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Quantifying the influence of arterial wave reflection on the heart and microvasculature

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Abstract

Hypertension is a leading risk factor for cardiovascular disease and accounts for significant healthcare expenditure. Furthermore, high systolic blood pressure (SBP) in childhood is associated with increased risk of cardiovascular events and mortality in adulthood. For more effective and targeted treatment, it is important to investigate the factors responsible for high SBP, both in the central arteries (causing elevated load on the left ventricle) and in the distal vasculature (causing end organ damage), and to better understand the effects of ageing on SBP. Wave reflection is thought to be a key factor modulating the pressure experienced by the microvasculature and the heart; however, controversies remain around its nature and effect on haemodynamics.

The first controversy investigated in this thesis relates to whether an increase in microvascular pressure with advancing age arises from decreased wave reflection in conduit arteries, causing an increase in transmission of pressure waves from the heart to the periphery. This paradigm is controversial because the theory underpinning wave reflection dictates a *decrease* (rather than an increase) in pressure wave transmission with a decrease in wave reflection. Using transmission line modelling techniques, it is shown that the increase in microvascular pulse pressure with ageing is most likely linked to a decrease in conduit arterial compliance, and hence an increase in the forward pressure wave amplitude, rather than increased transmission of the forward pressure wave.

The second controversy relates to the time when reflected waves arising in the arterial network return to the heart ('return time'). Reflected waves are thought to arrive at the heart during diastole in youth (promoting coronary perfusion) and during systole with ageing (increasing

SBP). However, current methods of estimating return time have only indicated systolic return times throughout life, which calls into question the traditional concept of wave reflection and/or the methodology used to estimate return time. To gain clarity on this, a computational model of the systemic vasculature of a young adult was developed. Given excellent agreement with human data, this model provides insights into the most likely origins of wave reflection and its effect on proximal and distal haemodynamics. In addition, a novel centroid method is developed whose higher accuracy (using the computational model) and sensitivity to diastolic and systolic return times (using *in vivo* experimental methods) than current methods is also demonstrated. Finally, the centroid method is applied to characterise return time across almost the entire life course, using data from various large cross-sectional studies in humans. Results provide the first quantitative evidence of a shift in return time from diastole towards late-to-mid-systole with age.

These studies provide clarity on the changes in wave reflection with age and its effect on proximal and distal haemodynamics. Future studies should investigate the effectiveness of wave reflection metrics such as return time as a risk factor for cardiovascular events and as a monitor of treatment effectiveness. Following this, the widespread adoption of wave reflection indices in clinical settings via automated devices such as those used to measure blood pressure may hold promise for improving diagnosis and treatment of cardiovascular diseases.

Declaration

This is to certify that:

- (i) This thesis comprises only my original work towards the PhD except where indicated.
- (ii) Due acknowledgement has been made in text to all other material used.
- (iii) This thesis is fewer than 100,000 words in length, exclusive of tables, figures, bibliographies, and appendices.

Avinash Kondiboyina

Preface

Included Publications

Chapter 3: Published in American Journal of Physiology – Heart and Circulatory Physiology in July 2020.

Kondiboyina A, Smolich JJ, Cheung MMH, Westerhof BE, Mynard JP. Conduit arterial wave reflection promotes pressure transmission but impedes hydraulic energy transmission to the microvasculature. Am J Physiol Heart Circ Physiol. 2020;319(1):H66-H75.

Author	Proportion	Contribution
Avinash Kondiboyina	75%	Study conception and design; data acquisition; data analysis and interpretation; draft and review of manuscript.
Joseph J Smolich	6%	Study design; data analysis and interpretation; review of manuscript.
Michael MH Cheung	2%	Data analysis and interpretation; review of manuscript.
Berend E Westerhof	2%	Study conception and design; review of manuscript.
Jonathan P Mynard	15%	Study conception and design; data analysis and interpretation; review of manuscript.

Chapter 4: Published in Journal of Physiology in Aug 2022.

Kondiboyina A, Harrington HA, Smolich JJ, Cheung MMH, Mynard JP. Optimized design of an arterial network model reproduces characteristic central and peripheral haemodynamic waveform features of young adults. J Physiol. 2022;600(16):3725-3747.

Author	Proportion	Contribution
Avinash Kondiboyina	75%	Study conception and design; data acquisition (doppler ultrasonography and applanation tonometry); data analysis and interpretation; draft and review of manuscript.
Hilary A Harrington	3%	Data acquisition (doppler ultrasonography and applanation tonometry); data analysis and interpretation; draft and review of manuscript

Joseph J Smolich	5%	Data analysis and interpretation; review of manuscript
Michael MH Cheung	2%	Data analysis and interpretation; review of manuscript
Jonathan P Mynard	15%	Study conception and design; data analysis and interpretation; review of manuscript

Chapter 5: Accepted for publication by IEEE Transactions on Biomedical Engineering.

Kondiboyina A, Smolich JJ, Cheung MMH, Mynard JP. Novel centroid method for robust evaluation of return time of reflected waves in the systemic arterial network. IEEE Trans Biomed Eng.

Author	Proportion	Contribution
Avinash Kondiboyina	75%	Study conception and design; data acquisition; data analysis and interpretation; draft and review of manuscript.
Joseph J Smolich	8%	Design and surgical preparation of in vivo experimental studies; data analysis and interpretation; review of manuscript
Michael MH Cheung	2%	Data analysis and interpretation; review of manuscript
Jonathan P Mynard	15%	Study conception and design; data analysis and interpretation; review of manuscript

Included Material

Chapter 2: Parts of this chapter were included in a published book chapter titled “Wave reflection in the arterial tree” in Textbook of Arterial Stiffness and Pulsatile Hemodynamics in Health and Disease.

Mynard JP, Kondiboyina A. Wave reflection in the arterial tree. *Textbook of Arterial Stiffness and Pulsatile Hemodynamics in Health and Disease*. 2022:169:191.

A/Prof Jonathan Mynard and I were each responsible for certain sections in this book chapter. Only the portions of this book chapter that I wholly contributed towards have been included in Chapter 2, along with additional content that I have written.

Co-authored Publications not Included in the Thesis

Mynard JP, Kondiboyina A, Kowalski R, Cheung MMH, Smolich JJ. Measurement, analysis and interpretation of pressure/flow waves in blood vessels. *Front Physiol.* 2020;11:1085. (Review)

Mynard JP, Kondiboyina A, Clarke MM, Kowalski R, Cheung MMH, Smolich JJ. Noninvasive assessment of carotid arterial wave speed and distensibility. *Am J Physiol Heart Circ Physiol.* 2018;315(5):H1495. (Letter to the Editor)

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Conference Abstracts

Mynard JP, Harrington HA, Kowalski R, Glenning J, Kondiboyina A, Smolich JJ, Cheung MMH. Suitability of a representative aortic flow waveform for pressure-only wave separation in children and adolescents. Artery Research. 2021. (Online)

Kondiboyina A, Smolich JJ, Cheung MMH, Mynard JP. Experimental validation of a novel centroid method for estimating return time of reflected pressure waves in arteries. North American Artery 2021. (Online)

Kondiboyina A, Smolich JJ, Cheung MMH, Mynard JP. Validation of a novel centroid method for estimating return time of reflected pressure waves in arteries. Faculty of Medicine, Dentistry and Health Sciences Graduate Research Student Conference. 2020. (Online)

Kondiboyina A, Smolich JJ, Cheung MMH, Mynard JP. Development and validation of a novel centroid method for estimating effective reflection time. Murdoch Children's Research Institute Research Student Symposium. 2020. (Online)

Kondiboyina A, Smolich JJ, Cheung MMH, Westerhof BE, Westerhof N, Mynard JP. Does wave reflection protect the microvasculature from high pulse pressure? Artery 18. 2018. Guimaraes, Portugal.

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List of Symbols and Abbreviations

Uncommon symbols that are only used in a small section will be defined in the text only.

Abbreviations

0D	Zero-dimensional
1D	One-dimensional
ACCTIII	Anglo-Cardiff Collaborative Trial
Aix	Augmentation index
BIS	Barwon Infant Study
BLIP	Balloon-induced pulse
cfPWV	Carotid-femoral pulse wave velocity
DBP	Diastolic blood pressure
ERD	Effective reflection distance
GTRT	Ground truth return time
ICC	Interclass correlation coefficient
LV	Left ventricle
PWV	Pulse wave velocity
RCT	Randomised controlled trials
RM	Reflection magnitude
RMSE	Root mean squared error
RTI	Return time index
RV	Right ventricle
SBP	Systolic blood pressure
TDI	Transition distance index

Symbols

A	Vessel area
c	Vessel wave speed
C	Compliance
dQ	Change in flow
dP	Change in pressure
HE	Hydraulic energy
P	Pressure
PPd	Distal pulse pressure
PPp	Proximal pulse pressure
Q	Flow
R_{bed}	Vascular bed resistance
T_P	Transmission coefficient of pressure
T_Q	Transmission coefficient of flow
TAC_{wk}	Total arterial compliance (windkessel method)
TAC_m	Total arterial compliance (model)
Z_c	Characteristic impedance
Γ_Q	Reflection coefficient of flow
γ_A	Asymmetry ratio of area
γ_c	Asymmetry ratio of wave speed
ρ	Blood density
τ	Time constant ($R_{bed} \times C_{bed}$)

Chapter 1: Introduction

Hypertension is the leading risk factor for attributable deaths globally (160) and a major risk factor for ischemic heart disease, stroke, and heart failure, which account for a significant portion of global healthcare expenditure (25). Every 20 mmHg and 10 mmHg increase in systolic blood pressure (SBP) and diastolic blood pressure (DBP), respectively, is associated with two-fold increased risk, respectively, starting from as low as 115 mmHg for SBP and 75 mmHg for DBP (134, 217); SBP in particular was found to be the greater risk factor (160). Importantly, although the prevalence of high SBP increases with age (9, 48, 125, 270), even mild elevations in childhood SBP appear to become amplified with age (90). Importantly, high childhood SBP has recently been directly associated with an increased risk of cardiovascular events and mortality in adulthood (106). High SBP can be caused by a variety of mechanisms; however, treatments often ignore the specific cause and offer blanket solutions. Understanding the biomechanical causes across the entire age range would offer more granular risk stratification and may assist with development of more targeted and effective treatments.

High SBP increases cardiovascular risk predominantly by exposing 1) the microvasculature and 2) the heart to increased mechanical stress. High SBP in the conduit arteries is commonly related to increased pressure pulsatility. Furthermore, increased pressure pulsatility in the microvasculature is thought to damage low-resistance, high-perfusion organs such as brain and kidneys and lead to cognitive decline (103, 274) and kidney dysfunction, respectively (114, 273, 293). Studies have noted increased brain atrophy (67), endothelial dysfunction (274), and increased plaque formation (229) with increased SBP, which help explain the cognitive decline. Similarly, high SBP in kidneys leads to vasoconstriction, which further increases pressure in a vicious cycle that can eventually lead to chronic kidney disease (251). High SBP also increases

left ventricular afterload, which increases the stress on the myocardium and can lead to left ventricular hypertrophy, and eventually congestive heart failure (97, 98, 252).

Blood is ejected from the ventricle in a pulsatile nature into the central conduit arteries, and both mean pressure and pulsatility progressively diminish towards the small feeding vessels (20), notwithstanding an initial rise in pulsatility as the pulse propagates in large arteries—a phenomenon known as pulse pressure amplification (181). Furthermore, conduit arteries are thick and composed primarily of elastin and smooth muscle cells, whereas smaller feeding vessels are thinner and have lesser elastin content (20). Due to these differences in local haemodynamics and vessel structure, it may be that the mechanisms that give rise to increased pressure pulsatility in the microvasculature differ from those acting in the central arteries. Understanding these mechanisms could help pinpoint the factors that lead to high SBP throughout the systemic circulation. However, despite the well-known relationship between high left ventricular stroke volume, large arterial stiffness, and systemic vascular resistance, and high SBP (69, 179, 187, 201, 221), questions remain as to the specific effects of these and other factors on proximal and distal haemodynamics. In particular, *wave reflection* is thought to be a key factor modulating the pressure experienced by both the microvasculature and the heart. However, a number of controversies surround the source, nature, and consequences of wave reflection, hindering progress towards its use in clinical settings. Resolving these controversies by advancing understanding of wave reflection, and how to best quantify it, is a primary motivation for the work in this thesis.

As the left ventricle contracts and ejects blood into the ascending aorta, a forward pressure wave is generated that propagates into the arterial system. The speed of propagation, or “wave speed”, of an artery is determined by its cross-sectional area and compliance. For a given cross-

sectional area, a more compliant artery will have a lower wave speed while a stiffer artery will have a higher one. When the forward-travelling pressure wave encounters a change in arterial properties (or, more precisely, an 'impedance mismatch'), it undergoes some degree of wave reflection: a portion of the wave's energy is transmitted forward to distal vessels and another portion is reflected back towards the heart (180); the magnitude of wave reflection depends on the degree of mismatch. In this manner, wave reflection has an impact on both proximal and distal haemodynamics.

Regarding the impact of wave reflection on distal haemodynamics, the transition between large elastic arteries (which are less stiff, particularly in youth) and smaller muscular arteries (which have greater stiffness) is thought to be important. Mitchell proposed that the mismatch in arterial properties gives rise to substantial wave reflection, which limits transmission of pulsatile pressure and thus protects the microvasculature from high pulsatility (153). With ageing, elastic arteries get stiffer while muscular arteries do not undergo an appreciable change in their properties (27, 129, 300). Thus, Mitchell also proposed that this reduces the mismatch in arterial properties with ageing, leading to a lesser magnitude of wave reflection and allowing more pressure to be transmitted to the microvasculature, leading to end-organ damage in delicate organs like the brain and kidneys (153).

There are two key inconsistencies with this proposed paradigm that have given rise to controversy regarding this view. First, a major site of wave reflection at the transition point between elastic and muscular arteries has not been found; in fact, extensive in vivo measurements have suggested that minimal wave reflection occurs in healthy conduit arteries (including both elastic and muscular) (199). Second, the concept that wave reflection limits transmission of pulsatile pressure to the microvasculature is inconsistent with a fundamental

principle in transmission line theory, which underlies the concept of wave reflection. As will be explored in Chapter 2, this principle states that greater wave reflection leads to *greater* transmission of pulsatile pressure, implying that a *lower* magnitude of wave reflection with ageing would be needed to prevent transmission of pulsatile pressure. There is therefore a significant need to study what factor(s) are likely to be responsible for increasing microvascular pulse pressure with ageing.

While the effect of wave reflection on the microvasculature has important implications for understanding the haemodynamic causes of end-organ damage, most studies of wave reflection have focussed on its impact on ventricular afterload. Representative central pressure waveforms of a young adult (17-year-old male) and an older adult (72-year-old male) are shown in Figure 1.1, which is adapted from Kelly et al (116). A pressure hump (red arrow) is evident during diastole in the younger waveform, and this shifts towards systole in the older waveform, causing an increase in systolic pressure.

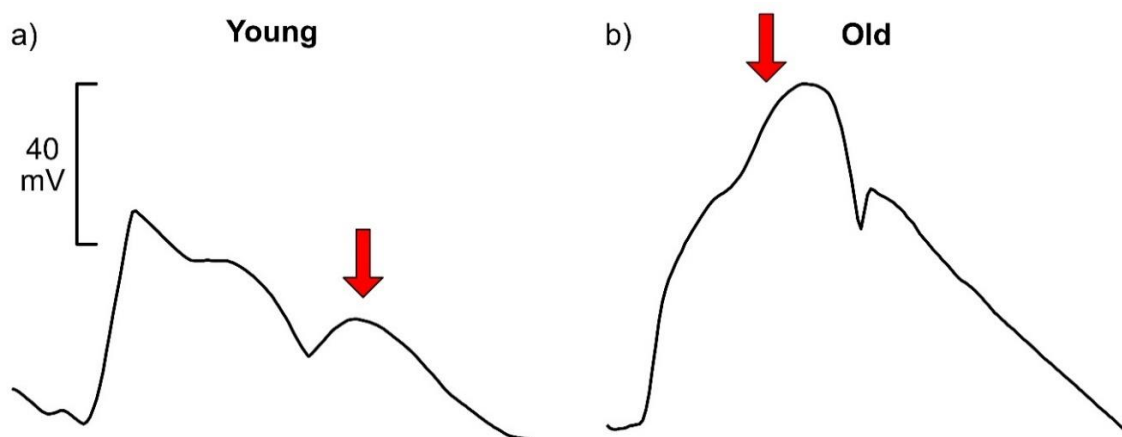


Figure 1.1: CENTRAL PRESSURE WAVEFORMS OF YOUNG ADULTS AND OLDER ADULTS. Representative central pressure waveforms of young adults (a) and older adults (b). The red arrows indicate the approximate location of the hump (or 'pressure augmentation' due to reflection) in both panels. This figure is adapted from Kelly et al (116), and pressure is given in mV units.

Based on these qualitative changes in pressure waveforms observed with ageing, it is widely thought that compliant arteries in youth (associated with a low wave speed) cause reflected waves to return to the heart during diastole, which causes the distinct diastolic hump (45, 180, 190). This is considered to support coronary perfusion pressure, as it is during this time that the myocardium is relaxing and there is the least impediment to coronary flow (191). However, stiffening of arteries with ageing increases wave speed (145) and therefore it is thought that this causes reflected waves to return to the heart earlier, and importantly, during systole (45, 180, 190). This shift reduces support for coronary perfusion, whilst also increasing SBP, left ventricular afterload, and myocardial energy requirements, resulting in poorer energy efficiency of ventricular pumping dynamics. This paradigm therefore revolves around the concept that the 'return time' of reflected waves shifts from diastole to systole with ageing.

Although a well-established paradigm, the shift in return time from diastole to systole remains controversial, as no studies have demonstrated this shift with quantitative methods; rather, it is most often supported by qualitative description of illustrative examples such as that in Figure 1.1. The most widely used methods for quantifying return time are the inflection point, foot, and zero crossing methods, the details of which will be explored in Chapter 2. While each method does show a decrease in return time with ageing, the return times appear to occur within systole throughout life (12, 239, 266). This is because these methods capture only the start of the reflected waves, which indeed remains in systole throughout life. Thus, these methods are not suited to investigate the diastolic-to-systolic shift with ageing, which is based on a qualitative description of the entire waveform. Furthermore, each method provides different absolute values for return time, and it is therefore unclear which method (if any) provides an adequate quantification of return time. Indeed, methodological shortcomings—such as those noted for the inflection point method (94, 100) —may be a major factor limiting the assessment of

changes in wave reflection with age and/or in disease conditions. The development of an improved, well-validated method for quantifying return time is therefore a significant need in the field of arterial haemodynamics.

A powerful tool for providing insights into the influence of wave reflection on arterial haemodynamics, as well as assisting in the development of new techniques in the field, is one-dimensional (1D) modelling (3, 7, 123, 170, 255, 281). 1D models are used to simulate blood pressure and flow in an arterial network and are generally coupled to lumped parameter (zero-dimensional; 0D) models of the heart and microvascular beds. 1D modelling offers multiple advantages. First, they offer substantial flexibility in manipulating key physiological parameters independently or in combination, as well as the arterial network structure or properties, which would be impossible to do in animal experiments or clinical studies. Such flexibility can help tease out important insights from the complex haemodynamics of the arterial system (4, 168). Second, 1D models allow virtual experiments to be performed that would not be practically achievable or even ethical in clinical settings, such as changing arterial stiffness (24), to analyse their effects on haemodynamics. Finally, 1D models provide comprehensive pressure and flow information throughout the arterial network, constituting an ideal platform for validating new techniques (2, 123).

The overarching aim of this thesis is to improve understanding of arterial wave reflection and its impact on the microvasculature and ventricle through novel methodology that harnesses 1D modelling as well as in vivo experimental and human measurements. This thesis is arranged as follows. Chapter 2 provides an in-depth review of the theory of wave reflection and methods used to quantify and study it, including 1D modelling. Chapter 3 employs a bifurcating fractal tree 1D model to elucidate the influence of wave reflection on transmission of pulsatile haemodynamic forces towards the distal microvasculature. Chapter 4 describes an improved 1D

model of the systemic arteries that provides an accurate representation of the haemodynamics of a healthy young adult, sheds light on the wave reflection properties of the fully developed non-diseased arterial network, and serves as an important baseline model for studying haemodynamic changes with ageing. In Chapter 5, a novel ‘centroid method’ of estimating return time is developed, which overcomes key methodological issues limiting previous methods; the model developed in Chapter 4 is used to assess the accuracy of all methods via a novel model-based ground truth. Using data from three large cohort studies spanning most of the human lifespan, Chapter 6 investigates whether the centroid method supports or refutes the concept of a diastolic-to-systolic shift in return time with ageing, and also investigates other factors that affect return time, such as height, which is particularly relevant during childhood. Finally, Chapter 7 contains an overall discussion and considerations regarding limitations and future work.

Chapter 2: Modelling Wave Reflection in the Systemic Arterial Network

This chapter introduces key concepts regarding wave reflection in systemic arterial network. First, it describes the physical phenomenon of wave reflection and its effect on pressure and flow. Second, it introduces and critically assesses the methods that are commonly used to quantify the timing and magnitude of wave reflection. Finally, it discusses modelling techniques best suited for computational investigation of wave reflection and associated methods development. The concepts and techniques presented here are also used in subsequent chapters to shed light onto controversies about the effects of wave reflection and how it changes with age. Certain sections of this chapter were published in a book chapter titled “Wave reflection in the arterial tree” in *Textbook of Arterial Stiffness and Pulsatile Hemodynamics in Health and Disease*.

2.1 Introduction

As the left ventricle contracts and ejects blood through the arterial lumen, it also produces a forward-traveling mechanical wave that propagates to distal arteries through the elastic arterial wall at a finite speed known as wave speed. It is important to distinguish between the velocity of blood, which occurs at a slower speed (in the order of $\text{cm}\cdot\text{s}^{-1}$), and that of the mechanical wave, which occurs at a much higher speed (in the order of $\text{m}\cdot\text{s}^{-1}$). Like electromagnetic waves, this mechanical wave is also partially reflected at locations where there are changes in arterial properties. In the systemic arterial network, these backward-traveling reflected waves primarily cause an increase in pressure and flow (141), which has three important implications. First, the pressure and flow waveforms in arteries are determined not only by the properties of the heart, but also by those of the arterial tree. Second, the time when these reflected waves return to the

heart ('return time') is important, and it is determined by the distance from the reflection sites and the wave speed of all arteries en route. In youth, the reflected waves are thought to predominantly return during diastole, which helps promote coronary perfusion (181, 190). With ageing, there is an increase in wave speed owing to arterial stiffening (263). This shifts the return time earlier to systole, which presents an additional afterload to the ventricle and reduces its efficiency (181, 190). Thus, there is an expected diastolic-to-systolic shift in return time with ageing. Finally, both the timing and magnitude of reflected waves can provide insights into cardiovascular health (92, 141, 276, 298).

2.2 Pressure and Flow in the Absence of Wave Reflection

To understand the impact of wave reflection, it is useful to first consider what the relationship between blood pressure and blood flow would be in a theoretically reflection/less scenario—an infinitely long distensible vessel with uniform mechanical properties. If a pulse of fluid is injected into the vessel, a change in flow (dQ_+) and pressure (dP_+) is produced that travels as a wave in the forward direction ('+' subscript). The mathematical description of wave travel in a distensible vessel was originally formulated by Euler in 1775 (although published in 1862) (65). Von Kries later identified that dQ_+ and dP_+ in an elastic tube are intrinsically linked via a simple equation, now known as the 'water hammer' equation (203, 264):

$$dP_+ = Z_c dQ_+ \quad (\text{Equation 2.1})$$

where Z_c is called characteristic impedance, a term that is borrowed from electrical transmission line theory (110), noting that voltage and current are the electrical equivalents of pressure and flow respectively. The next section explains the details of a transmission line and the equations that describe voltage and current flowing through it.

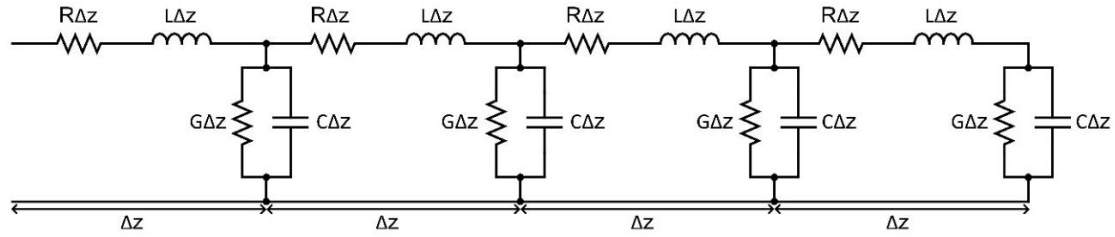


Figure 2.1: REPRESENTATION OF AN INFINITELY LONG TRANSMISSION LINE. An infinitely long transmission line represented by infinitesimally small transmission lines of length Δz , with each section having some capacitance ($C\Delta z$), inductance ($L\Delta z$), resistance ($R\Delta z$), and conductance ($G\Delta z$).

