Non-Invasive, MRI-Based Calculation of the Aortic Blood Pressure Waveform by 0-Dimensional Flow Modelling
Development and Testing Using In Silico and In Vivo Data

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Non-Invasive, MRI-Based Calculation of the Aortic Blood Pressure Waveform by 0-Dimensional Flow Modelling: Development and Testing Using In Silico and In Vivo Data

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Title:
Non-Invasive, MRI-Based Calculation of the Aortic Blood Pressure Waveform by 0-Dimensional Flow Modelling: Development and Testing Using In Silico and In Vivo Data

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Abstract:
Clinical evidence shows that central (aortic) blood pressure (CBP) is a better marker of cardiovascular risk than brachial pressure. However, CBP can only be accurately measured invasively, through catheterisation. We propose a novel approach to estimate CBP non-invasively from aortic MRI data and a non-invasive peripheral (brachial) pressure measurement, using a one-dimensional (1-D) model of aortic blood flow. We created a population of ‘virtual’ (computed) subjects, each with distinctive arterial pulse waveforms available at multiple arterial locations, to develop and assess our approach. This population was created by varying cardiac (stroke volume, cardiac period, time of systole) and arterial (stiffness, peripheral resistance) parameters of a distributed 1-D model of the largest systemic arteries within a wide range of physiologically plausible values. After optimising our algorithm for the 1-D aortic model in silico, we tested its accuracy in a clinical population of 8 post-coarctation repair patients. Results from our in silico study, after varying cardiac and arterial parameters by ± 20% and ± 40%, respectively, showed average relative errors for systolic, mean and diastolic aortic model CBP estimations of 2.9%, 0.2% and 2.2%, respectively. Corresponding average errors from our clinical study were 5.4%, 1.5% and 8.0%. We have provided a proof of concept for the non-invasive estimation of patient-specific CBP using computational aortic blood flow modelling in combination with MRI data and a non-invasive peripheral pressure measurement.

Keywords:
1-D blood flow modelling; patient-specific modelling; central blood pressure; haemodynamics; magnetic resonance imaging
Conference Proceedings and Abstracts:
Below is a list of the conference proceedings and abstracts which I have authored or co-authored to date.


CHAPTER 1

Introduction

Hypertension and cardiovascular disease

High blood pressure (BP), also known as hypertension, is the main risk factor for mortality worldwide. In the year 2000, over 25% of the world’s adult population had hypertension. By 2025, the incidence of hypertension is estimated to increase to 29% [1]. Hypertension is diagnosed for levels of systolic BP (SBP) ≥ 140 mmHg and/or diastolic BP (DBP) ≥ 90 mmHg measured at the brachial artery [2, 3]. Hypertension can result in heart attack, stroke, aneurysm, heart failure, kidney disease, vision loss, metabolic syndrome, memory loss or impaired cognitive function [4, 5].

According to the World Health Organisation, 17.7 million people died from cardiovascular disease (CVD) in 2015, representing 31% of all global deaths. Approximately 7.4 million of these deaths were due to coronary heart disease and 6.7 million were due to stroke [6].

Although cancer was the largest (29%) cause of death in the United Kingdom in 2014, CVD followed closely as the second largest (27%) [7]. Dementia and Alzheimer disease has replaced ischaemic heart disease as the leading cause of death in England and Wales, accounting for 11.6% of all deaths registered in 2015. Ischaemic heart disease was the second leading cause of death in England and Wales, with 11.5% of all deaths registered in 2015. For males, ischaemic heart disease was the leading cause of death accounting for 14.3% of all male deaths in 2015, compared with 14.8% in 2014. For females, the leading cause of death was dementia and Alzheimer disease accounting for 15.2% of all female deaths, up from 13.4% in 2014 [8].

1.1 Cardiovascular anatomy and physiology

The main functions of the cardiovascular (CV) system are to provide the rapid convection of oxygen, nutrients and metabolites to the body and to quickly get rid of metabolic waste products like carbon dioxide, urea and creatinine. The CV system is also part of a control system since it distributes and secretes hormones; plays a vital role in temperature regulation; and is crucial in the defence of the body by the immune system [9, 10].

From an engineering point of view, the cardiovascular system is composed of a fluid (the blood) moving under the action of a pump (the heart) within a closed
network of flexible tubes of varying diameter and thickness (the blood vessels). Such system can be analysed according to the physical laws of fluid mechanics, accounting for the fluid-structure interaction between the blood (fluid) and the blood vessels (structure).

1.1.1 The heart and the circulation of blood

![Diagram of the cardiovascular system showing the arterial (red) and venous (blue) circulation.](image)

Figure 1.1: Diagram of the cardiovascular system showing the arterial (red) and venous (blue) circulation [11].

The heart can be thought of as two adjacent and synchronised muscular pumps, the right and left ventricles. Each pump is filled from a blood collection chamber, the right and left atrium, respectively. The right ventricle receives deoxygenated blood from the right atrium and pumps this blood to the lungs; this process is part of the pulmonary circulation (shown in blue in Figure 1.1). The left ventricle, which receives oxygenated blood from the left atrium, simultaneously pumps blood through the aorta to the rest of the body; this process is part of the arterial circulation (shown in red in Figure 1.1). The blood follows a closed circuit due to the action of one-way valves located in the heart and the veins [9]. In the current study, we are focusing on the systemic circulation as opposed to the pulmonary circulation.

