Comprehensive Assessment of Vascular Haemodynamics by Magnetic Resonance Imaging

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I, Michael Quail, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.
Acknowledgements

I would like to thank my principal supervisor Dr Vivek Muthurangu for his support and friendship during my research. Vivek is a superb scientist and this work would not be possible without him. I am grateful for all he has taught me.

My wife, Teresa, my children, my parents and family for their love and patience, thank you for supporting me in my endeavors. This work is dedicated to you.

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Finally I would like to thank the British Heart Foundation for funding my research, and all the patients who kindly volunteered to participate in this work.
Abstract

Haemodynamics is concerned with the physiological and mechanical factors that determine pressure and flow in the circulation. Currently no diagnostic modality in clinical practice provides simultaneous pressure and flow data, and therefore our analysis of fundamental haemodynamic problems is limited. Cardiac catheterisation with conventional technology can measure pressure as a function of time but can only provide estimates of mean flow. In contrast cardiac magnetic resonance imaging (CMR) can measure flow as a function of time, but cannot directly measure pressure. It is desirable that both pressure and flow signals be acquired and integrated using non-invasive techniques to measure fundamental haemodynamic components. In this thesis it is proposed to develop methods for comprehensive haemodynamic assessment using non-invasive CMR data.

The cross-sectional area of a vessel is related to its intra-luminal pressure. The first experiment of this thesis tested the hypothesis that central aortic systolic blood pressure (c-SBP) could be derived from the time-varying cross-sectional area of the ascending aorta, using models of the pressure area relationship. The method was validated using carotid tonometry as a surrogate of central aortic pressure in 20 volunteers.

The second experiment tested the hypothesis that the principle components of central haemodynamics: systemic vascular resistance, central compliance, characteristic impedance and wave reflections could be measured non-invasively. The study utilised the previously developed techniques in a study of 50 patients with repaired coarctation of the aorta and 25 healthy controls. Pressure, area and flow data were further integrated to assess wave reflections in the aorta using a technique called wave intensity analysis. Using these methods it was demonstrated that patients with repaired coarctation have elevated c-SBP despite similar peripheral SBP to controls. Furthermore patients have increased vascular stiffness and abnormal wave reflections. These parameters were found to be important determinants of elevated LV mass in this population, and were superior to conventional biomarkers such as coarctation index and peripheral-SBP.
The final experiment tested the hypothesis that wave reflections could be assessed in the pulmonary circulation. 20 patients with pulmonary hypertension and 10 controls were recruited. It was hypothesized that wave intensity analysis could detect differences in reflections in PH patients compared to healthy controls and could also differentiate certain PH subtypes. This experiment showed that the presence of a backwards compression wave, reflected from the lungs, identified patients with PH and its magnitude showed discriminatory capacity for the presence of proximal PA clot in patients with Chronic Thromboembolic Pulmonary Hypertension (CTEPH).
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<tr>
<td>2D</td>
<td>2-Dimensional</td>
</tr>
<tr>
<td>3D</td>
<td>3-Dimensional</td>
</tr>
<tr>
<td>A</td>
<td>Area</td>
</tr>
<tr>
<td>AT</td>
<td>Acceleration Time</td>
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<tr>
<td>AUC</td>
<td>Area Under the Curve</td>
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<tr>
<td>B</td>
<td>Bulk Modulus</td>
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<tr>
<td>BCW</td>
<td>Backwards Compression Wave</td>
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<tr>
<td>BEW</td>
<td>Backward Expansion Wave</td>
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<tr>
<td>BMI</td>
<td>Body Mass Index</td>
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<tr>
<td>BNP</td>
<td>Brain Natriuretic Peptide</td>
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<tr>
<td>BP</td>
<td>Blood Pressure</td>
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<tr>
<td>BSA</td>
<td>Body Surface Area</td>
</tr>
<tr>
<td>C</td>
<td>Compliance</td>
</tr>
<tr>
<td>c</td>
<td>wave speed (PWV)</td>
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<tr>
<td>c-SBP</td>
<td>Central Aortic Systolic Blood Pressure</td>
</tr>
<tr>
<td>CHD</td>
<td>Congenital Heart Disease</td>
</tr>
<tr>
<td>CMR</td>
<td>Cardiac Magnetic Resonance</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
</tr>
<tr>
<td>CTEPH</td>
<td>Chronic Thromboembolic Pulmonary Hypertension</td>
</tr>
<tr>
<td>D</td>
<td>Diameter</td>
</tr>
<tr>
<td>dA</td>
<td>Delta Area</td>
</tr>
<tr>
<td>DBP</td>
<td>Diastolic Blood Pressure</td>
</tr>
<tr>
<td>Delta P</td>
<td>Pressure Drop</td>
</tr>
<tr>
<td>dI</td>
<td>Net Wave Intensity</td>
</tr>
<tr>
<td>DICOM</td>
<td>Digital Imaging and Communications in Medicine (file format)</td>
</tr>
<tr>
<td>DPAP</td>
<td>Diastolic Pulmonary Artery Pressure</td>
</tr>
<tr>
<td>dQ</td>
<td>Delta Q</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
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</tr>
<tr>
<td>E</td>
<td>Young's Modulus</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiograph</td>
</tr>
<tr>
<td>EF</td>
<td>Ejection Fraction</td>
</tr>
<tr>
<td>EPI</td>
<td>Echo-Planar Imaging</td>
</tr>
<tr>
<td>EST</td>
<td>Estimated</td>
</tr>
<tr>
<td>exp</td>
<td>Exponential</td>
</tr>
<tr>
<td>FCW</td>
<td>Forward Compression Wave</td>
</tr>
<tr>
<td>FEW</td>
<td>Forwards Expansion Wave</td>
</tr>
<tr>
<td>FOV</td>
<td>Field of View</td>
</tr>
<tr>
<td>GRAPPA</td>
<td>Generalized autocalibrating partially parallel acquisition</td>
</tr>
<tr>
<td>HR</td>
<td>Heart Rate</td>
</tr>
<tr>
<td>IPAH</td>
<td>Idiopathic Pulmonary Hypertension</td>
</tr>
<tr>
<td>IQR</td>
<td>Interquartile Range</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
</tr>
<tr>
<td>l</td>
<td>Length</td>
</tr>
<tr>
<td>LV</td>
<td>Left Ventricle</td>
</tr>
<tr>
<td>LVH</td>
<td>Left Ventricular Hypertrophy</td>
</tr>
<tr>
<td>LVM</td>
<td>Left Ventricular Mass</td>
</tr>
<tr>
<td>MBP</td>
<td>Mean Blood Pressure</td>
</tr>
<tr>
<td>MPAP</td>
<td>Mean Pulmonary Artery Pressure</td>
</tr>
<tr>
<td>MR</td>
<td>Magnetic Resonance</td>
</tr>
<tr>
<td>P</td>
<td>Pressure</td>
</tr>
<tr>
<td>P&lt;sub&gt;dia&lt;/sub&gt;</td>
<td>Diastolic Pressure</td>
</tr>
<tr>
<td>P&lt;sub&gt;es&lt;/sub&gt;</td>
<td>End-Systolic Pressure</td>
</tr>
<tr>
<td>p-SBP</td>
<td>Peripheral (Brachial) Systolic Blood Pressure</td>
</tr>
<tr>
<td>PA</td>
<td>Pulmonary Artery</td>
</tr>
<tr>
<td>PAH</td>
<td>Pulmonary Arterial Hypertension</td>
</tr>
<tr>
<td>PAP</td>
<td>Pulmonary Artery Pressure</td>
</tr>
<tr>
<td>PCMR</td>
<td>Phase Contrast Magnetic Resonance</td>
</tr>
<tr>
<td>PCWP</td>
<td>Pulmonary Capillary Wedge Pressure</td>
</tr>
<tr>
<td>P&lt;sub&gt;d&lt;/sub&gt;</td>
<td>Diastolic Pressure</td>
</tr>
<tr>
<td>PH</td>
<td>Pulmonary Hypertension</td>
</tr>
</tbody>
</table>
$P_m$ Mean Pressure

$P_s$ Systolic Pressure

PVR Pulmonary Vascular Resistance

PWV pulse wave velocity

Q Flow

QA QA Method of PWV

R Resistance

$r$ radius

RAP Right atrial Pressure

RC Resistance*Compliance

ROC Receiver Operating Characteristics

ROI Region of Interest

RV Right Ventricle

RVEF Right Ventricle Ejection Fraction

SD Standard Deviation

SEM Standard Error of the Mean

SENSE Sensitivity encoding

SLE Systemic Lupus Erythematosus

SPAP Systolic Pulmonary Artery Pressure

SSFP Steady State Free Precession

t time

T Tesla

TE Echo Time

TPG Transpulmonary Gradient

TR Repetition time

UNFOLD UNaliasing by Fourier-encoding the Overlaps using the temporal Dimension

V Volume

$V_{enc}$ Velocity Encoding

VCG Vectorcardiography

W Frequency

WIA Wave Intensity Analysis
<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>x</td>
<td>Distance</td>
</tr>
<tr>
<td>Z_c</td>
<td>Characteristic Impedance</td>
</tr>
<tr>
<td>Z_i</td>
<td>Input Impedance</td>
</tr>
<tr>
<td>µ</td>
<td>Dynamic Viscosity</td>
</tr>
<tr>
<td>π</td>
<td>pi</td>
</tr>
<tr>
<td>ρ</td>
<td>Density</td>
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Chapter 1

1.1 Introduction

Haemodynamics is concerned with the physiological and mechanical factors that determine pressure and flow in the circulation. In clinical practice, however, periodic pressure and flow signals are not often assessed simultaneously and therefore a complete haemodynamic assessment is not usually obtained. The reasons for this are pragmatic: there is a growing emphasis on non-invasive assessment of haemodynamic problems using echocardiography and cardiac magnetic resonance (CMR). Unfortunately, although these modalities can accurately measure blood velocity or volume flow - they cannot directly measure pressure. Furthermore growing evidence for the diagnostic and prognostic capabilities of non-invasive imaging (without pressure data), has contributed to a wane in diagnostic cardiac catheterization for haemodynamic assessment. Consequently the availability of invasive pressure data for clinical and research purposes is much reduced.

If pressure and flow signals are not combined, fundamental properties of the cardiovascular system such as resistance, compliance and wave travel are left undetermined. Yet, it may be possible to derive estimates or surrogates of pressure from non-invasive CMR data using mathematical models of the cardiovascular system. The fundamental proposition of this thesis is that combining such models with directly measured CMR blood flow may overcome the shortcomings of examining pressure or flow in isolation, and allow for the development of novel biomarkers of vascular diseases.

In the first part of this thesis, relevant principles of cardiovascular haemodynamics and phase-contrast CMR imaging will be discussed. Chapter 2 will describe the use of CMR imaging to derive non-invasive central aortic pressure using models of the pressure-area relationship. The third component of the thesis will be the application of this methodology to assess the vascular physiology of repaired coarctation of the aorta. The final part will present the development of non-invasive wave intensity analysis in the pulmonary circulation – using vessel cross-sectional area as a
surrogate of pressure - and scrutinise the derived metrics as potential biomarkers for pulmonary hypertension.
1.2 Blood Flow

Descriptions of blood flow in arteries usually begin with discussion and analysis of steady flow of Newtonian fluids in straight, rigid tubes. Such models considerably simplify the reality of the cardiovascular system, but provide very useful models to understand haemodynamic phenomena.

1.2.1 Steady Flow

Poiseuille’s equation, which was formulated empirically in 1842 (published 1846) prior to its later analytical solution, describes the relationship between pressure drop (ΔP) and steady blood flow (Q) in a tube with circular cross section:

$$ Q = \frac{\pi r^4 (\Delta P)}{8 \mu l} $$  \hspace{1cm} \text{Equation 1-1}

Where \( r \) is the radius of the tube, \( l \) is the length and \( \mu \) is the dynamic viscosity of the liquid. Poiseuille’s equation demonstrates that resistance depends on the length and radius of the vessel and the viscosity of the blood. The 4th power relationship between radius and pressure drop means that resistance in the cardiovascular system is localized to the small muscular arterioles, whilst the capacitance vessels have intrinsically very low resistance.

However, Poiseuille flow occurs only under certain very restricted circumstances, the conditions of which will be described below.

1.2.1.1 Inlet Length and Developed Flow

Considering a tube with an inlet pressure \( P_1 \) and outlet pressure \( P_2 \): if the pressure drop across the length of the tube is examined at different regions, it is found that initially the pressure falls rapidly and non-linearly, but after a large distance from the inlet it decreases constantly as a function of distance, Figure 1-1. Within this inlet region, Poiseuille’s equation does not apply, as fluid is experiencing convective

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\(^{1}\) Newtonian fluids are homogenous liquids with constant viscosity at all rates of shear. Blood is non-Newtonian; a suspension of red blood cells in plasma. However in tubes, which have a large diameter compared to the cell size, it behaves as a Newtonian liquid.
acceleration – described as entrance effects. However, in the region distant from the inlet fluid exhibits a constant pressure drop with distance, and is called ‘developed’ flow. Indeed, Poiseuille recognised this in his original experimental work – although without precise conclusions – noting that with shorter tubes, his proportionality constant deviated from that obtained in longer tubes.

Figure 1-1 Variation in pressure drop across the length of a tube, with an initial rapid and non-linear pressure drop, followed by a constant linear pressure drop with increasing distance from the inlet. Figure adapted from.

1.2.1.2 Parabolic Velocity Profile

A property of developed flow is that it has a parabolic velocity profile, Figure 1-2. This occurs because of fluid viscosity: the particles of the fluid, flow in a series of laminae parallel to the sides of the tube with velocities dependent on radial position. Viscous forces retard the velocity of successive laminae; those adjacent to the wall have a velocity of zero - a property known as ‘no slip’ - whilst the maximum velocity occurs at the axis. The resultant velocity profile is axisymmetric and parabolic. At rates of flow higher than a critical value, laminar flow begins to deteriorate and become turbulent. Under such conditions Poiseuille’s equation no longer applies.
25

Figure 1-2 The parabolic velocity profile in steady laminar flow. The maximum velocity is at the axis, reducing progressively to zero as the wall is approached. The average velocity $\bar{V}$ is half the axial velocity $V_{axial}$. The flow is axisymmetric.

1.2.2 Resistance

Poiseuille’s equation can be re-arranged to a more general form, analogous to Ohm’s law for electricity: 

$$ R = \frac{\Delta P}{Q} $$  \hspace{1cm}  \text{Equation 1-2}

Where $R$ is resistance, $R = \frac{8\mu l}{\pi r^4}$

Using mean pressure drop and mean flow, $R$ can be calculated in the absence of actual geometric measurements. This simplification is clinically useful because it allows resistance to be estimated beyond its use in a single tube, and can be extrapolated to estimate the resistance of whole organs or indeed the entire systemic or pulmonary circulations. This makes it particularly useful for haemodynamic assessment in conditions such as pulmonary hypertension, where the chronic disease process induces changes in the pulmonary vasculature, one component of which is the reduction in the overall cross-sectional area of the pulmonary arterioles and therefore increasing vascular resistance.
Clinically pulmonary vascular resistance (PVR) is calculated by determining the mean pressure drop across the lungs; the inlet pressure is taken as the mean pulmonary artery pressure (PAP) and the outlet pressure is left atrial pressure (or pulmonary capillary wedge pressure, PCWP). Q is mean PA flow.

\[
PVR = \frac{\text{Mean PAP (mmHg)} - \text{PCWP (mmHg)}}{Q \text{ (L/min)}}
\]

Equation 1-3

Systemic vascular resistance (SVR) is calculated as the pressure drop across the systemic vasculature; the inlet pressure is mean aortic pressure (MAP) and the outlet pressure is right atrial pressure (which is often neglected for simplicity), and Q is mean aortic flow.

\[
SVR = \frac{\text{MAP (mmHg)} - \text{RAP (mmHg)}}{Q \text{ (L/min)}}
\]

Equation 1-4

1.2.3 Oscillatory Flow

The flow in the cardiovascular system is pulsatile, which introduces additional inertial forces through the acceleration and deceleration of blood; the assumptions of steady and developed flow for Poiseuille’s equation are therefore invalidated. The general equations describing the motion of fluids suitable for pulsatile flow are called the Navier-Stokes equations. Theses equations are non-linear partial differential equations, describing fluid motion in three spatial dimensions due to forces acting on the fluid (pressure, gravity) and include the effects of fluid viscosity and density. No general analytical solution is possible because of the non-linear components; therefore solutions for specific examples require numerical methods such as computational fluid dynamics.

An alternative approach is to use and accept simplifying assumptions: an important example of which is the work of Womersley in the 1950s who developed a linearized model of pulsatile blood flow; his model dropped non-linear terms of the Navier-Stokes equations after demonstrating that their contribution should be relatively small overall to the flow of blood in arteries. His analysis began with rigid tubes.
but later papers also described practical models of elastic \(^9\) and viscoelastic \(^{10}\) tubes including the effects of the reflection of pulse waves. \(^{11}\)

### 1.2.4 Compliance

An important consequence of oscillatory flow in the non-rigid arteries is the changing volume of the vessels due to changing pressure. The term that quantifies the relationship between pressure and volume is called compliance (or its inverse, elastance). Compliance, \(C\), is defined as the gradient of the tangent of the pressure-volume function at a given point, Figure 1-3.

\[
C = \frac{\Delta V}{\Delta P}
\]

Equation 1-5

![Figure 1-3 The Pressure-Volume relationship (blue). Compliance is given by the gradient of the tangent to the pressure-volume function at a given point. The green dashed line represents an altered pressure-volume relationship, representing a different location in the arterial tree, or alternatively changes associated with age or disease.](image)

The pressure-volume relationship is non-linear and it can be seen that the rate of change of volume, decreases with increasing pressure, this is because vessels become stiffer as they stretch. This is illustrated in Figure 1-3, which shows that compliance
changes according to the working point, and is reduced as we move to the right of the pressure-volume function. The pressure-volume relationship will be different at different points of the arterial tree, and in any given patient. Indeed, the pressure-volume relationship at any location also changes with age, and compliance decreases (vessels become stiffer) as we become older.

This definition allows for the assessment of the structural properties of the vessel in a given location or segment, and can also be described in terms of changing cross sectional area or diameter ($\Delta A$ or $\Delta D$). Compliance therefore depends on the size of the organ or vessel under examination and can be normalised with respect to the dimension used – for example $(\Delta V/V)/\Delta P$; this is referred to as distensibility.

Assessing the overall compliance of the systemic or pulmonary circulation could be achieved by adding the segmental compliances of every vessel in that circulation. This is clearly impractical and therefore, alternative models have been proposed. The simplest and crudest method to determine total arterial compliance, is the ratio of stroke volume to pulse pressure, and is referred to as capacitance. However, this approach assumes that if volume is added to the system, no volume is lost through the periphery; it therefore tends to overestimates true total arterial compliance.