2.2.1 Transmission Line Theory

In a similarly reflectionless scenario, a transmission line is represented by two infinitely long pieces of wires running parallel to each other separated by an insulator. The transmission line can be modelled using circuit theory components to understand the changes in voltage and current with position and time. First, two pieces of metal separated by a distance accumulate charges between them when electricity flows through them, generating capacitance (C). Second, wires carrying electricity also generate a magnetic field, which creates inductance (L). Third, there is some dissipation of energy as heat as electricity flows through the wires due to resistance (R). Finally, in the absence of a perfect insulator between the wires, some electricity will leak from one wire to the other, giving rise to conductance (G). These effects are distributed throughout the length of the transmission line and thus their values are given per unit length. It is useful to separate the infinitely long transmission line into infinitesimally small transmission lines of length Δz ; thus, the total compliance, inductance, resistance, and conductance of each section will be $C\Delta z$, $L\Delta z$, $R\Delta z$, and $G\Delta z$, respectively (Figure 2.1).

Applying Kirchhoff's laws and taking the limit as $\Delta z \rightarrow 0$, the "telegrapher's equations" are obtained.

$$\frac{\partial V(z, t)}{\partial z} = -RI(z, t) - L \frac{\partial I(z, t)}{\partial t} \quad (\text{Equation 2.2})$$

$$\frac{\partial I(z, t)}{\partial z} = -GV(z, t) - C \frac{\partial V(z, t)}{\partial t} \quad (\text{Equation 2.3})$$

where $V(z, t)$ and $I(z, t)$ are space- and time-varying voltage and current, respectively. To solve Equations 2.2 and 2.3, it is necessary to rewrite them in terms of purely $V(z, t)$ or $I(z, t)$ by converting them to the frequency domain. This involves replacing $\partial/\partial t$ with $j\omega$ and denoting the voltage and current as $V(z)$ and $I(z)$ (time-invariant).

$$\frac{dV(z)}{dz} = -(R + j\omega L)I(z) \quad (\text{Equation 2.4})$$

$$\frac{dI(z)}{dz} = -(G + j\omega C)V(z) \quad (\text{Equation 2.5})$$

where $j = \sqrt{-1}$ and ω is the angular frequency of the wave, with higher frequencies corresponding to faster changes in voltage and current. Differential equations purely in terms of $V(z)$ and $I(z)$ can now be obtained using Equations 2.4 and 2.5.

$$\frac{d^2V(z)}{dz^2} - \gamma^2 V(z) = 0 \quad (\text{Equation 2.6})$$

$$\frac{d^2I(z)}{dz^2} - \gamma^2 I(z) = 0 \quad (\text{Equation 2.7})$$

where $\gamma = \sqrt{(R + j\omega L)(G + j\omega C)}$. Equations 2.6 and 2.7 are second-order differential equations, which can be solved to yield:

$$V(z) = V_0^+ e^{-\gamma z} + V_0^- e^{\gamma z} \quad (\text{Equation 2.8})$$

$$I(z) = I_0^+ e^{-\gamma z} + I_0^- e^{\gamma z} \quad (\text{Equation 2.9})$$

where $V(z)^+ = V_0^+ e^{-\gamma z}$ and $I(z)^+ = I_0^+ e^{-\gamma z}$ are forward-travelling waves, while $V(z)^- = V_0^- e^{\gamma z}$ and $I(z)^- = I_0^- e^{\gamma z}$ are backward-travelling waves. However, in a reflectionless scenario, $V(z)^- = I(z)^- = 0$.

2.2.2 Characteristic Impedance

In transmission line theory, Z_c is defined as the ratio of the forward-travelling voltage and current. Substituting Equation 2.8 in Equation 2.4 and using Equation 2.9, Equation 2.10 is obtained:

$$I_0^+ = \frac{\gamma}{R + j\omega L} V_0^+ \quad (\text{Equation 2.10})$$

Finally, characteristic impedance can be defined as:

$$Z_c = \frac{V_0^+}{I_0^+} = \sqrt{\frac{R + j\omega L}{G + j\omega C}} \quad (\text{Equation 2.11})$$

These equations can also be applied to the propagation of waves in a fluid-filled elastic vessel. V and I are equivalent to pressure and flow, respectively. Characteristic impedance is thus defined as the ratio of forward-traveling pressure and flow. R is viscous resistance to flow, L is inertia of the fluid, C is compliance of the vessel and G is leakage of blood through the vessel wall. The parameters L , C , and R can be related to measurable quantities as follows:

$$L = \frac{\rho}{A} \quad (\text{Equation 2.12})$$

$$C = \frac{A}{\rho c^2} \quad (\text{Equation 2.13})$$

$$R = \frac{8\eta}{\pi r^4} \quad (\text{Equation 2.14})$$

where ρ is blood density, η is blood viscosity, A is lumen cross-sectional area, r is lumen radius, and c is wave speed (which increases with vessel stiffness). Importantly, resistance is negligible in large vessels but becomes significant in smaller vessels because it is inversely proportional to the fourth power of radius (Equation 2.14). Thus, by ignoring resistance in large vessels ($R = 0$) and assuming no leakage of blood through the vessel wall ($G = 0$), Equation 2.11 reduces to $Z_c = \sqrt{L/C}$, which is frequency-independent and, via Equations 2.12 and 2.13, becomes:

$$Z_c = \frac{\rho c}{A} \quad (\text{Equation 2.15})$$

Z_c is an important haemodynamic parameter that is used as a metric of arterial stiffness (26, 101, 303). To understand the physical meaning of characteristic impedance, let us consider a large vessel where resistance to flow is negligible and thus Equation 2.15 is valid—the ascending aorta. Considering Equations 2.1 and 2.15, an increase in wave speed (as accompanied by increased vessel stiffness) increases Z_c , causing an increase in pressure for a given flow. This helps explain the increase in blood pressure with the ageing-related increase in aortic stiffness (72, 122, 209). However, it is important to note that aortic cross-sectional area increases with ageing (57, 204, 219), thus offsetting the increase in Z_c . The extent of this offset is controversial because some studies show an increase (148, 182), while others show a decrease (240), or no change (85) in Z_c with ageing.

To summarise the key points in this section, in the absence of wave reflection 1) pressure and flow waveforms will have the same shape; 2) the ratio of pressure and flow is called characteristic impedance (Z_c); and 3) Z_c is essentially independent of wave frequency in large vessels and depends on vessel size and stiffness (via A and c). The various methods of calculating Z_c are discussed in Section 2.5.

2.3 The Basis of Wave Reflection: Impedance Mismatching

Given the intrinsic link between pressure and flow in a reflectionless tube, *any differences* in the shape of measured pressure and flow waveforms must arise from wave reflection. Let us now consider two connected vessels of finite length with differing characteristic impedances (Z_1 and Z_2 , Figure 2.2); an ‘impedance mismatch’ therefore exists at the interface between these two vessels.

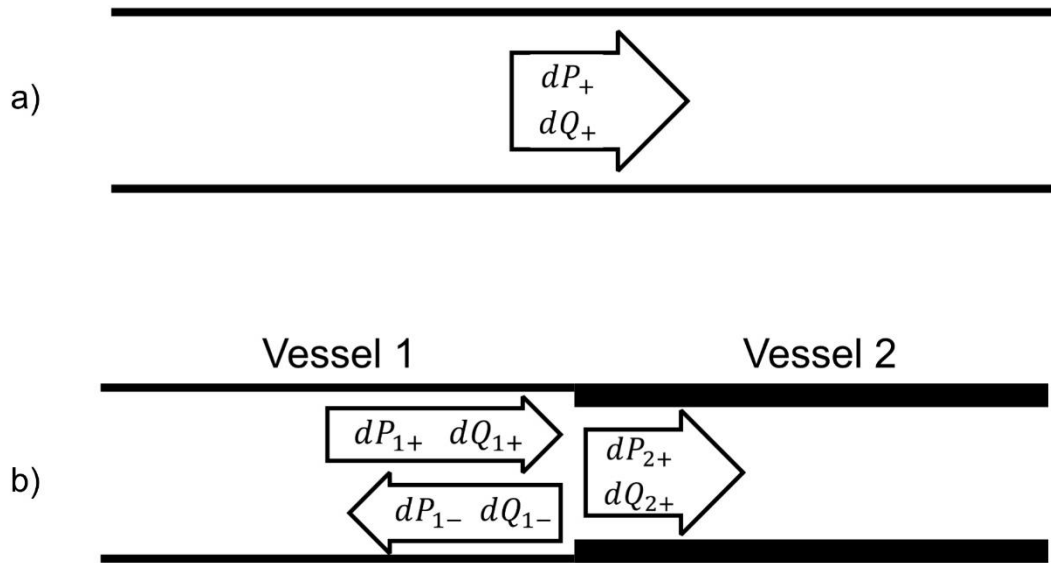


Figure 2.2: WAVE REFLECTION AT A SITE OF IMPEDANCE MISMATCH. a) In a uniform tube with infinite length, a forward-travelling wave undergoes no reflections and produces changes in pressure (dP_+) and flow (dQ_+). b) At the interface between two vessels that have differing characteristic impedance, a site of impedance mismatch exists. The incident forward wave produces pressure and flow changes in vessel 1 (dP_{1+} and dQ_{1+}) and the transmitted wave produces respective changes in vessel 2 (dP_{2+} and dQ_{2+}). A reflected wave produced at the site of impedance mismatch travels in the backward direction and produces further changes in pressure (dP_{1-}) and flow (dQ_{1-}) in vessel 1.

If a pulse of fluid is injected into the first vessel, a forward-travelling wave ('+' subscript) is produced that causes a change in pressure and flow in vessel 1 (dP_{1+} and dQ_{1+} , respectively). A portion of the wave energy is transmitted into vessel 2 (dP_{2+} and dQ_{2+} , respectively). In addition, wave reflection must arise at sites of impedance mismatch to satisfy the fundamental laws of conservation of energy and mass; this is akin to light or sound waves being partially reflected when they travel from one medium to another with different refractive indices or densities, respectively.

To understand this requirement, imagine a theoretical scenario where wave reflection does not occur at the interface between vessel 1 and 2 (Figure 2.2b). If this were so, the only pressure

and flow changes would be dP_{1+} and dQ_{1+} in vessel 1 and dP_{2+} and dQ_{2+} in vessel 2, respectively. Assuming no viscous dissipation (which is generally very small at vascular junctions), conservation of energy requires ‘continuity of pressure’, which means that the total pressure change in both vessels is the same ($dP_{1+} = dP_{2+}$). Re-writing both sides with the water hammer equation (Equation 2.1) would then imply that $Z_1 dQ_{1+} = Z_2 dQ_{2+}$. If the two vessels had the same characteristic impedance ($Z_1 = Z_2$), i.e., no impedance mismatch, then $dQ_{1+} = dQ_{2+}$, which satisfies conservation of mass. However, if there is an impedance mismatch ($Z_1 \neq Z_2$), then the water hammer equation requires that $dQ_{1+} \neq dQ_{2+}$, which would violate conservation of mass. Therefore, where an impedance mismatch is present, the only way for mass and energy to be conserved, while upholding the water hammer equation in both vessels, is for a reflected wave to arise in vessel 1.

The reflected wave travels in the backward direction (‘-’ subscript) and causes a further change in pressure (dP_{1-}) and flow (dQ_{1-}) in vessel 1 (Figure 2.2b). Hence, the overall pressure change in vessel 1 is $dP_{1+} + dP_{1-}$ and overall change in flow is $dQ_{1+} + dQ_{1-}$ (Figure 2.2). The laws of conservation of mass and energy require that the changes in pressure and flow in both vessels are equal, hence,

$$dP_{1+} + dP_{1-} = dP_{2+} \quad (\text{Equation 2.16})$$

$$dQ_{1+} + dQ_{1-} = dQ_{2+} \quad (\text{Equation 2.17})$$

2.4 Impact of Wave Reflection on Arterial Pressure and Flow

To understand how reflected waves affect pressure and flow, a key observation is that the water hammer equation expressed for backward-travelling waves includes a negative sign (in contrast to Equation 2.1 which is for forward-travelling waves):

$$dP_- = -Z_c dQ_- \quad (\text{Equation 2.18})$$

Where both forward and backward waves are present at a particular measurement site, the observed pressure (dP) and flow (dQ) changes are equal to the sum of the respective forward and backward waves ($dP = dP_+ + dP_-$ and $dQ = dQ_+ + dQ_-$), if the generally small influence of non-linearities is neglected (163, 212). These water hammer equations (Equations 2.1 and 2.18) have two very important implications for interpreting arterial haemodynamics. First, forward waves cause pressure and flow to change in the same direction (a pressure-increasing forward wave will accompany a flow increase). However, backward waves cause pressure and flow to change in opposite directions (a pressure-increasing backward wave will accompany a flow decrease). Consequently, it is backward waves that cause measured pressure and flow waveforms in arteries to differ in appearance (Figure 2.3).

With the exception of coronary arteries, where some backward waves are actively generated in the intramyocardial circulation (54, 172), wave reflection is therefore ultimately responsible for the well-known differences in the shape of arterial pressure and flow waveforms. These differences are virtually abolished by reducing wave reflection via infusion of vasodilators or the Valsalva manoeuvre, whereas the differences are accentuated when wave reflection is increased via the Mueller manoeuvre or infusion of vasoconstrictors (51, 159, 195, 269, 286).

2.5 Calculating Characteristic Impedance

As mentioned previously, characteristic impedance is defined as the ratio of forward-traveling pressure and flow. In the absence of wave reflection, the pressure and flow waveforms would have identical shapes; thus, Z_c can be obtained by simply taking the ratio of the two signals in the time domain. However, this method cannot be used in the presence of wave reflections because the shapes differ and dividing the two would give uninterpretable results. To overcome

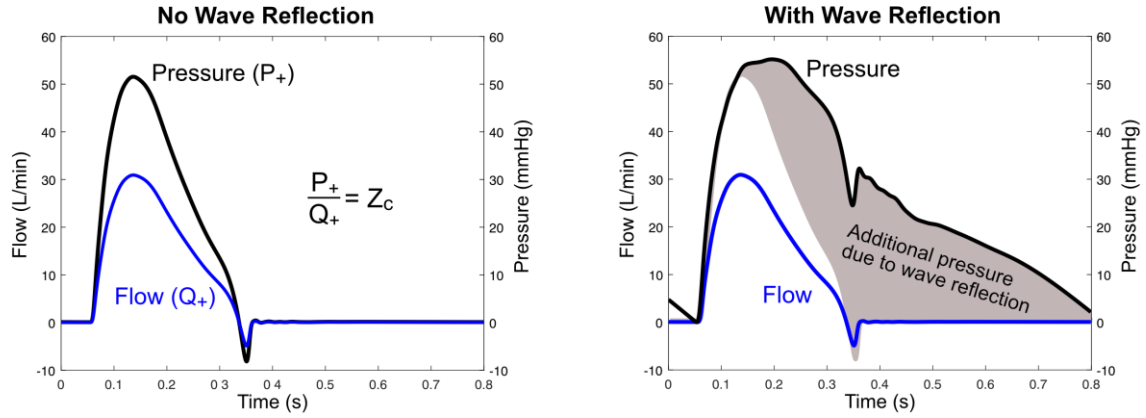


Figure 2.3: EFFECT OF WAVE REFLECTION ON PRESSURE. In the absence of wave reflection (left), flow and pressure waveforms have the same shape, scaled by the characteristic impedance ($1.67 \text{ mmHg} \cdot \text{min} \cdot \text{L}^{-1}$ in this case). In the presence of wave reflection (right), the pressure waveform diverges from the flow waveform. The grey shaded region of the pressure waveform is the additional pressure due to wave reflection. Note: the diastolic pressure in both cases is assumed to be zero for simplicity of representation, and the scales are different for the flow and pressure waveforms.

this, Z_c can be estimated using frequency-domain methods (average of pressure-flow harmonics at high frequencies) or time domain methods (pressure-flow loop method).

2.5.1 Frequency-Domain Method

A well-established method of calculating Z_c is via the input impedance (Z_{in}) spectrum, which is the ratio of the Fourier transforms (symbol $\mathcal{F}$) of the pressure (P) and flow (Q) waveforms measured simultaneously. The input impedance of the central arteries provides valuable information about wave reflection from the distal parts of the arterial tree and the afterload on the left ventricle (150, 194). Representative pressure and flow waveforms of the ascending aorta are shown in Figure 2.4a. The ratio of the Fourier transforms of the two produces the input impedance (Equation 2.19), whose modulus and phase spectra are shown in Figure 2.4b and 2.4c, respectively. Each datapoint is an integer multiple or ‘harmonic’ of the fundamental frequency (heart rate in beats per second).

$$Z_{in} = \frac{\mathcal{F}(P)}{\mathcal{F}(Q)} \quad (\text{Equation 2.19})$$

The impedance modulus has a large value at 0 Hz, which is the ratio of mean pressure and flow, and thus represents the systemic vascular resistance. It then falls sharply to a minimum at a critical frequency (f_c) and oscillates about a certain value (Z_c). The impedance phase also falls sharply from 0 Hz, crosses over from negative to positive around f_c , and oscillates about zero, indicating a cancellation of in-phase and out-of-phase reflected waves. The higher frequency region is consequently thought to be relatively free from wave reflection. Thus, Z_c is calculated as the average impedance modulus at frequencies higher than f_c (151). Ideally, the full modulus spectrum beyond f_c should be considered; however, there is low signal-to-noise ratio beyond ~ 25 Hz (151). Thus, a frequency band is usually used when calculating Z_c to avoid noise, with the exact frequency values being somewhat arbitrarily chosen (181). Some studies use a range of absolute frequency values (213); however, this has the drawback of being dependent on heart rate. To overcome this, some studies use a range of harmonics instead (213). The studies presented in this thesis use a harmonics range of 4 to 11 calculate Z_c , which is similar to that used by previous studies (101, 261).

2.5.2 Time-Domain Method

Given the mathematically involved nature of the frequency-domain method, Dujardin & Stone developed a simpler time-domain method of calculating Z_c from the slope of the pressure-flow loop during the initial upstroke (Figure 2.4d) (61). This period is assumed to be relatively free from wave reflection because it is thought that forward waves dominate due to ventricular ejection. Dujardin & Stone found that the time-domain method provided values of Z_c comparable to the frequency-domain method under a wide range of flow conditions (61), a finding confirmed by Qureshi et al. (213). Qureshi et al. provided a critical comparison of the two methods and noted that they provided qualitatively similar results (213).

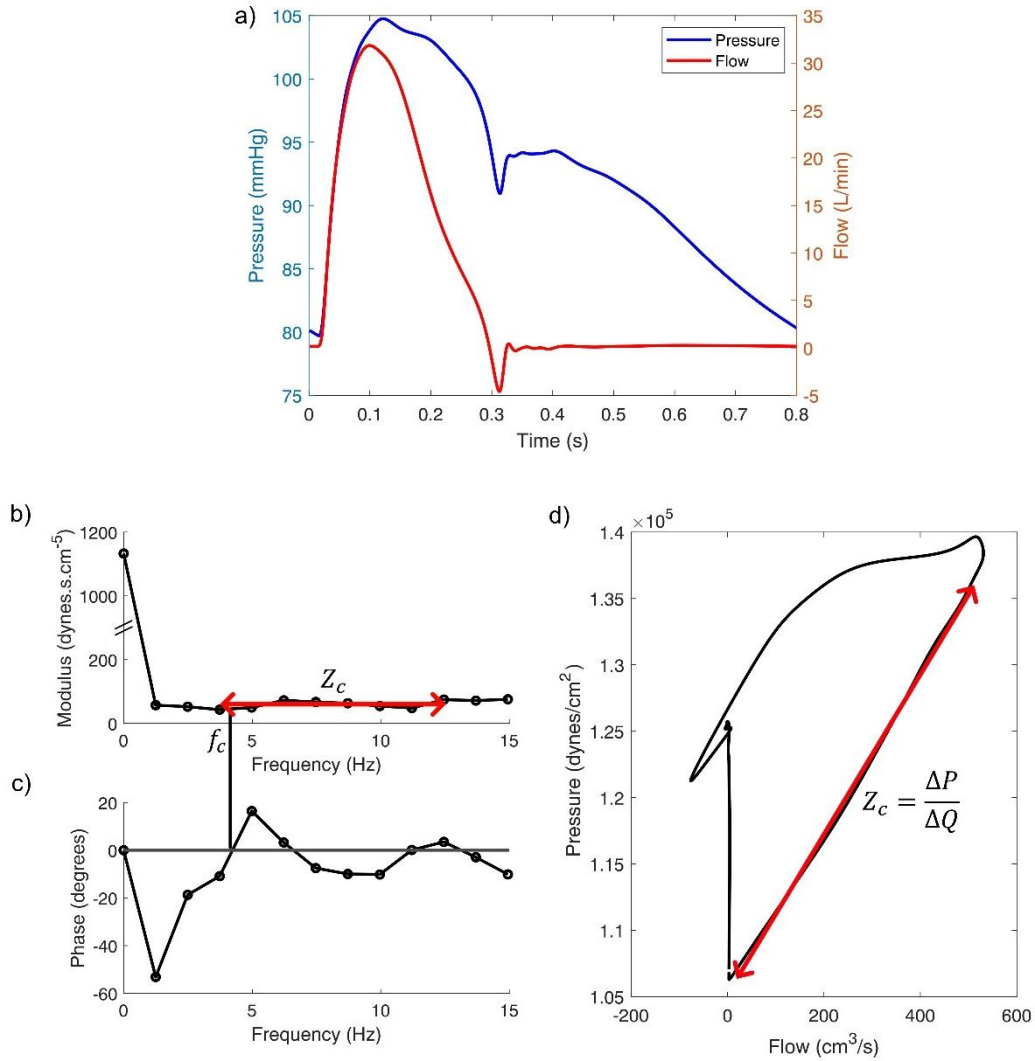


Figure 2.4: ESTIMATING CHARACTERISTIC IMPEDANCE. a) Representative pressure (blue) and flow (red) waveforms of the ascending aorta under normal conditions. Characteristic impedance (Z_c) can be obtained using frequency-domain (b and c) or time-domain methods (d). Frequency-domain: impedance modulus (b) and phase (c) obtained by the ratio of the Fourier transforms of pressure and flow. Z_c is obtained by taking the average modulus over a certain range of frequencies or harmonics beyond the critical frequency (f_c). d) Time-domain: Z_c is obtained as the slope of the pressure-flow loop during early systole where the relationship is somewhat linear. ΔP and ΔQ represent the amplitudes of the pressure and flow waveforms during the early systolic region.

2.6 Reflection and Transmission Coefficients

Characteristic impedance can be used to quantify the degree to which a pressure wave is reflected at the boundary between vessel 1 and vessel 2 (Figure 2.2b). The reflection coefficient

(Γ_P) is defined as the ratio of the reflected pressure wave (dP_{1-}) to the incident pressure wave (dP_{1+}). This can be expressed in terms of the mismatch in characteristic impedance using Equations 2.1, 2.16, 2.17, and 2.18 (110, 120):

$$\Gamma_P = \frac{dP_{1-}}{dP_{1+}} = \frac{Z_2 - Z_1}{Z_2 + Z_1} \quad (\text{Equation 2.20})$$

As mentioned previously, resistance is considered negligible in large vessels. Thus, the complex terms (j) cancel out (Equation 2.11) and Z_c becomes purely real, leading to a real Γ_P as well. However, when resistance becomes significant (e.g., in small vessels), the complex terms remain and Z_c is complex, making Γ_P complex as well. In such cases, Γ_P is more appropriately presented as a frequency-dependent spectrum (32, 286).

The pressure transmission coefficient (T_P) is defined as

$$T_P = \frac{dP_{2+}}{dP_{1+}} = \frac{2Z_2}{Z_2 + Z_1} \quad (\text{Equation 2.21})$$

By combining Equations 2.20 and 2.21, it can also be shown that T_P and Γ_P are related via $T_P = 1 + \Gamma_P$. At first this may seem counterintuitive because one might expect that a 40% reflection would be accompanied by 60% transmission. However, this intuition only applies to conserved quantities like flow and energy, whereas pressure is not a conserved quantity. On the other hand, pressure is essentially continuous at arterial junctions, which means that pressure does not exhibit large changes over very short distances; as will be shown in Chapter 3, the relation $T_P = 1 + \Gamma_P$ in fact arises from the requirement of the continuity of pressure and the conservation of momentum and energy. Reflection and transmission coefficients for flow Γ_Q and T_Q can also be defined and expressed in terms of Γ_P (Table 2.1). In addition, the coefficients of composite measures that combine pressure and flow (such as hydraulic power and wave intensity) can also be found by combining the respective coefficients in the same manner (Table 2.1).