Blood vessels can distend because they contain two elastic layers made of elastin and collagen. Elastin forms both very elastic fibres and sheets, while collagen only forms fibres that are about 1000 times stiffer than elastin fibres. Arteries are fairly thick-walled, elastic vessels that carry blood from the heart. They branch in a predominantly tree-like structure, called the arterial tree, although there are a number
of loops providing for some redundancy of perfusion. Arterial diameters range from 4 to 2 cm for the aorta and the main pulmonary artery down to 100 µm for the small arteries which perfuse the microcirculation. The microcirculation consists of arterioles which branch into the capillaries, form a complex network with vessel diameters between 8 and 6 µm. The capillaries merge into venules which also merge to form smaller veins. Veins are thin-walled vessels which present valves to prevent backflow. These valves usually have two cusps which consist of connective tissue membranes containing elastin fibres [10].

Blood is a fluid which consists of a suspension of blood cells in a liquid plasma, which is an aqueous solution containing proteins, mineral ions, hormones and glucose. Plasma behaves like a Newtonian fluid for in vivo shear rates. In large blood vessels, blood can be assumed to be a homogeneous, incompressible and Newtonian fluid, since its viscosity and density only depends on temperature [12].

1.1.2 Pulse wave propagation

During systole, the left-ventricular contraction injects blood into the aorta through the aortic valve distending the ascending aorta. This distension propagates as a wave, the so-called pulse wave, through the arterial network producing changes in blood flow and pressure in time and space. The pulse wave reflects multiple times at the aortic root, arterial bifurcations and due to arterial wall tapering. This physical phenomenon is known as pulse wave propagation and produces a variety of pressure and flow waveforms throughout the systemic arteries.

At the end of systole, the aortic valve closes and the flow of blood from the heart stops. During diastole, as blood leaves the larger arteries through the periphery and enters the microcirculation, pressure everywhere in large arteries tends to decrease exponentially [9].

How does pulse wave propagation affect BP?

The pressure waveform carries valuable information for the diagnosis and treatment of CVD and plays an important role in conditions such as hypertension. The shape of the BP waveform is determined by the physical properties of the cardiovascular system which are affected by disease, such as arterial stiffness, peripheral resistances and cardiac ejection patterns. As part of this project, we want to determine and quantify the properties of the cardiovascular system which produce the blood pressure increase in hypertension.

1.2 Motivation: central blood pressure (CBP)

Central blood pressure (CBP) is defined as the blood pressure in the ascending aorta, close to the heart. Current clinical evidence suggests that CBP is a more sensitive indicator of hypertension and cardiovascular risk than peripheral BP [5]. Peripheral measurements suffer from pulse amplification: as the pulse wave travels from the aortic root towards the periphery, the pulse pressure (PP), calculated as systolic BP minus diastolic BP, tends to increase. For this reason, peripheral BP is also a poor surrogate of CBP [5].
The gold standard of CBP measurements is aortic root BP, obtained using pressure-sensing wires or catheters during an invasive procedure. However, this methodology is risky, costly and not suitable for routine clinical practice [13].

The gold standard in the assessment of left-ventricular (LV) function is known as the pressure-volume (PV) loop, which requires simultaneous measurements of LV pressure and volume. Although blood volume can be obtained from MRI, blood pressure must be obtained via catheterisation to compute the PV loop. A good estimate of CBP using our methodology would take us closer to obtaining LV pressure non-invasively, allowing us to compute the PV loop non-invasively.

To estimate CBP non-invasively, a peripheral BP measurement is normally taken on the arm using a *sphygmomanometer* or pressure cuff. An alternative, more reliable approach may be to estimate CBP using magnetic resonance imaging (MRI), which currently provides accurate measurements of aortic geometry and blood flow. When coupled with a non-invasive pressure measurement, MRI could also provide patient-specific estimates of CBP using blood flow modelling. Testing this hypothesis is the main aim of this project.

**Current detection and monitoring of hypertension**

A consensus on a specific technique for the non-invasive detection and monitoring of hypertension does not currently exist [14]. However, the automated sphygmomanometer remains the device of choice for the non-invasive detection and monitoring of hypertension [2].

Carotid tonometry is a widespread method for the non-invasive assessment of hypertension, however it is only used in specialised clinics. Although carotid tonometry is advisable for the measurement of carotid-femoral pulse wave velocity (PWV<sub>cf</sub>), it is not recommended for routine estimation of central (aortic) blood pressure (CBP) waveforms, required for hypertension detection and monitoring [13, 15].

If carotid artery tonometry is not performed by an experienced professional, excessive applanation pressure increases the probability of unwanted baroreceptor activation [16]. This applanation pressure is influenced by a number of factors such as the thickness of the intervening tissue (skin, muscle, arterial wall), and the position and angulation of the tip of the probe. Without direct observation of the wall of the artery, the operators cannot ensure that the wall is flat under the probe, which implies that the recorded pressure may be an overestimation or underestimation of the true intra-arterial pressure.

Techniques based on the use of a generalised transfer function, which estimate CBP from a peripheral pressure measurement, have been widely adopted [17, 18, 19]. However, these methods do not currently provide subject-specificity: these CBP estimations rely entirely on the measured peripheral pressure waveform and do not take into account the characteristics of the cardiovascular system of a particular individual.

### 1.3 Objective: non-invasive CBP estimation

The aim of this PhD project is to develop a methodology to estimate patient-specific CBP non-invasively using a thoracic MRI scan and a peripheral pressure measurement. Using this data, we generate a 1-D aortic model (Figure 2.1) for each patient.
Our main hypothesis is that aortic geometry and flow combined with tonometry data are enough to accurately estimate CBP [20]. In fact, including additional information from peripheral arteries does not provide a substantial improvement to 1-D models [21]. If successful, this methodology would provide an alternative to risky, invasive procedures for measuring CBP, and would extend the range of measurements available during MRI scans.