A more satisfactory approach to determine total arterial compliance is to use the quantitative Windkessel models proposed by Frank in 1899. The two-element Windkessel is a so-called lumped parameter model of the circulation, describing the whole system as a combination of two parameters – compliance, $C$ and systemic (or pulmonary) vascular resistance, $R$. This model predicts that in diastole, when the aortic or pulmonary valve is closed, pressure decays exponentially with a decay time constant, $RC$, Figure 1-4.

\[
P_{\text{dia}}(t) = P_{\text{es}} e^{-t/RC}
\]

Where $P_{\text{dia}}$ is diastolic pressure, $P_{\text{es}}$ is end-systolic pressure, and $t$ is time.
Compliance based on the two-element Windkessel can be estimated using simultaneous flow (CMR) and pressure data by parameter optimization of the following equation:

\[ Q(t) = \frac{P(t)}{R} + C \frac{dP(t)}{dt} \]  

Equation 1-6

Where \( Q \) is volume flow, \( t \) is time, \( P \) is pressure, \( C \) is compliance, and \( R \) is resistance.\(^{14}\)

The 2-element Windkessel serves to illustrate the importance of both resistance and compliance to arterial load. Indeed for a given aortic flow, systolic and diastolic aortic pressures are almost completely determined by only 2 arterial parameters: peripheral resistance and total arterial compliance.\(^{15}\)

However, with the advent of analysis of pressure and flow signals in the frequency domain, important shortcomings of the 2-element Windkessel models become apparent, and are discussed in the next section.
1.2.5 Input Impedance

Impedance is the term used to represent opposition to oscillatory flow; and therefore contrasts distinctly to resistance, which represents opposition to non-oscillatory flow. In this section, we will restrict our discussion to input impedance which is defined as the ratio of pulsatile pressure and pulsatile flow at a particular site of the arterial system (considered the input to the distal vascular tree). Input impedance is a ratio of periodic pressure and flow signals expressed as Fourier series (Section 1.4.1 & Figure 1-8); impedance values are therefore complex numbers, expressed in terms of modulus (modulus of pressure divided by modulus of flow) and phase angle (delay between pressure and flow).

When reflected waves are present in a system, the observed pressure and flow waves are influenced by incident and reflected waves. Input impedance describes the system under these conditions.

Input impedance can be calculated experimentally by recording pulsatile pressure and flow simultaneously. The periodic signals are then subjected to frequency analysis, which represents the pressure and flow signals as a series of sinusoidal waveforms. The ratio of pressure and flow is then determined at each frequency, using the following approach.

In complex notation, the harmonic component of pressure, $P$ and flow, $Q$ respectively are given by $^{16}$:

$$P = |P|e^{i(\omega t - \phi)} \quad \text{Equation 1-7}$$

$$Q = |Q|e^{i(\omega t - \beta)} \quad \text{Equation 1-8}$$

The input impedance for a given harmonic term is:
\[
Z_i = \frac{|P| e^{i(\omega t - \phi)}}{|Q| e^{i(\omega t - \beta)}} = \frac{|P| e^{i(\beta - \phi)}}{|Q|} \quad \text{Equation 1-9}
\]

The real component of this equation is:

\[
Z_i = \frac{|P|}{|Q|} \cos (\beta - \phi) \quad \text{Equation 1-10}
\]

Where the modulus, \(|Z| = |P|/|Q|\) and the phase angle \(\theta = (\beta - \phi)\).

Expressing each complex harmonic term in modulus and phase form allows for input impedance to be plotted versus frequency, Figure 1-5.
Figure 1-5 Input impedance in the ascending aorta of a human (blue). *Ordinates*, impedance modulus, dyne sec/cm$^2$ (above); impedance phase, radians (below). Positive phase indicates that pressure leads flow. The dotted line is an example of the input impedance obtained using a 2-element Windkessel.

Figure 1-5 demonstrates the input impedance spectrum typical of a human aorta. It also shows the shortcomings of the 2-element Windkessel as a complete description of the systemic afterload, when considered in the frequency domain. For high frequencies the Windkessel modulus reduces to negligible values and its phase angle reaches -$90^\circ$, while the aortic input impedance derived in the humans shows an impedance modulus which decreases to a non-zero plateau value and a phase angle which remains close to zero at high frequencies. $^{17}$ Attempts to improve the performance of the 2-element Windkessel model have led to the creation of 3 and 4 element Windkessels, which include additional terms such as characteristic
The relatively constant level of impedance at higher frequencies in experimentally acquired data, Figure 1-5, is due to vascular characteristic impedance, which is analogous to input impedance in the absence of wave reflections, and physically has its origin in vessel stiffness – it therefore provides an evaluation of the transmission properties of a vessel. Characteristic impedance, $Z_c$, is related to the velocity of travelling waves, $c$ and blood density, $\rho$, by the water hammer formula, $dP/dU = c\rho = Z_c$. The 3-element improves its estimation of impedance at higher frequencies and also improves its reconstitution of pressure/flow waveforms.

Input impedance comprehensively describes the pulsatile pressure and flow relationship at its site of measurement, and so characterizes the properties of entire circulation distally. Furthermore, it also represents the hydraulic load presented by the circulation to the ventricles – it can therefore be considered the exemplar definition of afterload, because it is completely independent of cardiac properties.

### 1.3 Waves

A wave is a disturbance or vibration that transfers energy. Pressure and flow waves are generated in the cardiovascular system by periodic cardiac contraction. Waves travel at a velocity that is dependent on the physical properties of the medium – in the case of the cardiovascular system – the arterial wall and the blood. Waves transfer energy: mediating exchanges between kinetic and potential energy, which necessarily results in simultaneous changes in pressure and blood flow.

In this study we are primarily concerned with longitudinal waves that are parallel to the direction of wave travel, although other waves, including transverse and torsional waves are also present.

### 1.3.1 Wave Reflections

Milnor reflected that the existence of wave reflection is demonstrated by two phenomena which, ‘can scarcely be explained in any other way: (1) the amplification of pressure waves in some large arteries, notably the aorta; and (2) the radically different shapes of the flow and pressure pulses in the ascending aorta.’
Reflections arise in the cardiovascular system wherever there are discontinuities in the properties of the artery, termed impedance mismatches. Such areas of impedance mismatch cause the propagated wavefronts to produce reflected and transmitted waves according to the type of discontinuity. Alterations in vessel properties that induce reflections include; changes in cross-sectional area (stenoses or dilatations), bifurcations or local changes in the elastic properties of the arterial wall. The amount of reflection or transmission of waves at a site of impedance mismatch is given by the reflection co-efficient, R.

In a tube that narrows, R is positive, so that the leading forward compression wavefront reflects as a backward compression wave and the trailing expansion wave reflects as an expansion wave. Conversely in a tube that widens, R is negative so that the leading forward compression wavefront reflects as a backward expansion wave and the trailing expansion wave reflects as a compression wave.\(^\text{19}\)

Impedances are well matched at bifurcations, when R=0, and this occurs if the stiffness or cross-sectional areas of daughter and parent vessels are equal; analysis indicates that an ideal bifurcation parent daughter ratio, \(\alpha =1.15\). If \(\alpha\) is less than this, R is positive and the bifurcation acts as a partially closed tube. For \(\alpha\) greater than this value the bifurcation acts more like an open tube and R is negative. Parker\(^\text{19}\), notes that:

Interestingly, extensive measurements of area ratios of human arterial bifurcations found a mean value \(\alpha = 1.14 \pm 0.03\ldots\) The correspondence between the measured area ratios of arterial bifurcations and the well-matched condition \([1.15]\) could be a coincidence, but it could also be taken as evidence that the arteries are designed to be well-matched for waves generated by the heart.

Assessment of wave reflections is important in haemodynamics because they may contribute significantly to cardiac load by contributing to ventricular wall tension during cardiac ejection. Furthermore distinct patterns of reflection may occur in vascular pathologies such as coarctation of the aorta or thrombo-embolic pulmonary hypertension.\(^\text{20,21}\)
There are several methods that can be used to quantify wave reflections; two common methods are impedance analysis (frequency domain) and wave intensity analysis (time domain). In this thesis, wave intensity analysis will be the method utilised, because its time domain analysis makes interpretation more easily understood by clinicians. It is described in detail in chapter 3. Both techniques are compatible and produce similar results, as they are both 1-dimensional approximations, and are both dependent on the determination of wave speed, \(c\).

1.3.2 Wave Speed

The material properties of the arterial wall can be described in terms of its deformation to external forces. The force per unit area that produces such a deformation is called ‘stress’, whilst the deformation itself, called ‘strain’ can be defined as a ratio of the deformation to its original form (which is dimensionless).

The relationship between these two parameters can be expressed as a ratio called an elastic modulus – thereby allowing material properties to be quantified. In the cardiovascular system, tension or stress in the artery is related to arterial pressure \(P\), which exerts force in all directions.

The volumetric strain of the artery is defined as its change its volume \((\Delta V)\) from its original volume \((V_0)\), \(\Delta V/ V_0\). Therefore the ratio of stress \((P)\) to volumetric strain (or Bulk Modulus, \(B\)) can be given as

\[
B = -\frac{P_{V_0}}{\Delta V}
\]

Equation 1-11

The relationship between bulk modulus generally and wave speed can be examined by considering the velocity of a sound wave travelling in air, which was defined by Newton as

\[
c = \sqrt{B/\rho}
\]

Equation 1-12

where \(B\) is the bulk modulus and \(\rho\) is density. The speed of a sound wave is found to increase as the stiffness or bulk modulus increases, and decreases with density.
Substituting equation 1-11 for bulk modulus into equation 1-12 yields

\[ c = \sqrt{V \Delta P / \rho \Delta V} \]  
Equation 1-13

This derivation was first articulated by Thomas Young for the Croonian lecture in 1809. However, it is more often attributed to Frank and Bramwell and Hill, who derived it over a century later from the Moens-Korteweg equation

\[ c = \sqrt{Eh/2r \rho} \]  
Equation 1-14

where E is the Young’s modulus (ratio of stress/strain in the longitudinal direction), h is wall thickness and r is radius. The assumptions of the Moens-Korteweg equation are that the tube is thin walled, and contains an incompressible inviscid liquid. Equation 1-3 will be referred to as the Bramwell-Hill equation in this manuscript whilst acknowledging its earlier derivation by Young.

1.3.2.1 Measurement of Wave Velocity in Arteries

The time, \( t \) taken for a wave to travel between two points separated by a known distance, \( x \) can be used to measure wave speed, or pulse wave velocity, c:

\[ c = \frac{\Delta x}{\Delta t} \]  
Equation 1-15

‘Time-delay’ methods, using the carotid and femoral arteries as the sites of measurement, have been used extensively in hypertension research, Figure 1-6A. The mechanical properties of the aorta differ in different locations and therefore such methods provide an average ‘regional’ wave speed between points. Carotid-femoral PWV is considered the gold standard method to assess PWV, and has been shown to be predictive of cardiovascular events in epidemiological studies. The onset of the pulse-wave signal for this method is usually the ‘foot’ of the pressure wave measured transcutaneously with a tonometer. However, alternative waveforms, such

\[ \text{‡} \]  

\[ \text{The ‘foot’ is defined as the point at end of diastole, when the steep rise of the wavefront begins. This early point of the wave is assumed to be less affected by reflections, which render other features of the wave unreliable.} \]
as distension (diameter or area waves) or velocity waveforms using Doppler or MRI could also be used. The distance between the two sites is usually assumed to be the surface distance between the two sites, however the shape and curvature of the aorta can introduce error with this assumption. An alternative to transcutaneous methods is to measure the waveform using CMR, utilizing distension or flow waveforms measured simultaneously in the ascending and descending aorta, Figure 1-6B. This method differs by excluding the abdominal and iliac pathway from the assessment, and therefore may not be directly comparable to carotid-femoral methods.

An alternative to ‘regional’ estimation is to measure wave speed locally at a single location of the arterial tree. This could be performed using the Bramwell-Hill equation 1-3, substituting area for volume, and using the pulse pressure at that area:

\[ c = \sqrt{A \Delta P/\Delta A} \]

Equation 1-16
Figure 1.6 Pulse wave velocity (PWV) measured using the carotid femoral approach (above). PWV measured by MRI transit time method, utilizing flow or area waves travel between points A and B (below).
The advantage of this method is that arterial wave speed is determined directly from the change in pressure driving the change in area/volume. However, for the ascending aorta, pulse pressure would usually need to be obtained by cardiac catheterization, as brachial pulse pressure differs significantly from central pulse pressure, and would result in significant error.\textsuperscript{27}

An alternative method for calculating PWV in a single slice, without using pulse pressure was described by Vulliemoz \textit{et al.}\textsuperscript{28} using MRI and Rabban \textit{et al.}\textsuperscript{29} with ultrasound. It is predicated upon the following assumption: that during early systole, the aortic pressure and flow waves do not contain reflections. This assumption is reasonable, as reflected waves take a finite time to reach the aorta from the periphery. Early systole can therefore be assumed to be unidirectional and reflectionless. For unidirectional waves, the ratio between pressure variation ($\Delta P$) and flow variation ($\Delta Q$) is then equal to the characteristic impedance $Z_c$:

$$Z_c = \frac{\Delta P}{\Delta Q}$$

Equation 1-17

Local area compliance is given by:

$$C_A = \frac{\Delta A}{\Delta P}$$

Equation 1-18

where $\Delta A$ stands for the variation of cross-sectional area. $C_A$ is related to $Z_c$ through the following formula:

$$Z_c = \sqrt{\frac{\rho}{A C_A}}$$

Equation 1-19

where $\rho$ stands for the blood density and $A$ for the cross-sectional area at the end diastole. Eliminating $\Delta P$ from the above expression yields the following expression for $C_A$:

$$C_A = \left(\frac{\Delta A}{\Delta Q}\right)^2 \frac{A}{\rho}$$

Equation 1-20

$C_A$ is directly related to PWV (PWV$_{QA}$) by:
Therefore substituting the equation for \( C_A \) we obtain:

\[
PWV_{QA} = \frac{\Delta \frac{1}{\rho}}{\sqrt{\rho C_A}} \quad \text{Equation 1-21}
\]

\[
PWV_{QA} = \frac{\Delta Q}{\Delta A} \quad \text{Equation 1-22}
\]

This derivation leads to a simple and readily usable method to measure wavespeed non-invasively using CMR.
1.4 Cardiac Phase Contrast Imaging

CMR is the gold standard for the quantification of pulsatile blood flow in the cardiovascular system based on its intrinsic sensitivity toward motion.

Phase contrast MR (PCMR) is the most commonly used technique and is founded on the underlying observation that variation of MR signal along a magnetic field gradient is directly related to the blood flow velocity - as blood moves along the axis of an applied gradient, the spins in the blood, accumulate phase which is linearly proportional to its velocity.\(^{30}\)

Using bipolar velocity encoding gradients, flow-dependent phase changes can be detected by reading out two otherwise identical acquisitions except for different velocity-dependent signal phase. The phases of the two resulting images are subtracted on a pixel-by-pixel basis, which allows for the removal of the unknown background phase and calculation of velocity images\(^ {31}\), Figure 1-7.

Several important technical aspects need to be considered about the formation of the flow images. Standard CMR acquisitions are slow, and are not able to capture the dynamics of blood flow and vessel movements in real-time with sufficient resolution. This is because each line of k-space must be acquired twice in order to perform the background phase subtraction described above. Instead, time resolved images are produced (representing flow over the cardiac cycle) by acquiring data over multiple heartbeats using cardiac gating, triggered by the electrical activity of the heart, Figure 1-7.\(^ {32}\)

\(^{1}\) The vectorcardiogram (VCG) rather than electrocardiogram (ECG) is used for triggering, due to the ECGs susceptibility to radiofrequency and magnetic field artefacts. The VCG differs from the ECG in representing electrical activity in vector rather than scalar format. As the electrical axis of the heart and MR blood-flow artefacts have different orientations, using both time and space domain information inherent in VCG improves cardiac triggering in the MR environment.
Figure 1-7 Standard 2D PCMR with one-direction through-plane velocity encoding in the ascending aorta. Reference and velocity sensitive scan (added bipolar encoding gradient) are acquired in direct succession. The subtraction of both datasets provides phase difference images that contain quantitative blood flow velocities as shown in a 2D slice normal to the ascending (Ao) aorta. Due to time constraints, the MR data cannot be acquired during a single heartbeat and PC data are collected over several cardiac cycles. The measurement is synchronized with the cardiac cycle using a VCG-gated k-space segmented data acquisition. For each heartbeat and time frame only a subset (NSeg) of all required (Ny) phase-encoding steps are measured (k-space segmentation). The procedure is repeated until the full raw dataset is acquired and time-resolved (CINE) images can be derived depicting the dynamics of pulsatile through plane flow. The selection of the number of phase-encoding lines NSeg determines the temporal resolution (time to collect data for a single time frame $\Delta t = 2 TR NSeg$) and a total scan time $T_{acq} = Ny/NSeg TCC$ of the phase contrast CINE acquisition (TCC = duration of one cardiac cycle). For a typical TR on the order of 5–10 msec and NSeg = 3–4, measurements can be performed during breath-holding and with temporal resolutions of 30–80 msec. Typical velocity sensitivities are $V_{enc} = 150$ cm/s for aortic. Figure and Legend adapted from Markl et al. 2012.
PCMR requires the operator to prescribe a parameter called the aliasing velocity \(- V_{\text{enc}}\). \(V_{\text{enc}}\) is the maximum velocity which if exceeded results velocity aliasing. 31 Changing the \(V_{\text{enc}}\) changes the strength and duration of the bipolar gradients that encode velocity. The magnitude of the prescribed \(V_{\text{enc}}\) can influence the quality of the images because \(V_{\text{enc}}\) is directly proportional to velocity noise and inversely proportional to the signal-to-noise ratio (in associated magnitude images). A high \(V_{\text{enc}}\) increases noise, but an inadequate \(V_{\text{enc}}\) may induce aliasing. 33

### 1.4.1 PCMR for physiological assessment

For physiological assessment the acquisition of each time frame needs to be short relative to that of the object motion in order to obtain sufficient resolution. The acquisition time of conventional PCMR acquired using the standard Cartesian schema described above (Figure 1-7) depends on the number of phase-encoding steps and the heart rate; a 30-40 frame aortic flow acquisition might be in the region of 3-5 minutes for adults. Unfortunately, whilst such data may have adequate spatio-temporal resolution to resolve mass flow, it is inadequate for other dynamic information such as bulk vessel and wall motion resulting in blurring/smearing of the vessel wall. Shortening the length of acquisition to occur during a single breath hold is technically feasible and has the advantage of removing respiratory motion from the plane of interest.

The second important consideration is the temporal resolution of the data. Flow, pressure and area changes in a vessel are continuous functions, however, due to obvious technical limitations it is only possible to sample the functions at discrete intervals of time. If a continuous function is reduced to discrete samples and interpolated back to a continuous function, the fidelity of the result depends on the sample rate of the original sample. This is intuitive, but is formally expressed in the Nyquist-Shannon sampling theorem, as stated by Shannon 34:

If a function \(f(t)\) contains no frequencies higher than \(W\) (hertz), it is completely determined by giving its ordinates at a series of points spaced \(\frac{1}{2} W\) seconds apart.
A sufficient sampling frequency is therefore at least $2W$ samples per second, where $W$ is the highest frequency. The Nyquist-Shannon theorem indicates that a simple sine wave requires at least 2 points to be defined to reconstitute the function.

What sampling frequency is required for complex cardiovascular functions such as pressure and flow? This important question can be approached by considering the periodic cardiovascular function as a Fourier series – which is a way to represent any wave-like function as the sum of a (possibly infinite) set of simple oscillating functions: sines or cosines, called harmonics. Harmonics are multiples of a signals’ fundamental frequency, which in the case of pressure and flow waves is heart rate. At a heart rate of 75bpm or 1.25 Hz, the frequencies of the harmonics are 2.5 Hz, 3.75Hz, 5Hz etc.