Table 2.1: REFLECTION AND TRANSMISSION COEFFICIENTS. Reflection (Γ) and transmission coefficients (T) for pressure (subscript 'P'), flow (subscript 'Q'), and hydraulic power (subscript 'HP') where $HP = P \times Q$. Note: The reflection and transmission coefficients for wave power ($dP \times dQ$) are the same as those for hydraulic power.

Measurement	Reflection Coefficient	Transmission Coefficient
Pressure (P)	Γ_P	$T_P = 1 + \Gamma_P$
Flow (Q)	$\Gamma_Q = -\Gamma_P$	$T_Q = 1 + \Gamma_Q = 1 - \Gamma_P$
Hydraulic Power (HP)	$\Gamma_{HP} = \Gamma_P \times \Gamma_Q = -\Gamma_P^2$	$T_{HP} = 1 + \Gamma_{HP} = 1 - \Gamma_P^2$

A wave can either cause an increase in pressure ('compression' waves) or a decrease in pressure ('decompression' waves) (203). Furthermore, forward waves change pressure and flow in the same direction, while backward waves change them in the opposite direction (Equation 2.18). Thus, a forward compression wave (FCW) will increase both pressure and flow ($dP_+ > 0$ and $dQ_+ > 0$), while a forward decompression wave (FDW) will decrease both pressure and flow ($dP_+ < 0$ and $dQ_+ < 0$). On the other hand, a backward compression wave (BCW) will increase pressure but decrease flow ($dP_- > 0$ and $dQ_- < 0$), while a backward decompression wave (BDW) will decrease pressure but increase flow ($dP_- < 0$ and $dQ_- > 0$). Reflection and transmission coefficients interact differently with each type of wave; it is instructive to highlight three scenarios: no reflection, positive reflection, and negative reflection. The discussion here is limited to pressure and flow coefficients and note that Γ_P is positive when $Z_2 > Z_1$ and negative if $Z_2 < Z_1$.

1. *No reflection.* When the junction is well-matched, i.e., there is no impedance mismatch ($Z_2 = Z_1$), no reflected wave arises ($\Gamma_P = 0$ and $\Gamma_Q = 0$) and a pressure/flow wave is transmitted forward unaltered ($T_P = 1$ and $T_Q = 1$), regardless of its type.
2. *'Positive' reflection.* Positive reflection refers to a positive value of Γ_P , which will preserve the compression/decompression nature of the incident wave upon reflection. Thus, a FCW and FDW will produce a BCW and BDW, respectively. If vessel 2 were

progressively occluded (area approaches zero, i.e., $A_2 \rightarrow 0$), Z_2 would progressively increase. As $Z_2 \rightarrow \infty$ (i.e., complete occlusion), $\Gamma_P \rightarrow 1$ and $T_P \rightarrow 2$. On the other hand, $\Gamma_Q \rightarrow -1$ and $T_Q \rightarrow 0$, which means that (as expected) transmission of flow approaches zero and therefore the reflected flow wave must totally cancel out the incident flow wave (i.e., $\Gamma_Q = -1$). One may therefore consider positive reflection as involving a conversion from kinetic energy (flow) to potential energy (pressure).

3. *'Negative' reflection.* Negative reflection refers to a negative value of Γ_P , which will invert the compression/decompression nature of the incident wave upon reflection. Thus, a FCW and FDW will produce a BDW and BCW, respectively. If vessel 2 were progressively enlarged ($A_2 \rightarrow \infty$), Z_2 approaches zero, the pressure reflection coefficient becomes negative ($\Gamma_P \rightarrow -1$) and transmission of pressure falls toward zero ($T_P \rightarrow 0$). In the scenario where A_2 is infinite (i.e., vessel 1 opens out to an infinite reservoir), the reflected pressure wave entirely cancels the incident pressure wave, so that pressure at the interface does not change (just as flow does not change for a complete occlusion). The concept of negative reflection can be difficult to grasp but may be understood when considering the analogy of a wave propagating along a river (vessel 1) that meets the sea (vessel 2). A wave that increases water level in the river (analogous to an increase in pressure) cannot also raise sea level because the sea is effectively an infinite reservoir compared with the river. Hence to ensure continuity of pressure at the interface, the reflected pressure wave cancels the pressure effect of the incident wave. Negative reflection therefore involves a conversion from potential energy (pressure) to kinetic energy (flow), since as $Z_2 \rightarrow 0$, $\Gamma_Q \rightarrow 1$ and $T_Q \rightarrow 2$; hence the reflected wave augments flow in the same direction as the incident wave.

Although a single reflection site between two vessels has been considered, the same principles apply when considering wave reflection that is distributed through an arterial network. Positive

reflection ($\Gamma_p > 0$) is well-recognised to occur in systemic arteries, while there has been some evidence of negative reflection ($\Gamma_p < 0$) in the pulmonary circulation (30, 99). Moreover, negative reflection is just as prevalent (but less widely recognised) in systemic arteries as reflected waves travel from smaller distal vessels to larger proximal vessels (166).

2.7 Wave Reflection at Other Sites

So far, wave reflection at a point of impedance mismatch within a single vessel has been explored. Other features of the arterial system that can give rise to impedance mismatching include junctions, tapering, and resistance vessels.

2.7.1 Arterial Junctions

To understand wave reflection at junctions, Equation 2.20 can be extended to include two daughter vessels, instead of one. For simplicity, the equation can be written in terms of characteristic admittance, which is the inverse of characteristic impedance (i.e., $Y = 1/Z_c = A/\rho c$ in large vessels).

$$\Gamma_p = \frac{Y_0 - (Y_1 + Y_2)}{Y_0 + (Y_1 + Y_2)} \quad (\text{Equation 2.22})$$

where the subscripts 0, 1, and 2 refer to the parent and two daughters, respectively. Additional daughter branches could be included as additional terms in the brackets (Y_3, Y_4 etc), but only a bifurcation is considered here.

Assuming symmetrical daughter vessels ($A_1 = A_2$) and that $c \propto 1/A^4$ (as per the Moens-Korteweg equation), it can be shown that a bifurcation will be well-matched ($\Gamma_p = 0$) when the daughter-to-parent ratio ($\alpha = (A_1 + A_2)/A_0$) is approximately 1.15 (203, 292). For asymmetric bifurcations, the optimal area ratio is slightly lower (203). Interestingly, extensive measurements

of area ratios of the arterial tree in humans found that $\alpha = 1.14 \pm 0.03$, suggesting that the arterial bifurcations are indeed well-matched, facilitating the efficient transmission of forward waves from the heart to organs and tissues (199). This principle has been a key design feature of computational models of arterial haemodynamics, where it has been found that well-matched junctions are required to produce realistic pressure/flow waveforms (175, 275, 291). Alexander et al. had suggested that bifurcations provided sites of wave reflection (8). However, it was found that wave reflections can be almost entirely abolished by vasodilators, which directly increase the diameter of high resistance arterioles but have no effect on branching patterns of large conduit arteries (195). Hence, although wave reflection can occur at junctions that are not well-matched, it appears unlikely that this is the major source of wave reflection in the healthy arterial system.

2.7.2 Tapering

Arterial branching is a fundamental feature of the arterial system, but whether arterial junctions are a key source of wave reflection has been controversial. Arterial tapering refers to the gradual decrease in area (geometric tapering) or change in wall properties (elastic tapering) along the length of a vessel. Both kinds of tapering lead to a continuous change in Z_c and consequently, wave reflection also occurs in a continuous manner along the entire length of a vessel instead of at a discrete point (167). Interestingly, Segers et al. found that such continuous reflections had similar effects on measured pressure and flow signals as discrete reflections, thus making them indiscernible with measurements at a single site (241). Arterial tapering (which involves decreasing area and increasing stiffness) has been hypothesized to play a role in pulse amplification because the continuously increasing Z_c produces reflected waves that increasingly add to the pressure waveform as waves travel from the heart to the periphery (1, 14, 76).

2.7.3 Resistance Vessels

Viscous resistance is negligible in large arteries but becomes significant in smaller vessels such as arterioles. In these smaller vessels, resistance makes an appreciable or even dominant contribution to Z_c (Equation 2.11). This abrupt increase in resistance occurs over a very short length (181). Several lines of evidence support the long-held view that high resistance arterioles serve as the major sites of wave reflection (87, 188). First, as mentioned above, arterial bifurcations tend to be well-matched (200). Second, vascular beds have been shown to have a relatively high reflection coefficient, with a value of 0.8 estimated for the canine femoral vascular bed (195) and evidence of a relatively large backward compression wave in the distal radial artery in humans (299). Third, vasodilation of resistance vessels markedly reduces or even abolishes wave reflection, whereas vasoconstriction increases wave reflection (32, 41, 107, 195, 269).

These observations notwithstanding, the role of peripheral resistance in generating wave reflection is still debated, primarily because changes in wave reflection may be induced without a parallel change in systemic vascular resistance (282). For example, administration of glyceryl trinitrate, which mainly acts on muscular conduit arteries, results in a clear reduction in wave reflection, but unchanged peripheral resistance (68, 294). However, Yaginuma et al. suggested this could be explained by negative reflection arising at the interface between larger parent arteries and the dilated muscular arteries, which would offset the unchanged positive reflection occurring at the arteriolar level (294).

2.8 Methods for Assessing the Magnitude and Timing of Wave Reflection

As discussed in Section 2.1, both the timing and magnitude of wave reflection hold important clinical significance. Thus, clinically applicable methods have been established to provide an estimate of these parameters, which shall be explored in this section.

2.8.1 Pressure Augmentation

Aortic pressure waveforms are characterised by an initial rise in pressure accompanied by the increase in flow (caused by the heart contracting). In some cases, Murgo et al. noted a secondary rise in pressure following a visually evident inflection point (158). The inflection point occurred either after the peak systolic pressure (usually seen in younger patients) or before it (usually seen in older patients). This suggested that the inflection point may be an indicator of wave reflection timing.

Furthermore, Murgo et al. defined a quantity ΔP based on the inflection point: $\Delta P = P_{pk} - P_i$, where P_{pk} is peak systolic pressure and P_i is the pressure at the inflection point (158). Murgo et al. found that ΔP doubled in magnitude when wave reflections were increased by externally compressing the femoral artery (158); conversely, Yaginuma et al. found that ΔP decreased with the administration of a vasodilator and accompanying decrease in wave reflection (294). These findings point to ΔP as an index of wave reflection magnitude.

Kelly et al. (116) built on this work and defined a “shoulder point” on the central pressure waveform (located close to the inflection point and usually before it) and found that the shoulder point had a good correlation with, and was close to the point of peak flow, implying that any further rise or “augmentation” in pressure despite a decrease in flow must be due to

reflected waves. Thus, they used the shoulder point to quantify wave reflection timing and magnitude.

2.8.1.1 Wave Reflection Timing

Kelly et al. (116) analytically derived the shoulder point as the second zero-crossing of the fourth derivative of the pressure waveform in the direction from above to below the zero line. Segers et al. (239) determined the inflection point as the second peak of the second derivative of the pressure waveform. The time difference between the onset of the pressure waveform and the shoulder or inflection points are then taken as two definitions of return time (Figure 2.5). The exact reason for Kelly et al. defining a shoulder point instead of using the inflection point identified by Murgo et al. is unclear. Nevertheless, Segers et al. found that the return times obtained by either shoulder or inflection points were correlated and decreased with age as expected (239), a finding supported by the meta-analysis by Baksi et al (12).

2.8.1.2 Wave Reflection Magnitude

Kelly et al. (116) formalized the definition of ΔP by coining the term “augmentation index” (Alx; Equation 2.23)

$$\text{Alx} = \frac{P_{pk} - P_s}{PP} \times 100\% \quad (\text{Equation 2.23})$$

where P_s is the pressure at the shoulder point and PP is pulse pressure. Kelly et al. (116) found that Alx increased with age, consistent with the expectation of an increase in wave reflection with age (182) owing to increased peripheral resistance and impaired vasodilation of resistance vessels (78). A later meta-analysis also supported this finding (12), supporting the use of augmentation index as an estimate of wave reflection magnitude. Segers et al. found that Alx defined by the shoulder and inflection point both increased with age and were highly correlated, and that the shoulder point provided higher values for Alx than the inflection point (239).

Despite the extensive use of pressure augmentation (whether defined by the shoulder or inflection point) to estimate the timing and magnitude of reflected waves, there is significant controversy regarding the robustness of this technique (94, 100, 207, 237, 239), which has arisen due to the availability of another technique for quantifying the effect of reflected waves on the pressure waveform that is considered a “gold standard” method—wave separation.

2.8.2 Wave Separation

Deeper insights into the wave reflection properties of the arterial tree can be gathered by separating the measured pressure and flow waveforms into forward components (produced by the heart) and backward components (produced by the combined effects of all reflected waves arriving at the measurement site). Both frequency-domain (286) and time-domain methods (159) of wave separation have been developed, with both giving comparable results (101). Wave separation requires the measurement of both pressure and flow waveforms at a particular site, with respective forward and backward components calculated in the time domain via (176):

$$P_{\pm} = \frac{1}{2}(P_m - P_{ud} \pm Z_c Q_m) \quad (\text{Equation 2.24})$$

$$Q_{\pm} = \frac{1}{2} \left(\frac{P_m - P_{ud}}{Z_c} \pm Q_m \right) \quad (\text{Equation 2.25})$$

where the subscript ‘*m*’ refers to the measured waveform (Figure 2.6). P_{ud} is undisturbed pressure, which refers to the pressure that prevails when there is no pressure gradient and flow throughout in the system. For simplicity, P_{ud} is assumed to be 0 in this thesis.

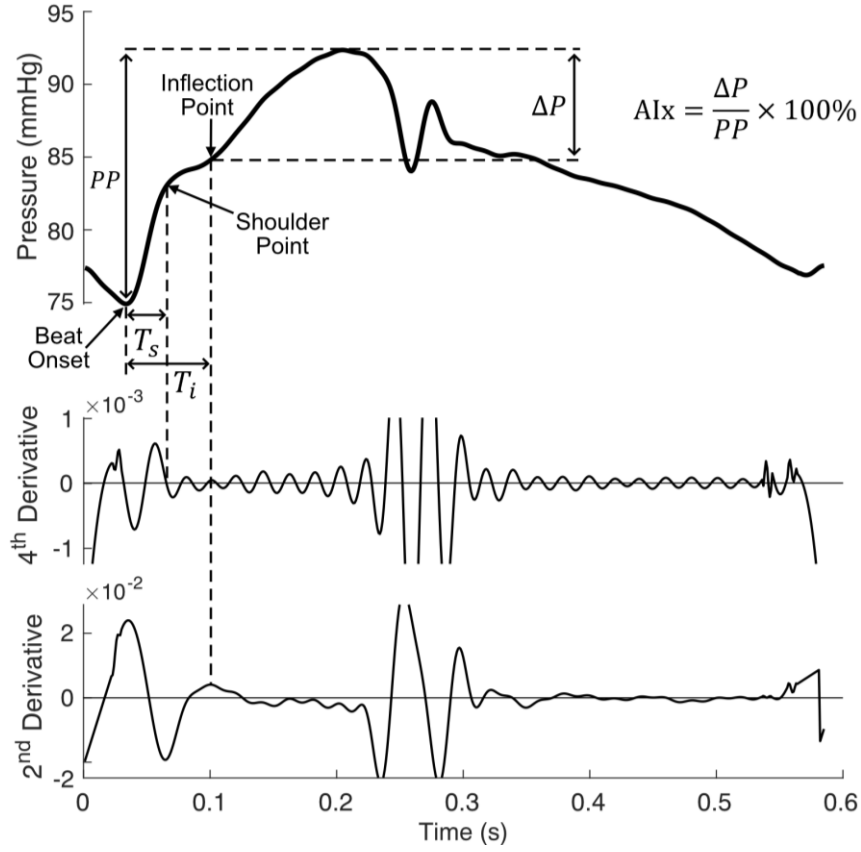


Figure 2.5: ESTIMATING RETURN TIME USING THE INFLECTION POINT METHOD. The shoulder point is identified by the second zero-crossing of the 4th derivative of the pressure waveform in the direction from above to below zero. The inflection point is identified by the second peak of the 2nd derivative of the pressure waveform. The shoulder point (T_s) or the inflection point (T_i) can be used to estimate return time by their time difference to beat onset time. ΔP is the pressure difference between the systolic pressure and the inflection point. Dividing ΔP by the pulse pressure (PP) gives augmentation index (Alx), an index of reflection magnitude. ΔP (and consequently Alx) can also be determined by the shoulder point. Note that the 2nd and 4th derivative waveforms have been cropped for better visualisation.

2.8.2.1 Wave Reflection Magnitude

Reflection coefficient is calculated as the ratio of the backward and forward waves (Equation 2.20). Based on this, reflection magnitude (RM) is defined as the ratio of the amplitudes of the backward (ΔP_-) and forward (ΔP_+) pressure waveforms (Equation 2.26).

$$RM = \frac{\Delta P_-}{\Delta P_+} \quad (\text{Equation 2.26})$$

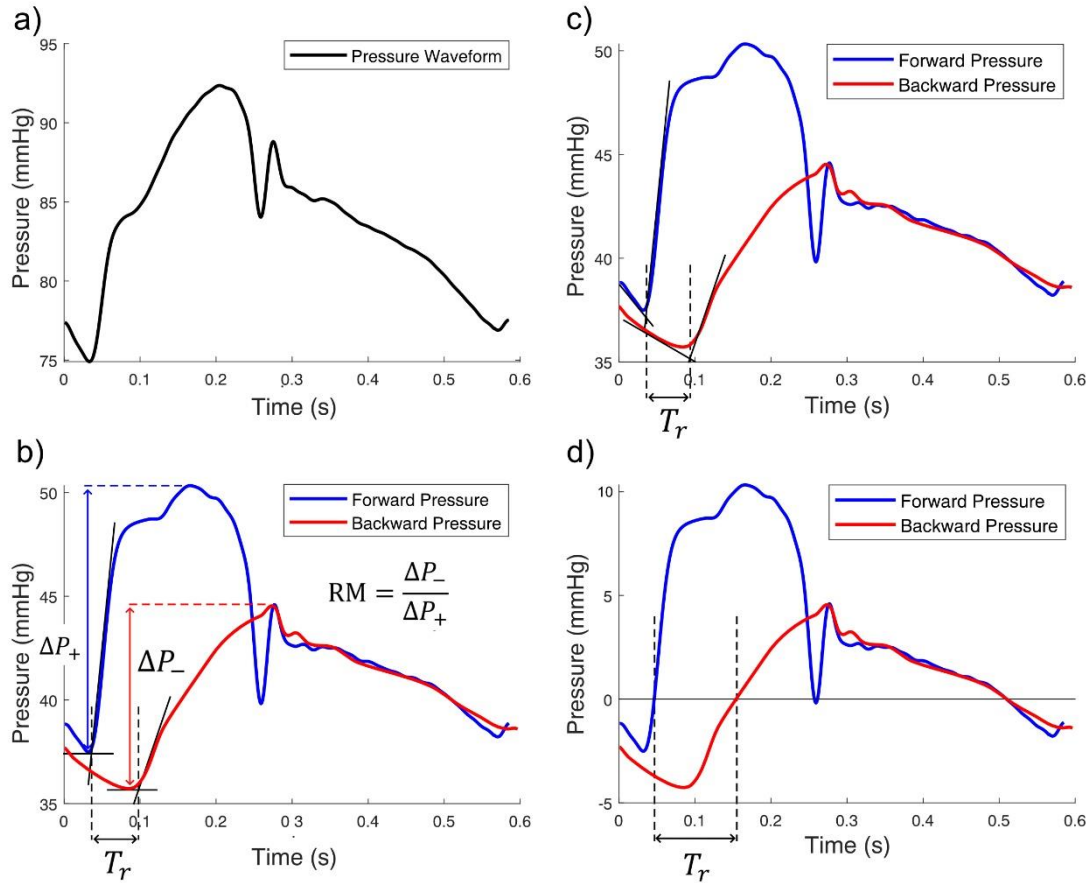


Figure 2.6: ESTIMATING RETURN TIME USING WAVE SEPARATION. Using wave separation, a pressure waveform (a) can be separated into its forward (P_+) and backward (P_-) components (b). From this, reflection magnitude (RM) is calculated as the ratio of the backward pressure amplitude (ΔP_-) to the forward pressure amplitude (ΔP_+). Return time (T_r) is calculated using the time difference of the feet of the backward and forward pressures. The foot can be found using the intersecting tangents of the maximum gradient of the pressure upstroke and a horizontal line from the minimum pressure (b) or a linear regression line formed from the minimum pressure and a few preceding points (c). T_r can also be calculated by subtracting the mean pressure before wave separation and taking the time difference between the first zero cross-over of the backward and forward pressures (d).

Interestingly, Segers et al. found a weak correlation (239) and Hughes et al. (100) found no correlation between Alx and RM. Unlike Alx , RM was found to be independent of height and gender (100). However, there is some controversy regarding the changes in RM with ageing; Hughes et al. found that it decreased (100) and Segers et al. found that it increased (239), while Mitchell et al. reported a slight increase until 50 years of age and a subsequent decrease (157).

It is important to note, however, that Hughes et al. (100) used the absolute peak values of P_- and P_+ instead of their amplitudes, which resulted in lower RM values than other studies.

2.8.2.2 Wave Reflection Timing

Compared with RM, there is less consensus regarding the best method for estimating wave return time using wave separation. One method is to take the difference between the onset (foot) of the backward and forward pressure waveforms as the return time. While the foot can be found by visual inspection, in some instances the exact location of the foot can be unclear (especially for backward waveforms that sometimes rise gradually). To help eliminate ambiguity, Chiu et al. developed a method to determine the foot of a pressure waveform using “intersecting tangents” (47). A tangent is drawn at the point of maximum gradient on the upstroke of the pressure waveform and a horizontal tangent is drawn through the point of minimum pressure at the foot; the point of intersection of the tangents is taken as the foot (Figure 2.6b). Some studies have taken a linear regression with the minimum pressure and a few preceding points, thus giving a downward-facing line instead of a horizontal line (Figure 2.6c) (155, 281). Return time obtained using this method (Figure 2.6b) was found to decrease with age, as expected (266).

However, the accuracy of the intersecting tangents method in determining the foot of noisy pressure waveforms has been called into question (113). Segers et al. therefore developed a new technique—the zero crossing method—that does not rely on finding the foot (239). Instead, the mean pressure is subtracted from the pressure waveform, which then undergoes wave separation. This subtraction causes the forward and backward waveforms to cross the x-axis and the difference between the first zero cross-over of the backward and forward waveforms is taken as the return time (Figure 2.6d). The return time obtained by this method

also decreased with age (207) and was only weakly correlated with that obtained by the shoulder and inflection point (239).

2.8.3 Wave Intensity

Parker et al. introduced wave intensity analysis as an intuitive time-domain method of extracting the forward and backward waves (both compression and decompression) from the pressure and flow waveforms (Equation 2.27).

$$dI = \frac{dP}{dt} \frac{dU}{dt} \quad (\text{Equation 2.27})$$

where dI is wave intensity, dt is the sampling rate, and dP and dU are obtained by taking the first derivative of the pressure and velocity waveform (flow waveform divided by vessel area), respectively. Figure 2.7 shows a typical wave intensity profile of the aorta obtained from Equation 2.27 and identifies the different types of waves (FCW, FDW, BCW, and BDW) by separating the profile into its forward and backward components. Wave reflection magnitude and timing can be quantified from the wave intensity profile.

2.8.3.1 Wave Reflection Magnitude

A positive overall reflection coefficient exists in the systemic circulation. Noting that a positive reflection coefficient will maintain the type of wave, a FCW will give rise to a BCW. Thus, wave reflection magnitude is usually estimated by the ratio of the peak amplitude of BCW to that of FCW, termed as wave reflection index (WRI) (Figure 2.7).