**In silico validation of the aortic model**

To test this hypothesis we first generated a population of 22 virtual (computed) subjects, each one with distinctive blood pressure and flow waveforms available at multiple arterial locations, using a 1-D model of the largest 116 arteries, as described in Section 2.2. This population was an initial step to test and develop our algorithm prior to validation using clinical data. We first generated a subject-specific 1-D aortic model for every virtual subject. We then compared the differences between the original in silico CBP and the aortic model CBP estimations (Figure 2.2).

**In vivo validation of the aortic model**

Following the in silico validation, we performed a preliminary in vivo assessment using clinical data with invasive measurements of aortic pressure and flow (Figure 3.6). As part of an on-going collaboration with Philips Healthcare, we integrated our 1-D blood flow solver within a prototype MRI segmentation tool which extracts arterial geometry and blood flow waveforms from 3-D magnetic resonance (MR) images (Figure 2.3, [22]). From this data we generated aortic models for patient-specific 1-D haemodynamic simulations.

### 1.4 Mathematical background

Computational fluid dynamics (CFD) allows us to simulate the flow of blood through the body. There are different dimensions for blood flow modelling: the higher the dimensionality, the greater the number of flow features captured by the model, but also the greater the computational cost (Figure 1.2).

In the clinic, regardless of the choice of modelling strategy, parameters describing the mechanical properties of the arteries cannot be directly measured and have to be estimated; e.g., arterial stiffness is estimated from the propagation speed of the pulse wave, the so-called pulse wave velocity (PWV).
1.4.1 Zero-dimensional (0-D) blood flow modelling

Zero-dimensional (0-D) models have a relatively low computational cost compared to other models, with a run time of a few seconds on a PC. Also known as lumped parameter models, they can capture the global characteristics of the arterial circulation during the cardiac cycle. Westerhof et al. [24] showed that the 0-D three-element Windkessel (3-WK) model is able to describe the pressure-flow relation for the systemic arterial system. As a proof of concept, Vennin et al. [25] recently showed that the CBP waveform could be estimated from a non-invasive blood flow measurement at the ascending aorta. However, these models are space-independent and cannot be used to study wave propagation or local changes in the properties of the arterial system. As part of this study, we will compare the performance of 0-D models at estimating CBP against our 1-D simulations.

1.4.2 One-dimensional (1-D) blood flow modelling

One-dimensional (1-D) models have a higher computational cost than 0-D models, with run times ranging from a few minutes to a few hours on a PC. They allow us to study the pulse wave propagation through the arterial system in the axial direction and during the cardiac cycle. Several in vivo [26, 20], in vitro [27], and three-dimensional (3-D) numerical [20] studies have shown that 1-D modelling can accurately reproduce the clinically relevant features of the pressure, flow and area waveforms. For these studies, direct measurements of all the parameters required by the corresponding 1-D models were available.
Modelling assumptions

In 1-D haemodynamic models, the arterial network is decomposed into arterial segments connected to each other at nodes. Each segment is modelled as a thin-walled, deformable cylindrical tube whose properties can be described by the axial coordinate \((x)\) alone. Pulse waves propagate in the \(x\)-direction, modifying the lumenal cross-sectional area, \(A(x,t)\), and the cross-sectional averages of blood velocity, \(U(x,t)\), flow, \(Q(x,t)\), and pressure, \(P(x,t)\). Blood is incompressible, Newtonian and laminar for \textit{in vivo} ranges [28].

Governing equations

The equations of mass and momentum conservation in terms of \(A\), \(Q\) and \(P\) are derived in [29] as

\[
\begin{align*}
\frac{\partial A}{\partial t} + \frac{\partial Q}{\partial x} &= 0 \\
\frac{\partial Q}{\partial t} + \frac{\partial}{\partial x}\left(\alpha \frac{Q^2}{A}\right) + \frac{A\frac{\partial P}{\partial x}}{\rho} &= \frac{f}{\rho},
\end{align*}
\]

where \(\rho\) represents blood density and \(\alpha\) is a velocity profile shape factor that affects the frictional term \(f = f(\alpha, U)\).

An explicit algebraic expression relating \(P\) and \(A\), known as the tube law, is used to close the system of equations:

\[
P(A, x) = P_d + \frac{\beta(x)}{A_d(x)} \left(\sqrt{A} - \sqrt{A_d(x)}\right),
\]

where \(\beta(x)\) is related to wall mechanical properties and \(P_d\) and \(A_d\) are the diastolic pressure and area, respectively. Since pulse wave velocity (PWV) is assumed to be constant for the whole 1-D model, \(\beta(x)\), only depends on vessel cross-sectional area values \(A_d(x)\) and \(A(x)\), as seen in Equation 1.3.

Rewriting equations 1.1 and 1.2 in non-conservative form and analysing them using Riemann’s method of characteristics results in the following expression for the PWV [30]:

\[
c = \sqrt{\frac{A \frac{\partial P}{\rho \partial A}}{A}} = \sqrt{\frac{\beta}{2 \rho A_d}} A^{1/4}.
\]

The previous 1-D equations are solved using the discontinuous Galerkin finite element method, as described in [10].

Boundary conditions

Boundary conditions (BC) are prescribed at the inlet and outlet of every segment. BCs are classified as \textit{inflow}, \textit{junction} and \textit{terminal}:

- The \textit{inflow} BC condition, a cardiac flow profile, \(Q_{in}(t)\), is imposed at the inlet of the ascending aorta.
• **Junction** BCs are prescribed at arterial segment connections and bifurcations.