The number of harmonics that need to be considered to define a given cardiovascular periodic function can be illustrated by using Fourier series to decompose an example signal – such as a vessel cross-sectional area–time function, Figure 1-8. Fourier analysis demonstrates that the amplitude of harmonics decrease with increasing frequency, and that at a certain point, no practical information is added to the signal by considering higher harmonics. It is typically suggested that the aortic pressure and flow curves can be almost completely reconstructed with 15-20 harmonics. With a heart rate of 60bpm, this equates to a minimum sampling frequency of 30-40Hz; which must be increased when sampling higher heart rates. However, certain very high frequency information such as the foot of the systolic upstroke (Figure 1-8), or the dicrotic/anacrotic notches may require consideration of higher harmonics and therefore need a higher sampling frequency. Unfortunately higher harmonics are also subject to more noise, and therefore the inclusion of higher harmonic information should be carefully considered.

Practically, a sampling frequency of 2-3 times the minimum sampling frequency should be used to ensure a sufficient safety net for heart rate variation and high
frequency information. For typical heart rates this equates to approximately 100Hz, or a temporal resolution of approximately 10ms per data point.
Fourier analysis allows representation of haemodynamic functions as their mean value and a series of harmonics (sine waves which are multiples of the fundamental frequency - heart rate). In the above example, area data was sampled at a rate of approximately 100 samples/second, in a patient with a heart rate of 50 bpm (0.83 Hz). It can be seen that as harmonics are progressively added, the original area curve is almost completely reconstructed with 20 harmonics (16 Hz). However even with 20 harmonics, very high frequency information, such as the foot of the systolic upstroke (zoom box), may not be completely reconstructed.
In conventional PCMR, the typical temporal resolution is 30-40ms or 25-33Hz. This is certainly adequate for the assessment of mass flow at normal heart rates, but may become increasingly inadequate for examining higher frequency data in waveform morphology – such as characteristic impedance or the systolic upstroke.

1.4.2 Accelerated PCMR

In the previous section, the need for shorter data acquisitions with sufficient sampling frequency (high temporal resolution) to measure dynamic features relevant to physiological assessment was described. Achieving high-spatiotemporal resolution phase-contrast MR imaging in a short breath hold requires innovative approaches to data acquisition. One particular solution is to use accelerated techniques, which attempt to increase the speed of data acquisition by reducing the amount of data acquired.

In MRI, image data is not acquired directly; rather spatial frequency information is collected in a domain called k-space, which is related to the actual image information through a mathematical operation called the Fourier transform. In a simple spin-echo pulse sequence, one line of imaging data (one line in k-space or one phase-encoding step) is collected within each repetition time (TR) period. The pulse sequence is then repeated until all phase-encoding steps are collected and k-space is filled. Reducing the amount of data acquired is only feasible if the acquisition of less data does not compromise image quality significantly. This is only possible because typical image data contains significant spatiotemporal correlations (redundancy); these can be exploited to reduce the amount of data collected.\(^{35}\)

Each point in k-space contains information about other points in k-space. If only a proportion of k-space is acquired, the missing information may be recoverable by utilizing the data contained in the other time frames. An example of this technique is parallel imaging; the two most commonly used methods are SENSE (sensitivity encoding) and GRAPPA (generalized autocalibrating partially parallel acquisition). In parallel imaging the acquisition time can be shortened by under-sampling k-space in the phase-encoding direction, however this leads to spatial aliasing in the image domain.\(^{36}\) Using an array of receiver coils to collect under-sampled k-space data
(thus producing an aliased image), SENSE uses knowledge of the coil sensitivities to unfold (unalias) and reconstruct the data in the image domain. GRAPPA differs from SENSE in that it seeks to regenerate the missing phase-encoding lines prior to the Fourier transformation. In GRAPPA, in addition to the under-sampled data, an additional region of sampled $k$-space called the autocalibration signal (ACS) is acquired. A convolution kernel is used to determine mathematical relationship between the ACS and missing data, which can be used to reconstruct the missing lines of $k$-space.  

A second potential area of data correlation is the time domain. Images in CMR are frequently comprised of a time series of cine images rather than single shots. It is therefore possible to use dynamic information contained within the data to exploit temporal correlations: an example of which is UNFOLD (UNaliasing by Fourier-encoding the Overlaps using the temporal Dimension). As with parallel imaging, an under-sampled $k$-space causes aliasing, therefore spatially distinct points within the object are overlapped at the same spatial position in the images. UNFOLD uses time to label the overlapped components, such that a Fourier transform through time can resolve them.

In addition to collecting an under-sampled dataset, the data itself can be acquired in a more efficient way. $k$-Space is typically filled line by line in a rectilinear fashion as described above for a simple spin-echo sequence – this is known as Cartesian $k$-space filling, Figure 1-9A. This technique is slow as each excitation fills only a portion of $k$-space, and the image therefore requires multiple excitations; the exact imaging time is equal to the product of the TR and the number of phase-encoding steps. Alternative trajectories attempt to fill $k$-space more efficiently, and may be able to fill a large proportion of $k$-space with a single excitation. Examples include echo-planar imaging (EPI) Figure 1-9B, and non-Cartesian radial and spiral trajectories Figure 1-9C & D.
Non-Cartesian spiral trajectories are particularly useful in dynamic and flow imaging because they relatively oversample the centre of k-space, which renders them less susceptible to flow and motion associated phase errors. However, the associated speed increases over Cartesian techniques provides their major advantage.

Steeden *et al.* combined both efficient k-space filling with spiral trajectories and acceleration with sensitivity encoding (SENSE) to reduce the acquisition time of flow imaging in a population of children and adults with congenital heart disease. Importantly this study demonstrated the utility and feasibility of integrating accelerated MR techniques such as parallel imaging with efficient k-space filling. Furthermore, the versatility in this scheme allows for data acquisition with sufficiently high spatiotemporal resolution to resolve bulk vessel motion, blood flow and arterial wall dynamics.
1.5 Aims

Using highly accelerated phase-contrast CMR flow imaging, measuring cardiovascular periodic signals with sufficient sampling rates becomes achievable. Flow and cross-sectional area data obtained using novel imaging sequences will form the basis of the work presented in this thesis.

In chapter 2, pressure-area relationship models will be used to derive pressure in the ascending aorta non-invasively from measured vessel areas and validated using carotid artery tonometry.

In chapter 3, the methodology developed in chapter 2 will be applied to patients with repaired coarctation of the aorta. An investigation of wave intensity analysis formulated for use with non-invasive imaging data will be incorporated to develop a comprehensive assessment of vascular function in this patient cohort.

Chapter 4 will conclude the experimental work with the development of novel haemodynamic pulmonary biomarkers, based upon non-invasive assessment of pathological wave reflections in pulmonary hypertension.
Chapter 2  Development and validation of a novel method to derive central aortic systolic pressure from the magnetic resonance aortic distension curve

2.1 Abstract

MR is used to assess cardiac sequelae of systemic arterial hypertension, but this data is limited without an accurate measure of cardiac load: central aortic systolic blood pressure (c-SBP). Unfortunately, c-SBP is difficult to measure using current methods during MR. In this study we report 3 methods of determining c-SBP by combining CMR-derived aortic area curves with different models of the pressure-area relationship.

c-SBP was derived by calibrating aortic area curves to the brachial mean and diastolic pressure, using: linear, exponential and arctangent models in 20 volunteers using a high temporal resolution spiral PCMR flow sequence. The arctangent model also required calibration with PWV. Carotid tonometry c-SBP was used as the standard comparator.

Brachial systolic pressure correlated only moderately with carotid c-SBP \( r^2=0.46 \) (p=0.01). However, arctangent, exponential and linear c-SBP correlated strongly with carotid c-SBP, \( r^2=0.90, r^2=0.86, r^2=0.85 \) respectively (p<0.0001). There was excellent agreement between carotid c-SBP and both arctangent (bias 1.5, SD 3.3) and exponential c-SBP (bias 0.6, SD 3.6). There was a slight underestimation using the linear model (bias -2.3, SD 3.8) and poor agreement and overestimation using brachial systolic pressure (bias 12.9, SD 8.0). We have shown that c-SBP can be derived from MR data: arctangent and exponential methods being superior to the linear method. The superior correlation of MR derived c-SBP over brachial systolic BP suggests these measures are useful in accurately defining cardiac load and will allow more comprehensive assessment of systemic arterial hypertension.
2.2 Background

The artery is a viscoelastic cylindrical structure that comprises three layers: intima, media and adventitia. The mechanically relevant constituents of these tissues are elastin, collagen and smooth muscle cells, the relative proportions of which determine the mechanical and physiological characteristics of the artery. The elastic modulus of collagen ($1300 \times 10^6$ dyne/cm$^2$) is considerably higher than that of elastin ($5 \times 10^6$ dyne/cm$^2$), so that arteries with lower elastin are stiffer. The elastin content decreases and collagen content increases with distance from the heart, therefore more peripheral arteries are less compliant; this transition occurs in the distal abdominal aorta in humans. Increasing stiffness of the central elastic arteries, due to fracture of elastin and transfer of stress to collagen combined with arterial wall hyperplasia, has emerged as the primary cause of increased systolic and pulse pressure with age and in patients with hypertension. Indeed, by middle age, the stiffness of the central elastic arteries may equal or exceed peripheral muscular arteries.

2.2.1 Arterial Distension

The cross-sectional area of an artery varies in time with pulsating pressure, which is generated by the periodic flow of blood ejected from the heart. Arterial walls are anisotropic and heterogeneous, having properties whose stress–strain relationships are nonlinear and frequency dependent, and exhibit creep (continuous extension at constant load), stress relaxation (tension decay at constant length), and hysteresis (different stress–strain relationship for loading and unloading). Nonlinearities are a function of the differential loading of elastin and collagen at different levels of pressure. Low levels of pressure result in a relatively linear level of resistance to stretch due to elastin alone; however, at higher levels of pressure a curvilinear pressure-diameter relationship results due to increasing participation of the stiffer collagen. Elastin therefore gives rise to elastic and viscoelastic deformation, while collagen contributes to the non-linear stiffening with increased pressure. In peripheral muscular arteries, smooth muscle cells contribute significantly to viscoelastic effects.
2.2.2 Pressure-Area Models

Determining the relationship between cross-sectional area (or diameter) of arteries and arterial pressure has interested physiologists and clinicians for decades. Understanding this relationship provides insight into the mechanical properties of the arterial wall, and also raises the possibility of deriving pressure non-invasively, using imaging techniques to measure arterial cross-section during pulsation (e.g. echo or MRI) in sites inaccessible other than by intravascular catheter, such as the ascending aorta.

In the literature, proposed models of the pressure-area or pressure-diameter relationships of arteries are wide-ranging. Models of increasing complexity have been developed to incorporate nonlinearities accounting for convective acceleration and the non-linear pressure-compliance relationship, whilst others have incorporated visco-elasticity and frequency-dependent effects. Comprehensive models of aortic pressure-area dynamics now exist which closely approximate in vivo conditions.

Early experimental animal data suggested that the relationship between pressure and diameter was linear in dogs. However, human phenomenological models based on empirical data have described the nonlinear elastic properties of the artery, whilst neglecting viscoelastic components. The pressure and area (diameter) relationship in models proposed by Hayashi et al. and Powalowski and Peńko utilised a two parameter exponential function. A more complex model by Langewouters et al. described the relationship with a three parameter arctangent function. Both models have been shown to fit clinical imaging data using least squares minimisation; however, the Langewouters model is superior.

2.2.3 Central Aortic Pressure

Hypertension is quantitatively the most important risk factor for premature cardiovascular disease, accounting for 54 percent of all strokes and 47 percent of all ischemic heart disease events globally. However, peripherally measured blood
pressure (p-SBP) does not directly reflect the pressure in the coronary and cerebrovascular beds and growing evidence suggests that central aortic pressure more accurately defines cardiovascular risk, and reflects cardiac load.

In patients with systemic hypertension, cardiovascular magnetic resonance (MR) is routinely used to assess cardiovascular sequelae (i.e. LV hypertrophy or ventricular dysfunction). However, this assessment is limited to secondary effects of hypertension, and currently does not provide more accurate estimates of cardiovascular risk and cardiac load, such as c-SBP.

The conventional method of assessing BP in the MR environment is oscillometric measurement of brachial artery pressure. However, due to the presence of arterial wave reflections, peripheral systolic BP (p-SBP) is often significantly higher than c-SBP, due to systolic pressure amplification. This phenomenon arises principally because of an increase in arterial stiffness moving away from the heart. As the pressure wave travels from the more elastic central arteries to the stiffer brachial artery, the upper portion of the wave becomes narrower, the systolic peak becomes more prominent, and systolic pressure increases, Figure 2-1. Furthermore, the person specific nature of pressure amplification results in only moderate correlation between measures.

Several non-invasive methods have been developed to assess c-SBP and have been shown to better predict cardiovascular events than p-SBP. Most rely on
applanation tonometry of the radial or carotid artery combined with calibration to the mean and diastolic brachial BP (the difference between diastolic and mean blood pressure is conserved throughout the vasculature). Unfortunately, these techniques are difficult to perform in the MR environment and an alternative approach is required.

One possibility is to use imaging-based methods, which rely on the fact that the arterial pressure-area relationship can be modelled by simple functions (i.e. linear or exponential). The fact that these functions can be optimized through calibration with mean and diastolic brachial BP, allows c-SBP to be estimated from area measurements anywhere in the vasculature. This approach has already been validated using ultrasound measures of the carotid artery and could easily be adapted to use MR measures of the aorta.

However, linear and possibly exponential models may inadequately describe the pressure-area relationship, leading to errors in c-SBP estimation and a more complex model may be desirable. For instance, the Langewouters arctangent model could be used, as it better describes the pressure-area relationship across a wider range of pressures. Unfortunately, this model requires 3 points for calibration, unlike the linear and exponential models that only require 2 points (typically mean and diastolic brachial BP). Nevertheless, several types of physiological information could be used as a third calibration point for the arctangent model, one of which is pulse wave velocity (PWV).

PWV can be assessed at a single position in the aorta, providing that flow and area measurements are made during the reflection free part of early systole (~30 ms). In MR, one way this can be accomplished is by using high temporal resolution spiral phase contrast MR, combined with sensitivity encoding (SENSE). As this sequence also provides area measurements throughout the cardiac cycle, it can be used to estimate c-SBP using all 3 of the described models. In this study, c-SBP (estimated using arctangent, exponential and linear models) was compared with the non-invasive reference standard carotid tonometry.
2.2.4 Hypotheses

1. c-SBP can be accurately estimated using MR derived area curves combined with pressure-area models.

2. Non-linear (arctangent and exponential) pressure-area models are superior to linear.
2.3 Methods

2.3.1 Study Population

20 healthy volunteers were recruited and imaged with local research ethics committee approval, and written informed consent was obtained from all participants.

2.3.2 MR Protocol

All imaging was performed on a 1.5T MR scanner (Avanto, Siemens Medical Solutions, Erlangen, Germany) using two spine coils and one body-matrix coil. Vectorcardiography was used for gating. The flow-imaging plane was planned using orthogonal long axis cine images of the ascending aorta and was placed just above the sinotubular junction. The sequence was a prospectively triggered, spiral, velocity encoded spoiled gradient echo acquisition accelerated with SENSE (TE/TR: 1.9/4.8 ms, FOV: 400×400×6 mm, matrix: 192×192, no. interleaves: 60, SENSE factor: 4, VENC: 180 cm/s). The temporal resolution was 9.6msec, the spatial resolution was 2.1×2.1 mm and the breath-hold was approximately 11s (16 R-R intervals).

2.3.3 Blood Pressure Measurement

Brachial systolic, mean and diastolic blood pressures were measured by automated oscillometric sphygmomanometry during flow imaging (Datex Ohmeda). Small-adult, adult and large-adult cuff sizes were chosen according to subject arm circumference. Volunteers lay supine in the scanner with arm at the level of the heart and there was a period of acclimatization (at least 10minutes) before measurements were taken.

2.3.4 Image Processing

All images were processed using an in-house plug-in for the open source DICOM software OsiriX (OsiriX Foundation, Geneva, Switzerland). Segmentation of the ascending aorta was performed on the modulus image using a previously validated semi-automatic registration-based algorithm. The aortic region of interest (ROI) could also be manually altered if necessary to ensure optimal vessel wall delineation.
The final ROI was used to both calculate the aortic cross-sectional area (A) and prescribe the region in the phase image from which mean velocity (V) and flow (Q) were calculated. For PWV analysis, Q and A curves were left uninterpolated and unfiltered. However, pressure wave synthesis requires curves that span the whole RR interval and the use of prospective gating resulted in missing data in the last 80-100ms of diastole. This missing data were recovered using linear interpolation between the last point and the first point. The curves were then linearly interpolated to 1ms temporal resolution and filtered using a zero-phase, low-pass, 2\textsuperscript{nd} order Butterworth filter with normalized cut-off frequency of 0.04 (Matlab 2012a, Mathworks).

2.3.5 Pulse Wave Velocity and Characteristic Impedance Measurement

Pulse wave velocity was calculated using the QA method. This method relies on the fact that:

\[ PWV = \frac{dQ}{dA} \]  \hspace{1cm} \text{Equation 2-1}

in the presumably reflection free part of early systole (with \( c \) in m/s, \( dQ \) in m\(^3\)/s and \( dA \) in m\(^2\)). In our implementation, the gradient of Q against A was calculated by linearly regressing the first 3 unfiltered and uninterpolated points of the Q and A curves at the start of systole.\(^{69}\) Only the first 3 points (first ~30ms of systole) were used to ensure that there was minimal signal contamination from wave reflections.\(^{65}\)

PWV was not directly used for calibration of the arctangent model; rather it was used to calculate characteristic impedance (\( Z_c \)) expressed in terms of velocity, rather than flow:

\[ Z_c = \rho \times PWV \]  \hspace{1cm} \text{Equation 2-2}

Where \( \rho \)=blood density, assumed to be 1060kg/m\(^3\). Characteristic impedance was subsequently used for calibration of the arctangent model (see further).
2.3.6 Derivation of c-SBP using Area-Distension Waveforms

The aortic area waveforms were calibrated using linear, exponential and arctangent schemes. The equation for the linear pressure-area relationship is:

\[ p(t) = p_d + \alpha \times A(t) \]  

Equation 2-3

Where \( p(t) \) is the synthesized pressure curve, \( p_d \) is the brachial diastolic BP, \( A(t) \) is the area curve and \( \alpha \) is the scaling factor, initially set as follows:

\[ \alpha = (p_s - p_d)/(A_s - A_d) \]  

Equation 2-4

Where \( A_s \) and \( A_d \) are the systolic and diastolic aortic areas respectively. \( p_s \) is the brachial systolic BP. As c-SBP is in general lower than p-SBP this initial starting \( \alpha \) is the theoretical maximum. The equation for the exponential pressure-area relationship is:

\[ p(t) = p_d \exp \left[ \alpha \left( \frac{A(t)}{A_d} - 1 \right) \right] \]  

Equation 2-5

With \( \alpha \) initially set as follows (which for the same reason as above is the theoretical maximum):

\[ \alpha = \frac{A_d \ln \left( \frac{p_s}{p_d} \right)}{A_s - A_d} \]  

Equation 2-6

Calibration of both these models consisted of iteratively reducing the scaling factor \( \alpha \) to minimize the difference between the measured mean brachial BP and the mean of the synthesized pressure curve. This calibration scheme was based on the validated assumption that the difference between diastolic and mean pressures \( (p_m) \) is constant in the large arteries. The estimated c-SBP was the peak of the optimized synthesized pressure curve.