FCW presents as a single distinct peak, making the identification of its peak amplitude unambiguous. However, BCW can be relatively diffuse, making the identification of a single peak subjective. To overcome this, reflection index is also sometimes taken as the ratio of the area

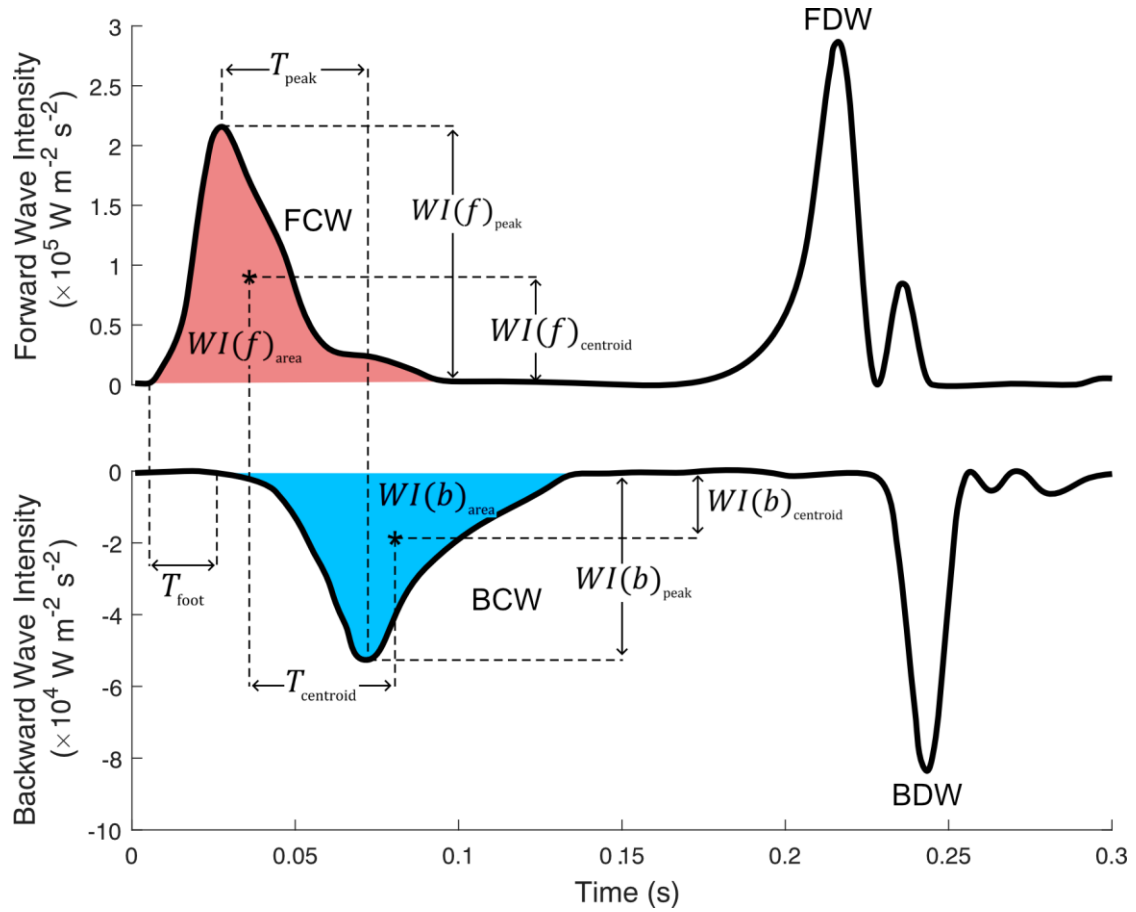


Figure 2.7: ESTIMATING RETURN TIME USING WAVE INTENSITY. From the wave intensity profile, reflection magnitude can be obtained by taking the ratio of the peak ($WI(b)_{\text{peak}}/WI(f)_{\text{peak}}$), centroid ($WI(b)_{\text{centroid}}/WI(f)_{\text{centroid}}$), or area under the curve ($WI(b)_{\text{area}}/WI(f)_{\text{area}}$) of the backward compression wave (BCW) and the forward compression wave (FCW). Return time can be obtained using the difference of the foot (T_{foot}), peak (T_{peak}), or centroid (T_{centroid}) of the BCW and FCW. The forward decompression wave (FDW) and backward decompression wave (BDW) are also shown here (note the different scales for the backward and forward wave intensity).

under BCW to that under FCW (161) or the ratio of their centroids (4) (Figure 2.7). Mynard et al. found that wave intensity was affected by the non-linear properties of arteries (dependence of wave speed on pressure), thus causing errors in estimating reflection magnitude from its profile (regardless of whether the peak or the area is used) (161). In fact, under some conditions, the calculated reflection index could be beyond the theoretical limits of a reflection coefficient (-1 to +1). Importantly, they found that the reflection magnitude obtained by wave separation of the pressure waveform was more accurate as it was less affected by non-linearity.

2.8.3.2 Wave Reflection Timing

Alastruey et al. proposed multiple methods of determining return timing using wave intensity: difference between timing of BCW and FCW 1) peak, 2) foot, and 3) centroid (Figure 2.7) (4). Using a simple computational model with a single reflection site, they found that the foot method gave an estimate of return time closest to the theoretical value. However, the accuracy of the methods in vivo is less clear owing to the diffuse nature of reflections. Wave intensity has not been used to determine age-related changes in return time to our knowledge.

2.9 Computational Modelling to Investigate Arterial Wave

Reflection

Reflected waves arrive at the heart in a continuum, with different magnitudes (depending on the reflection coefficient) and at different times (depending on arterial wave speeds and distance of the reflection site from the heart). However, the indices of wave reflection magnitude and timing described above only give a broad overview of the wave reflection properties downstream of the point of pressure and/or flow measurements. The concept of wave reflection arises from the equations that govern transmission lines, making it an inherently model-based construct. Thus, computational models rooted in transmission line theory are best suited to investigate wave reflection. One-dimensional (1D) models have been developed that use anatomically realistic arterial networks using 1D segments to represent the major arteries (10, 183, 256, 284). These models account for wave travel across the entire arterial tree, making them ideal for investigating the effect of complex patterns of wave reflection on haemodynamics at various locations on the arterial tree. Wave reflection in the systemic arteries is one of the major factors that underlies hypertension and elevated left ventricular afterload (181); hence, the focus shall only be on 1D models of the systemic arterial network in this thesis. Models of waves in arteries have 4 major components: 1) Navier-Stokes equations that define

the basic laws of fluid dynamics, 2) an empirical equation describing the relationship between pressure and arterial cross-sectional area (i.e., a wall law), 3) an inlet boundary condition (i.e., heart model), and 4) an outlet boundary condition (i.e., vascular bed model). The next sections describe each component in detail, focusing specifically on techniques employed in this thesis.

2.9.1 Navier-Stokes Equations

The Navier-Stokes equations (Equations 2.28 and 2.29) govern the spatial and temporal changes in pressure and velocity in any flowing fluid, and are derived from the laws of conservation of mass and momentum (245, 257). They are usually defined in three dimensions but can be reduced to a 1D form under the following assumptions:

1. Vessels have a uniformly circular cross-section.
2. The length of the vessel is much larger than the radius.
3. Pressure and velocity gradients in the radial and circumferential directions are negligible.

With these assumptions, the 1D Navier-Stokes equations may be expressed as (245, 257):

$$\frac{\partial A}{\partial t} + \frac{\partial Au}{\partial x} = 0 \quad (\text{Equation 2.28})$$

$$\frac{\partial u}{\partial t} + u \frac{\partial u}{\partial x} + \frac{1}{\rho} \frac{\partial P}{\partial x} = f \quad (\text{Equation 2.29})$$

where, A is area, u is velocity, P is pressure, ρ is blood density (1.06 g/cm^3), and f is a loss term related to viscous resistance that depends on blood viscosity ($\mu = 0.035 \text{ g/cm}\cdot\text{s}^{-1}$) and the assumed velocity profile. A simple form of f suitable for global haemodynamics is $f = -\xi\pi\mu u/A$, where ξ is calculated using the model described by Bessems et al (19). Note that Equation 2.29 assumes a flat velocity profile.

2.9.2 Pressure-Area Relationship (Wall Law)

To find solutions for the three variables (A , u , and P), a third equation is required to close the system that describes the relationship between pressure and area based on the vessel wall properties. Given the complex composition and properties of vessel walls, an empirical viscoelastic relationship has been proposed that provides a relatively good approximation of wall distention over a wide range of pressures (35, 175, 249).

$$P - P_{ext} = \frac{2\rho c_0^2}{b} \left[\left(\frac{A}{A_0} \right)^{\frac{b}{2}} - 1 \right] + \frac{\Gamma}{A\sqrt{A}} \frac{\partial A}{\partial t} + P_0 \quad (\text{Equation 2.30})$$

$$b = \frac{2\rho c_0^2}{P_0 - P_{collapse}} \quad (\text{Equation 2.31})$$

$$\Gamma = \frac{b_1}{D} + b_0 \quad (\text{Equation 2.32})$$

where P_{ext} is external pressure (assumed to be 0 in this thesis), P_0 is a reference pressure (taken to be 80 mmHg for systemic arteries), c_0 is the wave speed at P_0 , A_0 is the area at P_0 , Γ is a coefficient of wall viscosity, D is vessel diameter, $b_1 = 100 \text{ g}\cdot\text{cm}\cdot\text{s}^{-1}$, and $b_0 = 400 \text{ g}\cdot\text{s}^{-1}$. $P_{collapse}$ is the pressure at which $A \rightarrow 0$ and is taken as -10 mmHg by extrapolating the pressure-area relationship determined by Langewouters et al. (127) and to avoid complete collapse from occurring in any of the situations studied in this thesis. The values of b_1 and b_0 apply to arteries and were empirically derived by Mynard et al. (175) based on published dynamic pressure-area relationships in dogs and humans (16, 130). The value of A_0 is determined for each 1D artery in the model based on in vivo data (284). The in vivo value of c_0 is only known for major accessible arteries such as the ascending aorta, common carotid, and femoral arteries. Thus, an empirical relationship has usually been employed to assign a value of c_0 to every artery solely based on its value of A_0 (197, 223); an improved empirical relationship is proposed in Chapter 4.

2.9.3 Inlet Boundary Condition (Heart Model)

The inlet to the systemic arterial tree is the left heart. However, previous studies have prescribed either an aortic flow waveform (284) or pressure waveform (256) as the input for simplicity. It is now becoming common to prescribe a zero-dimensional (0D) heart model as the inlet boundary condition to the 1D model (34, 136, 247, 258) because it allows the investigation of ventriculo-vascular coupling. A 0D model is one where the chamber pressure (P_c) and volume (v) of the various chambers of the model only have temporal variation, but no spatial variation; indeed, wave propagation effects within the heart can be ignored for the purposes of this thesis. A commonly used model is to represent the relationship between P_c and v as a time-varying elastance (E) and to include a source resistance (R_s) that governs the relationship between p and ventricular flow (Q_{ven}) (Equation 2.33) (164). Elastance is the inverse of compliance and thus is the tendency of a chamber to recoil towards its original shape once a distending pressure is removed.

$$P_c = E(v - v_{p=0}) - R_s Q_{ven} \quad (\text{Equation 2.33})$$

where $v_{p=0}$ is the unstressed chamber volume. $R_s = K_s E(v - v_{p=0})$ where K_s is a source resistance constant. The time-varying elastance is well-described using a ‘two-Hill’ equation (Equations 2.34 and 2.35) (254). Elastance is thought to be relatively consistent between individuals and somewhat independent of preload (end-diastolic chamber volume) and afterload (mean arterial pressure) conditions (84, 147); this makes it an ideal candidate as an input to the 1D model.

$$E(t) = k \left(\frac{\left(\frac{t}{\tau_1}\right)^{m_1}}{1 + \left(\frac{t}{\tau_1}\right)^{m_1}} \right) \left(\frac{1}{1 + \left(\frac{t}{\tau_2}\right)^{m_2}} \right) + E_{min} \quad (\text{Equation 2.34})$$

$$k = \frac{E_{max} - E_{min}}{\max \left[\left(\frac{\left(\frac{t}{\tau_1} \right)^{m_1}}{1 + \left(\frac{t}{\tau_1} \right)^{m_1}} \right) \left(\frac{1}{1 + \left(\frac{t}{\tau_2} \right)^{m_2}} \right) \right]} \quad (\text{Equation 2.35})$$

where E_{max} and E_{min} are maximum and minimum elastance that govern systolic contractility and diastolic passive stiffness, respectively, k is a scaling factor that ensures that $\max(E(t)) = E_{max}$, τ controls the time translation, and m controls the slope of the elastance upstroke and downstroke. Since the studies in this thesis only relate to the systemic circulation, a 2-chamber left heart model is employed, with each chamber (atrium and ventricle) having unique values for Equations 2.33, 2.34, and 2.35 (Appendix A.3).

The left heart model also includes the mitral and aortic valve models, which have been previously described in detail (164). In brief, the relationship between the pressure difference (ΔP_v) and flow (Q_v) across a valve can be described by the Bernoulli equation:

$$\Delta P_v = B Q_v |Q_v| + L \frac{dQ_v}{dt} \quad (\text{Equation 2.36})$$

$$B = \frac{\rho}{2A_{eff}^2} \quad (\text{Equation 2.37})$$

$$L = \frac{\rho l_{eff}}{A_{eff}} \quad (\text{Equation 2.38})$$

where B is the Bernoulli resistance, L is the inertance of blood, and l_{eff} is an effective length. A_{eff} is the effective area of the valve and is determined by the valve's annulus area (A_{ann}) and an index of the valve's state (ζ),

$$A_{eff} = A_{ann} \zeta(t) \quad (\text{Equation 2.39})$$

where $0 \leq \zeta \leq 1$; $\zeta = 0$ denoted a closed valve while $\zeta = 1$ denoted an open valve. The valve begins to open once ΔP_v exceeds an opening threshold pressure (ΔP_{open}), governed by the following equation:

$$\frac{d\zeta}{dt} = (1 - \zeta) K_{vo}(\Delta P_v - \Delta P_{open}) \quad (\text{Equation 2.40})$$

Similarly, once $\Delta P_v < (\Delta P_{close})$, the valve begins to close according to the equation below:

$$\frac{d\zeta}{dt} = \zeta K_{vc}(\Delta P_v - \Delta P_{close}) \quad (\text{Equation 2.41})$$

The values for K_{vo} , K_{vc} , and A_{ann} used in this thesis are given in Appendix A.3.

2.9.4 Outlet Boundary Condition (Vascular Bed Model)

Modelling each arteriole and capillary within a circulatory region as a 1D segment is computationally intensive. Moreover, local wave propagation effects in these vessels are less important because their length is orders of magnitude smaller than arteries. Thus, the bulk properties of the large number of vessels distal to the large conduit arteries (referred to as ‘vascular bed’) can be condensed into a single 0D model to provide time-varying pressure and flow, which form the outlet boundary conditions for a terminal 1D artery. The venous system is represented as a constant outlet pressure (P_∞) of 5 mmHg (75).

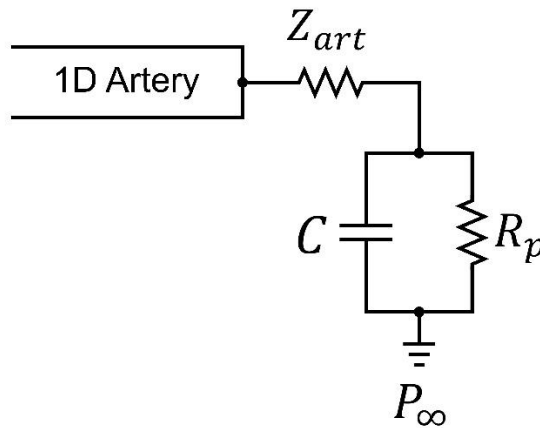


Figure 2.8: WINDKESSEL MODEL OF A VASCULAR BED. Schematic diagram of a 1D artery terminating in a vascular bed (windkessel model) depicting the characteristic impedance of the terminal 1D artery (Z_{art}), compliance (C) and peripheral resistance (R_p) of the vascular bed, and a constant venous pressure (P_∞).

The most common 0D model is a 3-element windkessel introduced by Westerhof et al. (285), which includes 2 resistance elements—characteristic impedance of the terminal 1D artery (Z_{art}) and peripheral resistance of the vascular bed (R_p)—and 1 capacitor element (C) that represents the compliance of the vascular bed (Figure 2.8). The pressure (P_w) and flow (Q_w) in the windkessel model are governed by the following equation:

$$P_w - P_\infty + R_p C \frac{dP_w}{dt} = (R_p + Z_{art}) Q_w + Z_{art} R_p C \frac{dQ_w}{dt} \quad (\text{Equation 2.42})$$

Mynard et al. (175) described a method for terminating multiple 1D segments into a common vascular bed encompassing certain anatomic regions or organs (e.g. shoulder, stomach etc) (Figure 2.9). The distribution of R_p values of each vascular bed determine the flow distribution; thus, the R_p values were adjusted to obtain a physiological flow distribution in every vascular bed (284).

Estimating the value of C for each vascular bed is more difficult and an approximation method is usually employed (256). First, total arterial compliance (C_{total}) is estimated using the aortic pressure and flow waveforms via the pulse pressure method (255). Second, the compliance of each 1D arterial segment is calculated using $LA_0/(\rho c_0^2)$, where L is the length of the artery, and the total compliance of all 1D arteries is determined (C_{1D}). Third, the total compliance of all vascular beds (C_{0D}) is calculated as $C_{total} - C_{1D}$. The value of C for an individual vascular bed (k) is then calculated based on its R_p value using

$$C_k = C_{0D} \frac{R_{total}}{R_p} \quad (\text{Equation 2.43})$$

where R_{total} is the systemic vascular resistance (combined resistance of all vascular beds).

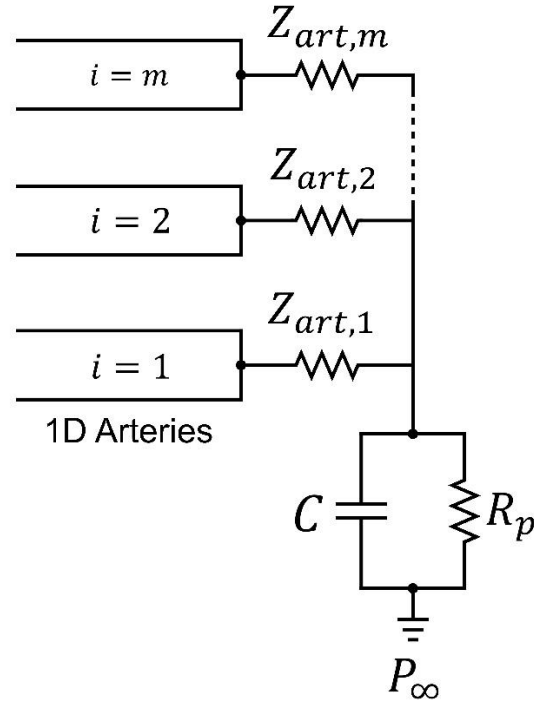


Figure 2.9: MULTIPLE ARTERIES TERMINATING IN A SINGLE VASCULAR BED. Schematic diagram of multiple 1D arteries ($i = 1, 2 \dots m$) terminating in a single vascular bed (windkessel model), with each 1D artery having its own characteristic impedance ($Z_{art,i}$).

2.9.5 Numerical Solution

Numerical methods are required to solve the non-linear 1D form of the Navier-Stokes equations (Equations 2.28 and 2.29). The two major steps involved are temporal discretization and spatial discretization, which have previously been described in detail (169). This thesis employed the numerical scheme described by Mynard and Nithiarasu (169). In brief, temporal discretization is obtained using the Taylor-Galerkin stabilization method (70, 245), wherein Equations 2.28 and 2.29 are first expressed in their conservative form:

$$\frac{\partial U}{\partial t} = S - \frac{\partial F}{\partial x} \quad (\text{Equation 2.44})$$

where $U = \begin{bmatrix} A \\ u \end{bmatrix}$, $S = \begin{bmatrix} 0 \\ f \end{bmatrix}$, and $F = \begin{bmatrix} uA \\ \frac{u^2}{2} + \frac{p}{\rho} \end{bmatrix}$. Taking the second derivative of Equation 2.44 with

respect to time and taking the first two terms of its Taylor series expansion from time n to $n + 1$ yields:

$$\frac{U^{n+1} - U^n}{\Delta t} = S^n - \frac{\partial F^n}{\partial x} - \frac{\Delta t}{2} \left[\frac{\partial}{\partial x} \left(\frac{\partial F^n}{\partial U} S^n - \frac{\partial F^n}{\partial U} \frac{\partial F^n}{\partial x} \right) - \frac{\partial S^n}{\partial U} \frac{\partial F^n}{\partial x} - \frac{\partial S^n}{\partial U} S^n \right] \quad (\text{Equation 2.45})$$

where Δt is the time step (taken as 3.5×10^{-6} s in this thesis).

Spatial discretization is achieved with the locally conservative Galerkin (LCG) finite element method (169), where each 1D segment is divided into a number of 1D elements (Ω_e). Equation 2.45 can then be expressed in its residual form, multiplied by a linear Galerkin weighting (N^T) and integrated over Ω_e :

$$\int_{\Omega_e} \left(N^T \frac{\Delta \hat{U}}{\Delta t} - N^T \hat{R}^n \right) d\Omega_e = 0 \quad (\text{Equation 2.46})$$

where $\Delta \hat{U} = \hat{U}^{n+1} - \hat{U}^n$ and $\hat{R}$ is the right-hand side of Equation 2.45. The values of any variables within an element can be found using linear interpolation. Equation 2.46 can be solved to yield the following set of equations:

$$[M_e] \{\Delta U\} = \Delta t \left([K_e] \{F\}^n + [L_e] \{S\}^n + \{f_{\Gamma_e}\}^n \right) \quad (\text{Equation 2.47})$$

$$[M_e] = \frac{l_e}{2} \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix} \quad (\text{Equation 2.48})$$

$$[K_e] = \left(\frac{1}{2} + \frac{\Delta t}{4} \frac{\partial \check{S}^n}{\partial U} \right) \begin{bmatrix} -1 & -1 \\ 1 & 1 \end{bmatrix} - \frac{\Delta t}{2l_e} \frac{\partial \check{F}^n}{\partial U} \begin{bmatrix} 1 & -1 \\ -1 & 1 \end{bmatrix} \quad (\text{Equation 2.49})$$

$$[L_e] = \left(\frac{l_e}{6} + \frac{\Delta t l_e}{12} \frac{\partial \check{S}^n}{\partial U} \right) \begin{bmatrix} 2 & 1 \\ 1 & 2 \end{bmatrix} - \frac{\Delta t}{r} \frac{\partial \check{F}^n}{\partial U} \begin{bmatrix} -1 & -1 \\ 1 & 1 \end{bmatrix} \quad (\text{Equation 2.50})$$

$$\{f_{\Gamma_e}\} = \begin{Bmatrix} \check{F}_i^n \\ -\check{F}_j^n \end{Bmatrix} \quad (\text{Equation 2.51})$$

where l_e is the length of the element, $\check{F}$ and $\check{S}$ are average values of F and S over the entire element with nodes (i, j) , respectively, and $\check{F}_i$ and $\check{F}_j$ are the average values of F from adjacent elements. For elements situated at either end of the 1D artery, f_{Γ_e} is determined from the boundary conditions. The 0D left heart and vascular bed models were discretised with a first-

order forward Euler time discretisation and coupled to the 1D segment by extrapolating the outgoing characteristic (for further details see Mynard et al. (169)).

2.9.6 Linear Wave Tracking

The Navier-Stokes equations and their numerical solutions provide a good description of arterial haemodynamics because they account for the non-linearities of blood flow in the cardiovascular system (e.g., viscous resistance). Thus, they provide pressure and flow waveforms that closely resemble those observed *in vivo*. The forward wave generated by the heart during contraction is reflected and re-reflected at various points along the arterial tree as determined by its geometry. Each wave exerts a different effect on local haemodynamics depending on its amplitude and timing. However, non-linearity in a system (*in vivo* and in the Navier-Stokes equations) causes dispersion and attenuation of waves as they traverse the network, making it impossible to ‘keep track’ of discrete waves. Towards this, linearised methods in the frequency domain (262) and time domain (222) have been developed—termed ‘linear wave tracking’—to track individual waves in the system. Such methods have provided important insights into wave reflection: 1) the majority of wave reflection occurs in the vicinity of vascular beds, not in the conduit arteries (5) and 2) the complex geometry of the arterial tree has a large influence on wave reflection patterns (275).