• **Terminal** BC are represented as 0-D lumped parameter models coupled to the outlet of terminal arterial segments. We have chosen the 3-element Windkessel (3-WK) model, as it represents the resistance \( R_T = R_1 + R_2 \) to flow and the compliance \( C_T \) of downstream vessels while minimising reflections by making \( R_1 \) equal to the terminal arterial characteristic impedance. \[ \text{Figure 1.3} \]

The 3-WK model relates pressure \( P \) and flow \( Q_{in} \) at the outlet of each terminal segment to \( P_{out} \), the pressure at the microcirculation level, through

\[
Q_{in} \left(1 + \frac{R_1}{R_2}\right) + C_T R_1 \frac{\partial Q_{in}}{\partial t} = \frac{P - P_{out}}{R_2} + C_T \frac{\partial P}{\partial t}. \tag{1.4}
\]

Figure 1.3: Reservoir [24] (left) and electrical (right) analogies for the 2-element (above) and 3-element (below) Windkessel models of arterial resistance and compliance.

### 1.4.3 Three-dimensional (3-D) blood flow modelling

Three-dimensional (3-D) models may be required for patients with complicated aortic geometries, such as those seen in severe aortic coarctation and aneurysms. 0-D and 1-D models cannot capture energy losses produced by turbulent flow and recirculation. However, 3-D flow modelling is unfeasible for current clinical settings due to its relatively high computational cost, with run times ranging from several hours to several days on a PC.

The main reasons for the choice of 1-D modelling over 0-D or 3-D modelling for this study are its computational cost (lower than 3-D approaches) and its ability to capture pulse wave propagation phenomena (which 0-D methods cannot capture).

### 1.4.4 Mathematical optimisation of 0-D and 1-D models

If the target CBP waveform is known, a mathematical optimisation of the 0-D and 1-D parameters should result in an optimal CBP estimation. For this optimisation we
used the Nelder-Mead algorithm \cite{31}, which is a simplex method for the minimisation of multivariable functions. We applied this minimisation technique to the 3-element Windkessel models of arterial compliance and resistance \cite{24} which are used both for the 0-D simulations and as outflow boundary conditions for the 1-D simulations.

1.5 Organisation of the report

Chapter 1 provides a background on the cardiovascular system and central blood pressure (CBP); describes the motivation for obtaining CBP non-invasively; outlines the main objectives of the current work; and introduces the main 1-D assumptions and the 1-D mathematical formulation.

Chapter 2 presents the 1-D aortic flow model which allows the calculation of CBP from \textit{in silico} and \textit{in vivo} data; explains the process of generating \textit{in silico} data for a population of ‘virtual’ healthy subjects; summarises the characteristics of the clinical data; and describes the error analysis for the validation of the 1-D aortic model.

Chapter 3 describes the characteristics of the \textit{in silico} cohort; provides a comparison between five different methods for non-invasive CBP estimation, including the 1-D aortic model; and contains the results for the \textit{in silico} and \textit{in vivo} validation of the aortic model, including a mathematical optimisation of the 0-D and 1-D models.

Chapter 4 analyses the results for the \textit{in silico} and \textit{in vivo} validation of the aortic model.

Finally, Chapter 5 summarises the main findings and limitations of the study, and proposes several ideas for future work.
CHAPTER 2

Methods

As both blood pressure and flow waveforms are generated by the propagation of the same pulse wave, it should be possible to use 1-D modelling to calculate aortic pressure and flow waveforms from the following non-invasive data: a peripheral BP measurement using applanation tonometry or a sphygmanometer; diastolic aortic geometry and aortic flow waveforms measured using MRI.

In Section 2.1 we describe the inputs of the 1-D aortic model. In Section 2.2 we describe how we generated the *in silico* cohort and used it for the validation of the 1-D aortic model. In Section 2.3 we describe how we post-processed the *in vivo* data for an initial clinical assessment of the 1-D aortic model. In Section 2.4 we describe the error metrics and the data analysis techniques chosen for this study.

2.1 1-D aortic model

The 1-D blood flow simulations in this study are run using a 1-D model of aortic geometry, which consists of the ascending aorta, part of the descending aorta and the three supra-aortic branches (Figure 2.1). Arterial length and diameter parameters are obtained from this geometry data. Volumetric flow profiles, obtained from MRI or otherwise, are required to calculate the cardiac inflow waveform and the pulse wave velocity (PWV), required for the estimation of aortic stiffness. *In vivo* PWV is obtained from these flow waveforms using the ‘foot-to-foot’ algorithm [32]. We combine flow and non-invasive pressure measurements to determine parameters describing vascular resistance and compliance. Parameter values for blood flow properties such as density and viscosity are taken from the clinical literature [10].
2.2 \textbf{In silico cohort: a ‘virtual population’}

We describe our methodology for building a population of virtual healthy subjects and how we used this virtual population for the \textit{in silico} validation of the aortic model. This \textit{in silico} study uses two different 1-D models of arterial haemodynamics (Figure 2.2): a ‘complete’ arterial model including the largest 116 human arterial segments; and the ‘reduced’ aortic model described in Section 2.1.

2.2.1 How do we generate virtual subjects?

We generate a ‘baseline subject’ using a 116-artery 1-D model whose parameters are obtained from the clinical literature [28, 33]. Obtaining all these parameters \textit{in vivo} is unfeasible, so this complete model is used as a source of \textit{in silico} data for the validation of our aortic model. Following Willemet’s approach [34] applied to our 116-artery model, a new population of virtual healthy subjects is generated by performing individual parameter variations of the baseline subject. Parameters are varied within the healthy \textit{in vivo} ranges shown in Table 2.1.
Table 2.1: Cardiovascular property variations of the virtual population based on clinical literature.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
<th>Variations, %</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke Volume [mL]</td>
<td>[66, 99]</td>
<td>-20 +20</td>
<td>[35, 36]</td>
</tr>
<tr>
<td>Cardiac Period [s]</td>
<td>[0.64, 0.96]</td>
<td>-20 +20</td>
<td>[35, 36]</td>
</tr>
<tr>
<td>End-Systolic Time [s]</td>
<td>[0.33, 0.50]</td>
<td>-20 +20</td>
<td>[37]</td>
</tr>
<tr>
<td>Peripheral Resistance [Pa·s/m³]</td>
<td>[1.08e8, 1.68e8]</td>
<td>-10 +40</td>
<td>[38]</td>
</tr>
<tr>
<td>Pulse Wave Velocity [m/s]</td>
<td>variable</td>
<td>0 +400</td>
<td>[39, 40]</td>
</tr>
</tbody>
</table>

2.2.2 *In silico* validation of the 1-D aortic model

Each virtual subject contains all the information required to generate an aortic model. We extracted aortic geometry; cardiac inflow waveforms; diastolic and mean pressures; and other parameters from every 116-artery model and generated their corresponding aortic models. We then compared the original virtual patient’s CBP (our target pressure) to the aortic model CBP estimation Figure 2.2.