The equation for the arctangent pressure area relationship is:
\[ p(t) = P_0 + P_1 \tan \left( \pi \left( \frac{A(t)}{A_m} - \frac{1}{2} \right) \right) \]  

Equation 2-7

Where the \( A_m \) is the maximal distension of the aorta, \( P_0 \) is the pressure at maximum aortic compliance and \( P_1 \) is the pressure at half-maximal aortic compliance. For calibration, multiple \( p(t) \) curves were calculated using a range of \( A_m \), \( P_0 \), and \( P_1 \) values. The range of values for \( P_0 \) and \( P_1 \) taken from 53 and the range of \( A_m \) was between \( A_s \) and twice \( A_s \). For each synthesized pressure curve, the minimum pressure (\( p_d \)-EST) and mean pressure (\( p_m \)-EST), as well as the characteristic impedance (\( Z_c \)-EST) were recorded. The \( Z_c \)-EST was the mean of quotients resulting from the division of the moduli of the 3rd to 10th harmonics of synthesized pressure and measured velocity spectra. Using the measured \( p_d \) and \( p_m \), as well as the \( Z_c \) calculated from the PWV, an error metric was then calculated for each synthesized pressure curve:

\[ e = |(p_d - p_d\text{-EST})/p_d| + |(p_m - p_m\text{-EST})/p_m| + |(Z_c - Z_c\text{-EST})/Z_c| \]  

Equation 2-8

The synthesized pressure curve that produced the lowest error was taken as the best estimate of central aortic BP and c-SBP was taken as the maximum value of this curve.

2.3.7 Measurement of Local Pressure by Tonometry

Carotid arterial waveforms were obtained during flow imaging by applanation tonometry using a custom-made fibre-optic pressure tonometer Figure 2-2, with a sampling frequency of 1000Hz (Samba Sensors AB, Gothenberg). The carotid pressure curve was determined by calibrating the ensemble-averaged tonometry waveform to the mean and diastolic brachial artery pressures. Waveforms were filtered using a zero-phase, low-pass, 2nd order Butterworth filter with normalized cut-off frequency of 0.04 (Matlab 2012a, Mathworks). The central aortic pressure was taken as the maximum of the calibrated curve.
Figure 2-2 Samba Sensor (A) with fibre optic tonometer (B) consisting of a machined plastic unit (concave surface) to which a diaphragm may be attached to form a tambour.

2.3.8 Statistics

A sample size of 18 was determined by power calculation, for the detection of an r-value 0.75, between MR derived c-SBP and carotid c-SBP, with alpha 0.01 and power 0.95 (2-tailed).

Statistical analysis of was performed using SPSS version 21.0.0.0 for Mac and Prism version 5f for Mac. Linear, exponential and arctangent c-SBP were compared with Carotid c-SBP and brachial oscillometric systolic pressure using Bland–Altman analysis, with limits of agreement expressed as mean difference ±1.96 times the standard deviation of the difference. Differences between linear, exponential, arctangent and carotid c-SBP were performed using repeated measures ANOVA with Bonferroni multiple-comparison post-hoc tests (alpha 0.05, two-tailed).
2.4 Results

2.4.1 Demographics

Mean age of participants was 38 years (SD 8.5, Range 24-52), 13/20 were male. The mean brachial systolic pressure was 123.8mmHg (SD 10.4, Range 104-143). Diastolic and mean brachial blood pressure was 70.2mmHg (SD 5.0, Range 61-79) and 90.6mmHg (SD 5.4, Range 80-99) respectively. Five subjects had normal systolic pressure (<119mmHg), 14 had prehypertension (120-139mmHg) and 1 had stage 1 hypertension (>140mmHg). The mean c-SBP measured using carotid tonometry was 110.9mmHg (SD 9.8, Range 92.4-130.1).

![Figure 2-3: Example of pressure curves derived using Arctangent (blue), Exponential (green) and Linear (red) calibration methods, compared with simultaneous Carotid tonometry (black dotted).](image)
2.4.2 Feasibility

Phase contrast MR and tonometric data were successfully acquired in all volunteers within a breath hold. Assessment of PWV using the QA method was feasible in all subjects. The mean aortic PWV was 3.77 m/s (SD 1.25, Range 1.84-7.14). There was a significant linear relationship between PWV and age (p=0.04). Area and flow curves were also successfully acquired allowing c-SBP to be determined using all 3 models and compared with carotid tonometry, Figure 2-3.

![Figure 2-4: Correlations between Carotid c-SBP and (A) Brachial SAP, (B) Arctangent c-SBP, (C) Exponential c-SBP and (D) Linear c-SBP.](image-url)
2.4.3 MR derived c-SBP compared to carotid tonometry c-SBP

Arctangent, exponential and linear c-SBP correlated strongly with carotid tonometry c-SBP, $r^2=0.90$, $r^2=0.87$, $r^2=0.85$ respectively (all $p<1\times10^{-6}$). This contrasted with brachial systolic pressure which correlated only moderately with carotid c-SBP $r^2=0.47$ ($p<0.01$), Figure 2-4.
There was excellent agreement between carotid c-SBP and both arctangent c-SBP (bias 1.5mmHg, SD 3.3) and exponential c-SBP (bias 0.6, SD 3.6). There was a slight underestimation using the linear model (bias -2.3mmHg, SD 3.8) and poor agreement and overestimation using brachial systolic BP (bias 12.9mmHg, SD 8.0) (Figure 2-5). Repeated measures ANOVA and Bonferroni post-hoc testing confirmed statistically significant differences between mean carotid c-SBP and linear c-SBP (mean difference 3.8mmHg, 95% CI of difference, 0.65-3.95, p<0.01). There were no significant statistical difference between either mean carotid c-SBP and mean arctangent c-SBP or mean carotid c-SBP and mean exponential c-SBP.

2.4.4 Inter-Model Differences

Repeated measures ANOVA confirmed significant inter-model differences (F=30.8, p<0.0001). Bonferroni post-hoc testing demonstrated significant differences between the mean linear c-SBP and both arctangent (mean difference 3.8mmHg, 95% CI 2.5-5.0, p<0.0001) and exponential c-SBP (mean difference 2.9mmHg, 95% CI 1.6-4.2, p<0.0001). There was no significant difference between arctangent and exponential c-SBP.

2.4.5 Pressure-Area Relationship in the Physiological Range

The pressure-area relationships estimated using the linear, exponential and arctangent model for a representative patient is shown in Figure 2-6. This shows that in the physiological range of central blood pressures, the exponential and arctangent models are very similar and the linear model only deviates at peak pressures.
Figure 2-6 Pressure-Area relationship of Arctangent (blue), Exponential (green) and Linear (red) models in a representative subject with central pressure 120/61 (interrupted lines). Demonstrating coincidence of models in this pressure range with separation of arctangent and exponential models from linear at higher pressures.
2.5 Discussion

It has been shown that it is possible to accurately measure c-SBP using MR combined with exponential and arctangent models of the pressure area relationship. No significant benefit of the arctangent model over the exponential model in normal and pre-hypertension pressure ranges was observed. However, both the exponential and arctangent model did seem to outperform the linear model in our study population. Importantly, all MR c-SBP metrics were superior to oscillometric brachial systolic pressure. This study shows MR estimates of c-SBP could be a useful addition to the MR investigation of hypertension.

It is increasingly recognized that c-SBP is an important metric in hypertension. This is because i) most organs at risk of hypertensive damage are exposed to central rather than brachial pressure and ii) the relationship between central and peripheral blood pressure is non-linear. Our results are in agreement with previous studies showing that p-SBP is non-linearly related to, and significantly higher than c-SBP. In fact several studies have demonstrated the superiority of c-SBP over p-SBP for predicting cardiovascular events and evaluating response to therapy.

The reference standard non-invasive method of assessing c-SBP is carotid tonometry as it has previously been validated against invasive cardiac catheterization. However, it is difficult to perform and its accuracy is dependent on patient factors such as obesity, as well as operator skill. Furthermore, in older patients with severe hypertension and possible carotid atheroma it may be dangerous. Therefore, c-SBP is generally measured using radial tonometry combined with generalized transfer functions. Unfortunately, there are concerns about the validity of the generalized transfer functions used for radial tonometry. A previously validated ultrasound method was adapted to estimate c-SBP using aortic area measurements. This method is reliant on the fact the pressure can be derived from area using calibrated models of the pressure area relationship. The simplest model is the linear model, which assumes that arterial compliance is constant at all pressures. An improvement on this is the exponential model, where arterial stiffness increases with increasing pressure. This model has been shown to
outperform the linear model when using ultrasound data suggesting that it more accurately reflects the in-vivo properties of the aorta. However, both clinical and ex-vivo studies have shown that the best approximation of the pressure area relationship is an arctangent model. Thus, in this study we compared c-SBP estimated using all of these models against c-SBP measured using tonometry. In this population, both the arctangent and exponential models performed extremely well with small biases and narrow limits of agreement. In addition, they both outperformed the linear model, which underestimated c-SBP. The reasons for this can be understood from inspection of pressure-area curves. They show that in the physiological range of pressures the exponential and arctangent curves are almost coincident and therefore produce similar estimates of c-SBP. The linear prediction on the other hand deviates at higher physiological pressures, leading to underestimation of c-SBP. Thus, our results suggest that in normal or pre-hypertensive subjects, the arctangent model is not necessary for accurate assessment of c-SBP. This is pertinent because our implementation of the arctangent model required measurement of PWV and this necessitated high temporal resolution flow imaging. Although feasible to acquire such data, it does require specialized sequences, more complex image processing and a relatively long breath hold. The exponential model only requires area curves and thus c-SBP could be estimated using cine imaging alone. This would have significant advantages including easier segmentation and more widespread availability of sequences.

Nevertheless, the arctangent model may have a theoretical advantage over the exponential model in patients with severe hypertension. In this group, the aortic pressures may no longer be in the range where the exponential and arctangent curves are coincident. Thus, in hypertension the arctangent model may better describe the pressure-area relationship and produce better estimates of c-SBP. Our study did not include this group of patients and further work is necessary to assess any potential benefits of the arctangent model in this population. We also did not include any subjects with low pressure (in particular children) where once again the arctangent model may be superior for similar reasons.
An important limitation of this study is the lack of simultaneous invasive pressure as a reference standard. Unfortunately, micro-manometer pressure catheters are not available for the MR environment and the alternative, fluid filled catheters, have unfavourable frequency response and damping characteristics, which limit their use for this purpose. Furthermore, our use of carotid tonometry for the determination of central systolic pressure has previously been validated for this purpose. However, it is acknowledged that optimal validation of MR c-SBP metrics would be performed using high fidelity, intravascular measuring devices, e.g fibre-optic catheters.

In this study a relatively small (although adequately powered) population was used, covering normal and pre-hypertension ranges of blood pressure. Our study did not include a hypertension population, but describes a methodology that could be used to investigate this group. Further work is therefore required to validate this methodology in severe hypertension.

In summary, we have demonstrated the feasibility of central aortic pressure assessment using MR derived aortic area curves and models of the pressure-area relationship. Both the arctangent and exponential models correlated equally strongly with central aortic pressure as measured by carotid tonometry. Therefore, in subjects with normal or mildly increased blood pressure the exponential model may be sufficient for accurate estimation of c-SBP. This opens up the possibility of better MR characterization of patients without the availability of specialized sequences or processing, using MR derived aortic area curves and models of the pressure-area relationship. Both the arctangent and exponential models correlated equally strongly with central aortic pressure as measured by carotid tonometry. Therefore, in subjects with normal or mildly increased blood pressure the exponential model may be sufficient for accurate estimation of c-SBP. This opens up the possibility of better MR characterization of patients without the availability of specialized sequences or processing.
Chapter 3  Non-invasive haemodynamic assessment of repaired coarctation of the aorta

3.1 Abstract

The basis of late cardiovascular mortality following coarctation repair is poorly understood. Although hypertension has been implicated, peripheral systolic pressure (pSBP) has not been shown to be definitively higher in this group. This may be because mortality is more related to central systolic pressure (cSBP) than pSBP. We have developed a novel cardiovascular magnetic resonance (CMR) protocol that allows assessment of cSBP and its components: resistance, compliance and wave reflections. The main aims of this study were i) characterize hemodynamic differences between patients and controls ii) define hemodynamic determinants of cSBP in patients and iii) Identify possible biomarkers amongst covariates associated with LV mass (LVM).

75 subjects, 50 patients with repaired coarctation, median age 23.5yrs (74% male) and 25 matched controls; 21.0yrs (72% male) were recruited. Ascending aorta area and flow waveforms were obtained using a high temporal resolution (10ms) spiral phase-contrast MR flow sequence. This data was used to derive cSBP and perform wave intensity analysis (WIA) non-invasively using previously validated techniques. The determinants of cSBP and LVM were assessed using multivariable linear regression analysis.

Central SBP was significantly higher in patients compared to controls (115±13 vs 107±9mmHg [mean±sd], p=0.002). However, there was only a trend towards higher pSBP (123±15 vs 117±11mmHg, p=0.052). Patients had reduced arterial compliance, increased characteristic impedance and larger backward compression waves (BCW) than controls; and these parameters were independently associated with cSBP. LVM index was significantly higher in patients than controls (73.1±14.6 vs 58.9±9.7g/m², p=0.0001). Independent predictors of LVM included cSBP (p=0.001) and BCW (p=0.002), but importantly not pSBP or coarctation index.
Non-invasive assessment of fundamental arterial hemodynamics by CMR is feasible. Using these techniques we have shown elevated cSBP in patients after coarctation repair. Elevated cSBP and BCW are important determinants of increased LVM following coarctation repair. These metrics represent superior biomarkers of afterload than coarctation index and pSBP.
3.2 Introduction

Patients with repaired coarctation of the aorta have increased cardiovascular mortality late after repair. The reasons for this are not fully understood, although hypertension is thought to be an important factor. However, hypertension is not a consistent finding, creating uncertainty regarding the link between high blood pressure and excess mortality in this population.

Another important issue is related to measurement of peripheral (brachial) rather than central (aortic) systolic blood pressure. Peripheral systolic blood pressure (pSBP) is generally higher than central systolic blood pressure (c-SBP). Nevertheless, it is possible for subjects to have similar p-SBP, but widely different c-SBP. However, as the coronary and cerebral vascular beds are exposed to c-SBP, it would be more appropriate to measure c-SBP in these patients.

Several non-invasive methods have been used to convert radial pressure measurements to aortic pressure. Most rely on generalized transfer functions, which are not patient specific and may not be valid in repaired coarctation. We have recently shown that c-SBP can be determined from CMR data in a patient-specific manner. Our technique relies on calibration of aortic area curves to brachial mean and diastolic pressure using models of the pressure-area relationship. One of the main aims of this study was to use this technique to determine if patients with repaired coarctation have higher c-SBP than age- and sex-matched controls.

Combining CMR derived c-SBP and flow imaging also allows calculation of systemic vascular resistance, central arterial compliance and local pulse wave velocity. In addition, area and flow data acquired at high temporal resolution can be used to evaluate the final important component of hemodynamics – wave reflections. Thus, using CMR it is possible to accurately assess all aspects of conduit vessels function and determine their relationship to c-SBP. This might have important implications for therapy in this patient population.

In addition, CMR provides accurate assessment of left ventricular (LV) hypertrophy. The LV remains one of the most important target organs for hypertension, and
hypertrophy is associated with adverse cardiovascular events and death. Consequently, evaluating the relationship between LV hypertrophy, c-SBP and conduit vessel function is important in understanding the causes of late mortality after coarctation repair.

In this study, we recruited 50 patients with repaired coarctation of the aorta and 25 age and sex matched healthy controls. The aims of the study were to utilize high temporal resolution CMR imaging to perform a comprehensive non-invasive haemodynamic assessment.

3.2.1 Hypotheses

1. Patients and controls are characterized by differences in c-SBP, p-SBP, arterial resistance, arterial compliance, characteristic impedance and wave reflections.

2. Hemodynamic and geometric parameters are associated with variation in c-SBP.

3. c-SBP is more strongly associated with variation in LV mass than p-SBP.

4. Wave reflections are associated with variation in LV mass.
3.3 Materials and Methods

3.3.1 Subjects

50 Patients with coarctation of the aorta repaired in childhood and 25 healthy controls were recruited. Exclusion criteria were: (i) Irregular heart rates; (ii) Contraindications to cardiovascular magnetic resonance (CMR) such as MR-incompatible implants; (iii) Pregnancy; (iv) Aortic stenosis; (v) Coarctation associated with major congenital heart disease (exception non-stenotic bicuspid aortic valve, or repaired ventricular/atrial septal defects); or (vi) Coarctation stents. Patients receiving antihypertensive medications were included if this was reported as stable, chronic therapy. The study was performed with local research ethics committee approval and written informed consent was obtained.

3.3.2 CMR Protocol

All imaging was performed on a 1.5 T MR scanner (Avanto, Siemens Medical Solutions, Erlangen, Germany) using two spine coils and one body-matrix coil. A vector electrocardiographic system was used for cardiac gating. The flow-imaging plane was planned using orthogonal long axis cine images of the ascending aorta and was placed just above the sinotubular junction. The sequence was a prospectively triggered, spiral, velocity encoded spoiled gradient echo acquisition, accelerated with SENSE (TE/TR: 1.9/4.8 ms, FOV: 400×400×6 mm, matrix: 192×192, spiral interleaves: 60, SENSE factor: 4, VENC: 180 cm/s). The temporal resolution was 9.6msec, the spatial resolution was 2.1×2.1 mm and the breath-hold was approximately 11s (16 R-R intervals).

Aortic arch morphology was assessed in patients using gadolinium-enhanced MR angiography as previously described with a coronal 3D fast-field-echo sequence.
Gadolinium (Dotarem, Guerbet) was injected into a peripheral vein and tracked into the heart with a dynamic coronal 2D fast-field-echo sequence. The gadolinium dose was 0.2 mmol/kg. The MR angiographic sequence was started when contrast reached the left ventricle. Two consecutive angiograms were acquired in a single 15- to 20-second period of apnea. In 7 patients intravenous contrast was not administered for clinical reasons (IV access could not be obtained [n=2] or no consent for contrast [n=5]). Aortic anatomy was assessed in these patients using a diastolic ‘whole-heart’, magnetization-prepared 3D balanced, steady-state free precession sequence with navigator respiratory gating as previously described.92

A radial k-t SENSE sequence was used to calculate LV volumes and mass as previously described.93 Images were acquired in the ventricular long-axis, four chamber, and the short axis covering both ventricles (9-12 slices). Assessment of the LV volume was performed by manual segmentation of the endocardial contour of short-axis cine images at end-diastole and end-systole using a built-in plug-in for OsiriX. End diastolic volume and end systolic volume were calculated using Simpson’s rule. From these volumes, stroke volume and ejection fraction (EF) were calculated. Epicardial contours were manually segmented at end systole. Ventricular mass was calculated as the difference between the epicardial and endocardial contours multiplied by the slice thickness and a specific gravity of ventricular mass of 1.05g/ml. LV mass was adjusted for body surface area (BSA) to provide the indexed LV mass (g/m$^2$).

3.3.3 Blood Pressure Measurement

Brachial systolic (p-SBP), diastolic (DBP) and mean (MBP) blood pressures were measured by automated oscillometric sphygmomanometry during flow imaging (Datex Ohmeda) on the patient’s right arm. Small-adult, adult and large-adult cuff sizes were chosen according to subject arm circumference. Volunteers lay supine in
the MR scanner with the arm at the level of the heart and there was a period of acclimatization (at least 15 minutes) before measurements were taken.