By ignoring non-linearities of the system, individual waves can be treated independent of each other. A detailed description of linear wave tracking is provided in Chapter 5. Briefly, using a 1D model of the systemic arterial network (with the ascending aorta as the first artery), an ‘input’ wave of amplitude 1 at time 0 is prescribed at the proximal end of the ascending aorta. This input wave ‘traverses’ the first vessel segment over a given time, calculated by dividing the length of the ascending aorta by its wave speed. At the distal end of the ascending aorta, three waves are produced: two waves that are transmitted into each of the daughter vessels and one

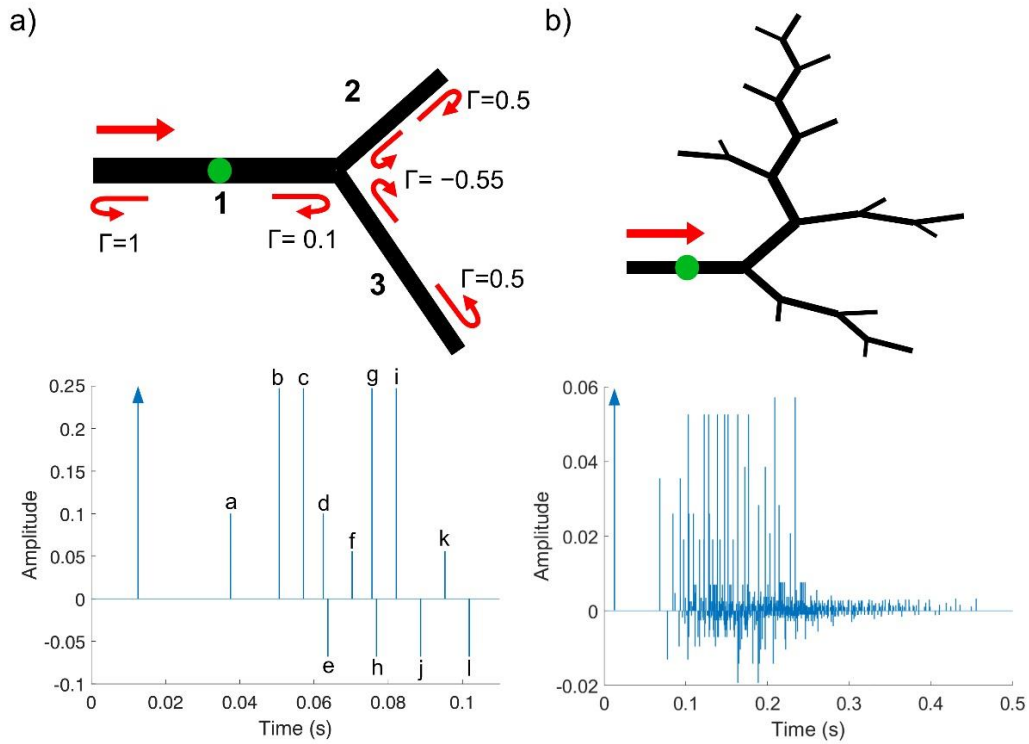


Figure 2.10. IMPULSE RESPONSE OF ARTERIAL TREES. Schematic of a simple asymmetric bifurcation (a) and a complex fractal tree with multiple generations (b) and their respective impulse responses showing the amplitude and timing of reflected waves arriving at the monitoring point (green dot). The arrow in the impulse response represents the input wave with amplitude 1.

reflected wave that propagates back towards the parent vessel. The amplitude of each wave is determined by the reflection coefficient at the junction (Equation 2.22). As the input wave traverses the model, numerous reflected and transmitted waves are produced, with each wave being ‘tracked’. The amplitude and timing of every reflected wave arriving at the inlet can be precisely measured, producing an impulse response (275). Figure 2.10 shows the impulse response for a simple bifurcation model and a more complex branching network. The pattern of reflection and re-reflection would continue indefinitely throughout the model, with wave amplitude becoming progressively smaller. Since it would not be feasible to keep track of every wave, once the amplitude of a wave falls below a specified threshold, it is no longer tracked.

2.10 Summary

This chapter introduced the basis of wave reflection (impedance mismatch) and the differing effects of forward and backward waves on pressure and flow. It also discussed the relationship between the reflection and transmission coefficients of pressure ($T_p = 1 + \Gamma_p$) and flow ($T_Q = 1 - \Gamma_Q$), which will be used in Chapter 3 to clarify the role of wave reflection on pressure transmission to the distal microvasculature. This chapter also provided a detailed description of 1D computational models of the systemic arterial tree. Chapter 4 highlights certain drawbacks in current models and suggests improvements in key aspects of 1D models that help generate more realistic arterial properties and haemodynamics representative of a young adult. Finally, this chapter introduced the current methods of estimating return time. Chapter 5 will introduce a novel centroid method and Chapter 6 will apply these methods to data spanning most of the human lifespan to investigate how return time changes with normal ageing.

Chapter 3: Effect of wave reflection on microvascular pressure

This chapter first examines a prevailing hypothesis that reduced wave reflection with ageing is a key factor responsible for increased pulse pressure in the microvasculature. It then explains the inconsistency of this hypothesis with the theory underpinning wave reflection. Finally, it provides clarity using computational means on the more likely factor responsible for increased microvascular pulse pressure. This chapter is published as a peer-reviewed article titled “Conduit arterial wave reflection promotes pressure transmission but impedes hydraulic energy transmission to the microvasculature” in the American Journal of Physiology – Heart & Circulatory Physiology (doi: 10.1152/ajpheart.00733.2019).

3.1 Introduction

With ageing, increased pressure pulsatility is thought to occur in distal feeding vessels (49). While this has not been measured directly, evidence from clinical studies suggests that this occurs in conjunction with increased flow pulsatility, elevating risk of damage to high perfusion, low impedance organs such as the brain and kidneys, and contributing to cognitive decline and kidney dysfunction, respectively (114, 273, 293). However, the precise mechanism for increased distal pulse pressure (*PPd*) with ageing has not been fully identified.

One prominent paradigm proposed by Mitchell et al. (153) holds that increased *PPd* arises from altered wave reflection with ageing. Wave reflection occurs when an incident wave encounters an impedance mismatch, which can be caused by a net change in area or stiffness, e.g., at bifurcations or with tapering. The degree of impedance mismatch determines the degree of reflection and transmission of the incident wave, which are quantified by the pressure reflection

coefficient (R) and transmission coefficient (T_p), respectively. Mitchell (153) suggested that the higher compliance of the elastic arteries compared with muscular arteries in youth creates a stiffness gradient, leading to impedance mismatching and hence wave reflections. It was postulated that these reflections limit the transmitted pressure and protect the distal feeding vessels from high pulse pressure. The paradigm also suggests that with ageing, stiffening of the elastic arteries reduces the stiffness gradient in the arterial network, leading to reduced wave reflection and increased pressure transmission, and consequently, increased PPd . This mechanism was assumed to underlie an association between reduced stiffness gradient and increased cardiovascular events in dialysis patients (71). Mitchell et al. (156) also proposed that reduced wave reflection with ageing may also increase transmission of hydraulic energy. Hydraulic energy, defined as the integral of the product of pressure (P) and flow (Q), relates to the potential for work, with changes in this quantity manifesting as changes in flow and/or pressure depending on the conditions.

However, a potential issue with the view that pressure transmission increases with reductions in conduit arterial wave reflection arises from consideration of transmission line theory, which forms the widely accepted mathematical framework for analysing wave reflection and transmission. Transmission line theory states that pressure reflection and transmission coefficients are related via $T_p = 1 + R$ (see Appendix A.1). This implies that wave reflection would not protect against high PPd in youth because reduced reflection with ageing would reduce pressure transmission, not increase it (207). Furthermore, it is not known whether hydraulic energy follows the same principles of wave transmission as pressure.

Another mechanism that could account for increased PPd is increased magnitude (rather than transmission) of the forward pressure wave generated by the left ventricle. It is known that the decrease in aortic compliance and associated increase in characteristic impedance with age

leads to increased forward wave magnitude and proximal pulse pressure (PPp) (157, 253). Whether aortic compliance modulates PPd and PPp in similar ways is not known.

Thus, the aims of this study were: 1) To investigate whether increased *transmission* of the forward pressure wave (caused by a decrease in wave reflection) or increased *magnitude* of the forward pressure wave (caused by a reduction in large artery compliance) could account for increased PPd with ageing; 2) To explore whether PPp and PPd are linked via arterial compliance; and 3) To determine and compare the influence of wave reflection on transmission of hydraulic energy and pressure into distal feeding vessels.

3.2 Methods

3.2.1 Fractal Arterial Tree Model

Systematically altering conduit arterial wave reflection to investigate its effect on haemodynamics would be essentially impossible in vivo. Hence, the most effective method to explore the aims of this study was to use established modelling techniques to investigate arterial wave dynamics (170, 174, 176). A one-dimensional model of a bifurcating fractal tree (each parent branch having two daughter branches) was used rather than an anatomical model, as in Mynard et al. (175). This allowed a systematic investigation of the influence of wave reflection on haemodynamics in a vascular network from large proximal arteries down to the distal feeding vessels (Figure 3.1).

The fractal tree comprised 1816 vessels across 21 generations. The branching structure of the fractal tree was governed by the following equations:

$$r_0^\xi = r_1^\xi + r_2^\xi \quad (\text{Equation 3.1})$$

$$\gamma_A = \frac{r_1^2}{r_2^2} = \frac{A_1}{A_2} \quad (\text{Equation 3.2})$$

$$\gamma_c = \frac{c_1}{c_2} \quad (\text{Equation 3.3})$$

$$R = \frac{Y_0 - Y_1 - Y_2}{Y_0 + Y_1 + Y_2} \quad (\text{Equation 3.4})$$

where r is radius, A is area, c is wave speed (referring to values at a reference initial pressure) of a parent vessel (subscript 0) and daughter vessels (subscripts 1 and 2), ξ is the fractal exponent with fixed value of $\xi = 2.76$ (197), γ_c is the wave speed asymmetry ratio, γ_A is the

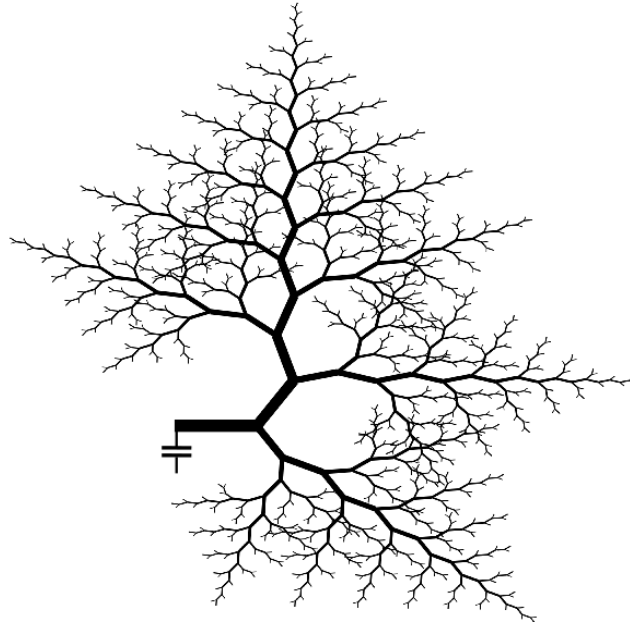


Figure 3.1: ARTERIAL NETWORK REPRESENTED BY A FRACTAL TREE. Fractal tree representing an arterial network spanning from large proximal arteries to the distal feeding vessels. The capacitor represents an additional compliance used in some simulations to maintain proximal pulse pressure or proximal forward pressure despite parameter changes applied to the network.

area asymmetry ratio, and $Y = A/c$ is characteristic admittance. The value of γ_A was fixed at 0.48 based on the average area asymmetry ratio in a previous anatomical model of the large systemic arteries (175). Appendix A.2 details how the value of γ_c was set based on γ_A , ξ , and Γ_p . A length-to-radius ratio of 8 was chosen as this produced physiological pressure and flow waveforms. A time-varying elastance heart model was used, as in Mynard (162), with two Hill equations used to describe the evolution of ventricular contraction and relaxation; the parameter values are detailed in Appendix A.3. This model was connected to the inlet branch of the fractal tree, whose cross-sectional area was set to 650 mm^2 (radius = 14.4 mm), which is within the normal range for the adult aorta (radius = 10–17 mm) (64, 142). The network was terminated when the radius was $<1.5 \text{ mm}$, and the terminal vessels were connected to 3-element windkessel compartments that represented downstream vessels (total resistance $1.2 \text{ mmHg}\cdot\text{s}\cdot\text{mL}^{-1}$ and total compliance $1.2 \text{ mL}\cdot\text{mmHg}^{-1}$, distributed according to terminal vessel cross-sectional area).

3.2.2 Distal and Proximal Stiffening

Each simulation involved the same fractal geometry, but the distribution of arterial stiffness (as determined by the prescribed reference wave speed) was altered. For a given simulation, every junction was assigned the same reflection coefficient, based on the reference area and wave speed of the parent and daughter branches (Equation 3.4). Reflection coefficients employed in this study were $R = -0.01, 0, 0.01, 0.02, 0.03$, or 0.04 ; noting that these are reference reflection coefficients, i.e., calculated via Equation 3.4, and that the actual reflection coefficients are complex (frequency-dependent) and non-linear (pressure-dependent). All fractal trees were geometrically identical; R values were prescribed by changing only the wave speed values in Equation 3.4 through progressive stiffening of 1) distal vessels or 2) proximal vessels. For distal stiffening, the effects of wave reflection on PPd without accompanying changes in the forward component of proximal pulse pressure (PPp_+) were investigated. This was achieved by keeping

proximal wave speed constant at $4.6 \text{ m}\cdot\text{s}^{-1}$ and progressively increasing distal wave speed to achieve the specified reflection coefficient at junctions (Figure 3.2a). For proximal stiffening, progressive stiffening of proximal vessels was simulated by keeping distal wave speed constant (starting from the $R = 0.04$ case) and increasing proximal wave speed (Figure 3.2b). For a detailed explanation of how proximal stiffening was achieved, refer to Appendix A.4. Note that wave speeds as high as $50 \text{ m}\cdot\text{s}^{-1}$ have been predicted to exist in small vessels (234). The highest wave speed in terminal vessels of our simulations ($106.8 \text{ m}\cdot\text{s}^{-1}$), although probably not physiological, was allowed purely to understand the mechanistic principles relating wave reflection to *PPd*.

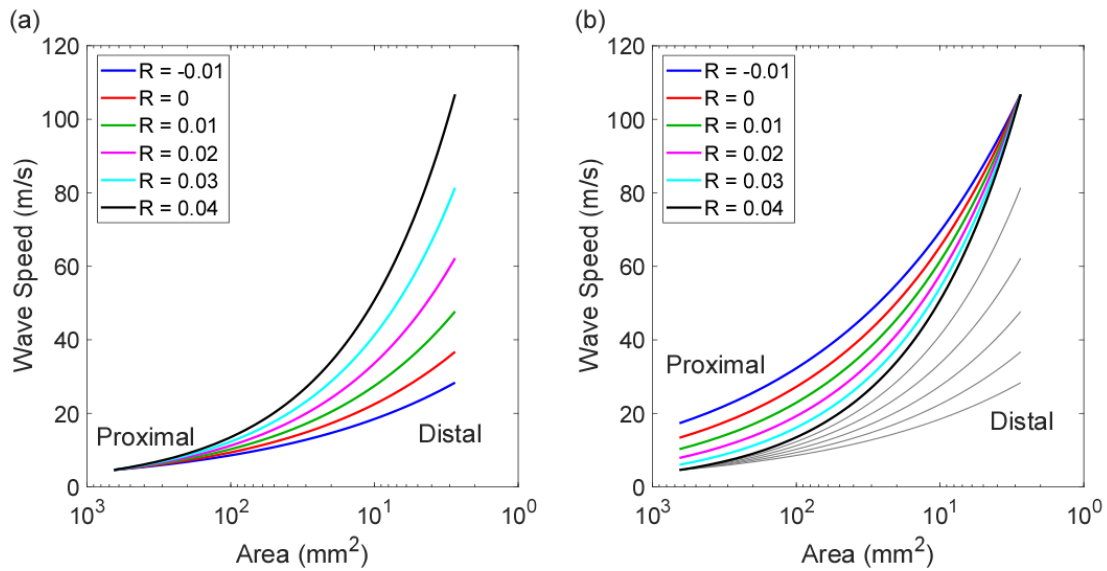


Figure 3.2: PROXIMAL AND DISTAL STIFFENING. Plots of (a) distal stiffening and (b) proximal stiffening of the one-dimensional arterial network, showing wave speeds from the proximal (large) vessels to the distal (small) vessels. Note that the x-axis is logarithmic and in reverse order. a) Distal stiffening: the proximal wave speeds remain constant and the distal wave speeds increase with an increase in reflection coefficient. b) Proximal stiffening: the distal wave speeds remain constant and the proximal wave speeds increase with a decrease in reflection coefficient. The grey lines show the wave speed trends from the distal stiffening group for comparison. Note that the curve for $R = 0.04$ is the same for both groups because it was used as the reference for proximal stiffening.

3.2.3 Arterial Compliance

Total compliance of the fractal trees changed substantially as distal or proximal vessels were stiffened; changes in proximal wave speed also led to substantial changes in PPp_+ . Thus, an additional compliance (i.e., capacitor) was attached to the inlet of the fractal tree (Figure 3.1) to equalize compliance or PPp_+ across the fractal trees. To elucidate the role of wave reflection on PPd without the confounding effect of varying PPp_+ , the value of this compliance was

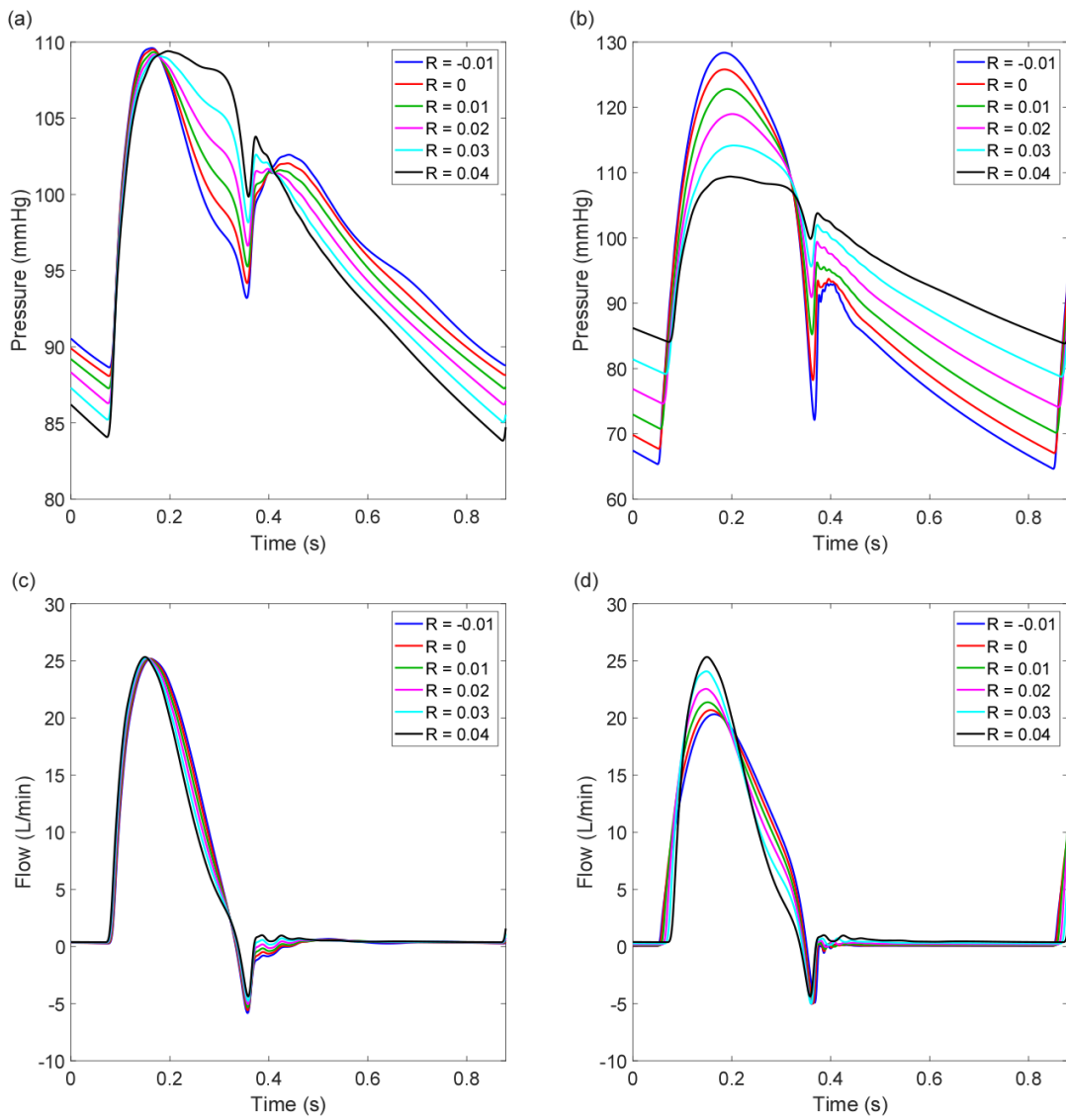


Figure 3.3: PRESSURE AND FLOW WAVEFORMS WITH PROXIMAL AND DISTAL STIFFENING. Pressure waveforms in the largest (proximal) vessel of all fractal trees with a) distal and b) proximal stiffening. Flow waveforms in the largest (proximal) vessel of all fractal trees with c) distal and d) proximal stiffening.

iteratively adjusted for each simulation to attain the same PPp_+ as that of the $R = -0.01$ case for the distal stiffening simulation (since this network had the highest compliance). Similarly, to investigate the role of compliance on PPd , the value of the additional compliance was changed to attain the same total compliance across all fractal trees. In all other simulations (unless otherwise stated), the value of the additional compliance was zero.

3.2.4 Hydraulic Energy

To investigate the effect of wave reflection on the transmission of hydraulic energy (HE), it is necessary to consider its forward component (Equation 3.5), which is given by

$$HE_+ = \int_0^{HP} P_+ Q_+ dt = \int_0^{HP} \frac{1}{4} \left[2PQ + Z_c Q^2 + \frac{P^2}{Z_c} \right] dt \quad (\text{Equation 3.5})$$

where HP is heart period, $Z_c = \rho c/A$ is characteristic impedance, ρ is blood density, P is pressure, Q is flow, and the subscript '+' refers to the forward wave component (174). Transmission and reflection coefficients for pressure waves are related via $T_P = 1 + R$ (subscript 'P' refers to pressure), whereas flow wave transmission relates to R_P via $T_Q = 1 - R$ (subscript 'Q' refers to flow). Since hydraulic energy is equal to the integral of hydraulic power (i.e., pressure $\times$ flow),

$$T_{HE} = T_P \times T_Q = (1 + R) \times (1 - R) = 1 - R \quad (\text{Equation 3.6})$$

where subscript 'HE' refers to hydraulic energy. This implies that greater pressure reflection is accompanied by lower transmission of hydraulic energy, which makes sense given the limiting case of an occlusion where $\Gamma_p = 1$ and clearly $T_{HE} = 0$. Thus, it is hypothesized that, unlike pressure, a decrease in conduit arterial wave reflection with ageing would lead to an increased hydraulic energy transmission (153). To demonstrate this, the peak-to-peak amplitudes of HE_+ , P_+ , and Q_+ at the terminal vessels of the fractal trees are calculated across both stiffening groups, normalized to their respective values at the inlet (designated ΔHE_+ , ΔP_+ , and ΔQ_+ respectively).

Blood flow simulations in the fractal trees were performed in MATLAB (version R2018a; The MathWorks Inc., Massachusetts, USA) using a previously established one-dimensional flow solver (169, 175). Appendix A.5 details the equations employed by the flow solver.

3.3 Results

Pressure and flow waveforms in the largest (proximal) vessel of all fractal trees are shown in Figure 3.3. Distal stiffening caused increased pulse pressure with increasing reflection, whereas proximal stiffening caused increased pulse pressure with decreasing reflection. In both cases, decreasing wave reflection in the arterial network caused the proximal pressure waveform to become progressively more similar in shape to the proximal flow waveform during systole (Figure 3.3). Pressure waveforms in progressively distal locations in the fractal tree are shown in Figure 3.4 (for the $R = 0$ case). Pulse pressure amplification was seen in both distal and proximal stiffening scenarios but was less pronounced when proximal vessels were stiffened.

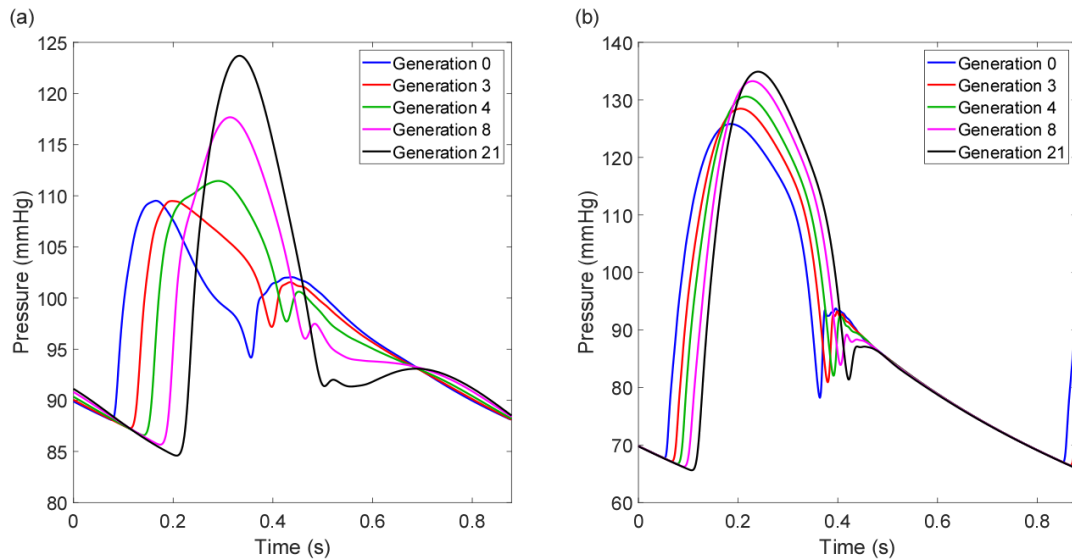


Figure 3.4: PRESSURE WAVEFORMS ALONG THE FRACTAL TREE. Pressure waveforms in the proximal (Generation 0) to the distal (Generation 21) vessels of the fractal tree with 0 reflection coefficient from the a) distal stiffening and b) proximal stiffening simulation sets.