To assess the *in silico* performance of the aortic model, we used four metrics: systolic BP (SBP), mean BP (MBP), diastolic BP (DBP) and root mean square (RMSE) errors. We performed a correlation analysis followed by a Bland-Altman analysis on this data, as described in (Section 2.4).

Figure 2.2: Each virtual patient (116-artery model) has a distinct CBP waveform (top). Virtual patients contain the information required to generate a corresponding aortic models (bottom).
2.2.3 Five methods for CBP estimation using the virtual population

In order to determine whether the aortic model provides an improvement compared to other non-invasive methods for CBP estimation, we estimated CBP for each subject using five different methods:

- **Brachial measurement**: CBP is estimated as the pressure at the midpoint of the brachial artery for each virtual subject.
- **Carotid measurement**: CBP is estimated as the pressure at the midpoint of the carotid artery for each virtual subject.
- **2-element Windkessel**: CBP is estimated by lumping each arterial network into a 0-D, 2-element Windkessel model.
- **2-element Windkessel**: CBP is estimated by lumping each arterial network into a 0-D, 3-element Windkessel model.
- **Aortic model**: CBP is estimated using our 1-D aortic model.

2.3 Clinical cohort: 8 post-coarctation repair patients

The clinical cohort used in this study contains 8 patients (7 male, 1 female), aged 20 ± 9 years, showing mild to severe aortic coarctation. A description of some clinical characteristics of these patients is provided in Table 2.2.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [years]</td>
<td>20 ± 9</td>
</tr>
<tr>
<td>Height [cm]</td>
<td>168 ± 25</td>
</tr>
<tr>
<td>Weight [kg]</td>
<td>61 ± 22</td>
</tr>
<tr>
<td>Heart Rate (HR) [bpm]</td>
<td>68 ± 16</td>
</tr>
<tr>
<td>Stroke Volume (SV) [mL]</td>
<td>75 ± 28</td>
</tr>
<tr>
<td>Cardiac Output (CO) [L/min]</td>
<td>5.0 ± 2.1</td>
</tr>
<tr>
<td>Central SBP [mmHg]</td>
<td>91 ± 14</td>
</tr>
<tr>
<td>Central MBP [mmHg]</td>
<td>68 ± 9.7</td>
</tr>
<tr>
<td>Central DBP [mmHg]</td>
<td>53 ± 6.7</td>
</tr>
</tbody>
</table>

Table 2.2: Characteristics of the clinical cohort. SBP, MBP and DBP stand for systolic, mean and diastolic blood pressure, respectively. PWV stands for pulse wave velocity. The values are reported as mean ± standard deviation.
2.3.1 Clinical data post-processing

Patient-specific parameters of the aortic model were obtained from MRI data using a prototype segmentation tool developed by our collaborators at Philips Healthcare \[22\]. The geometry for the aortic model was segmented from contrast-enhanced magnetic resonance angiography (MRA) of the thorax (resolution 1.3±0.3 mm in-plane, 2.3±0.5 mm slice thickness). Volumetric blood flow profiles at the ascending and diaphragmatic aorta were extracted from time-resolved 2-D phase contrast (PC) MRI data (89±46 time points, resolution 1.8±0.4 mm, thickness 7.6±0.7 mm). Invasive CBP was obtained via catheterisation at the ascending aorta over several cycles. For some patients, non-invasive brachial pressure was acquired using a sphygmomanometer.

Figure 2.3: MRI data post-processing for one patient using the prototype segmentation software being developed by Philips Healthcare. The segmentation centrelines (red lines) and contours (blue rings), together with the ascending and descending aortic flow waveforms (pink and purple signals, respectively) are shown in this image.

2.3.2 Clinical validation of the 1-D aortic model

We performed a Bland-Altman analysis to assess the \textit{in vivo} performance of the aortic model, as described in Section 2.4.

2.4 Error calculation

To assess the performance of the aortic model using \textit{in silico} and \textit{in vivo} data, we used four error metrics throughout the study: relative systolic BP (SBP), relative mean BP (MBP), relative diastolic BP (DBP) and root mean square (RMSE) errors. The RMSE is calculated as the square root of the average of squared errors between the reference (target) and the estimated CBP waveform. The RMSE was normalised by the subject-specific mean CBP for comparison.
We chose systolic, mean and diastolic CBP errors for our analysis since they are commonly found in the clinical literature; these pressure values are used for the assessment of cardiovascular risk and are therefore useful to clinicians. The RMSE was chosen to quantify the overall disagreement between the reference and estimated CBP waveforms for the \textit{in silico} cohort (Figure 3.3).

A correlation analysis using the Pearson correlation coefficient, $r$, was performed on the \textit{in silico} to determine the linear correlation between reference and estimated values of systolic, mean and diastolic CBP (Figure 3.4).

A Bland-Altman analysis was also performed to assess the agreement between these reference and estimated CBP values. Bland-Altman plots allow us to visually identify the bias (mean difference) and the 95\% limits of agreement (calculated as the bias $\pm$ 1.96 standard deviations (SD)) \cite{41}. 