3.3.4 Image Processing

All images were processed using an in-house plug-in for the open source DICOM software OsiriX (OsiriX Foundation, Geneva, Switzerland).\(^67\) Segmentation of the ascending aorta was performed on the modulus image using a previously validated semi-automatic registration-based algorithm.\(^68\) The aortic region of interest (ROI) was manually adjusted as necessary to ensure optimal vessel wall delineation. The final ROIs were used to both calculate the aortic cross-sectional area (A) and prescribe the region in the phase image from which mean velocity (V) and flow (Q) were calculated. However, pressure wave synthesis requires curves that span the whole RR interval and the use of prospective gating resulted in missing data in the last 80-100ms of diastole. This missing data were recovered using linear interpolation between the last point and the first point. The curves were then linearly interpolated to 1ms temporal resolution and filtered using a zero-phase, low-pass, 2\(^{nd}\) order Butterworth filter with normalized cut-off frequency of 0.04 (20Hz), (Matlab 2014b, Mathworks).

Aortic arch anatomy was evaluated using multiplanar reformatted 3D images in OsiriX. Residual coarctation was assessed by measurement of diameter at the site of minimum lumen in the aortic arch. The diameter of the descending aorta was measured at the level of the diaphragm. To adjust for body size, a coarctation index was calculated by dividing the minimum aortic arch diameter by the descending aorta diameter at the level of the diaphragm. To assess aortic arch hypoplasia, the diameter of the aortic arch was measured distal to the right common carotid artery and an ‘arch hypoplasia index’ was calculated by dividing by the diaphragmatic aortic diameter. Aortic arches were characterised as ‘gothic’ if the arch had an acutely angulated triangular conformation.\(^94\)
3.3.5 Derivation of c-SBP using Area-Distension Waveforms

The aortic area waveforms were calibrated using a previously validated exponential pressure-area model. The equation of an exponential pressure-area relationship is:

\[ p(t) = p_d \exp \left[ \alpha \left( \frac{A(t)}{A_d} - 1 \right) \right] \]

Equation 2-5

Where \( p(t) \) is the synthesized pressure curve, \( p_d \) is the brachial diastolic BP, \( A(t) \) is the area curve and \( \alpha \) is the scaling factor, initially set as follows:

\[ \alpha = \frac{A_d \ln \left( \frac{p_s}{p_d} \right)}{A_s - A_d} \]

Equation 2-6

Where \( A_s \) and \( A_d \) are the systolic and diastolic aortic areas respectively. As c-SBP is in general lower than p-SBP this initial starting \( \alpha \) is the theoretical maximum.

Calibration of this model consisted of iteratively reducing the scaling factor \( \alpha \) to minimize the difference between the measured brachial mean BP and the mean of the synthesized pressure curve. This calibration scheme was based on the validated assumption that the difference between diastolic and mean pressures is constant in the large arteries. The estimated c-SBP was the peak of the optimized synthesized pressure curve.

3.3.6 Wave Speed (Characteristic Impedance)

Due to the possible early reflection site related to the repaired coarctation, conventional single cut methods of calculating wave speed (such as the Q/A method) are unreliable. Therefore, the Bramwell-Hill equation was used to obtain local pulse wave velocity, \( c \), in the ascending aorta, using the aortic area waveform and c-SBP:

\[ c = \sqrt{A \Delta P / \Delta A} \]

Equation 1-16
where \( A_d \) is the diastolic cross-section area, \( \Delta A \) is \( A_s - A_d \), and \( \Delta P \) is the central pulse pressure (c-SBP-DBP). This method has been shown in computer simulations to be robust in the presence of early wave reflections.\(^9\) Characteristic impedance, \( Z_c \), was calculated by:

\[
Z_c = \rho \frac{c}{A_d}
\]

Equation 3-1

where \( \rho \) is assumed to be 1060kg/m\(^3\).

### 3.3.7 Arterial Resistance and Compliance

Arterial resistance (Woods Units) was calculated by dividing MBP (mmHg) by cardiac output (L/min). Central arterial compliance (ml.mmHg\(^{-1}\)) was calculated in Matlab using a 2-element windkessel model as previously described,\(^1^4\) using single cardiac cycle phase contrast flow curves and central pulse pressure (c-SBP – DBP). Resistance was indexed to body size by multiplication with BSA and compliance by dividing by BSA.

### 3.3.8 Wave Intensity Analysis

In WIA, waves are regarded as a summation of incremental wave fronts; it is therefore possible to separate the \( Q \) and \( A \) curves into the respective forward (+) and backward (-) components by expressing the relationship between \( c \), and changes in flow and cross-sectional area.

\[
c = \pm \frac{dQ}{dA}
\]

Equation 3-2

Equation 3-1 combined with Equations 3-2 and 3-3:

\[
dA = dA_+ + dA_-
\]

\[
dQ = dQ_+ + dQ_-
\]

Equation 3-3

Equation 3-4

can be solved for the changes in the forward and backward flow and cross-sectional area; this results in Equations 3-4 and 3-5:
\[
\begin{align*}
    dQ_\pm &= \frac{1}{2} (dQ \pm cdA) \quad \text{Equation 3-5} \\
    dA_\pm &= \frac{1}{2} \left(A \pm \frac{1}{c} dQ\right) \quad \text{Equation 3-6}
\end{align*}
\]

Net wave intensity \( dI_a \) was defined as the product of the differentials of cross-
sectional area and flow.

\[
dI_a = dA \, dQ \quad \text{Equation 3-7}
\]

Similarly it can be shown that the net wave intensity \( dI_a \) (Equation 3-6) can be
divided into the forward and backward intensities, Equation 3-7:

\[
dI_a = dI_{a(+)} + dI_{a(-)} \quad \text{Equation 3-8}
\]

with the separated \( dI_a \) expressed as:

\[
dI_{a(\pm)} = \pm \frac{c}{4} \left[dA \pm \frac{dQ}{c}\right]^2 \quad \text{Equation 3-9}
\]

Using this formulation and \( c \) calculated using the Bramwell-Hill equation (Equation
1-16), forwards and backwards \( dI_a \) were calculated and plotted. As per convention,
the direction of waves was referenced to the direction of blood flow. Waves arising
from the heart were defined as forward running and those arising from the
vasculature as backward running. Waves causing an increase in area were classified
as compression waves and those causing a decrease in area as expansion waves by
examination of \( dA_\pm \) plots. Thus, a forward running wave was held to be a
compression wave if \( dA_+ \) was greater than zero and an expansion wave if \( dA_- \) was
less than zero. Similarly, a backward-running wave was considered as a compression
wave if \( dA_- \) was greater than zero and an expansion wave if \( dA_- \) was less than zero.

Using this system four different waves may be characterised: Forwards Compression
Waves (FCW), Forwards Expansion Waves (FEW), Backwards Compression Waves
(BCW) and Backwards Expansion Waves (BEW).

The type of wave and their magnitude (area under the wave) were determined by
analysis of the net and separated WIA plots in Matlab. The areas under the separated
waveforms were calculated by numerical integration.
3.3.9 Statistics

STATA 13 and Graphpad Prism 5f for mac were used for statistical analysis and Figures. Data were examined for normality and where appropriate, non-normally distributed variables were log transformed to ensure normal distribution prior to analysis. Descriptive statistics are expressed as mean (±95% confidence interval) when normally distributed, and geometric mean (±95% confidence interval of geometric mean) when non-normally distributed, unless specified. Proportions are expressed as percentages.

Pearson’s correlation coefficient was used to analyze simple linear relationships between variables. The independent samples t-test was used to compare differences in parametric data between coarctation patients and controls; Welch’s correction was employed for unequal variances. Proportions test was used to compare proportions amongst groups. The level of alpha considered for statistical significance was 0.05.

Multivariable linear regression analysis was used to determine covariates independently associated with c-SBP and LV mass. For c-SBP, the model was adjusted for previously described predictors: BSA, sex, age, heart rate, characteristic impedance, cardiac output, and vascular resistance. For LVM, the model was adjusted for: BSA, sex, and age to ascertain independent associations.
3.4 Results

3.4.1 Study Population Characteristics

The characteristics of the study population are shown in Table 3-1. There were no significant differences in age or gender between patients and controls. Control subjects were taller on average than patients (p=0.04), however there was no difference in BMI or BSA between groups.

The median age of repair was <1year (25th-75th percentile <1year – 4years) and 32/50 patients (64%) underwent coarctation repair at <1 year of age. End-to-end anastomosis was performed on 39/50 patients (78%), left subclavian flap angioplasty in 10 patients (20%) and Dacron patch augmentation in 1 patient. A bicuspid aortic valve was present in 27/50 (54%) patients.

Patients had predominately no or mild re-coarctation with 92% of patients having a coarctation index >0.7. The group median coarctation index was 0.88 (10th-90th percentile, 0.71-1.14). There were no cases of significant aortic arch hypoplasia with all patients having an aortic arch hypoplasia index >0.7; the median arch hypoplasia index was 1.04 (10th-90th percentile, 0.89-1.23). 12/50 patients (24%) had a ‘gothic’ arch.

3.4.2 Blood pressure: Normal vs. Repaired Coarctation patients

There were no significant differences in age or gender between patients and controls. Control subjects were taller on average than patients (p=0.04), however there was no difference in BMI or BSA between groups.

The median age of repair was <1year (25th-75th percentile <1year – 4years) and 32/50 patients (64%) underwent coarctation repair at <1 year of age. End-to-end anastomosis was performed on 39/50 patients (78%), left subclavian flap angioplasty in 10 patients (20%) and Dacron patch augmentation in 1 patient. A bicuspid aortic valve was present in 27/50 (54%) patients.
Patients had predominately no or mild re-coarctation with 92% of patients having a coarctation index >0.7. The group median coarctation index was 0.88 (10th-90th percentile, 0.71-1.14). There were no cases of significant aortic arch hypoplasia with all patients having an aortic arch hypoplasia index >0.7; the median arch hypoplasia index was 1.04 (10th-90th percentile, 0.89-1.23). 12/50 patients (24%) had a ‘gothic’ arch.

3.4.3 Blood pressure: Normal vs. Repaired Coarctation patients

Central SBP was significantly higher (p=0.002) in patients (115mmHg [111-118mmHg]) compared to controls (107mmHg [103-110mmHg]). On the other hand, there was only a trend (p=0.052) toward higher brachial systolic blood pressure (p-SBP) in patients (123mmHg [119 - 127 mmHg] vs. 117mmHg [112 - 121 mmHg]). There were no significant differences in MBP or DBP between patients and controls (p=0.4 and p=0.6 respectively). Only 6/50 (12%) patients had evidence of brachial systolic hypertension (p-SBP>140mmHg). However, 10/50 (20%) had evidence of central systolic hypertension (c-SBP>125mmHg)27,96 and 23/50 (46%) had c-SBP >90th centile for the normal population.97 By contrast, no control patients had c-SBP>125mmHg or p-SBP>140mmHg. There were no differences in p-SBP or c-SBP between patients with and without a ‘gothic’ arch.

Nine patients were receiving stable anti-hypertensive therapy. A single agent was prescribed in 7 patients and a combination of agents in 2 patients. Medications included: ACE inhibitors (4 patients), angiotensin receptor blockers (2 patients), dihydropyridine-type calcium channel blockers (2 patients), and beta blockers (4 patients). There was a trend towards higher p-SBP in treated compared to untreated patients (135mmHg [121-148mmHg] vs. 121mmHg [117-125mmHg], p=0.2) as well as c-SBP (121mmHg [109-133mmHg] vs. 113mmHg [110-117mmHg], p=0.2).
<table>
<thead>
<tr>
<th></th>
<th>Patient n=50</th>
<th>Control n=25</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>37 (74%)</td>
<td>18 (72%)</td>
<td>p=0.9</td>
</tr>
<tr>
<td>Age (years) *†</td>
<td>24 (22-26)</td>
<td>23 (21-25)</td>
<td>p=0.5</td>
</tr>
<tr>
<td>Weight (kg) *</td>
<td>72 (67-76)</td>
<td>76 (69-83)</td>
<td>p=0.3</td>
</tr>
<tr>
<td>Height (cm) *</td>
<td>171 (168-175)</td>
<td>177 (173-180)</td>
<td>p=0.04</td>
</tr>
<tr>
<td>Body Surface Area (m²) *</td>
<td>1.8 (1.8-1.9)</td>
<td>1.9 (1.8-2.0)</td>
<td>p=0.1</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)*</td>
<td>24 (23-26)</td>
<td>24 (22-26)</td>
<td>p=0.9</td>
</tr>
<tr>
<td>Brachial Systolic BP (mmHg)</td>
<td>123 (119-127)</td>
<td>117 (112-121)</td>
<td>p=0.052</td>
</tr>
<tr>
<td>Brachial Mean BP (mmHg)</td>
<td>87 (85-90)</td>
<td>85 (82-89)</td>
<td>p=0.4</td>
</tr>
<tr>
<td>Brachial Diastolic BP (mmHg)</td>
<td>63 (61-66)</td>
<td>64 (61-68)</td>
<td>p=0.6</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>68 (65-72)</td>
<td>64 (59-68)</td>
<td>p=0.1</td>
</tr>
<tr>
<td>LV ejection fraction (%)†</td>
<td>65 (63-67)</td>
<td>63 (61-65)</td>
<td>p=0.2</td>
</tr>
<tr>
<td>LV mass index (g/m²) †</td>
<td>73 (69-78)</td>
<td>59 (55-63)</td>
<td>p&lt;0.0005</td>
</tr>
<tr>
<td>Cardiac Index (l.min⁻¹.m⁻²)*</td>
<td>3.1 (3.0-3.3)</td>
<td>3.3 (3.1-3.5)</td>
<td>p=0.3</td>
</tr>
<tr>
<td>Resistance Index (Wood units.m²) †</td>
<td>28 (27-30)</td>
<td>26 (25-28)</td>
<td>p=0.06</td>
</tr>
<tr>
<td>Aorta Diastolic Area (cm²) *†</td>
<td>5.5 (4.9-6.2)</td>
<td>4.8 (4.5-5.1)</td>
<td>p=0.03</td>
</tr>
</tbody>
</table>

Table 3-1 Study Population Demographics. *T-test on log transformed data: geometric mean and (95% confidence interval of geometric mean) †Welch correction for unequal variance.
<table>
<thead>
<tr>
<th></th>
<th>Patient n=50</th>
<th>Control n=25</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>c-SBP (mmHg) †</td>
<td>115 (111-118)</td>
<td>107 (103-110)</td>
<td>p=0.002</td>
</tr>
<tr>
<td>Central Compliance Index (ml.m⁻².mmHg⁻¹) *</td>
<td>0.61 (0.56-0.66)</td>
<td>0.79 (0.72-0.86)</td>
<td>p=0.0003</td>
</tr>
<tr>
<td>Pulse Wave Velocity (m/s) *</td>
<td>4.3 (4.0-4.7)</td>
<td>3.7 (3.4-4.1)</td>
<td>p=0.02</td>
</tr>
<tr>
<td>Characteristic Impedance (kg.m⁻².s⁻¹) *†</td>
<td>8.3e⁴ (7.5e⁴-9.2e⁴)</td>
<td>8.3e⁴ (7.6e⁴-9.1e⁴)</td>
<td>p=0.98</td>
</tr>
<tr>
<td>BCW (cm³) †</td>
<td>1e⁻³ (7.7e⁻³ - 1.3e⁻³)</td>
<td>6.6e⁻³ (5.0e⁻³ - 8.6e⁻³)</td>
<td>p=0.02</td>
</tr>
<tr>
<td>FCW (cm³) *</td>
<td>8.6e⁻³ (7.2e⁻³ - 0.01)</td>
<td>0.01 (8.5e⁻³ - 0.001)</td>
<td>p=0.2</td>
</tr>
<tr>
<td>FEW (cm³) *</td>
<td>1.8e⁻³ (1.5e⁻³ - 2.2e⁻³)</td>
<td>1.6e⁻³ (1.2e⁻³ - 2.1e⁻³)</td>
<td>p=0.3</td>
</tr>
</tbody>
</table>

Table 3-2 Central Haemodynamics, Characteristic Impedance and Wave Intensity Analysis in Patients and Control subjects. *T-test on log transformed data: geometric mean and (95% confidence interval of geometric mean) †Welch correction for unequal variance.
3.4.4 Arterial Function: Normal vs. Repaired Coarctation patients

Differences in arterial function between patients and controls are shown in Table 3-2. Pulse wave velocity was significantly (p=0.02) higher in patients (4.3m/s [4.0 - 4.7m/s]) compared to controls (3.7m/s [3.4 - 4.1m/s]). Compliance index was lower in patients than controls, (0.61ml.m⁻².mmHg⁻¹ [0.56-0.66ml.m⁻².mmHg⁻¹] vs. 0.79ml.m⁻².mmHg⁻¹ [0.72-0.86 ml.m⁻².mmHg⁻¹], p=0.0003).

The magnitude of the reflected backwards compression wave was higher (p=0.02) in patients (10 e⁻⁴ cm⁵ [7.7e⁻⁴ – 13 e⁻⁴ cm⁵]) compared to controls (6.6e⁻⁴ cm⁵ [5.0e⁻⁴ - 8.6e⁻⁴ cm⁵]) as seen in Figure 3-1. There were no significant differences in the magnitude of the forward compression wave or forward expansion wave between patients and controls. There were no group differences in cardiac index or resistance index, Table 3-1.
Figure 3-1 WIA in representative repaired coarctation patient (A-C) and Control (D-F). Three main types of waveforms were found to arise during systole in study participants using wave separation analysis: (1) A forward compression wave, characterized by: increasing area and increasing flow representing cardiac ejection, Panel B & E, labeled ‘*’ (2) A protodiastolic forward expansion wave: decreasing area [pressure] and decreasing flow, Panel B & E labeled ‘‡’, and (3) A backwards compression wave: increasing area [pressure] and decreasing flow, Panel B labeled ‘†’ (not seen in panel E in this particular control). The identification of the waves as compression or expansion can be seen from examination of panels C and F, showing the dA± plots. Time=0 corresponds to the onset of data acquisition as triggered by the R wave on CMR vectorcardiograph.
Simple linear relationships between indices of arch geometry and haemodynamic variables are shown in Table 3-3. Both c-SBP and p-SBP were found to increase with decreasing coarctation index, and c-SBP increased with decreasing arch hypoplasia index. There was no significant relationship between arch geometry indices and resistance, compliance, characteristic impedance or BCW.

<table>
<thead>
<tr>
<th></th>
<th>Coarctation Index</th>
<th>Arch Hypoplasia Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-SBP</td>
<td>-0.43</td>
<td>-0.2</td>
</tr>
<tr>
<td>c-SBP</td>
<td>-0.41</td>
<td>-0.3</td>
</tr>
<tr>
<td>Resistance Index</td>
<td>0.005</td>
<td>0.13</td>
</tr>
<tr>
<td>Central Compliance Index*</td>
<td>0.27</td>
<td>0.2</td>
</tr>
<tr>
<td>Pulse Wave Velocity*</td>
<td>-0.09</td>
<td>-0.12</td>
</tr>
<tr>
<td>BCW*</td>
<td>-0.18</td>
<td>-0.14</td>
</tr>
</tbody>
</table>

Table 3-3 Simple Linear Relationships between indices of arch geometry: coarctation index and arch hypoplasia index and haemodynamic parameters. *Log normalised variables.
The results of the fully adjusted model for c-SBP including all subjects are shown in Table 3-4. Central compliance, BCW, characteristic impedance and HR were all independent predictors of c-SBP. These metrics were also significant in a model only including patients. However, in this model there was no significant association between c-SBP and either coarctation index (p=0.1), arch index (p=0.3), or the presence of a ‘gothic arch’ (p=0.8).