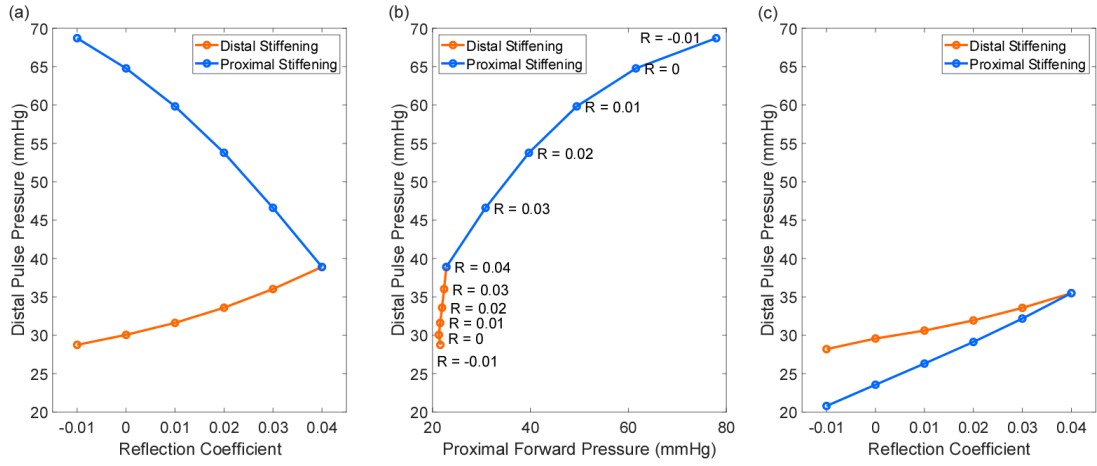


Figure 3.5: CHANGES IN DISTAL PULSE PRESSURE. a) Distal pulse pressure (PPd) vs reflection coefficient (R). b) PPd vs proximal forward pressure (PPp_+). c) PPd vs R with constant PPp_+ .

When stiffening distal vessels, decreasing wave reflection was accompanied by decreasing PPd , while PPp_+ was essentially constant (Figure 3.5a,b). On the other hand, stiffening proximal vessels led to increasing PPd with decreasing wave reflection. Importantly, however, this increase in PPd was also accompanied by an increase in the forward wave amplitude, or PPp_+ . When PPp_+ was held constant with the additional compliance, PPd decreased with a decrease in wave reflection regardless of whether proximal or distal vessels were stiffened (Figure 3.5c).

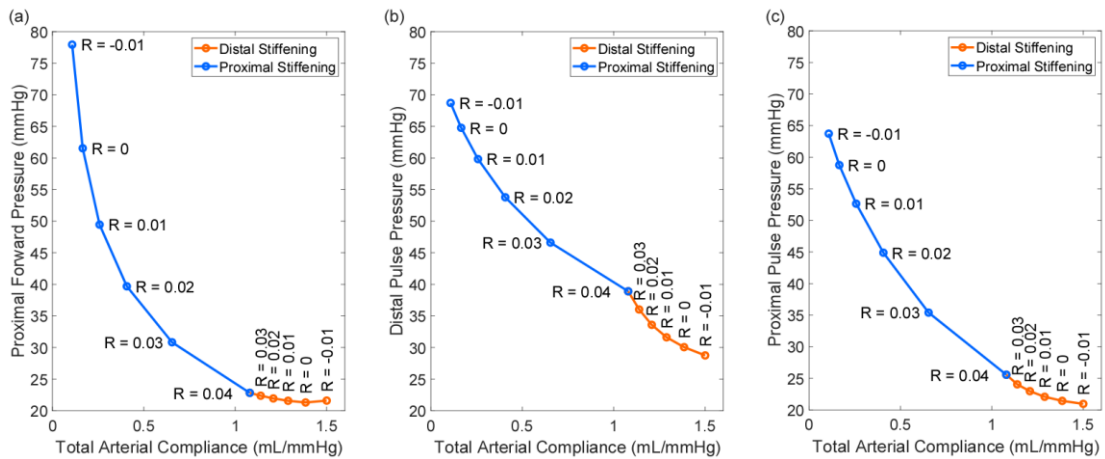


Figure 3.6: EFFECT OF TOTAL ARTERIAL COMPLIANCE ON PRESSURE. a) Proximal forward pressure (PPp_+) vs arterial compliance. b) Distal pulse pressure (PPd) vs arterial compliance. c) Proximal pulse pressure (PPp) vs arterial compliance.

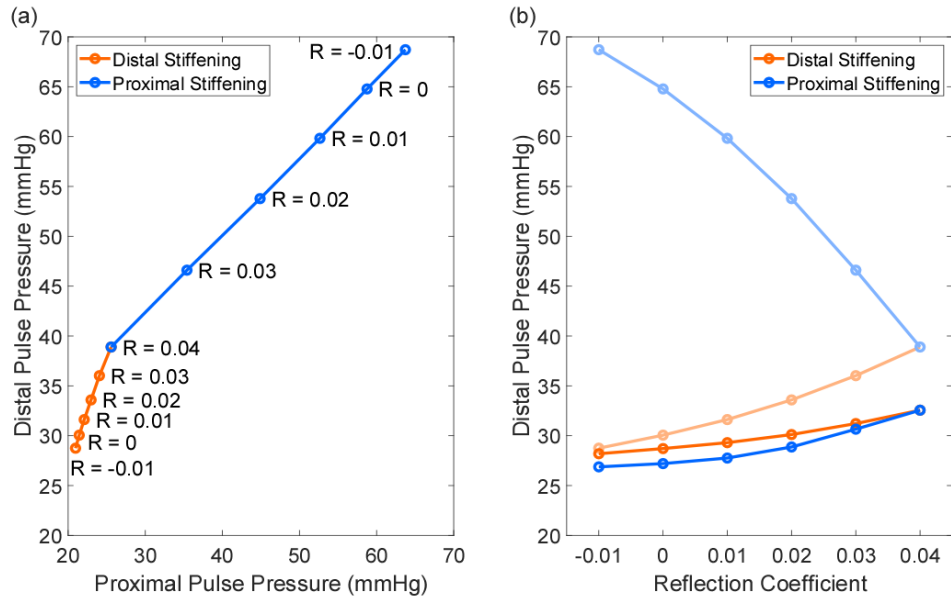


Figure 3.7: FACTORS UNDERLYING CHANGES IN DISTAL PULSE PRESSURE. a) Proximal pulse pressure (PPp) vs Distal pulse pressure (PPd) b) PPd vs reflection coefficient (R) with constant compliance. The faded lines shows PPd vs R with varying compliance.

Investigating the effect of arterial compliance, PPp_+ (Figure 3.6a), PPd (Figure 3.6b), and PPp (Figure 3.6c), all monotonically increased with decreasing compliance, regardless of the mode of stiffening (proximal or distal). An approximately proportional relationship between PPp and PPd was suggested in Figures 3.6a and 3.6c and confirmed in Figure 3.7a. A strong dependence of PPd on arterial compliance was revealed by using the additional compliance to hold compliance constant across all reflection coefficient values—the variation in PPd was then small (5.6 mmHg) compared to that with variable compliance (40 mmHg) (Figure 3.7b).

Finally, as predicted by transmission line theory, ΔHE_+ and ΔQ_+ increased with a decrease in wave reflection (Figure 3.8a,c), while ΔP_+ decreased with a decrease in wave reflection (Figure 3.8b) regardless of the pattern of stiffening.

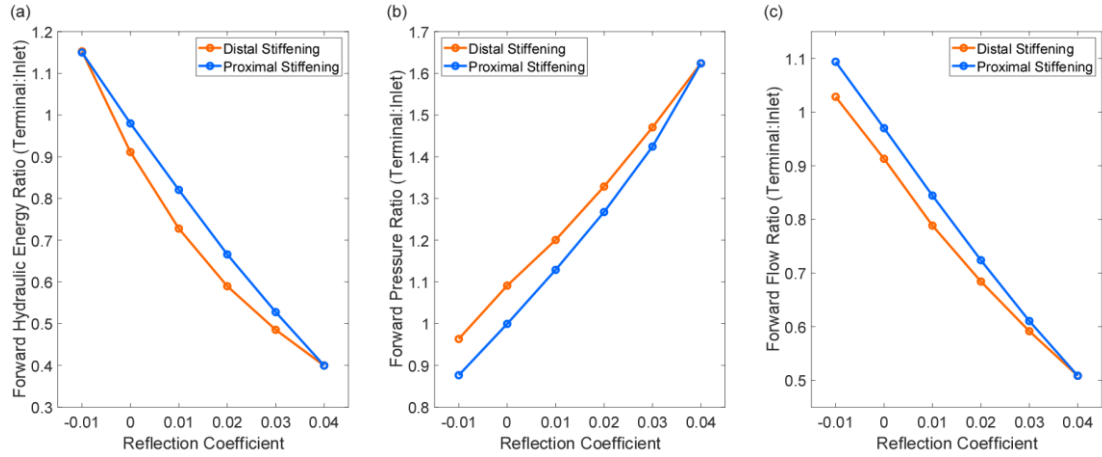


Figure 3.8: TRANSMISSION OF HYDRAULIC ENERGY, PRESSURE, AND FLOW. The ratio of the forward peak-to-peak a) total hydraulic energy, b) average pressure, and c) total flow at the terminal branches to that at the inlet of the fractal tree with respect to the reflection coefficient.

3.4 Discussion

This study has shown that reduced wave reflection in the conduit arteries could accompany, but not cause, increased *PPd* with ageing, tending instead to reduce pressure transmission due to the positive link between pressure reflection and transmission ($T_p = 1 + R$). Our data suggest that increased *PPd* with ageing likely occurs mainly due to an increase in the magnitude, not the transmission, of the forward pressure wave (PPp_+) and a decrease in large artery compliance. Indeed, when PPp_+ was held constant, *PPd* decreased with a decrease in wave reflection across all simulations in accordance with transmission line theory. Finally, this study provided evidence that, unlike pressure, hydraulic energy transmission increases with decreasing wave reflection in the conduit arteries, as suggested by Mitchell (153), which is also consistent with transmission line theory.

3.4.1 Wave Reflection

Uniform changes in wave reflection were produced at all junctions of the network to systematically investigate the effect of wave reflection on haemodynamics. The progressive

similarity between flow and pressure waveforms with decreasing reflection occurs because in a reflectionless system (i.e. $R = 0$), the pressure waveform is equal to the flow waveform scaled by the characteristic impedance (288). Additionally, pulse pressure amplification was evident in Figure 3.4 when moving from proximal to distal vessels, with stiffening of proximal vessels leading to lesser amplification (by $\sim 35\%$), as occurs in ageing (11, 208).

While the model produced physiological pressure and flow waveforms, the precise spatial distribution of wave reflection *in vivo*, and how it changes with ageing, is controversial because of challenges in measuring it. Commonly used indices of wave reflection, including augmentation index and the ratio of forward/backward pressure waves, increase with age (66, 239). However, these indices quantify the net effect of many reflections as seen at a particular measurement site and do not provide site-specific information. Wave reflection is thought to occur at unmatched arterial junctions, due to arterial tapering (173, 241, 281), and in the vicinity of resistance vessels. However, the proportion of wave reflection occurring at these sites and how this changes with ageing remains unclear (181, 233).

Some information on the spatial distribution of wave reflection along the arterial tree can be provided by an 'effective' reflection site. This is obtained by modelling the arterial network as a single tube and calculating an effective length ($L_{eff} = c \times t_r/2$) from wave speed (c) and the arrival time of the reflected wave to central arteries (t_r). Mitchell et al. (154) and Sugawara et al. (259) found that L_{eff} increased with age, suggesting a distal shift in wave reflection. Mitchell explained this finding by reasoning that ageing-related stiffness matching in conduit arteries reduced wave reflection at these sites and caused a larger proportion of reflection to occur at the distal resistance vessels (153).

However, there are two potential limitations to this proposed paradigm. First, ‘stiffness’ matching does not guarantee impedance matching because impedance depends on both stiffness and vessel area (207). Moreover, a positive impedance gradient (i.e., comparing individual daughter vessels with a parent vessel) is required for a well-matched (reflectionless) arterial network (Equation 3.4). There is evidence that the young aorta and its branches are exceptionally well matched, i.e., very little wave reflection occurs (174, 199); furthermore, there is no clear evidence that impedance matching emerges with ageing. Second, the distal shift in reflection sites with ageing implied by this paradigm is controversial (12, 193, 236, 281), in part because some studies have found a proximal shift in reflection sites with ageing, suggesting that wave reflections at arterial junctions may not necessarily decrease with age (207, 239). This difference in results could be due to differences in methodology used to calculate t_r ; the most appropriate method to calculate t_r is still being debated. While further investigations are needed to precisely elucidate whether wave reflection at arterial junctions increases or decreases with ageing, this study nevertheless investigated the effect of the proposed age-related decrease in wave reflections at arterial junctions on pressure and hydraulic energy transmission.

Another potential issue with this paradigm is that the impedance mismatching and wave reflection proposed to exist in conduit arteries in youth would be detrimental to ventricular afterload while purportedly protecting against high *PPd*. Furthermore, with ageing, reduced wave reflection would be favourable for ventricular afterload but detrimental to the microvasculature (increasing *PPd*). This trade-off would imply that ventriculo-vascular coupling is less optimized in youth than in the elderly, which runs counter to principles of biological optimality. On the contrary, our results suggest that wave reflection does not limit pressure transmission; thus, decreased conduit arterial wave reflection per se would cause a decrease in

both ventricular afterload and PPd . Hence, wave reflection does not create a trade-off between the two.

3.4.2 Arterial Compliance

Our finding of an increase in forward pressure magnitude with a decrease in arterial compliance is supported by clinical and modelling studies (154, 198); this relationship is mediated by an increase in aortic characteristic impedance with age (157, 182). Furthermore, this study has shown that proximal and distal pressures were closely related to each other and were both modulated in a similar way by changes in arterial compliance. PPd increased with a decrease in arterial compliance regardless of the distribution of wave reflection in the conduit arteries, as did PPp_+ and PPp . This indicates that arterial compliance modulates both central and peripheral haemodynamics.

3.4.3 Hydraulic Energy and Pressure

Our results suggest that a decrease in wave reflection in the conduit arterial network would be accompanied by an increased transmission of hydraulic energy. This is necessarily related to increased flow wave transmission because there is a concurrent decrease in pressure wave transmission. Thus, this study suggests that with ageing, increases in distal hydraulic energy may occur due to a combination of increased amplitude of the forward energy wave and increased transmission of flow waves; however, increases in distal pulse pressure likely occur due to increased forward pressure wave amplitude and potentially increased wave reflection in the distal resistance vessels. The latter (distal reflection) has not been investigated in our study but would have opposite effects on distal hydraulic energy and pulse pressure. It is currently not known whether excess hydraulic energy or pulse pressure is more deleterious to vascular beds. Increased pulse pressure could cause excessive stretch of vessel walls, while increased hydraulic energy could give rise to high shear stress related to increased flow pulsatility. Mitchell et al

(156) showed that an increase in flow pulsatility with a decrease in wave reflection is associated with cognitive decline, and an association between proximal pulse pressure and distal flow pulsatility has also been established (49). However, to clarify the relative importance of pulse pressure and hydraulic energy in vascular beds, future studies may need to measure flow and pulse pressure in distal feeding vessels, which would be challenging.

3.4.4 Conclusion

This study sheds new light on the mechanisms underlying increased PPd with ageing. It showed that reduced arterial compliance and increased forward wave pressure were the main determinants of increased PPd with ageing, not a decrease in wave reflection at arterial junctions. Furthermore, PPd , PPp , and PPp_+ are closely related, with a similar dependence on arterial compliance. Finally, it showed that the relationships of conduit arterial wave reflection to transmission of pressure and hydraulic energy are opposite, with decreasing wave reflection reducing pressure transmission but increasing hydraulic energy transmission.

Chapter 4: Optimised arterial network model of a young adult

This chapter introduces a computational model of the systemic arterial network by optimising key aspects of previous models such as wave speed, vascular bed compliance, and arterial taper to better represent the haemodynamics of a healthy young adult. It also presents the validation of the pressure and velocity waveforms of the model against in vivo waveforms. This chapter is published as a peer-reviewed article titled “Optimised design of an arterial network model reproduces characteristic central and peripheral haemodynamic waveform features of young adults” in the *Journal of Physiology* (doi: 10.1113/JP282942).

4.1 Introduction

It is widely recognised that a healthy arterial system limits the rise in pressure during systole and maintains pressure during diastole (181, 185). One prominent view is that this occurs, in part, due to the “beautifully designed... tuning” of the arterial tree (190), with junctions that are well-matched in the forward direction (199) resulting in reflected pressure waves predominantly arriving at the left ventricle during diastole. In the ascending aorta, this is evidenced by a Type C waveform, which has a similar shape to the flow waveform during systole—with an early systolic peak and negative augmentation index (116)—and a pressure ‘hump’ during diastole that supports coronary perfusion (158, 182, 190). According to this paradigm, arterial stiffening with ageing causes wave reflections to arrive during systole, which contributes to systolic hypertension, elevated left ventricular afterload and, ultimately, cardiovascular events and increased mortality (40, 43, 131, 248, 265, 301).

One-dimensional (1D) mathematical modelling of the arterial network is a powerful approach for gaining insight into the structural and functional properties that lead to this “beautiful tuning”, as well as mechanisms underlying the detrimental effects of vascular ageing and disease (5, 36, 256). It therefore stands to reason that establishing a representative model of a healthy young adult is a crucial starting point for studying processes that might cause a departure from an ‘ideal’ arterial design. In particular, an accurate model of a young adult would be expected to exhibit the following characteristic features in the ascending aorta: 1) an early systolic peak, 2) a negative augmentation, and 3) a prominent diastolic hump. However, although the detailed model of Blanco et al. (23) produced a diastolic hump, to our knowledge no prior models have predicted an early systolic peak and negative augmentation (36, 175, 224).

The reason(s) that these features have not been well-captured in existing 1D models is unclear, given that input variables such as wave speed in the ascending aorta (83, 117, 178, 230), and general haemodynamic variables e.g. systolic and diastolic blood pressures (144, 192, 228) and cardiac output (31, 112), have been representative of young adults. Nonetheless, at least four possible reasons may be involved in current 1D models not capturing all key features of young adult blood pressure waveforms. The first is that the wave speeds for the other arteries may not have been sufficiently representative of in vivo values. Since it is not feasible to obtain in vivo data from every artery in the body, previous investigators have estimated wave speeds of all arteries via an empirical equation that uses arterial diameter as the independent variable (197, 223). However, since the common carotid and femoral arteries have comparable diameters—0.69 cm (210) and 0.77 cm (139), respectively—this approach leads to similar estimated wave speeds for both arteries. By contrast, in vivo measurements indicate that wave speed in the carotid artery—397–485 $\text{cm}\cdot\text{s}^{-1}$ (63, 108, 149, 205, 215)—is substantially lower than in the femoral artery—926–1029 $\text{cm}\cdot\text{s}^{-1}$ (28, 56, 214, 268), most likely because the common carotid is

an “elastic artery” (i.e. has a higher elastin content), whilst the femoral artery is a “muscular artery” (higher smooth muscle content) (130, 132, 137). As a rule of thumb, systemic arteries that are closer to the heart (e.g. aorta and carotid) are elastic while those further away (femoral and radial) are muscular (20, p892-893). This study proposes a novel method for estimating the wave speed of all systemic arteries that accounts for the relative distance to transition points from elastic to muscular arteries.

A second possibility for the lack of young adult features in previous models is non-representative wave reflection properties of the arterial tree, given the profound influence of wave reflection on haemodynamic waveforms (269). As previous models have exhibited positive systolic augmentation (23, 36, 175, 224), wave reflection in these models likely occurred more proximally than is typical in young adults due to certain features of these geometrically simplified models. For example, similar to the related models by other authors (10, 23, 223, 245, 256, 284), the model by Mynard et al. (175) incorporated a substantial amount of taper in the brachial and femoral arteries (70% and 50% area reduction, respectively) and no side branches along their substantial length (35 and 44 cm, respectively). Such taper in the models is likely to produce substantial wave reflection (241); although the exact origin of wave reflection in the arterial system is controversial (241, 280), one widely-held theory is that wave reflection mainly occurs in the vicinity of resistance vessels (87, 188). If this is the case, it is likely that the progressive decline in diameter of conduit arteries with distance from the heart occurs primarily in a stepwise manner (decreasing where side branches arise), which allows for the preservation of impedance and minimises wave reflection of forward waves in the main conduit arteries. This stepwise reduction in diameter may therefore be considered “impedance-preserving taper” in contradistinction to “within-segment taper” that increases impedance and gives rise to wave reflection.

A third issue concerns the degree of wave reflection occurring at the distal vascular beds. In many previous models, the simulated velocity waveforms in peripheral arteries (such as the femoral artery) have been monophasic (forward flow throughout the cardiac cycle) (223, 256), whereas in vivo waveforms are triphasic (forward flow during systole, reverse flow during early diastole, and forward flow again during late diastole) (102, 118). It has been suggested that the early diastolic reverse flow arises due to the high resistance of peripheral vascular beds (140, 227), which in turn is likely to be associated with lower vascular bed compliance. Importantly, vascular bed compliance (not resistance per se) governs the reactive (or pulsatile) components of impedance, and hence the degree of wave reflection (282). However, while vascular bed compliance (C_{bed}) is therefore likely to be a key parameter governing systemic arterial wave reflection, current methods for estimating C_{bed} for modelling studies are highly approximate. Thus, the in vivo value of C_{bed} is not known. Therefore, this study investigates the effect of C_{bed} on central and peripheral haemodynamics.

The fourth issue is that while most junctions in the systemic vasculature appear to be well-matched in the forward direction (199), some studies suggest that the aorto-iliac bifurcation could be an exception to this rule, with a reflection coefficient (R_p) as high as 0.2 in some individuals (82, 199). However, the effect of wave reflection at the aorto-iliac bifurcation on the wave reflection patterns in the aorta has not been explored in previous models.

This study had three main aims. The first was to determine the effect of incorporating the following improved physiological variables on large artery pressure and flow waveforms into a previously-described one-dimensional model by Mynard et al. (175): a) a more accurate

empirical equation that approximates arterial wave speeds based on cross-sectional area *and* relative distance to known elastic-muscular arterial transition points; and b) eliminating within-segment taper, and ensuring any taper in major arteries is impedance-preserving (e.g. by adding additional side branches). It is hypothesized that this improved ‘YoungAdult’ model would predict early systolic peak, negative augmentation, and diastolic hump in the ascending aortic pressure waveform, and triphasic flow in peripheral arteries. The second aim was to validate model predictions with non-invasively acquired in vivo pressure and velocity waveforms obtained from young adults, with a focus on whether the model reproduced key features of waveform morphology. The third aim was to determine the influence of the following key aspects of the model: a) compliance of distal vascular beds (C_{bed}), b) reflection coefficient of the aorto-iliac bifurcation, and c) employing impedance-preserving vs within-segment arterial taper on arterial wave reflection.

4.2 Methods

4.2.1 Wave Speed Relationship - Conventional Approach

Previous modelling studies defined the relationship between arterial diameter and wave speed by fitting exponential (197) or power (223) curves to in vivo data. In doing so, the elastic/muscular nature of arteries has not been explicitly accounted for. To evaluate this approach, in vivo data on the wave speeds of various arteries in young adults (18-30 years) were gathered from literature, the details of which are presented in Appendix B.1. Similar to previous work, a power relationship (Equation 4.1) was fitted to the data points using the Curve Fitting toolbox of MATLAB (Mathworks, Massachusetts, USA). Furthermore, an anchor point for the fitted curve at the wave speed of the ascending aorta (Segment 2) was imposed, as this is considered to be the most important value for achieving representative arterial compliance. To achieve this, a weight of 1 was given to the wave speeds of all other arteries, while the weight

of the ascending aortic wave speed was arbitrarily increased to a value of 50, which forced the curve to pass exactly through this wave speed. This manipulation did not significantly alter the shape of the curve compared to using no weights (data not shown). The resulting power law equation was:

$$c = \frac{577.3}{A^{0.23}} \quad (\text{Equation 4.1})$$

where c is wave speed ($\text{cm}\cdot\text{s}^{-1}$) and A is artery area (cm^2). This relationship yielded an R^2 value of 0.79 and a root mean square error (RMSE) of $177 \text{ cm}\cdot\text{s}^{-1}$ (Figure 4.1a). However, there were substantial differences between the in vivo wave speeds and those calculated using this equation (Figure 4.1b). For example, the in vivo wave speeds of the carotid and femoral arteries were $438 \text{ cm}\cdot\text{s}^{-1}$ and $905 \text{ cm}\cdot\text{s}^{-1}$ (average of literature values – refer to Appendix B.1), respectively, whereas Equation 4.1 yielded $679 \text{ cm}\cdot\text{s}^{-1}$ (difference = $-241 \text{ cm}\cdot\text{s}^{-1}$) and $703 \text{ cm}\cdot\text{s}^{-1}$ (difference = $202 \text{ cm}\cdot\text{s}^{-1}$), respectively.