15
Results

We first describe the characteristics of our virtual population in Section 3.1. In Section 3.2 we show a comparison between 5 different methods (including the 1-D aortic model) for non-invasive CBP estimation, together with the in silico validation of the 1-D aortic model. We show preliminary clinical CBP estimation results using the aortic model for 8 post-coarctation repair patients in Section 3.3.

3.1 Properties of the virtual population

We generated a population of 22 virtual healthy subjects following the methodology described in Section 2.2. Table 3.1 contains the characteristics of the virtual population. Figure 3.1 shows the central, carotid and brachial BP waveforms grouped by parameter variation. The baseline pressure is shown in black; positive parameter variations are given in red and negative parameter variations are given in blue. Whereas variations in stroke volume, cardiac period and peripheral vascular resistance do not significantly affect the shape of the pressure waveform, ejection time and pulse wave velocity variations result in waveform shape changes.
Table 3.1: Characteristic of the virtual cohort. SBP, MBP and DBP stand for systolic, mean and diastolic blood pressure, respectively. PWV stands for pulse wave velocity. The values are reported as mean ± standard deviation.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Range of values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Rate (HR) [bpm]</td>
<td>75 ± 5.4</td>
</tr>
<tr>
<td>Stroke Volume (SV) [mL]</td>
<td>83 ± 5.7</td>
</tr>
<tr>
<td>Cardiac Output (CO) [L/min]</td>
<td>6.2 ± 0.6</td>
</tr>
<tr>
<td>Carotid-femoral PWV (PWV&lt;sub&gt;cf&lt;/sub&gt;) [m/s]</td>
<td>6.2 ± 1.9</td>
</tr>
<tr>
<td>Central SBP [mmHg]</td>
<td>128 ± 22.5</td>
</tr>
<tr>
<td>Central MBP [mmHg]</td>
<td>104 ± 13.0</td>
</tr>
<tr>
<td>Central DBP [mmHg]</td>
<td>77.3 ± 20.9</td>
</tr>
<tr>
<td>Brachial SBP [mmHg]</td>
<td>145 ± 18.6</td>
</tr>
<tr>
<td>Brachial MBP [mmHg]</td>
<td>101 ± 13.0</td>
</tr>
<tr>
<td>Brachial DBP [mmHg]</td>
<td>71.2 ± 20.2</td>
</tr>
</tbody>
</table>
Figure 3.1: Pressure waveform comparison depending on parameter variation for each virtual subject at three locations: (a) ascending aorta, (b) carotid artery and (c) brachial artery. Each row shows the effect of specific model parameter variations. The pressure waveform for the baseline subject is shown in black. Positive and negative parameter variations are shown in red and blue, respectively.
Figure 3.2 shows an increase in SBP as we move away from the ascending aorta (SBP around 15 KPa) towards the carotid and brachial arteries (SBP around 16 and 18 KPa, respectively). There is also a decrease in DBP towards the periphery. These changes in SBP and DBP result in an even larger pulse pressure (calculated as SBP minus DBP) increase towards peripheral arteries.

3.2 Aortic model performance: an *in silico* assessment

We compared the performance of the aortic model to four alternative methods for non-invasive CBP estimation.

Table 3.2 shows the median and interquartile ranges for the relative errors of each method. Systolic CBP is better estimated by the 2-element Windkessel (2-WK) method (median error of 0.28% and 1.27% for the physical and optimised estimations, respectively), followed by the carotid measurement (-1.52%) and the 1-D aortic model (2.96% and 2.36%). The 1-D aortic model shows smaller mean (-0.05% and -0.32%) and RMSE (2.20% and 1.81%) metrics than any other comparators. Diastolic CBP is better estimated by the 2-WK model (-1.89% and -1.45%) followed by the 1-D aortic model (-0.47% and -0.85%).

Figure 3.3 shows a comparison between the reference (virtual subject) and estimated CBP waveforms corresponding to the smallest and largest root mean square errors (RMSE) for each method. The smallest RMSE (1.92% and 1.62% for the physical and optimised estimations, respectively) corresponds to the 1-D aortic model.

Figure 3.4 shows correlation plots comparing estimated and reference (a) systolic, (b) mean and (c) diastolic CBP for each method. The highest linear correlation is found for the carotid ($r > 0.998$) and brachial ($r > 0.995$) measurement methods. The lowest linear correlation is found for the systolic CBP estimation using the 2-WK ($r = 0.980$) and 3-WK ($r = 0.994$) models.

Figure 3.5 shows a Bland-Altman analysis of these same error metrics. The greatest bias for systolic, mean and diastolic CBP is found for the brachial measurement (>10 mmHg), the 2-WK and 3-WK models (±2 mmHg), and the brachial measurement (≤3 mmHg), respectively.
Table 3.2: Systolic, mean, diastolic and root mean square (RMSE) errors for each CBP estimation method: a) brachial measurement; b) carotid measurement; c) 2-element Windkessel model; d) 3-element Windkessel model; and e) 1-D aortic model. Relative errors for the physical (top row) and optimised (bottom row) estimations are shown for the last three methods.