<table>
<thead>
<tr>
<th></th>
<th>Coefficient</th>
<th>Beta</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central Compliance*</td>
<td>-20.7</td>
<td>-0.55</td>
<td>p&lt;0.0005</td>
</tr>
<tr>
<td>Cardiac Output*</td>
<td>73.8</td>
<td>1.31</td>
<td>p&lt;0.0005</td>
</tr>
<tr>
<td>Vascular Resistance</td>
<td>4.3</td>
<td>1.11</td>
<td>p&lt;0.0005</td>
</tr>
<tr>
<td>BCW*</td>
<td>4.2</td>
<td>0.31</td>
<td>p&lt;0.0005</td>
</tr>
<tr>
<td>Characteristic Impedance*</td>
<td>8.9</td>
<td>0.22</td>
<td>p=0.01</td>
</tr>
<tr>
<td>Heart Rate*</td>
<td>-18.6</td>
<td>-0.26</td>
<td>p=0.001</td>
</tr>
</tbody>
</table>

Table 3-4 Multiple Linear Regression Analysis of Covariates associated with central SBP, Model $R^2$: 0.89. Adjusted for BSA, age and gender *Log normalised variables.
Figure 3-2 Predictive margins from regression equation for c-SBP for levels of (a) BCW (ln) at 75% centile and 25% centile, and (b) Central compliance at 0.9 mL/mmHg\(^{-1}\) (25th centile) and 1.3 mL/mmHg\(^{-1}\) (75th centile) and (c) Coarctation index at median 0.8, and improvement to index of 1.
Figure 3-2 A-B shows the c-SBP at patients’ 25th and 50th centiles of BCW and central compliance. It can be seen that variability in these metrics predicts significant differences in c-SBP. Figure 3-2 C shows c-SBP at the 25th centile coarctation index (0.8) and a normal index of 1.0, with little difference in c-SBP.

3.4.5 Determinants of LV Mass

There was a significant difference (p<0.00005) in LV mass index between patients and controls, 73 g/m² (69-78 g/m²) vs. 59 g/m² (55-63 g/m²). There was no difference in LV mass index between patients with bicuspid and those with tricuspid aortic valves, p=0.6.

The determinants of LV mass were assessed using multivariable linear regression analysis. Models were adjusted for known predictors of LV mass: BSA, age, and sex, Table 3-5. Independent associations of LV mass were found with c-SBP (p=0.004) and BCW (log) (p=0.001). There was no significant independent association of LV mass with p-SBP, vascular resistance, cardiac output, or central compliance. Adjustment for coarctation index or arch index in patients demonstrated no significant relationship between LV mass and these variables.

When c-SBP and BCW (log) were included in combination in the adjusted regression model, statistically significant independent associations remained with LV mass.
<table>
<thead>
<tr>
<th></th>
<th>Coefficient</th>
<th>Beta</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>c-SBP</td>
<td>0.80</td>
<td>0.28</td>
<td>p=0.003</td>
</tr>
<tr>
<td>p-SBP</td>
<td>0.41</td>
<td>0.17</td>
<td>p=0.1</td>
</tr>
<tr>
<td>Central Compliance*</td>
<td>-11.6</td>
<td>-0.11</td>
<td>p=0.3</td>
</tr>
<tr>
<td>BCW*</td>
<td>12.0</td>
<td>0.31</td>
<td>p=0.001</td>
</tr>
<tr>
<td>Resistance*</td>
<td>12.4</td>
<td>0.08</td>
<td>p=0.47</td>
</tr>
<tr>
<td>Cardiac Output*</td>
<td>-8.2</td>
<td>-0.05</td>
<td>p=0.65</td>
</tr>
<tr>
<td>Coarctation Index†</td>
<td>-29.8</td>
<td>-0.13</td>
<td>p=0.2</td>
</tr>
<tr>
<td>Arch Hypoplasia Index†</td>
<td>0.67</td>
<td>0.03</td>
<td>p=1.0</td>
</tr>
</tbody>
</table>

Table 3-5 Multiple linear regression analysis of covariates with LV mass (g). Each row represents separate model adjusted for BSA, age, and gender. *Log normalised variables. †Coarctation patients only.
3.5 Discussion

In this study, we used advanced CMR techniques to simultaneously assess all the components of central pulsatile pressure – vascular resistance, arterial compliance, pulse wave velocity and wave reflections – in patients with repaired coarctation.

The main findings of the study were: i) Central SBP was higher in patients than controls, even though there was no significant difference in brachial SBP; ii) Patients post-coarctation repair were characterised by lower arterial compliance, higher local wave speed and increased backwards compression wave reflections; and iii) Higher LV mass observed in patients is significantly determined by c-SBP and BCW reflections, but not by coarctation index or p-SBP.

3.5.1 Blood Pressure Differences

In this study, there was only a trend toward higher p-SBP in patients with repaired coarctation. On the other hand, central SBP was significantly higher and a significant proportion of patients would be reclassified as hypertensive using c-SBP. We believe this demonstrates the importance of measuring c-SBP in this patient population, rather than simply relying on brachial blood pressure.

Our study is not the first to measure c-SBP following repair of coarctation. Swan et al. measured central blood pressure in post-coarctation repair patients and normal volunteers, and in contrast to our study observed no difference in c-SBP. This may be partly due to their exclusion of any patient with high brachial artery blood pressure. However, another possible reason was their use of the SphygmoCor device to measure c-SBP. This device uses a generalized transfer function to derive central blood pressure from radial tonometric data. The algorithms used are based on a non-congenital population and may not be valid in subjects with very abnormal arterial function. In particular, generalized transfer functions may not adequately control for the abnormal wave reflections that may be present in patients post coarctation repair.
We used a novel CMR technique to derive c-SBP that is based on exponential modeling of the aortic distension curve.\(^{56}\) As this method uses patient specific data as its initial starting point and for calibration, it should be able to better model pressure amplification. This is backed up by the fact that there was a strong relationship between c-SBP and LV mass in our study.

Currently, CMR is primarily used to identify re-coarctation and help decide if further intervention is required. However, the ability to measure c-SBP opens up new uses, such as titration of antihypertensive therapy. This is particularly pertinent as certain anti-hypertensive classes affect peripheral and central blood pressure differently. The CAFE study examined the impact of atenolol ± thiazide versus amlodipine ± perindopril; despite similar effects in peripheral BP, there were substantial reductions in c-SBP in favor of the amlodipine-based treatment.\(^{75}\) Another important use of CMR in these patients is to better interrogate the underlying pathophysiology of central hypertension. In this study, we achieved this by comprehensively assessing the components of arterial function.

Interestingly, these clinical findings are concordant with data that was recently obtained from a complex 3D computational model of the aortic arch, studying the differential impact of a stiff and/or narrowed segment in the descending aorta on central aortic hemodynamics as model of repaired coarctation.\(^{100}\) The simulations predicted a maximally increased central blood pressure of 8 mmHg due to the presence of a stiff zone in the descending aorta, which is consistent with the observed differences between patients and controls.

### 3.5.2 Arterial Stiffness

We have shown important group differences between patients and control subjects in terms of central arterial compliance and local wave speed. Importantly, variation in these parameters has been shown to account for the majority of variability in c-SBP between patients and controls. Specifically, c-SBP increases with reducing compliance and increased characteristic impedance. Importantly, we did not demonstrate a significant association of coarctation index or arch hypoplasia index\(^{101}\) after adjusting for these fundamental hemodynamic parameters.
Abnormal aortic stiffness following repair\textsuperscript{94,102} is a consistent finding across studies, and it is confirmed in the present study. The aetiology of increased vascular stiffness and remodelling after repair is still unclear, but may be due to changes in the phenotypic expression of vascular smooth muscle cells. Remodelling may also occur as a compensatory mechanism to restore tensile stress to homeostatic levels.\textsuperscript{103} One particular concern is that there are no effective medical therapies to modulate vascular compliance. Nevertheless, our findings highlight the need for such putative therapies in this patient population.

### 3.5.3 Wave Reflections

The increased magnitude of the BCW in patients and its significant contribution to c-SBP and LV mass is a novel finding. Reflections are known to arise at areas of impedance mismatch (e.g. branches, changes in wall stiffness or calibre). In patient post coarctation repair, the most obvious cause of an impedance mismatch is recoarctation. However, in our study of patients with mainly ‘good’ anatomical repairs there was no relationship between coarctation index and the magnitude of the BCW. Therefore, the observed increased wave reflections were probably due to changing material properties around the area of coarctation repair. In particular, the transition from the ascending to descending aorta may represent an important impedance mismatch due to differences in the elastic properties of these segments.\textsuperscript{104} Irrespective of their cause, our data demonstrates that a) increased BCW’s have important hemodynamic consequences and, b) they are unlikely to be remedied by simple anatomical interventions such as stenting.

### 3.5.4 Arch morphology

We found no difference in any hemodynamic parameters between patients with and without ‘gothic’ aortic archs.\textsuperscript{94} Our data was acquired at rest and studies have observed greater exercise hypertension in patients with a ‘gothic arch’.\textsuperscript{105} However, Ntsinjana \textit{et al.}\textsuperscript{106} using quantitative (rather than qualitative) analysis of arch angulation found no association with exercise blood pressure after adjustment for coarctation index. In addition, in this study there was no relationship between coarctation or arch hypoplasia index and any hemodynamic parameter. Thus, in our
population of patients with ‘good’ repairs, arch geometry does not seem to be an important factor in determining central hemodynamics.

### 3.5.5 Determinants of LV mass

We, and others, have noted elevated LV mass in patients with repaired coarctation. Importantly, this end-organ effect has been shown to be strongly associated with increased cardiovascular morbidity and mortality.\(^{89,90}\)

In our study, the most important determinant of LV mass was c-SBP, which is unsurprising as c-SBP is an excellent measure of LV afterload. However, there was no significant relationship between p-SBP and LV mass. This result is in keeping with several previous studies. For instance, De Divitiis et al.\(^{107}\) showed there was no relationship between one off resting p-SBP and LV mass measured by echocardiography. While Swan et al.\(^{108}\) showed no relationship between either resting or exercise brachial blood pressure and LV mass. The poor performance of p-SBP is probably due to the patient specific nature of pressure amplification, which results in variable mapping of peripheral to central SBP. This reinforces the importance of measuring c-SBP in this patient population.

A slightly more surprising finding was that the magnitude of the BCW was also an independent determinant of LV mass. The mechanism by which early backwards compression waves contribute to the development of increased LV mass is uncertain. The early arrival of such waves, may contribute to ‘front loading’ of the pressure waveform, when LV volume and wall tension are higher (Law of Laplace). Further work is required to fully understand the relationship with LV mass and wave reflections. Nevertheless, WIA may have a role to play in follow-up of these patients, particularly in the era of novel therapeutic interventions.

### 3.5.6 Novel MR Imaging

Comprehensive non-invasive assessment of hemodynamics was made possible in this study because of the novel CMR and signal processing techniques utilized. All of the hemodynamic data was derived from a single high temporal resolution phase contrast acquisition, obtained during a breath-hold. This data provides the
prerequisite area and flow data needed to derive central systolic pressure, resistance, compliance, local pulse wave velocity and wave intensity when combined with simultaneous brachial non-invasive blood pressure measurement.

Arterial compliance was assessed using a technique based on 2-element Windkessel modelling; an improvement upon the stroke volume/pulse pressure method known to overestimate compliance. We used the Bramwell-Hill equation for derivation of local pulse wave velocity/characteristic impedance, rather than the flow-area (QA) method because we anticipated significant early reflections during the early part of systole, which prevent accurate measurement.95

Wave intensity analysis provides useful insight into wave reflections in the time domain, it is relatively simple to implement but requires high temporal resolution data flow imaging to resolve waveforms, which have short durations.

The ability to assess c-SBP, central compliance and characteristic impedance during routine CMR assessment is feasible; whilst performing non-invasive WIA may be more challenging to implement. However, the strong association with LV mass, and potentially other end organs strongly suggests these parameters as useful biomarkers. Further studies assessing their relationship to outcomes and response to therapies are necessary.

3.5.7 Limitations

Central SBP was derived by calibrating aortic area curves to mean and diastolic BP using an exponential pressure-area relationship. This method was originally validated using non-invasive carotid tonometry, rather than using preferred invasive pressures. Unfortunately, micro-manometer pressure catheters are not available for the MR environment and the alternative, fluid filled catheters, have unfavorable frequency response and damping characteristics, which limit their use for this purpose. However, the strong relationship between LV mass and this measurement in contrast to peripheral BP, supports its overall validity.
In this study, we assessed hemodynamics in the ascending aorta. An important area of further work is to assess other regions of the aorta, in particular the descending aorta, which may contribute to the pathophysiological development of significant wave reflection by acting as an area of impedance mismatch.

The units of non-invasive WIA in this study, cm$^5$ do not have an easily understandable physical meaning: in contrast to the W/m$^2$ units of invasive WIA. Nevertheless, the waveforms produced by non-invasive WIA are qualitatively similar to invasive WIA in the literature – and given a linear pressure-area relationship would be directly proportional. Area and flow waves can therefore be considered analogous to pressure and velocity waves as found in the WIA literature.

### 3.5.8 Conclusion

This study aimed to describe all relevant conduit vessel haemodynamic parameters underlying the vascular abnormalities in coarctation of the aorta. We have shown that this can be performed within a single breath-hold, using a high temporal resolution phase contrast acquisition in the ascending aorta with simultaneous oscillometric blood pressure measurement. These data provide systemic vascular resistance, total arterial compliance, local pulse wave velocity/characteristic impedance and wave reflections, which describe central aortic systolic pressure in this population.

We have shown that both c-SBP and BCW are important determinants of the elevated LV mass in this group, in contrast to p-SBP and coarctation index. These parameters are important biomarkers, and at least c-SBP may be modifiable through therapeutic interventions with current therapy. Therapies that can influence arterial compliance and wave reflections may represent important drug development targets for the future.
Chapter 4  Non-Invasive Pulmonary Artery Wave Intensity Analysis in Pulmonary Hypertension

4.1 Abstract

Pulmonary wave reflections are a potential hemodynamic biomarker for pulmonary hypertension (PH) and can be analyzed using wave intensity analysis (WIA). In this study we used pulmonary vessel area and flow obtained using cardiac magnetic resonance to implement WIA non-invasively. We hypothesized that this method could detect differences in reflections in PH patients compared to healthy controls and could also differentiate certain PH subtypes.

20 patients with PH (35% CTEPH, 75% female) and 10 healthy controls (60% female) were recruited. Right and left pulmonary artery (LPA & RPA) flow and area curves were acquired using self-gated golden-angle, spiral, phase-contrast MR with a 10.5ms temporal resolution. This data was used to perform WIA on patients and controls. The presence of proximal clot in CTEPH patients was determined from contemporaneous CT/angiographic data.

A backwards-travelling compression wave (BCW) was present in both LPA and RPA of all PH patients, but was absent in all controls \((p=6e^{-8})\). The area under the BCW was associated with a sensitivity of 100% (95% CI 63-100%) and specificity of 91% (95% CI 75-98%) for the presence of clot in the proximal pulmonary arteries of patients with CTEPH.

In conclusion WIA metrics were significantly different between patients and controls; in particular the presence of an early BCW was specifically associated with PH. The magnitude of the area under the BCW showed discriminatory capacity for the presence of proximal PA clot in patients with CTEPH. These results demonstrate that WIA could be used in the non-invasive assessment of PH.
4.2 Introduction

Pulmonary hypertension (PH) is primarily characterized by increased pulmonary vascular resistance (PVR) and reduced pulmonary arterial compliance. However arterial wave reflections, which are caused by abrupt changes in vessel area or compliance, also contribute to right ventricular (RV) load. As PH is characterized by widespread vascular changes, it has been postulated that abnormal wave reflections may be an additional source of increased afterload.

Semi-quantitative studies of wave reflection have been attempted before in pulmonary hypertension; however, most have been limited to assessment of either pressure or flow. In chronic thromboembolic hypertension (CTEPH) for example, a ‘notch index’ on pulmonary artery Doppler velocity profiles has been used to estimate the effects of wave reflection on flow deceleration. This ratio has been associated with greater in-hospital mortality and persistent post-operative PH. Attempts to differentiate CTEPH from other forms of PH using pressure only metrics such as inflection time and augmentation index have unfortunately shown conflicting results.

Parker and Jones proposed a method called wave intensity analysis (WIA) to quantify wave reflections as a function of time and which allows both the direction and the type of wave to be evaluated. The main problem with conventional WIA is that it requires invasive measurement of pressure and velocity, hindering its use in the clinical environment. Nevertheless, both animal and limited human studies do suggest that pathological wave reflections are present in pulmonary vascular disease.

Recently, it has been demonstrated that WIA can be performed non-invasively using image-based measures of arterial area or diameter and flow. Phase contrast magnetic resonance (PCMR) is the reference standard method of measuring flow and can also provide area measurements. However, high temporal resolution data is necessary to accurately assess wave speed, which conventionally requires long free breathing acquisitions. Unfortunately, in this setting, respiratory motion can blur the vessel wall, rendering such data unsuitable for WIA.
In this study, a previously validated respiratory self-navigated golden angle spiral PCMR sequence was used to acquire vessel area and flow data in order to perform WIA in volunteers and patients with PH. This sequence provides data with a sampling frequency 3-4 times higher than conventional CMR flow imaging and overcomes the problems of vessel wall blurring due to breathing.

### 4.2.1 Hypotheses

1. CMR Wave intensity analysis in the Pulmonary artery is feasible.
2. Differences in Wave reflection can be identified between patients with PH and healthy Controls.
3. WIA can discriminate patients with proximal chronic thromboembolic pulmonary hypertension (CTEPH), disease from other forms of PH.
4. Wave reflections are independent of steady-state haemodynamics.
4.3 Methods

4.3.1 Subjects

20 consecutive patients with pulmonary hypertension undergoing right heart catheterization and 10 healthy volunteers were recruited. PH was diagnosed by right heart catheterization as a mean pulmonary artery pressure greater than 25 mmHg and a pulmonary capillary wedge pressure less than 15 mmHg. Exclusion criteria were: (i) Irregular heart rates; (ii) Contraindications to cardiovascular magnetic resonance (CMR) such as MR-incompatible implants; (iii) Known independent left-sided cardiac disease unrelated to PAH; (iv) Clinically significant restrictive or obstructive lung disease identified by pulmonary function tests; or (v) Pregnancy. The study was performed with local research ethics committee approval and written informed consent was obtained.