4.2.2 Wave Speed Relationship - Accounting for Elastic-Muscular Transition Points

In addition to elastic arteries being closer to the heart and muscular arteries being further away, there are known transition points along a given arterial pathway where there is a substantial increase in wave speed and a distinct change in morphological features from one artery to the next; this indicates a transition from a predominantly elastic to more muscular arteries. These points are the distal ends of the axillary artery for the upper limbs (21) and abdominal aorta for the lower limbs (128), and 1 cm from the origin of the external carotid artery for the head and neck region (184) (the same distance for internal carotid artery is assumed, consistent with its classification as a muscular artery (220)). Using this, a “transition distance index” (TDI) of an artery is proposed as a surrogate marker for an artery’s degree of elasticity/muscularity. TDI is defined as the distance between the proximal end of an artery and the left ventricle

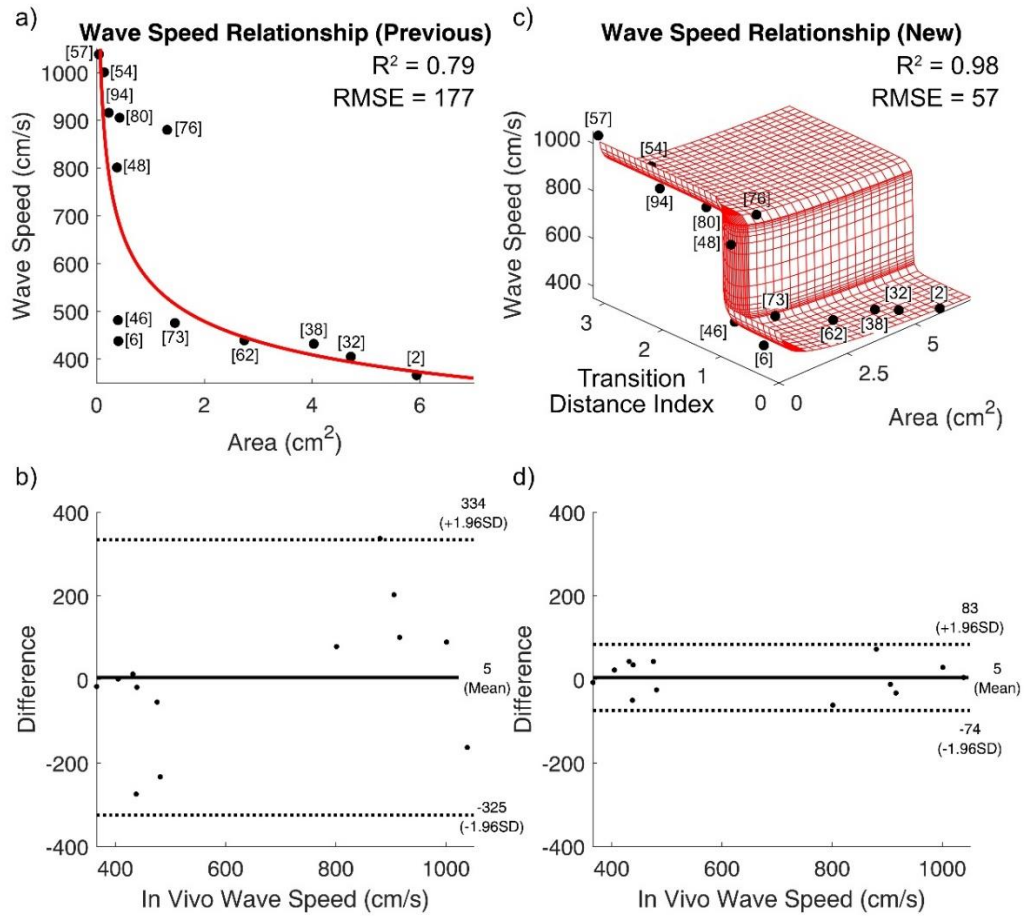


Figure 4.1: AREA-WAVE SPEED RELATIONSHIPS. Wave speed estimated only from artery area as in previous studies (a), and that estimated from the artery area and transition distance index in this study (b). The numbers in square brackets correspond to the segment number of the artery (see Figure 4.2). Bland Altman plots depict the difference between in vivo wave speeds and those calculated using the previous and new relationships are show in (b) and (d), respectively.

divided by the distance between the transition point and the left ventricle. Thus, $TDI < 1$ indicates an elastic artery and $TDI > 1$ a muscular artery.

The transition points at the axillary artery, abdominal aorta, and external carotid artery were assigned to the arm arteries (subclavian to ulnar and radial arteries), the entire aorta and leg arteries (ascending aorta to posterior tibial artery), and the cerebral arteries (all arteries distal to the common carotid and vertebral arteries inclusive), respectively. The TDI of arteries with

available in vivo data on wave speed and area are shown in Appendix B.1. Power and sigmoid functions were used to govern the area- and TDI-dependence of wave speed, respectively. Thus, a 3D surface was obtained with area and TDI as independent variables and wave speed as the dependent variable (Equation 4.2). After weighting towards the ascending aortic data point in the same way as for Equation 4.1, the final expression was:

$$c = \frac{661}{A^{0.058}} + 145.3 \times \arctan(167 \times TDI - 164.8) \quad (\text{Equation 4.2})$$

This relationship yielded an R^2 value of 0.98 and RMSE of $57 \text{ cm}\cdot\text{s}^{-1}$ (Figure 4.1c). The differences between the in vivo wave speeds and those calculated using the new relationship were substantially reduced compared to those obtained with Equation 4.1 (Figure 4.1d), with values of $462 \text{ cm}\cdot\text{s}^{-1}$ and $921 \text{ cm}\cdot\text{s}^{-1}$ for the carotid and femoral arteries (differences of only $-24 \text{ cm}\cdot\text{s}^{-1}$ and $-15 \text{ cm}\cdot\text{s}^{-1}$ from the in vivo values, respectively, see Appendix B.1).

4.2.3 Model Development

The YoungAdult 1D model described herein is an adaptation of a previously developed closed-loop model of the entire circulation and 4-chamber heart, herein referred to as ‘Mynard2015’ (175). Since the present study only relates to systemic arterial haemodynamics, only those model components likely to have a substantial impact on large artery haemodynamics were incorporated; therefore the coronary arteries, veins and the pulmonary circulation were removed, whereas the cerebral arteries were retained, as these have been shown to have an effect on central waveforms (223). The input to the YoungAdult model was a 2-chamber elastance-based heart model (left atrium and ventricle) that has been described previously (120). The distal arteries were terminated with lumped parameter 3-element windkessel compartments representing downstream vascular beds.

Eliminating the veins, pulmonary and coronary circulations, and inter-ventricular interactions caused small changes in the preload, mean arterial pressure, and chamber elastance, respectively, compared with the closed-loop model. To achieve results that were similar to those of the Mynard2015 model, an algorithm was used to iteratively adjust the preload, vascular resistance, and chamber elastance until the maximum chamber volume, mean aortic pressure, and maximum effective chamber elastance, respectively, of the YoungAdult model were within a 0.5% tolerance of those of the Mynard2015 model. Further details about the model are provided in Appendix B.2.

4.2.3.1 Tapering and Arterial Side Branches

To obtain impedance-preserving taper and reduce early wave reflection, side branches were added to the major arterial segments of the YoungAdult model—such as the internal carotid, radial, brachial, and femoral arteries. The brachial artery, which originally had a 71% area taper, was divided into 4 non-tapered segments of successively smaller diameter by adding side branches along its length based on the detailed model of Blanco et al. (23). Similarly, the femoral artery, which originally had an area taper of 43%, was divided into 5 non-tapered segments of successively smaller diameter by adding 4 equally spaced side branches representing the muscular branches of the femoral artery that perfuse the surrounding tissue. Furthermore, a more detailed lower limb arterial network was included in the model by including the genicular, popliteal and peroneal arteries, which have been neglected in most previous models. Figure 4.2 depicts a schematic representation of the model and the detailed list of all arteries included in the YoungAdult model can be found in Appendix B.4.

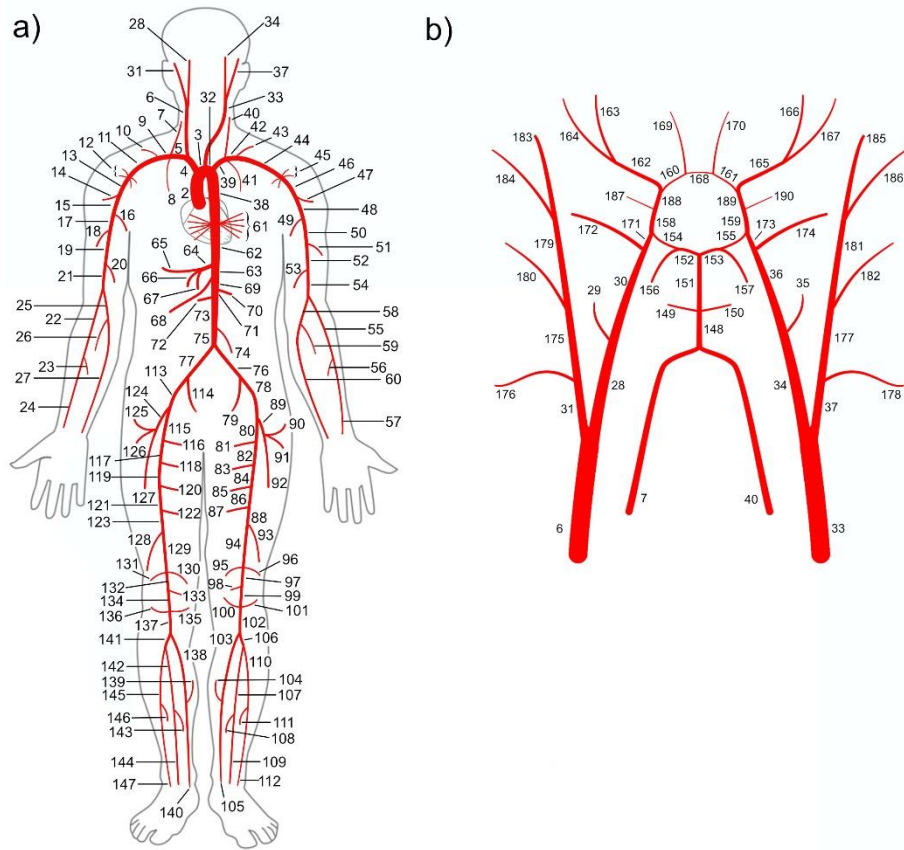


Figure 4.2: YOUNGADULT MODEL. Schematic diagram of the systemic (a) and cerebral (b) arteries of the YoungAdult model.

4.2.3.2 Impedance Matching of Branch Junctions

Arterial junctions have been found to be relatively well-matched (i.e. R_p of approximately zero) in vivo, implying an efficient transmission of energy in the forward direction (199). However, simply eliminating within-segment taper from arteries of the YoungAdult model would result in unmatched junctions. An optimization algorithm was therefore developed to produce well-matched junctions for all arteries in the YoungAdult model. The R_p value at a junction can be calculated using Equation 4.3.

$$R_p = \frac{\frac{A_0}{c_0} - \frac{A_1}{c_1} - \frac{A_2}{c_2}}{\frac{A_0}{c_0} + \frac{A_1}{c_1} + \frac{A_2}{c_2}} \quad (\text{Equation 4.3})$$

where the subscript '0' refers to the parent artery while '1' and '2' refers to the two daughter arteries. As part of the optimization algorithm (Equation 4.3), the area and wave speed of the parent artery was kept fixed, while A_1 and A_2 were multiplied by a scaling factor (x); the corresponding wave speeds (c_1 and c_2) were calculated using Equation 4.2. Using the `fminsearch` function of MATLAB (Mathworks, Massachusetts, USA), the value of x was iteratively changed until a reflection coefficient of 0 was achieved (within a tolerance of ± 0.001). The optimization algorithm did not significantly alter the diameters of the downstream arteries, as evidenced by the terminal posterior tibial (22, 232) and radial arteries (15, 296, 297), which had diameters within physiological ranges. Note that the within-segment taper of the cerebral arteries downstream of the internal carotid artery from the Mynard2015 model was retained because the looping nature of the cerebral arterial tree meant that some cerebral arteries had two parents. This is not conducive for the optimization algorithm, which requires a simple bifurcating tree structure.

To explore the influence of reflection at the aorto-iliac bifurcation, the optimization algorithm was used to obtain a second model in which a R_p value of 0.2 was enforced at the aorto-iliac bifurcation, along with well-matched junctions in the downstream junctions of the legs.

4.2.3.3 Vascular Bed Compliance

The compliance of distal vascular beds (C_{bed}) is difficult to measure in vivo and estimation techniques are therefore used for model parameterisation. In most studies, total arterial compliance (TAC_{wk}) has first been estimated from aortic pressure and flow waveforms via the pulse pressure method that uses a 2-element windkessel model (255). Vascular bed compliance is then estimated by subtracting the combined compliance of all 1D arterial segments from TAC_{wk} and distributing the remaining compliance among the vascular beds (in inverse

proportion to their resistances). While the windkessel method is well established to estimate arterial compliance, it is not known whether this ‘subtraction approach’ accurately captures both central arterial compliance (C_{art}) and C_{bed} .

Appendix B.3 shows that although TAC_{wk} is sensitive to C_{art} , it is relatively insensitive to C_{bed} in the YoungAdult model, with a 153% increase in total compliance of the model, produced by changing only C_{bed} leading to an increase of only 1.6% in TAC_{wk} . This suggests that currently used methods of estimating C_{bed} may be inaccurate. Thus, this study investigated the effect of varying C_{bed} on the model waveforms. C_{bed} and R_{bed} (windkessel resistance) are related via an assumed time constant ($\tau = R_{bed} \times C_{bed}$). Starting from a value of $\tau = 0.55$, as used in Mynard2015, a value of $\tau = 1.3$ was found to produce the characteristic features of a young adult aortic pressure waveform (early systolic peak, diastolic hump, and negative augmentation) and in the peripheral flow waveforms (triphasic flow). Thus, C_{bed} of all vascular beds was calculated using R_{bed} and $\tau = 1.3$ as the baseline model. The details of the vascular beds of the YoungAdult model with baseline C_{bed} values can be found in Appendix B.5. The sensitivity of the model to the value of τ was also tested by performing simulations with $\tau = 0.5$ and $\tau = 2.5$.

4.2.3.4 Impact of Impedance-Preserving vs Within-Segment Taper

To elucidate the impact of employing impedance-preserving taper on central wave reflection, the closed-loop Mynard2015 model (with a substantial degree of within-segment taper) was first converted to an open-loop model, as described above, but without any other changes to the arterial tree geometry or wave speed. The C_{bed} of all vascular beds was then calculated based on R_{bed} and a value of τ of 1.3 (baseline) and 100 (used to markedly reduce wave reflection at vascular beds and thereby reveal the contribution of tapering to wave reflection). The same procedure was followed for the YoungAdult model, which has no within-segment

taper (i.e., only impedance-preserving taper), except in the cerebral arteries. The waveforms at the aorta of the two models were then compared for both values of τ .

To quantify the effects of taper on central wave reflection, the system ‘input pressure’ (P_{in} , elsewhere called the water hammer pressure (271), which signifies the pressure that would occur in the absence of any wave reflection) was calculated as $P_{in} = QZ_c$ (206), where Q is flow and Z_c is characteristic impedance calculated using the frequency-domain method (194). Conversely, the ‘total reflected pressure’ (P_{ref}), defined as the pressure arising from vascular wave reflection and any re-reflections occurring at the ventricle, is given by $P_{ref} = P - P_{in} = 2P_{bk}$, where P is the total pressure and P_{bk} is the traditionally-defined backward component of pressure obtained by wave separation (286). In summary, $P = P_{in} + P_{ref}$ and as wave reflection decreases, $P_{ref} \rightarrow 0$ and $P \rightarrow P_{in}$ (206).

4.2.3.5 Model Computation

The model was implemented using previously described methods (169, 175). In brief, the non-linear 1D form of the Navier-Stokes equations, combined with a non-linear viscoelastic pressure-area relationship (175), were solved using a finite element method (169), with conservation of mass and continuity of total pressure enforced at junctions.

4.2.4 Model Validation with In Vivo Data

4.2.4.1 Non-Invasive Study

Model-predicted pressure and velocity waveforms were validated by performing applanation tonometry and Doppler ultrasound measurements, respectively, of accessible arteries in 7

healthy young adults aged between 21 and 25 years. Informed consent was obtained from all participants and this study conformed to the standards set by the Declaration of Helsinki. This study was approved by the Ethics Committee of the Royal Children's Hospital, Victoria, Australia. Participants were asked to refrain from consuming caffeine or alcohol for 3 hours prior to the study and all participants were non-smokers. They were placed in a supine position and were allowed to rest for 5 minutes before recording their brachial blood pressure with an oscillometric device (WatchBP Office Central, Microlife, Switzerland). Pressure waveforms in the left brachial, radial, common carotid, superficial femoral, superficial temporal, and posterior tibial arteries were then measured with applanation tonometry (SPT-301, Millar Instruments, Texas, USA). The pressure waveform of the ascending aorta was obtained by applying a validated transfer function to the common carotid pressure waveform (37). Finally, Doppler ultrasound was performed using a GE Vivid ultrasound machine (10-15 MHz; GE Healthcare, NSW, Australia) for the left common carotid and femoral arteries and a VisualSonics Vevo 3100 ultrasound machine (30-70 MHz; FUJIFILM VisualSonics, Toronto, Canada) for the left brachial, radial, and posterior tibial arteries owing to the difference in depth of the arteries. The sampling gate was over the middle two-thirds of the artery with an insonation angle of less than 60° (77). Doppler ultrasound of the superficial temporal artery was not performed.

4.2.4.2 In Vivo Data Analysis

Pressure waveforms from tonometry were ensemble-averaged over approximately 20 heart beats. Systolic and pulse pressures for each artery were obtained by calibrating waveforms to diastolic and mean pressures in the brachial artery, since these pressures are similar throughout the arterial network (88, 115). The upper and lower spectral envelopes of the Doppler ultrasound data were automatically segmented using a custom program written in MATLAB (R2020b, The MathWorks Inc., Natick, Massachusetts). In each artery, the mean velocity

waveform across 3 cycles was calculated from the spectrum-weighted average, which were then ensemble averaged.

To facilitate visual comparison of in vivo and model waveforms, pressure, and velocity waveforms were normalized to an amplitude of 1. To normalize the systolic duration, pressure waveforms with a distinct dicrotic notch (common carotid, superficial temporal, and ascending aortic waveforms) were normalized to a systolic duration of 0.3 s (the same as that of the model). The waveforms in other arteries did not always have a sharply defined dicrotic notch indicating the end of systole, and so these waveforms were scaled horizontally to minimise the root mean squared error compared with the corresponding model waveform. These were then

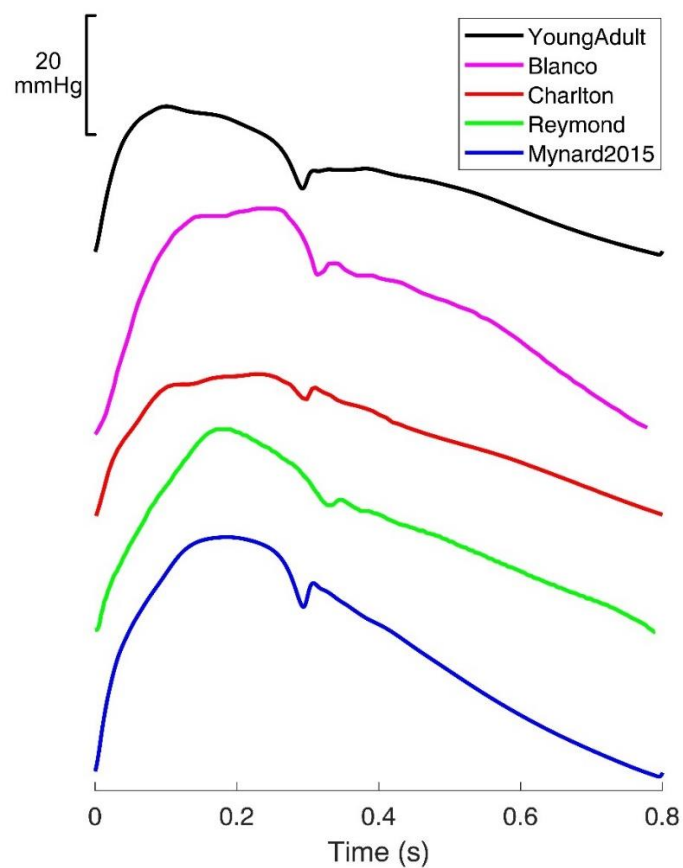


Figure 4.3: COMPARISON OF PRESSURE WAVEFORMS. Comparison of the ascending aortic pressure waveform of the YoungAdult model with models described by Blanco et al. (23), Charlton et al. (36), Reymond et al (224), and Mynard et al. (Mynard2015) (175).

ensemble-averaged to visually validate the corresponding waveforms produced by the model. Validation of raw absolute values of pressure and velocity (systolic and pulse) are also tabulated.

4.3 Results

4.3.1 Comparison with Previous Models

Figure 4.3 compares the aortic pressure waveforms from the YoungAdult model with those from previous models. The YoungAdult model displayed all features typically found in young adults: early systolic peak (at 35% of systolic duration), negative augmentation ($Alx = -3.6\%$), and a clear diastolic hump. By comparison, previous models exhibited later systolic peaks (between 53% and 75% of systolic duration) and positive augmentation (Alx between 3.4%, and 24%), while only the Blanco model displayed a diastolic hump.

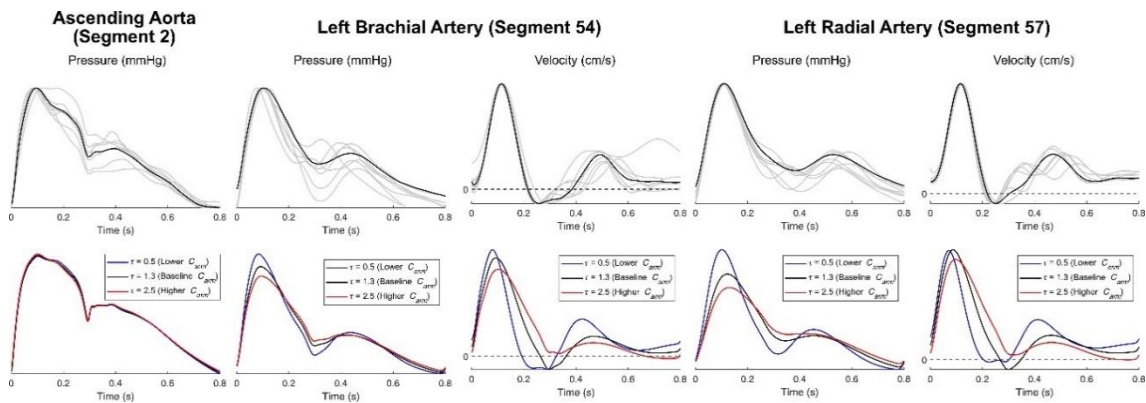


Figure 4.4: IN VIVO VALIDATION OF ARM WAVEFORMS. Comparison of the ascending aortic, left brachial, and left radial artery waveforms produced by the YoungAdult model (bottom panel) and in vivo data (top panel). The individual waveforms for each participant are shown in grey and the average waveform in black. The effect of varying the compliance of the arm vascular beds (C_{arm}) by varying the time constant (τ) on the waveforms is also shown. The in vivo waveforms have been normalized for visualization purposes.

Table 4.1: PARTICIPANT CHARACTERISTICS. Characteristics of participants in the in vivo validation study (n = 7).