<table>
<thead>
<tr>
<th>Relative error (%)</th>
<th>Systolic</th>
<th>Mean</th>
<th>Diastolic</th>
<th>RMSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q2 (Q1 Q3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brachial measurement</td>
<td>-10.71 (-12.49, -9.17)</td>
<td>0.63 (0.55, 0.70)</td>
<td>4.03 (3.78, 4.54)</td>
<td>96.57 (79.02 106.11)</td>
</tr>
<tr>
<td>Carotid measurement</td>
<td>-1.52 (-2.03, -1.33)</td>
<td>0.33 (0.29, 0.36)</td>
<td>1.73 (1.55, 1.91)</td>
<td>3.41 (2.91, 3.82)</td>
</tr>
<tr>
<td>2-element Windkessel</td>
<td>0.28 (-0.94, 0.92)</td>
<td>-1.89 (-2.70, -1.50)</td>
<td>-0.35 (-0.45, -0.30)</td>
<td>4.58 (3.82, 5.42)</td>
</tr>
<tr>
<td></td>
<td>1.27 (0.53 1.74)</td>
<td>-1.45 (-1.63, -1.36)</td>
<td>-0.38 (-0.45, -0.32)</td>
<td>4.27 (3.74, 4.85)</td>
</tr>
<tr>
<td>3-element Windkessel</td>
<td>9.04 (7.56, 9.70)</td>
<td>2.05 (1.73, 2.29)</td>
<td>-1.57 (-1.82, -1.36)</td>
<td>6.81 (6.03 7.71)</td>
</tr>
<tr>
<td></td>
<td>2.02 (0.60, 2.71)</td>
<td>-0.47 (-0.84, -0.35)</td>
<td>0.00 (-0.01, 0.00)</td>
<td>2.20 (1.88, 2.43)</td>
</tr>
<tr>
<td>1-D aortic model</td>
<td>2.96 (1.67 3.27)</td>
<td>-0.05 (-0.14, 0.06)</td>
<td>-0.47 (-1.18 0.06)</td>
<td>2.20 (2.07, 2.48)</td>
</tr>
<tr>
<td></td>
<td>2.36 (1.50, 2.62)</td>
<td>-0.32 (-0.38, -0.25)</td>
<td>-0.85 (-1.10, -0.27)</td>
<td>1.81 (1.73, 1.98)</td>
</tr>
</tbody>
</table>
Figure 3.3: Comparison of reference (black line), physically estimated (blue dotted line) and optimally estimated (red dotted line) CBP waveforms with (a) lowest and (b) highest root mean square (RMS) errors using five different methods. Each plot shows RMS, systolic (sys), diastolic (dias), pulse pressure (PP) and mean (mean) errors for CBP estimation. Errors for the optimised CBP estimation are shown on the right column.
Figure 3.4: Scatter plots for (a) systolic, (b) mean and (c) diastolic CBP estimation using five different methods. The dashed line represents the identity line. The correlation coefficient, $r$, is calculated for the physical CBP estimation (blue circles) for every method.
Figure 3.5: Bland-Altman plots for (a) systolic, (b) mean and (c) diastolic CBP estimation using five different methods. The solid line represents the bias and the dotted lines represent the limits of agreement (calculated as ± 1.96 standard deviations from the bias). Bias and limits of agreement are calculated for the physical CBP estimation (blue circles) for every method.
3.3 Clinical feasibility study: initial results

Figure 3.6 contains Bland-Altman plots for systolic, diastolic and pulse pressure CBP comparing in vivo invasive CBP to the aortic model estimations for 8 patients. There is a 1.6 mmHg and -3.6 mmHg bias in systolic and diastolic CBP estimation, respectively. 1-D aortic model estimations of CBP lie within the limits of agreement.

Figure 3.6: Bland-Altman plots for (a) systolic, (b) mean and (c) pulse pressure CBP estimation using the aortic model on 8 patients. Data points are shown as black circles. The solid black line represents the bias and the solid blue lines represent the limits of agreement (calculated as ± 1.96 standard deviations from the bias).
Discussion

During the initial stages of algorithm development, *in vivo* data acquisition errors and inconsistencies in the way whereby clinicians record patient data add additional complexity to the task. *In silico* data is an alternative to *in vivo* data for the optimisation and testing of our CBP estimation algorithm, since it eliminates both acquisition errors and data inconsistencies.

We analysed other approaches for the non-invasive estimation of CBP to compare them to the 1-D aortic model method. Using the brachial and carotid measurements for each virtual subject as a surrogate for CBP resulted in large overestimations of systolic CBP and underestimations of diastolic CBP. We know from the clinical literature that the mean pressure slowly decreases towards peripheral arteries due to energy losses, which explains the < 1 mmHg difference between estimated and target mean CBP using these two methods. The 2-element Windkessel model is a better estimator of systolic and diastolic blood pressure than the brachial and carotid measurements. We know that the 3-element Windkessel model should outperform the 2-element Windkessel model, however this is not the case. We have identified a problem with the implementation for both 0-D approaches: although we impose the mean CBP, the results show an average error of 2 mmHg. We will investigate these issues next, as they may explain some of the problems with the boundary conditions of our 1-D aortic model.

### 4.1 Virtual population and aortic model

Results from the virtual cohort show the ability of the *in silico* model to replicate pulse amplification observed *in vivo* (Figure 3.2); e.g. for the baseline subject, pressure amplifications of 3.7 mmHg and 17 mmHg are observed between the aortic root and the carotid and brachial arteries, respectively.

The correlation study did not offer a clear insight on the agreement between target and estimated CBP (Figure 3.4). Therefore, we chose to analyse the *in silico* data using Bland-Altman plots (Figure 3.5) as they provide direct information of (a) the value of the mean difference (bias) and (b) the spread of the difference between the target and estimated CBP values (limits of agreement). This analysis showed that the aortic model consistently overestimates systolic CBP (bias = 2.5 mmHg), however we believe that this is due to an issue with the algorithm and that we
should be able to remove this systolic CBP overestimation. We have identified an issue with four virtual subjects (those created by modifying the arterial stiffness) which result in non-physiological values of CBP. We decided to include them in this study as we will address this problem soon.