4.3.2 MR Protocol

All imaging was performed on a 1.5T CMR scanner (Magnetom Avanto, Siemens Healthcare, Erlangen, Germany), using two rows of spine coil elements and two rows of body-matrix elements, giving a total of 12 coil elements. A vector electrocardiographic system was used for cardiac gating. All flow imaging for WIA was performed using a self-navigated, cardiac gated, golden-angle spiral PCMR sequence. In brief, an image-based navigator was first produced by reconstructing low temporal resolution (315ms) real-time images by combining the data in consecutive groups of 30 spiral pairs. This navigator was then used to select the spiral interleaves acquired in expiration for final reconstruction of the retrospectively cardiac-gated data. Sequence parameters: TE/TR 2.7/5.26ms, FOV 450x450mm, Matrix: 192x192, uniformly distributed spiral interleaves required to fill k-space: 80, slice thickness: 7mm, VENC: 150cm/s, Flip angle: 25°, pixel bandwidth: 1628Hz/pixel. This achieved a temporal resolution of 10.5ms, with a spatial resolution 2.34x2.34mm, giving approximately 90 cardiac phases, in a scan time of approximately 4 minutes. Pulmonary artery flow imaging was performed at the approximate midway point of both the left and right pulmonary arteries (PA). The right and left PAs were used to avoid the through plane motion of the pulmonary trunk, and to facilitate the investigation of asymmetric lung involvement.
4.3.3 Image Processing

All images were processed using an in-house plug-in for the open source DICOM software OsiriX (OsiriX Foundation, Geneva, Switzerland).\(^{67}\) Segmentation of the branch PAs was performed on the modulus image using a previously validated semi-automatic registration-based algorithm.\(^{68}\) The branch PA region of interest (ROI) could also be manually altered if necessary to ensure optimal vessel wall delineation. The final ROI was used to both calculate the cross-sectional area (A) and prescribe the region in the phase image from which flow (Q) were calculated.

4.3.4 Signal Processing

For wave speed analysis, A and Q curves were not interpolated or filtered. For wave intensity analysis the A and Q curves were interpolated to 1ms temporal resolution using a cubic spine and filtered using a zero-phase, low-pass, 2\(^{nd}\) order Butterworth filter with cut-off frequency of 20Hz. All signal processing was performed in Matlab 2012a (Mathworks).

4.3.4.1 Wave Speed Calculation

Wave speed (\(c\)) was calculated using the QA method,\(^{28,29}\) as deduced from the water hammer equations. Wave speed is equivalent to pulse wave velocity (PWV). This method relies on the fact that:

\[
c = \pm \frac{dQ}{dA} \pm \frac{dQ}{dA} \pm \frac{dQ}{dA} \quad \text{Equation 4-1}
\]

in the presumably reflection free part of early systole (with \(c\) in m/s, \(dQ\) in m\(^3\)/s and \(dA\) in m\(^2\)). In our implementation, the gradient of Q against A was calculated by linearly regressing the first three unfiltered and uninterpolated points of the Q and A curves at the start of systole.\(^{69}\) Only the first three points (first ~30ms of systole) were used to ensure that there was minimal signal contamination from wave reflections.\(^{65}\)
4.3.4.2 Wave Intensity Analysis

In WIA, waves are regarded as a summation of incremental wave fronts; it is therefore possible to separate the $Q$ and $A$ curves into the respective forward (+) and backward (-) components by expressing the relationship between $c$, and changes in flow and cross-sectional area. Equation 1 combined with Equations 2 and 3:

$$dA = dA_+ + dA_- \quad \text{Equation 4-2}$$
$$dQ = dQ_+ + dQ_- \quad \text{Equation 4-3}$$

can be solved for the changes in the forward and backward flow and cross-sectional area; this results in Equations 4 and 5:

$$dQ_\pm = \frac{1}{2} (dQ \pm cdA) \quad \text{Equation 4-4}$$
$$dA_\pm = \frac{1}{2} \left( A \pm \frac{1}{c} dQ \right) \quad \text{Equation 4-5}$$

Net wave intensity $dI_a$ was defined as the product of the differentials of cross-sectional area and flow.

$$dI_a = dA \ dQ \quad \text{Equation 4-6}$$

Similarly it can be shown that the net wave intensity $dI_a$ (Equation 6) can be divided into the forward and backward intensities, Equation 7:

$$dI_a = dI_a(+) + dI_a(-) \quad \text{Equation 4-7}$$

with the separated $dI_a$ expressed as:

$$dI_a(\pm) = \pm \frac{c}{4} \left[dA \pm \frac{dQ}{c}\right]^2 \quad \text{Equation 4-8}$$

Using this formulation forwards and backwards $dI_a$ were calculated and plotted. As per convention, the direction of waves was referenced to the direction of blood flow. Waves arising from the heart were defined as forward running and those arising from the vasculature as backward running. Waves causing an increase in area were classified as compression waves and those causing a decrease in area as expansion waves by examination of $dA_\pm$ plots. Thus, a forward running wave was held to be a
compression wave if $dA_+ > 0$ and an expansion wave if $dA_+ < 0$. Similarly, a backward-running wave was considered as a compression wave if $dA_- > 0$ and an expansion wave if $dA_- < 0$. Using this system three different early to mid systolic (flow onset to flow peak) waves were characterised: Forwards Compression Waves (FCW), Backwards Compression Waves (BCW) and Backwards Expansion Waves (BEW).

4.3.4.3 Wave Intensity Analysis Post-Processing

The type, duration, magnitude and time to peak (time from onset of ejection to waveform peak) of waves were determined by analysis of the net and separated WIA plots in Matlab. The areas under the separated waveforms were calculated by numerical integration.

As well as separate quantification of magnitude, timing and waveform areas: the average of all WIA metrics of both branch pulmonary arteries was also calculated ($FCW_{\text{mean}}$, $BCW_{\text{mean}}$, $BEW_{\text{mean}}$, $PWV_{\text{mean}}$).

4.3.5 Catheterization and Clinical Data

Right heart catheterization was performed in all patients with PH according to standard procedures, within 30 days of MR imaging using a Swan-Ganz catheter. Cardiac output was measured using thermodilution. Systolic (SPAP), diastolic (DPAP) and mean (MPAP) PA pressures, pulmonary capillary wedge pressure and PVR data were obtained. All patients had serum N-terminal pro-brain natriuretic peptide (NT-pro-BNP) levels and 6-minute walk test measured. The clinical subtype of PH was determined by review of patient records. For patients with CTEPH, the presence and location of proximal clot was determined and differentiated from distal disease by review of contemporaneous computed tomography and selective digital subtraction angiographic clinical data. RV ejection fraction (RVEF) was calculated as previously described\textsuperscript{119} from a RV transaxial stack using a radial k-t SENSE real-time sequence. Branch PA flow ratio was used to assess any asymmetry in lung blood flow; calculated by dividing branch PA flow by total pulmonary blood flow.
Acceleration time for both branch pulmonary arteries, and their average was calculated as the time from the onset of ejection to peak flow.

4.3.6 Statistics

STATA 13 and Graphpad Prism 5f for mac were used for statistical analysis and Figures. Data were examined for normality using the Shapiro-Wilk normality test. Descriptive statistics are expressed as mean ± Standard Error of Mean (SEM) when normally distributed and median (inter-quartile range, IQR) when non-normally distributed. Proportions are expressed as percentages.

Pearson’s correlation coefficient was used to analyze simple linear relationships between variables. The independent samples t-test was used to compare differences in parametric data between PH patients and controls; Welch’s correction was employed for unequal variances. The Mann-Whitney-U test was used for non-parametric data. Fisher’s exact test was used to compare proportions data.

Stepwise binary logistic regression analysis was used to identify covariates with independent association with the diagnosis of pulmonary hypertension.

Area under the receiver operating characteristics (ROC) curve was used to assess the diagnostic accuracy of WIA metrics for the identification of proximal clot in patients with CTEPH. For this analysis, the 40 branch pulmonary arteries (left and right in 20 PH patients) were coded according to the presence (8 lungs) or absence (32 lungs) of proximal clot on contemporaneous CT or angiographic imaging. The optimum cut off value was chosen to maximize the Youden index (sensitivity + specificity -1).

Multivariable linear regression analysis was used to determine covariates independently associated with transpulmonary gradient (TPG) and pulmonary vascular resistance. Probability values, p<0.05 were considered statistically significant.
4.4 Results

4.4.1 Study Population Characteristics

Mean age of PH patients was 54±3 years (15 female, 5 male) and mean age of controls was 47±3 years (6 female, 4 male); there was no significant difference in age or gender between groups.

The diagnoses in the patient group were: 8 systemic sclerosis (7 limited cutaneous, 1 diffuse cutaneous), 7 CTEPH, 2 systemic lupus erythematosus (SLE), 2 mixed connective tissue disease, 1 idiopathic pulmonary arterial hypertension (IPAH).

The median interval between right heart catheterization and CMR was 6 days (IQR 2-11 days). Hemodynamic data were available for all patients. Mean MPAP was 43±3 mmHg, SPAP 70±5 mmHg, DPAP 27±2 mmHg. Mean pulmonary capillary wedge pressure was 11±1 mmHg and mean PVR was 7.4±0.8 Wood units (WU).

In patients the mean 6-minute walk test was 338±28 m and median serum NT-pro-BNP was 145 pmol/L (IQR 225 pmol/L). PH mean CMR RVEF was 41±3%.

In the CTEPH group, 5/7 patients had proximal disease (2 right lobe, 3 bilateral). There was no significant difference between CTEPH patients with proximal disease (n=5) and other PH patients (n=15, other PH etiologies) based on cardiac catheterization data: PVR (p=0.4), MPAP/TPG (p=1.0/p=0.7), pulse pressure (p=0.6) or clinical parameters: 6-minute walk test (p=0.9), serum NT-pro-BNP (p=0.8), and CMR RVEF (p=0.9).
Figure 4-1 WIA in representative PH patient (A-D) and Control (E-H). Three types of waveforms were found to arise during early and mid systole in study participants using wave separation analysis: (1) A forward compression wave, characterized by: increasing area and increasing flow representing cardiac ejection, Panel C & G, labeled ‘*’ (2) A backwards compression wave: increasing area [pressure] and decreasing flow, Panel C labeled ‘†’, and (3) A backwards expansion wave: decreasing area [pressure] and/or increasing flow, Panel G labeled ‘‡’. The identification of the backwards compression and expansion waves can be seen from examination of panel D and H, showing the ΔA± plots. The dotted line across panels A-D shows the timing of peak flow used to measure acceleration time (AT), demonstrating it arises as a consequence of the arrival of the backwards compression wave overcoming the forward compression wave (arrow). Time=0 corresponds to the onset of data acquisition as triggered by the R wave on CMR vectorcardiography.
4.4.2 WIA in Patients and Controls

The PWV was approximately two times higher in patients compared with controls Table 4-1(PWV_{mean}: 1.36±0.08m/s vs. 0.72±0.05m/s, p=3e^{-7}).

Early- and mid-systolic forward and backward waves were often found to be coincident on net wave intensity, $dl_a$ (Figure 4-1). Following wave separation into forward and backward components, important group differences were apparent (Figure 4-1). Peak wave intensity (cm$^5$/s), time to peak wave intensity (ms) and wave intensity area (cm$^5$) for FCW, BCW and BEW are described in Table 4-1.

FCW area was significantly lower in patients than controls as shown in Figure 4-2, and Table 4-1 (FCW_{mean}: 0.003 cm$^5$ [IQR 0.002] vs. 0.006 cm$^5$ [IQR 0.005], p=0.002). The time to peak FCW_{mean} was earlier in patients with PH, mean 31±2ms compared with controls 38±1ms, p=0.03.

A backwards-travelling compression wave (BCW) was present in both the LPA and RPA of all PH patients, but was absent in all controls ($p=6e^{-8}$, OR: 861 [15-∞]), Figure 4-2. Patients’ median BCW_{mean} area was 0.0004cm$^5$ (IQR 0.0006cm$^5$), and the time to peak BCW_{mean} was 76±6ms.

A backwards-travelling expansion wave (BEW) was present in the RPA of 9/10 controls, but was absent in all patients ($p<0.0001$, OR: 260 [10-6988]). A BEW was present in the LPA of all controls but only in 4/20 of PH patients ($p<0.0001$, OR: 77 [4-1583]). The median control BEW_{mean} area was 0.0005cm$^5$ (IQR 0.0008cm$^5$), Figure 4-2. The mean time to peak BEW_{mean} was 45±5ms.

Acceleration time was significantly lower in patients than controls as shown in Figure 4-2, Table 4-1 (AT_{mean}: 67±4 m/s vs. 121±11 m/s, p=0.001). However, there was still overlap between the two groups. The phenomenon of reduced acceleration time in PH was found to arise as a consequence of the interaction between the FCW and the timing and magnitude of the reflected BCW, Figure 4-1.
Stepwise binary logistic regression analysis of variables listed in Table 4-1 identified the presence of a backward compression wave as the covariate most strongly associated with the presence of PH, discriminating groups completely (-2 log-likelihood: 0).

Figure 4-2 Scatter diagrams of WIA metrics in patients and controls. (A) Acceleration Time (AT) mean. (B) Forward compression wave (FCW) mean area. (C) Backward compression wave (BCW) mean area. (D) Backward Expansion Wave (BEW) mean area.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patient</th>
<th>Control</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>PWV (m/s) ‡</td>
<td>Right 1.26 (0.07)</td>
<td>0.73 (0.07)</td>
<td>4e-5</td>
</tr>
<tr>
<td></td>
<td>Left 1.46 (0.12)</td>
<td>0.70 (0.06)</td>
<td>1e-5</td>
</tr>
<tr>
<td></td>
<td>Mean 1.36 (0.08)</td>
<td>0.72 (0.05)</td>
<td>3e-7</td>
</tr>
<tr>
<td>Acceleration Time (ms) ‡</td>
<td>Right 60 (4)</td>
<td>108 (9)</td>
<td>0.0004</td>
</tr>
<tr>
<td></td>
<td>Left 74 (5)</td>
<td>135 (16)</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>Mean 67 (4)</td>
<td>121 (11)</td>
<td>0.001</td>
</tr>
<tr>
<td>FCW Peak (cm$^3$/s) †</td>
<td>Right 0.09 (0.11)</td>
<td>0.18 (0.14)</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>Left 0.06 (0.06)</td>
<td>0.06 (0.08)</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>Mean 0.08 (0.08)</td>
<td>0.15 (0.11)</td>
<td>0.06</td>
</tr>
<tr>
<td>FCW Peak time (ms) ‡</td>
<td>Right 29 (2)</td>
<td>33 (3)</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>Left 33 (2)</td>
<td>42 (4)</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>Mean 31 (2)</td>
<td>38 (3)</td>
<td>0.03</td>
</tr>
<tr>
<td>FCW Area (cm$^3$) †</td>
<td>Right 0.003 (0.004)</td>
<td>0.005 (0.005)</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>Left 0.002 (0.002)</td>
<td>0.003 (0.003)</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Mean 0.002 (0.002)</td>
<td>0.005 (0.003)</td>
<td>0.006</td>
</tr>
<tr>
<td>BCW Peak (cm$^3$/s) †</td>
<td>Right 0.01 (0.02)</td>
<td>0 (0)</td>
<td>6e-8</td>
</tr>
<tr>
<td></td>
<td>Left 0.006 (0.02)</td>
<td>0 (0)</td>
<td>6e-8</td>
</tr>
<tr>
<td></td>
<td>Mean 0.01 (0.01)</td>
<td>0 (0)</td>
<td>6e-8</td>
</tr>
<tr>
<td>BCW Peak time (ms) ‡ *</td>
<td>Right 73 (6)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Left 79 (8)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Mean 76 (6)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>BCW Area (cm$^3$) †</td>
<td>Right 0.0004 (0.0005)</td>
<td>0 (0)</td>
<td>6e-8</td>
</tr>
<tr>
<td></td>
<td>Left 0.0003 (0.0006)</td>
<td>0 (0)</td>
<td>6e-8</td>
</tr>
<tr>
<td></td>
<td>Mean 0.0004 (0.0006)</td>
<td>0 (0)</td>
<td>6e-8</td>
</tr>
<tr>
<td>BEW Peak (cm$^3$/s) †</td>
<td>Right 0 (0)</td>
<td>0.02 (0.02)</td>
<td>9e-6</td>
</tr>
<tr>
<td></td>
<td>Left 0 (0)</td>
<td>0.01 (0.01)</td>
<td>1e-6</td>
</tr>
<tr>
<td></td>
<td>Mean 0 (0)</td>
<td>0.01 (0.01)</td>
<td>1e-6</td>
</tr>
<tr>
<td>BEW Peak time (ms) ‡ *</td>
<td>Right -</td>
<td>30 (4)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Left 40 (2)</td>
<td>56 (7)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Mean 41 (2)</td>
<td>45 (5)</td>
<td>-</td>
</tr>
<tr>
<td>BEW Area (cm$^3$) †</td>
<td>Right 0 (0)</td>
<td>0.0005 (0.0008)</td>
<td>9e-6</td>
</tr>
<tr>
<td></td>
<td>Left 0 (0)</td>
<td>0.0004 (0.0002)</td>
<td>3e-7</td>
</tr>
<tr>
<td></td>
<td>Mean 0 (0)</td>
<td>0.0005 (0.0005)</td>
<td>1e-7</td>
</tr>
</tbody>
</table>

Table 4-1 Comparison of WIA metrics between PH patients and controls. † Non-normally distributed, Median (IQR), Mann-Whitney-U test. ‡ Normally distributed, Mean (SEM), t-test ± Welch correction for unequal variances. *Waveform absent in the majority of one group, therefore statistical testing of timing parameters or ratios not performed.
4.4.3 PH Subtype Differentiation

BCW area and AT showed statistically significant discriminatory capacity for the presence of clot (Figure 4-3, Table 7); PWV, FCW area, FCW peak time, BCW peak time and branch PA flow ratio were non-significant (Table 7).

The area under the curve (AUC) for BCW area was 0.97 (95% confidence interval [CI] 0.91-1.0), p=0.00006. A BCW area threshold of >0.0006cm$^5$ was associated with a sensitivity of 100% (95% CI 63-100%) and specificity of 91% (95% CI 75-98%) for the presence of clot in the proximal pulmonary arteries. Example WIA in patients with and without proximal clot, Figure 4-4.

The AUC for AT was 0.84 (95% CI 0.70 to 0.90). An AT threshold of <57.6ms was associated with a sensitivity of 88% (95% CI 47-99%) and specificity of 81% (95% CI 64-93%) for the presence of proximal clot.

Figure 4-3 Receiver operating characteristics analysis for the detection of proximal PA clot: Sensitivity (y axis) 1-Specificity (x axis). BCW area (blue) AUC 0.97, Acceleration Time (red) AUC 0.84. Interrupted black line – line of identity.
Table 7 Receiver operating characteristics analysis for the detection of proximal PA clot. AUC, area under the ROC curve. Significant parameters in bold.

<table>
<thead>
<tr>
<th>Variable</th>
<th>AUC</th>
<th>AUC 95% CI</th>
<th>p</th>
<th>Threshold</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCW Area</td>
<td>0.97</td>
<td>0.92-1.0</td>
<td>0.0005</td>
<td>&gt;0.0006cm&lt;sup&gt;5&lt;/sup&gt;</td>
<td>100% (63-100)</td>
<td>91% (75-98)</td>
</tr>
<tr>
<td>Acceleration Time</td>
<td>0.84</td>
<td>0.70-0.98</td>
<td>0.003</td>
<td>&lt;57.6ms</td>
<td>88% (47-99)</td>
<td>81% (64-93)</td>
</tr>
<tr>
<td>PWV</td>
<td>0.70</td>
<td>0.47-0.92</td>
<td>0.09</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>FCW Area</td>
<td>0.61</td>
<td>0.38-0.85</td>
<td>0.3</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>BCW Peak Time</td>
<td>0.60</td>
<td>0.40-0.79</td>
<td>0.4</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>FCW Peak Time</td>
<td>0.50</td>
<td>0.27-0.74</td>
<td>1.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Figure 4-4 RPA WIA in 2 patients with CTEPH. (A) Patient with proximal clot in right lower lobe artery and (B) patient with disease limited to distal vessels. Note larger BCW in patient A.
4.4.4 Steady state Haemodynamics and WIA

There was no observed association between steady state hemodynamic parameters and BCW\textsubscript{mean} area, acceleration time or PWV (Table 8).

