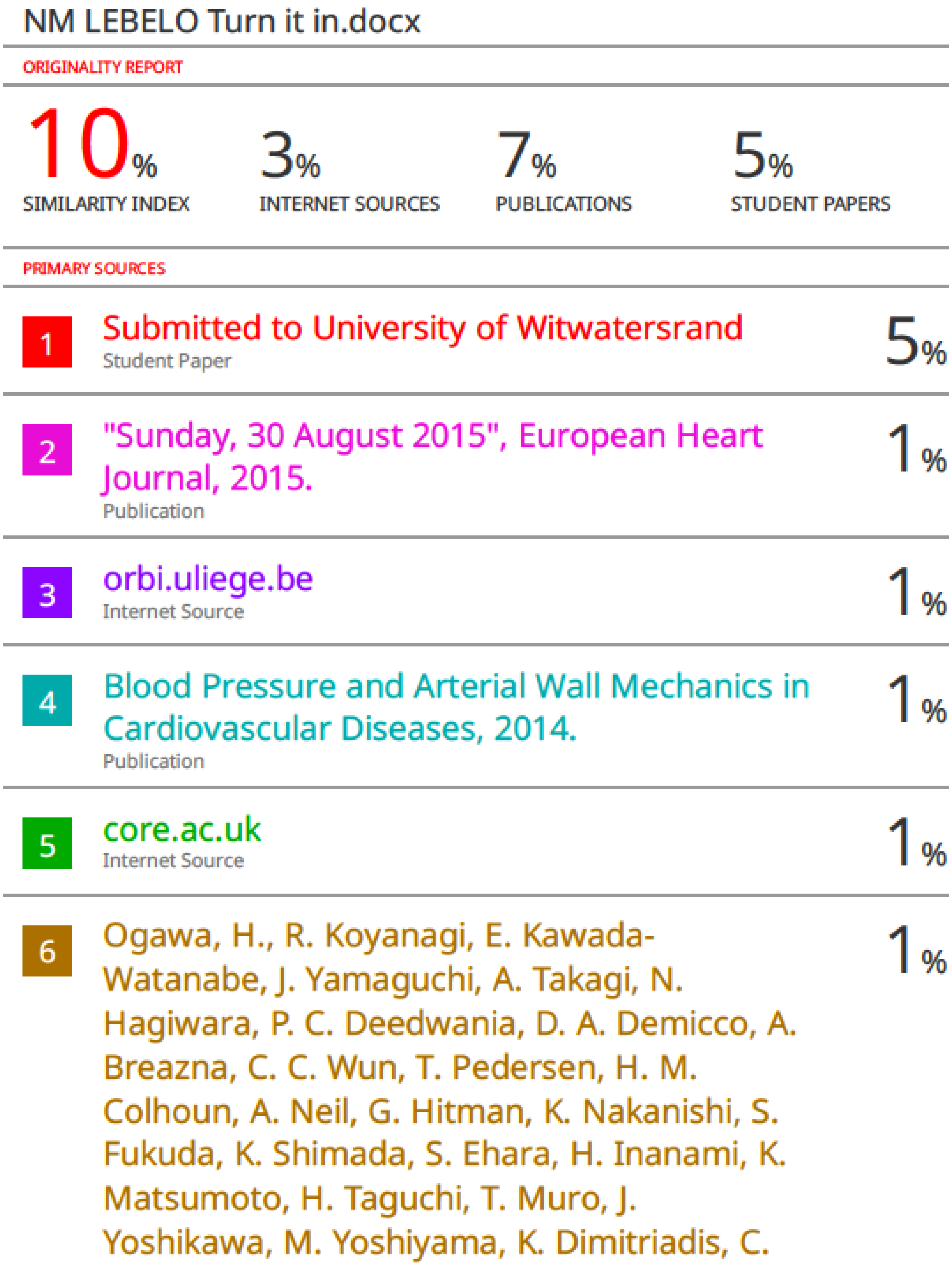
To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **2023/08/01** and therefore reports and re-certification will be due in the month of **2023/08/01** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator

Date

Appendix II: Turn-it-in Plagiarism Report



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Publication

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7 Paul K. Whelton, Robert M. Carey, Wilbert S. Aronow, Donald E. Casey et al. "2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines", Hypertension, 2018 — 1%

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