4.2 Mathematical optimisation

Model parameters for the 0-D and 1-D approaches are estimated according to physical considerations. However, these parameters do not necessarily lead to an optimal CBP estimation. The mathematical optimisation of the CBP waveform shows how well different methods perform for a given set of optimal parameters.

From the previous results we can conclude that, although optimised 2-element and 3-element Windkessel models are able to estimate central SBP, MBP and DBP with < 5% errors, they are not able to capture waveform features such as the early systolic upstroke or the second peak, as seen in Figure 3.3. These features, which are measured in the clinic (e.g. to calculate aortic pulse wave velocity or augmentation index), are only captured by the optimised 1-D aortic model.

4.3 Clinical feasability study

Preliminary clinical results show a similar agreement for the systolic and diastolic CBP estimation compared to the in silico validation. The current study was performed on 8 patients, but a larger cohort with a range of aortic geometries and cardiac conditions is required.
CHAPTER 5

Conclusion

The current study provides a proof of concept for the non-invasive estimation of patient-specific CBP using a 1-D model of aortic flow coupled with MRI data and a non-invasive peripheral pressure measurement. The current estimation errors for central systolic and pulse pressures are within clinically acceptable ranges. However, the algorithm for CBP estimation is still work in progress and can be improved further: we know from unpublished data from one of our collaborators that the aortic model is able to better estimate the CBP waveform. We have already identified some potential culprits for the suboptimal performance of the aortic model, namely the estimation of peripheral compliance and aortic PWV, and will work on this next.

5.1 Current findings, relevance and limitations

We showed that the reduced aortic model of 1-D blood flow is able to accurately capture the main features of the pressure and flow waveforms from \textit{in silico} and \textit{in vivo} data. In silico assessment of our model using 1-D modelling led to average relative errors of 2.9\%, 0.2\% and 2.2\% for the estimated systolic, mean and diastolic CBP. Similarly, average errors from our clinical study were 5.4\%, 1.5\% and 8.0\%. The current work with \textit{in silico} data provides a proof of concept of the non-invasive estimation of CBP, and allows us to decide on new strategies to account for the possible inconsistencies of \textit{in vivo} data.

The aortic model estimates CBP using information which is readily available in the cardiac MRI set up, such as MRI data and brachial pressure measurements, and could provide valuable insight into cardiovascular health. As part of our collaboration with PHILIPS Healthcare, we are integrating our 1-D blood flow modelling framework within their segmentation tool.

The main limitation of this study arises from model parameters which have a large impact on the model output. Some of these parameters, such as the arterial wall stiffness (which is obtained non-invasively from the pulse wave velocity), can only be roughly estimated from \textit{in vivo} data.
5.2 Future work

The subject-specific calculation of CBP from non-invasive data constitutes the core of this PhD project. The main elements for the continuation of our current study together with a number of ideas for future work are listed below:

- The current virtual population only includes 22 healthy subjects generated by individually varying cardiac or arterial properties. To study the interaction between these cardiovascular properties, we want to generate thousands of virtual subjects by simultaneously varying multiple model parameters using the range of values in Table 5.1. Although we currently work with healthy subjects only, we will include subjects with cardiovascular property ranges from population studies of cardiovascular diseases affecting CBP.

- We will compare 1-D and 3-D modelling, starting with idealised geometries such as a simple shaped tube. The geometry will be progressively modified to assess the effect of local geometry and mechanical property on 1-D model results. This comparison will be performed to identify the limits of applicability of the 1-D formulation in aortic geometries seen in stenosis (coarctation or atherosclerosis), aneurysms, and in patients with stents.

- Once we identify the optimal algorithm for the aortic model using the virtual population, we want to test it on a larger clinical cohort to determine which aortic geometries result in pressure losses due to turbulent blood flow which cannot be neglected.

- We want to investigate the additional computational cost of mathematical optimisation techniques (e.g. Kalman filters [42]) which optimise aortic model parameters as the 1-D blood flow simulation runs: first using 0-D models applied to clinical data of simultaneous aortic pressure and flow for a normotensive and hypertensive population ( >100 patients) under normal physiological conditions or under the effect of pharmacological drugs which affect the cardiac or vascular properties [43]; then using 1-D aortic models generated from MRI data and non-invasive peripheral pressure measurements. We will also assess the effect which cardiovascular parameter uncertainties have on the model [44].

- The pressure-volume (PV) loop is the gold standard for the assessment of cardiac function, and it requires simultaneous left-ventricular (LV) blood pressure and volume measurements, which are normally aquired using an impedance catheter. Coupling a 0-D model of the heart [45] to the 1-D aortic model, and using non-invasive in vivo heart data to obtain parameters for each heart model, we will try to estimate LV pressure to obtain a non-invasive PV loop.
Table 5.1: Future database variations based on clinical literature, literature review by [34].

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Range of values</th>
<th>Variations, %</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elastic arteries PWV</td>
<td>-20 +125</td>
<td></td>
<td>[46, 39]</td>
</tr>
<tr>
<td>Muscular arteries PWV</td>
<td>-20 +30</td>
<td></td>
<td>[47, 48]</td>
</tr>
<tr>
<td>Elastic arteries diameter</td>
<td>-10 +40</td>
<td></td>
<td>[49, 50]</td>
</tr>
<tr>
<td>Muscular arteries diameter</td>
<td>-10 +21</td>
<td></td>
<td>[49, 50]</td>
</tr>
<tr>
<td>Heart rate</td>
<td>-15 +15</td>
<td></td>
<td>[35, 36]</td>
</tr>
<tr>
<td>Stroke volume</td>
<td>-20 +20</td>
<td></td>
<td>[35, 36]</td>
</tr>
<tr>
<td>Peripheral Vascular Resistance</td>
<td>-10 +10</td>
<td></td>
<td>[38]</td>
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Bibliography