There was a strong negative correlation between FCW\textsubscript{mean} area and TPG, (R=-0.56, p=0.01) and PVR (R=-0.68, p=0.001). Of note, the FCW\textsubscript{mean} area also correlated significantly with RVEF (R=0.65, p=0.002)

The BCW\textsubscript{mean} peak time was negatively associated with TPG, (R=-0.49, p=0.03).
Table 8 Simple linear correlations between WIA metrics and acceleration time with haemodynamic and clinical variables. Significant parameters in bold.

<table>
<thead>
<tr>
<th></th>
<th>FCW&lt;sub&gt;mean&lt;/sub&gt; Area</th>
<th>BCW&lt;sub&gt;mean&lt;/sub&gt; Area</th>
<th>FCW&lt;sub&gt;mean&lt;/sub&gt; Peak Time</th>
<th>BCW&lt;sub&gt;mean&lt;/sub&gt; Peak Time</th>
<th>Acceleration Time&lt;sub&gt;mean&lt;/sub&gt;</th>
<th>PWV&lt;sub&gt;mean&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p</td>
<td>r</td>
<td>p</td>
<td>r</td>
<td>p</td>
</tr>
<tr>
<td>PVR</td>
<td>-0.66</td>
<td>0.001</td>
<td>-0.13</td>
<td>0.59</td>
<td>-0.44</td>
<td>0.05</td>
</tr>
<tr>
<td>TPG</td>
<td>-0.56</td>
<td>0.01</td>
<td>0.21</td>
<td>0.93</td>
<td>-0.44</td>
<td>0.05</td>
</tr>
</tbody>
</table>
4.5 Discussion

In this proof of concept study, the feasibility of performing noninvasive WIA in the pulmonary arteries using phase contrast MR imaging has been demonstrated for the first time. The main findings were: i) There was a significant difference in WIA metrics between patients and controls; ii) The presence of a BCW was specifically associated with the presence of PH; and iii) The magnitude of the BCW area showed discriminatory capacity for the presence of proximal PA clot in patients with CTEPH. These preliminary results demonstrate that WIA could be used in the non-invasive assessment of patients with PH.

The primary finding of this study was the marked difference in the pattern of early backward wave reflections seen in patients and controls. Specifically, patients were characterized by BCWs (absent in controls), while BEWs predominated in normal subjects.

These observations are consistent with the experimental work of Hollander et al. who observed BEWs in normal canine pulmonary arteries and BCWs in experimentally vasoconstricted pulmonary arteries. These findings can be attributed to the different types of reflecting sites found in the 2 models. In normal pulmonary arteries, the increasing total vessel area at each bifurcation results in reflection sites with predominately negative reflection coefficients and consequent backward expansion waves. Conversely, the reduced vessel area and increased stiffness found in the vasoconstricted state creates reflection sites with positive reflection coefficients and results in compressive reflections.

In this study, the reflection site of the BCW was approximately 2-3cm from the site of measurement in the branch PAs (based on wave timing and PWV). Thus, quantifiable reflections in the branch PAs seem to arise from the next generation of vessels rather than the terminal branches. This initially appears surprising as the majority of vascular remodeling in PH occurs in the peripheral pulmonary arteries. However, recent work in the systemic vasculature has demonstrated that wave reflections do not arise from a single discrete reflecting site, rather they are an amalgamation of reflections, with more proximal arising waves being exponentially
more important. This so-called ‘horizon effect’ is due to re-reflection and entrapment of reflected waves, and may be even more important in the highly fractal pulmonary circulation. This effect may also explain the lack of correlation between steady state haemodynamics and BCW, as they reflect different attributes of the vasculature.

Our data is also concordant with studies of the fetal pulmonary circulation, where large BCWs were observed to arise in the setting of the high pulmonary vascular resistance in utero. An invasive WIA study by Lau et al. also reported the presence of a BCW in PH. However, in this study small BCWs were also observed in the control patients. This is probably because hemodynamic measurements were made in the more distal pulmonary lobe branches in order to obtain a stable catheter position. The greater proximity to the terminal branches likely explains the presence of BCWs in normal controls.

These results suggest that it may be possible to use the presence of an early BCW in the branch PAs as a screening test for PH. It may be particularly useful in situations where diagnostic indictors such as septal curvature are less reliable (i.e. patients with PH related to complex congenital heart disease). Nevertheless, this was not a diagnostic cohort study and further work must be performed in order to evaluate true diagnostic accuracy.

Another significant finding was that BCW area was able to discriminate between patients with proximal CTEPH and those with other forms of PH. This was in spite of the fact that there were no invasive hemodynamic differences between the two groups. Combined with the lack of correlation between steady state haemodynamics and BCW, this reiterates the fact that BCW provides ‘novel’ hemodynamic information. This ‘novel’ information could be used as the basis for a non-invasive and non-ionizing test for patients with treatable proximal clot. Of course, a larger comparative study would be required to show that it has benefit over current MR perfusion methods. Another intriguing possibility is that this ‘new’ information may provide additional prognostic information over conventional hemodynamic
measures. This cannot be predicted from this small study and warrants further investigation.

Our data also confirms that abnormal wave reflections explain the shorter acceleration time \(^{124-126}\) and notched/scalloped flow/velocity curves \(^{111}\) observed in PH. Specifically, notching of the flow curve in PH – also the point of measurement of AT – occurs when the abnormally large BCW exceeds the incident FCW. Shortened acceleration times can therefore be considered an epiphenomenon of disease-associated wave reflection. It is for this reason, we believe that AT performs less well than the WIA components.

In addition, the FCW may provide insight into ventricular function, being lower in patients with PH and correlating significantly with RVEF and inversely with PVR. Furthermore, it has been shown that peak aortic FCW is proportional to \((\max dp/dt)^2\) \(^{127}\) and responds to alterations in the inotropic state of the ventricle. \(^{128, 129}\)

A prerequisite of WIA is the acquisition of high temporal resolution data in order to accurately evaluate PWV and correctly perform wave separation. In this study, this was achieved using a respiratory self-navigated, cardiac gated, golden-angle spiral PCMR sequence. This sequence has the benefit of being able to acquire area and flow data at 10.5ms temporal resolution, while also maintaining edge sharpness. However, any navigated high temporal resolution PCMR could be used for WIA, although with less temporal efficiency. Importantly, data was acquired in the branch pulmonary arteries rather than the main pulmonary trunk. This reduced any corruption of the data due to through-plane motion and also allowed assessment of each lung separately.

An important difference between this study and other WIA studies is the use of the QA method rather than the Pressure-Velocity (PU) method for the determination of wavespeed. The QA-method has recently been shown to underestimate PWV whilst the PU method overestimates PWV in the presence of reflections. \(^95\) Importantly, the PU method overestimates wavespeed to a greater extent than the QA method underestimates it. In presence of a positive reflection, \(\gamma\), the PU loop overestimates
with a proportionality factor \((1+ \gamma)/(1- \gamma)\), while the QA-loop method underestimates with \((1- \gamma)/(1+ \gamma)\). For a value of \( \gamma = 0.3 \), for instance, the PU-loop method overestimates by 86%, while the QA-loop method underestimates by 46%. As reflections are more pronounced in PH, it is possible that PWV is (more) underestimated than in controls, thereby artificially reducing the group difference. This is preferable; as it provides a more conservative difference than would be the case if using the PU method, which could conflate group differences.

A major benefit of the WIA implementation described in this study is that it does not require cardiac catheterization. Furthermore, as the noninvasive area and flow data is acquired in the same time frame there is no need to align pressure and flow signals to enforce a straight-line segment for calculation of wave speed.

PWV using PU methods in instrumented animal pulmonary arteries have been reported in the region of 2-3m/s. 113,130 Lau et al. reported PWV of 3.8m/s in human controls and 6.9m/s in patients with PAH. 114 Using the QA method in the pulmonary trunk, Peng et al. reported wave speeds of 1.84m/s in healthy volunteers, and 1.96m/s including other patients without pulmonary hypertension. 131 Ibrahim et al. reported values 2-3m/s in cardiac patients without pulmonary hypertension and 5.2m/s in those with PH. 132

A difficulty in comparing our wavespeed with other pulmonary QA or PU methods lies in our use of only the first 30ms after ejection to calculate wavespeed. Other studies have reported higher wave speeds, but have assessed PWV over intervals of 100ms or more, when empirically this would be considered contaminated by reflections, and also when arterial pressure is much higher (pressure dependency of PWV).

Furthermore the use of the pulmonary trunk rather than the branch pulmonary arteries may be associated with higher QA values due to the complex through-plane movement of the vessel. The pulmonary trunk has an ‘hourglass’ shape, and moves inferiorly in systole; as the narrower waist of the vessel moves into the imaging plane, a reduced \( \Delta A \), would artifactually increase PWV.
4.5.1 Limitations

The purpose of this study was to demonstrate the feasibility of non-invasive WIA and characterize differences between patients and controls. The significant finding of a BCW only present in PH patients suggests utility as a potential diagnostic test. However a diagnostic testing cohort would be necessary to confirm this.

The role of BCW area for the detection of clot similarly shows potential as an adjunct to non-invasive PH assessment. However, the modest sample size necessitates further work, as reflected in the confidence intervals for sensitivity and specificity.

In this study, cardiac catheterization data and CMR data were not simultaneously acquired; however, the intervening period between catheterization and CMR was short, and patients did not have any significant clinical changes between studies. Catheter based calculations of flow were also made from thermodilution. The possibility, that given simultaneous catheter and CMR assessment, there would be stronger correlations with haemodynamics cannot be excluded.

This technique does not presuppose a particular pressure-area relationship, and therefore the units of non-invasive WIA in this study, m$^3$/s do not have an easily understandable physical meaning: in contrast to the W/m$^2$ units of invasive WIA. However, the waveforms produced by non-invasive WIA are qualitatively similar to invasive WIA in the literature – and given a linear pressure-area relationship would be proportional.

4.5.2 Conclusion

In conclusion, it has been shown that noninvasive pulmonary WIA reveals important abnormalities in patients with PH, distinguishing the disease state from normality, and shows potential as a tool to identify PH and differentiate PH subtypes.
4.5.3 Appendix

In the absence of a ‘reference standard’ method for measuring PWV in the pulmonary vasculature, we compared the PWV estimated using the QA method with a novel method developed by Davies et al. (4) for use in the coronary arteries in the presence of significant reflections. This method works by minimizing net wave energies, and was designed to use simultaneously acquired pressure (P) and velocity data (U) from a single position within a vessel. It does not require the vessel to be long enough for two measurements nor does it rely on a period during which there is only a single wave impulse. The method can be modified for use with flow and area measurements:

\[ c = \sqrt{\frac{\sum d q^2}{\sum d A^2}} \]  

Equation 4-9

Using Bland-Altman analysis, we observed good agreement between the two methods, bias 0.07m/s (standard deviation of bias, 0.45m/s), and 95% limits of agreement -0.83-0.97m/s, Figure 4-5.

Figure 4-5 Bland-Altman of bias (black solid line) and 95% limits of agreement (Gray broken lines). Data is presented as difference between QA method and minimisation of net wave energy method (y-axis), versus the average of both (x-axis).
Chapter 5  Conclusions And Future Work

"Je n'ai fait celle-ci plus longue que parce que je n'ai pas eu le loisir de la faire plus courte." Blaise Pascal 1657

"If I had more time, I would have written a shorter letter"

In this thesis, novel signal processing techniques have been combined with advanced phase contrast flow imaging to acquire vascular haemodynamic data non-invasively. The techniques have been applied to diseases of the systemic and pulmonary circulations in order to better understand their pathophysiology and to develop potential non-invasive clinical biomarkers.

In Chapter 2 the development and validation of a novel method to derive central systolic blood pressure was described. This experiment tested the hypothesis that central pressure could be derived from area-time data acquired in the ascending aorta using models of the pressure area relationship. Pressure-area models were calibrated to brachial blood pressure (linear and exponential models) and characteristic impedance (arctangent model) and validated against pressure measured by carotid tonometry. Such methods are attractive because they allow for the acquisition of central pressure data during routine PCMR flow acquisition, and could readily be incorporated into clinical workflows. Whilst the arctangent has certain hypothetical advantages, we showed no differences between this and the simpler exponential method (used in the subsequent chapter). This is important for clinical generalizability, as the exponential method obviates the need for flow data (by not requiring PWV). This means that such data could be easily acquired using balanced SSFP cine imaging in the ascending aorta, which is more easily processed using automatic segmentation methods, Figure 5-1.
In Chapter 3, non-invasive haemodynamic assessment for patients with coarctation of the aorta was implemented. This study tested the hypothesis that the principle components of central haemodynamics: systemic vascular resistance, central compliance, characteristic impedance and wave reflections could be measured non-invasively. The population studied was repaired coarctation of the aorta, in which it was hypothesised that important haemodynamic differences compared to healthy controls would be observed. An important component of this experiment was the implementation of non-invasive wave intensity analysis (defined in terms of area and flow) to examine the contribution of reflected waves to LV load. This experiment demonstrated that central-systolic blood pressure and backwards travelling wave reflections were important determinants of afterload and LV mass. In addition to
providing corroborative evidence for our method central blood pressure derivation, this work calls for fundamental reconsideration of surveillance in patients with coarctation by showing that conventional biomarkers of the disease do not parallel end organ effects – such as changes in LV mass.

Chapter 4 describes the experimental application of the previously developed techniques to the pulmonary circulation. The pulmonary circulation is inherently more difficult to study than the systemic circulation, in part because pressure cannot be directly measured non-invasively and also there exist several obstacles to successful imaging. The pulmonary trunk is the most obvious candidate vessel for investigation. However significant through-plane motion limited its use for our purposes, as area data could not be reliably obtained. Instead the branch pulmonary arteries were used, which advantageously also provides separate lung data. Moreover, patients with pulmonary hypertension, find it difficult to breath-hold for the 10-15secs required using the high-resolution spiral prospectively triggered flow sequence. To overcome this, a self-navigated, cardiac gated, golden-angle spiral PCMR sequence was used. In this scheme, an image-based navigator was first produced using low temporal resolution real-time images. This navigator was then used to select the spiral interleaves acquired in expiration for final reconstruction of the retrospectively cardiac-gated data.

As PH is characterized by widespread vascular changes, we postulated that abnormal wave reflections arising in this condition might provide novel hemodynamic information with potential application as a biomarker. In this study we showed that the presence of a backwards compression wave, reflected from the lungs, identified patients with PH and its magnitude showed discriminatory capacity for the presence of proximal PA clot in patients with CTEPH.

In this thesis, innovative signal processing has been combined with advanced flow imaging to achieve the principle aim of this work – non-invasive haemodynamic assessment.
5.1 Future Work

5.1.1 Clinical Adoption of Tools

Development and implementation of the signal processing tools has been a significant proportion of the work presented in this thesis, however there remain several obstacles that prevent direct translation to the clinical workflow. Providing these tools in an easily accessible form for clinical end-users is an important next step in its dissemination.

Each high temporal resolution image may contain 70-100 frames; however despite semi-automatic image registration, manual correction can be time consuming. This is particularly problematic in diastole, when signal intensity is lower, and registration tools tend to mis-register the vessel wall. As alluded to above, a balanced SSFP image (rather than PCMR) can be used to obtain area data only, which can be used for calculation of central blood pressure using the exponential method. Vessel edge delineation is maintained through the cardiac cycle, and therefore makes registration trivial, Figure 5-1. Preliminary work in this area indicates that this may be an important future direction; biomarkers, which are time consuming to acquire, are unlikely to transition to the clinical arena.

All the signal-processing techniques are currently implemented in Matlab. To facilitate uptake and utilisation in the clinical environment, it is essential that an easy to use tool be incorporated into the software used by clinicians to analyse imaging data. I plan to implement a plugin for the open source OsiriX software that will output central pressure, resistance, compliance, local pulse wave velocity and wave intensity using phase contrast data.

5.1.2 Alternative Applications

The techniques developed in this thesis have the potential for wider application. Other systemic vascular diseases of interest include connective tissue diseases such as Marfan syndrome or vascular Ehlers-Danlos syndrome. These disorders are inherited conditions with alterations in genes affecting the synthesis and processing of different forms of connective tissue proteins. Consequential abnormalities in vessel
properties are responsible for an increased risk of life-threatening spontaneous vascular rupture in these conditions. It is possible that non-invasive assessment of vascular properties in particular c-SBP, aortic compliance and wave reflections could provide clinically useful information allowing improved phenotyping or better risk assessment for vascular rupture events.

Pulmonary wave intensity could also easily be applied to other forms of pulmonary hypertension, in particular congenital heart disease or left heart lesions. The assessment of pulmonary hypertension in congenital heart disease (CHD) is challenging, partly because this group may have elevated pulmonary pressure caused by a range of hemodynamic mechanisms (sometimes coexisting), including increased pulmonary flow (left-to-right shunts), elevated pulmonary vascular resistance or elevated pulmonary venous pressure. An important clinical problem is identification of patients who have developed pulmonary vascular disease secondary to unrepaired left to right shunts (PDA, VSD or ASD). Our study demonstrated abnormal wave reflections in patients with PH due to pulmonary vascular disease. It is presently unknown whether patients with elevated PA pressure due to high pulmonary blood flow or elevated pulmonary venous pressure have normal or abnormal backward reflections – if a different or indeed a normal pattern of wave reflection were observed, this could represent an important tool for excluding pulmonary vascular disease in these patients. This methodology may also be useful for the detection of pulmonary vascular disease complicating left heart disease (combined post-capillary PH and pre-capillary PH, or ‘out of proportion’ PH).

An outstanding and important question arising from this work is whether the developed haemodynamic markers track disease progression or response to therapy. Therefore, a planned extension is to measure c-SBP or BCW in response to therapies in the systemic and pulmonary circulations (e.g anti-hypertensive therapy in systemic circulation and pulmonary vasodilators or pulmonary endarterectomy in pulmonary hypertension).

This thesis has focused exclusively on arterial hemodynamics, however examination of the venous circulation may provide equally interesting insights. For example, caval wave intensity analysis in the superior and total cavopulmonary circulation for
single ventricle palliation in congenital heart disease or pulmonary venous wave intensity in left ventricular diastolic dysfunction. However an important obstacle to venous wave intensity analysis is the definition and measurement of wave speed in the venous system.

5.2 Conclusion

This thesis aimed to describe the development and application of novel signal processing techniques to derive haemodynamic data non-invasively from high temporal resolution phase-contrast data. For the systemic circulation, all the components of pulsatile central haemodynamics can be acquired in a single breath-hold, and we have shown that this data deepens our understanding of the vascular problems in patients with repaired coarctation of the aorta. The pulmonary circulation poses greater challenges, despite this, it has been shown that wave reflections are abnormal in pulmonary hypertension, and can be used to differentiate both health from disease and identify disease subtypes.

It is hoped that the data from these experiments will positively benefit the care of patients in the future.
Appendix A  Academic Outputs During PhD

Prizes

Melvin Judkins Young Clinical Investigator Award  American Heart Association, Council on Cardiovascular Radiology and Intervention (2014)

Book Chapters


Manuscripts


Quail MA, Taylor AM. Computer Modelling to Tailor Therapy for Congenital Heart Disease. *Curr Cardiol Rep* 2013; 15(395);


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