Characteristic	Value
Age (years)	22.6 ± 1.5
Height (cm)	172.2 ± 7.8
Weight (kg)	64.4 ± 15.7
Sex (% Male)	29%

4.3.2 In Vivo Validation

Participant characteristics are presented in Table 4.1 and their pressure and flow waveforms are presented in the top panels of Figures 4.4-4.6. There are no pressure scales in these figures because our primary aim was to visually compare the model waveforms with in vivo ones. Overall, pressure and velocity waveforms produced by the baseline YoungAdult model ($\tau = 1.3$) were similar to those found in vivo. Importantly, the model captured key features of young adult waveforms such as triphasic flow in distal arteries (brachial, radial, femoral, and tibial) and an aortic pressure waveform that matched the in vivo waveform. Furthermore, Table 4.2 shows that the systolic and pulse pressures, and maximum and pulse velocity values of all arteries of

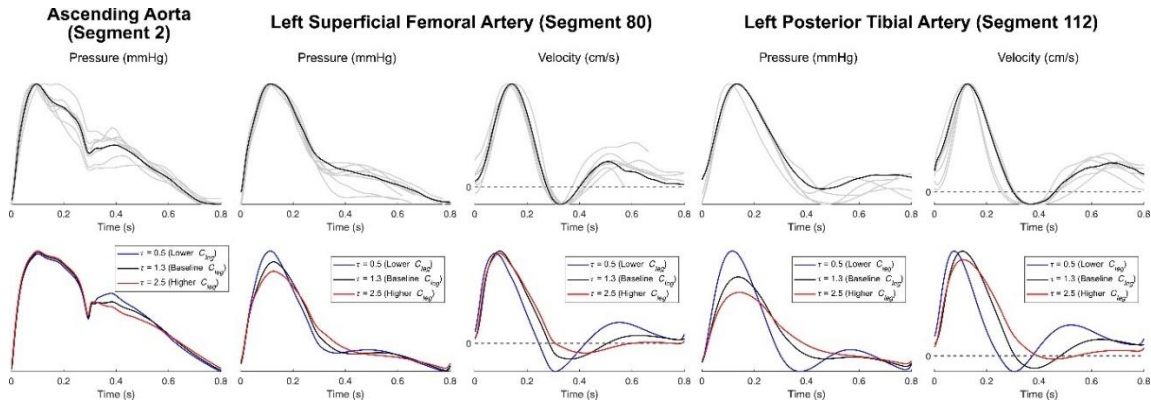


Figure 4.5: IN VIVO VALIDATION OF LEG WAVEFORMS. Comparison of the ascending aortic, left superficial femoral, and left posterior tibial artery waveforms produced by the YoungAdult model (bottom panel) and in vivo data (top panel). The individual waveforms for each participant are shown in grey and the average waveform in black. The effect of varying the compliance of the leg vascular beds (C_{leg}) by varying the time constant (τ) on the waveforms is also shown. The in vivo waveforms have been normalized for visualization purposes.

the model were within the range of values found in vivo, with the exception of ascending aortic pulse pressure (although the model values were similar to the central pulse pressure reported in 18-29-year-olds in a much larger study (145)).

4.3.3 Influence of Vascular Bed Compliance

Decreasing the compliance of the arm vascular beds by decreasing τ increased the triphasic nature of the velocity waveforms of the brachial and radial arteries, with increasing amplitudes of the systolic forward velocity, early diastolic reverse velocity and late diastolic forward velocity, and earlier diastolic velocity reversal. Similar changes were also observed in the pressure waveforms, with an increased systolic peak, lower early diastolic trough, and a higher late diastolic peak. This also augmented the late systolic portion of the ascending aortic pressure

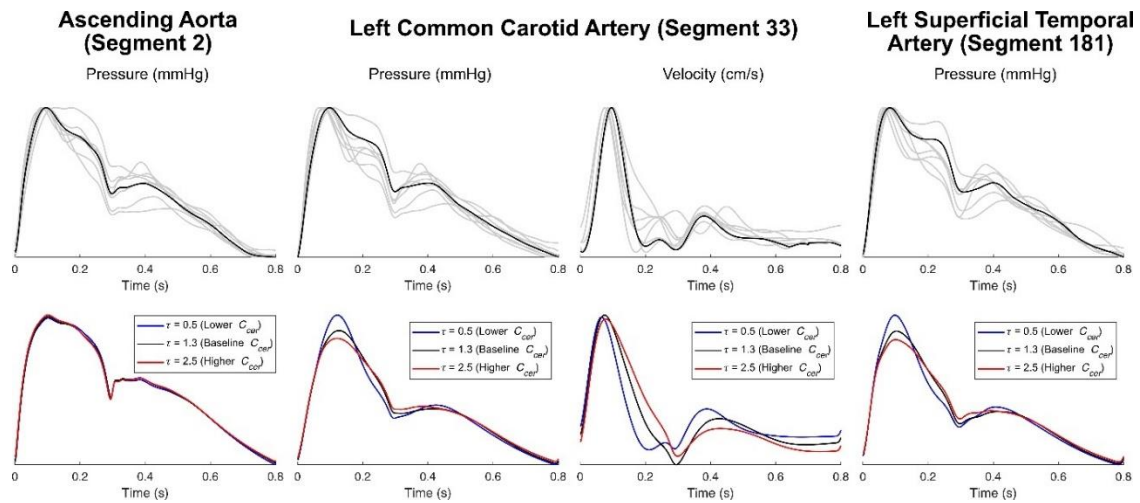


Figure 4.6: IN VIVO VALIDATION OF CEREBRAL WAVEFORMS. Comparison of the ascending aortic, left common carotid, and left superficial temporal artery waveforms produced by the YoungAdult model (bottom panel) and in vivo data (top panel). The individual waveforms for each participant are shown in grey and the average waveform in black. The effect of varying the compliance of the cerebral vascular beds (C_{cer}) by varying the time constant (τ) on the waveforms is also shown. The in vivo waveforms have been normalized for visualization purposes. The velocity profile of the superficial temporal artery was not measured.

waveform. Increasing compliance had the opposite effect, with decreasing flow and pressure amplitudes and reduced late systolic augmentation (Figure 4.4).

A similar effect was seen when decreasing and increasing leg vascular bed compliance (Figure 4.5). Importantly, decreasing compliance augmented the diastolic hump of the ascending aortic pressure waveform, while increasing compliance had the opposite effect. Increasing the cerebral vascular bed compliance also caused similar changes in the pressure waveforms of the common carotid and superficial temporal arteries, and slightly augmented the late systolic portion of the ascending aortic pressure waveform (Figure 4.6).

4.3.4 Wave Reflection at the Aortoiliac Bifurcation

Introducing $R_p = 0.2$ at the aortoiliac bifurcation and adjusting the downstream leg vasculature to maintain well-matched junctions thereafter affected the late systolic and diastolic portions of the ascending aortic pressure waveform and abolished the diastolic hump. It also increased the

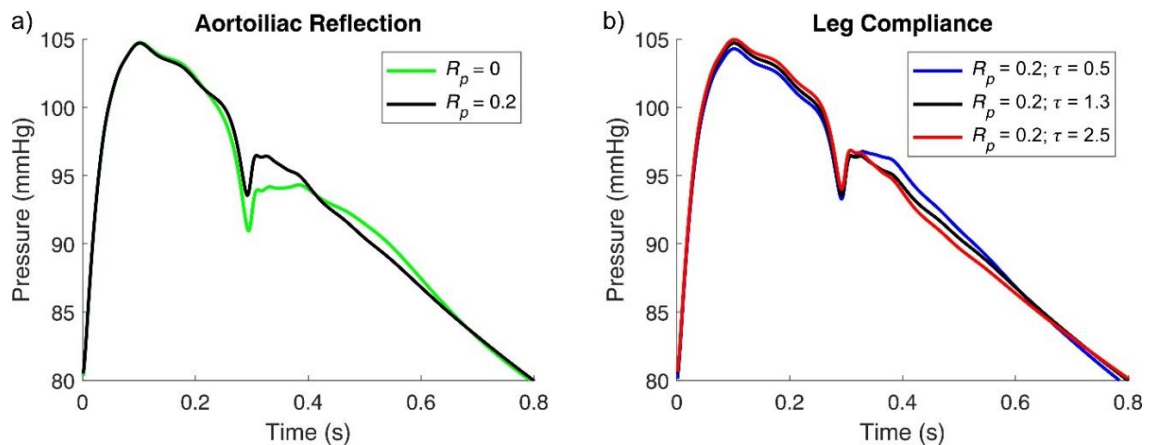


Figure 4.7: WAVE REFLECTION AT THE AORTOILIAC BIFURCATION. a) Comparison of the ascending aortic pressure waveform of the YoungAdult model with an aortoiliac bifurcation reflection coefficient (R_p) of 0 (baseline) and 0.2. b) Effect of changing leg vascular bed compliance on the ascending aortic pressure waveform when aortoiliac $R_p = 0.2$.

height of the diastolic notch (Figure 4.7a) and masked the effect of changing leg vascular bed compliance on the ascending aortic pressure waveform, with decreasing compliance causing lesser modulation of the diastolic hump (Figure 4.7b) when compared to the changes seen in Figure 4.5 (where $R_p = 0$).

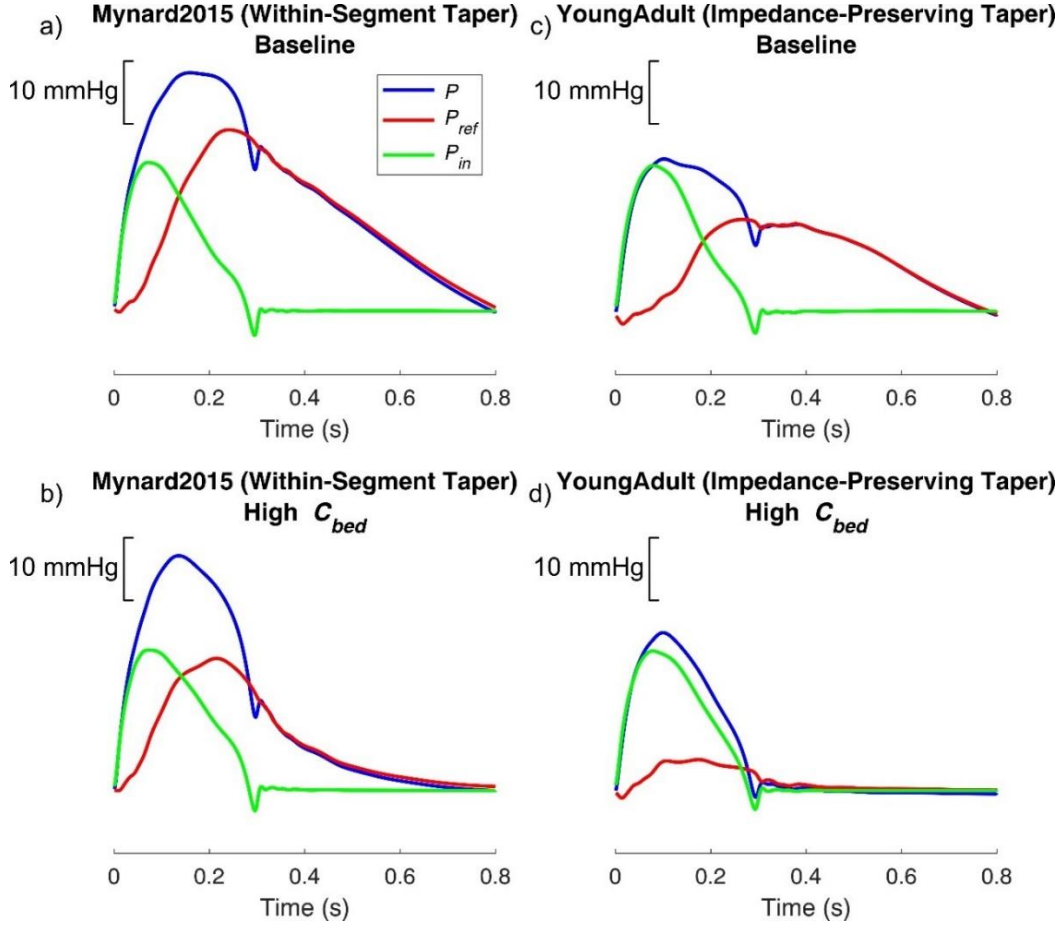


Figure 4.8: INVESTIGATING THE EFFECT OF ARTERIAL TAPER ON WAVE REFLECTION. The Mynard2015 incorporated substantial within-segment taper (as in most other models), whereas the YoungAdult model eliminated within-segment taper by adding impedance-preserving side branches. The total pressure (P), input pressure (P_{in}), and total reflected pressure (P_{ref}) waveforms of the aorta are shown for the Mynard2015 and YoungAdult models with baseline vascular bed compliance (C_{bed}) (a and c, respectively) and, to evaluate the influence of substantially reducing wave reflection from all distal vascular beds via a 100-fold increase in C_{bed} (b and d, respectively). The ascending aortic pressure waveform has been shifted to start at zero for better visual comparison with the input and reflected pressure waveforms.

Table 4.2: VALIDATION OF PRESSURE AND VELOCITY VALUES. Comparison of the systolic/maximum and pulse pressure and velocity values as median (range) across various arteries from the YoungAdult model and the in vivo study (subject characteristics given in Table 4.1).

Artery	Pressure/Velocity	Units	Model Values	In Vivo Values
Ascending Aorta	Pressure (Systolic)	mmHg	105	102 (96 – 122)
	Pressure (Pulse)	mmHg	25	35 (33 – 52)
Left Common Carotid Artery	Pressure (Systolic)	mmHg	111	102 (95 – 120)
	Pressure (Pulse)	mmHg	32	37 (31 – 50)
	Velocity (Max)	cm·s ⁻¹	54	44 (38 – 89)
	Velocity (Pulse)	cm·s ⁻¹	52	36 (30 – 69)
Left Brachial Artery	Pressure (Systolic)	mmHg	117	112 (105 – 126)
	Pressure (Pulse)	mmHg	39	41 (34 – 56)
	Velocity (Max)	cm·s ⁻¹	35	49 (26 – 64)
	Velocity (Pulse)	cm·s ⁻¹	40	57 (34 – 79)
Left Radial Artery	Pressure (Systolic)	mmHg	113	116 (114 – 145)
	Pressure (Pulse)	mmHg	36	49 (45 – 75)
	Velocity (Max)	cm·s ⁻¹	30	20 (15 – 39)
	Velocity (Pulse)	cm·s ⁻¹	33	29 (21 – 43)
Left Superficial Femoral Artery	Pressure (Systolic)	mmHg	122	106 (98 – 127)
	Pressure (Pulse)	mmHg	45	41 (30 – 57)
	Velocity (Max)	cm·s ⁻¹	36	37 (32 – 68)
	Velocity (Pulse)	cm·s ⁻¹	42	48 (32 – 89)
Left Posterior Tibial Artery	Pressure (Systolic)	mmHg	118	124 (114 – 134)
	Pressure (Pulse)	mmHg	43	52 (43 – 68)
	Velocity (Max)	cm·s ⁻¹	36	21 (13 – 43)
	Velocity (Pulse)	cm·s ⁻¹	40	31 (18 – 59)
Left Superficial Temporal Artery	Pressure (Systolic)	mmHg	113	105 (94 – 129)
	Pressure (Pulse)	mmHg	35	36 (30 – 59)

4.3.5 Impact of Tapering on Wave Reflection

To investigate the impact of impedance-preserving vs within-segment tapering on arterial wave reflection, Figure 4.8 shows the effect of a large increase in C_{bed} that markedly reduced wave reflection in the distal vascular beds (thus revealing the contribution of wave reflection within the 1D network). In the Mynard2015 model (which includes substantial within-segment taper), the amplitude of P_{ref} (red) at the aorta was 29 mmHg at baseline and reduced by only 27% when C_{bed} was increased; there also remained a large difference between P (blue) and P_{in} (green, Figure 4.8b). On the other hand, the amplitude of P_{ref} in the ascending aorta of the YoungAdult model (with mostly impedance-preserving taper) was 17 mmHg at baseline (43% less than the Mynard2015 model) and reduced by 63% with increased C_{bed} ; the ascending aortic pressure and input waveforms also became very similar in shape (Figure 4.8d), demonstrating that most of the wave reflection in the YoungAdult model arises at the level of the vascular beds.

4.4 Discussion

This study described an optimised arterial network model that is the first to predict the characteristic features of the ascending aortic pressure waveform in young adults (early systolic peak, negative augmentation, and a diastolic hump (158, 182, 190)) as well as clearly triphasic velocity profiles in peripheral arteries. The properties of the YoungAdult model that led to this improvement over prior models were: 1) an improved wave speed relationship that accounted for the degree of elasticity/muscularity of arteries in addition to area, 2) optimally matched junctions, 3) impedance-preserving taper and 4) increased vascular bed compliance. Model results imply that the arterial network must be exquisitely well-matched to exhibit the observed waveform features that are typical of healthy young adults, with minimal reflection in the main conduit arteries (i.e., at junctions or due to within-segment taper), and wave reflection predominantly occurring in the distal vascular beds. Furthermore, a major strength of our study

is that both pressure and velocity waveforms produced by the model across major central and peripheral arteries were in close agreement with observed in vivo data measured in young adults.

A novel empirical equation is proposed that uses both area and distance from the heart indexed to known transition points as a surrogate marker of the degree of elasticity/muscularity. Owing to the paucity of data on the wave speed of every artery, prior studies have employed different estimation techniques for the purpose of model parameterisation. Westerhof et al. (284) assigned an elastic modulus (E) to each artery and then calculated wave speed using the Moens-Korteweg equation: $c = \sqrt{Eh/2r\rho}$, where ρ is blood density, and h and r are wall thickness and artery radius, respectively, using data from Noordegraaf et al. (183). Although the value of E increased in a stepwise manner ($4, 8$, and $16 \times 10^6 \text{ g cm}^{-1} \text{ s}^{-2}$) with increasing distance along an arterial path (284), the common carotid and femoral arteries were both assigned the same value of E ($4 \times 10^6 \text{ g cm}^{-1} \text{ s}^{-2}$) and thus had similar wave speeds ($582 \text{ cm}\cdot\text{s}^{-1}$ and $625 \text{ cm}\cdot\text{s}^{-1}$, respectively). This approach was also employed by Stergiopulos et al. (256) and Avolio et al. (10), although Avolio increased the value of E for the femoral artery to $8 \times 10^6 \text{ g cm}^{-1} \text{ s}^{-2}$, which increased its wave speed to $910 \text{ cm}\cdot\text{s}^{-1}$ and was therefore more representative of in vivo values.

To avoid the need to estimate E and h for every artery, Olufsen et al. (197) used data from Westerhof et al. (284) and Stergiopulos et al. (256) to develop an empirical relationship between Eh/r and r . This allows the estimation of the wave speed of an artery based solely on its radius. This relationship has been employed in multiple studies (36, 175), although Reymond et al. (223) later developed a similar empirical relationship based on published in vivo wave speeds. The drawback of these empirical relationships is that they provide similar wave speeds for arteries of similar radius but different wall properties (e.g., common carotid and femoral arteries). This

study has shown that our improved relationship provides substantially more accurate estimates of wave speed across a wide range of central and peripheral arteries in the young adult compared to previously employed relationships because it accounts for different wall properties as well as radius.

Impedance-preserving taper was incorporated in the YoungAdult model, which moved the major reflection sites distally to the vascular beds. Many previous studies have incorporated substantial within-segment taper (of up to 70% by area (175)) into cardiovascular models (223, 256). Although arterial diameter is known to decrease with distance from the heart, Suwa et al. (260) and Milnor et al. (152) found little to no taper in sections of arteries between successive branching points. This led Papageorgiou et al. (200) to conclude that the reduction in diameter of an artery does not occur continuously (as assumed in previous models), but in steps, with each step occurring due to branching of the vascular tree. Implementing such impedance-preserving tapering in the YoungAdult model led to substantial changes in both central and peripheral arteries, compared with the Mynard2015 model (175), i.e. leading to an ascending aortic pressure waveform exhibiting the typical features of a young adult, as well as triphasic velocity profiles in peripheral arteries.

Additional evidence towards the lack of within-segment taper arises when considering model findings in Figure 4.8 in light of experimental data presented by van den Bos et al. (269). These authors found that substantial reduction of peripheral resistance and vascular bed wave reflection, via administration of the potent vasodilator sodium nitroprusside in dogs, led to pressure and flow waveforms in the ascending aorta having similar shapes. This indicated that vascular beds are likely to be the main sites of wave reflection. Our results are consistent with this conclusion, since increasing C_{bed} in the YoungAdult model produced similar pressure and

flow waveforms in the ascending aorta (Figure 4.8d) as in van den Bos et al. (269), noting that C_{bed} is likely to increase with vasodilation. By contrast, even with a large increase in C_{bed} in the Mynard2015 model (that includes substantial within-segment taper), the ascending aortic pressure and flow waveforms still had dissimilar shapes, indicating that significant arterial wave reflection was still present within the 1D network (i.e., conduit arteries).

Our findings therefore support the contention by Papageorgiou et al. (200) that ‘true’ arterial taper (i.e. within-segment taper) is unlikely to be a typical (or at least haemodynamically significant) feature in healthy young adults, and that vascular beds are the main sites of wave reflection in the vasculature (191). Indeed, from a design point of view, it is unclear why such within-segment taper would be beneficial. It was therefore not surprising that eliminating this impedance-increasing taper from the major arteries in the YoungAdult model caused wave reflection to occur more distally in the network, and the reflected waves to arrive in the ascending aorta during diastole. The reflected waves thus exerted minimal effect during systole (resulting in an early systolic peak and negative augmentation) but a prominent influence during diastole (resulting in the diastolic hump), which is an optimal situation when considering cardiac energetics (190).

The influence of C_{bed} in 1D models has received little attention, but this parameter was observed to have a substantial effect on wave reflection properties in the vasculature. Importantly, this study showed that the ‘subtraction approach’ to approximate C_{bed} , may not provide accurate values since calculated total arterial compliance (using model waveforms) is relatively insensitive to this quantity (Appendix B.3). Hence, the effect of varying C_{bed} on flow waveforms of distal arteries was explored. Reflection from systemic vascular beds would produce a backward compression wave (BCW) on wave intensity analysis (167, 203), the

amplitude of which would be inversely related to C_{bed} (given that reducing C_{bed} increases reflection). The BCW would decrease arterial flow (203), tending to produce backward flow and the triphasic velocity profiles seen under healthy conditions (216). This explains why decreasing C_{bed} (increased wave reflection) increased the triphasic nature of velocity and caused earlier diastolic velocity reversal but increasing C_{bed} (reduced wave reflection) decreased it and made it more monophasic in nature. In fact, a monophasic velocity profile in distal arteries can point to a pathological condition such as stenosis (60, 216, 256). Previous models have produced monophasic femoral flow waveforms (223, 256), suggesting that the C_{bed} values and/or vascular geometry may have been underestimated. Given that the precise value of C_{bed} is not currently known, our results suggest that the dominant effect of C_{bed} on the triphasic nature of velocity in distal arteries may be useful in guiding estimation of C_{bed} .

It is of interest that reducing C_{bed} had a similar effect on both the pressure and flow waveforms: increased early systolic peak, lower early diastolic trough, and increased late systolic hump. This may be counterintuitive because a BCW has opposite effects on pressure and flow (167, 203). However, the similar effects of C_{bed} observed in conduit arteries likely relates to the fact that at arterial bifurcations, reflected waves from a given branch are transmitted into all other branches (not just the parent artery) (168); therefore, they give rise to backward waves as well as forward waves in peripheral arteries. Although the complex ensemble of reflected, re-reflected, and transmitted waves makes it difficult to precisely establish the basis for all waveform features, changes in pressure and flow that are in the same direction indicate a predominant effect of forward waves whereas changes in the opposite direction indicate a predominant effect of backward waves.

While it is known that the diastolic hump in the ascending aortic pressure waveform is caused by the reflected waves arriving during diastole (196), the exact origin of these reflected waves is unclear. Based on in vivo experiments, O'Rourke et al. (194) proposed that there were two distinct 'effective' reflection sites in the body roughly corresponding to the upper and lower body. They consequently likened the systemic arterial network to an asymmetric T-Tube model, with the shorter tube representing the upper body and the longer tube representing the lower body (186). They also proposed that, in young adults, reflections from the upper body and lower body affect the early and later part of the cardiac cycle, respectively (189). Our simulations were consistent with this concept given that increasing reflection from the arm/cerebral and leg arteries increased the late systolic portion and diastolic hump of the ascending aortic pressure waveform, respectively, thus providing insight into the effect of wave reflection from different regions of the body on the ascending aortic pressure waveform.

Given the clear influence of wave reflection from the legs on the diastolic hump (see Figure 4.5), it was not surprising that this waveform feature was affected by the reflection properties of the aortoiliac bifurcation. While most arterial junctions appear to be well matched in the forward direction, the aortoiliac bifurcation is thought to be a potential exception due to observed lower daughter-to-parent area ratios (199). Ex vivo analysis of abdominal aortic and common iliac arteries by Greenwald et al. suggested that R_p at the aortoiliac bifurcation might reach 0.2 or even higher in some young individuals, although most values in young adults were between 0 and 0.1 (82). Our results show that introducing $R_p = 0.2$ at the aortoiliac bifurcation abolished the diastolic hump, indicating that the earlier wave reflection arriving at the aorta due to the unmatched junction obscures the impact of reflection in the legs (as revealed by comparison with $R_p = 0$ (Figures 4.5 and 4.7). These findings suggest that the aortoiliac bifurcation (in addition to other arterial junctions in the lower body) may need to be well-matched to obtain a

prominent diastolic hump. Interestingly, a study found $R_p = 0.07$ at the aortoiliac trifurcation in dogs (135), which is within the range of values found by Greenwald et al. ($R_p = 0 - 0.1$). Thus, there is no strong evidence that there is a difference between species. Importantly, Greenwald et al. determined the R_p value at the bifurcation using ex-vivo methods, which may not be representative of in-vivo conditions. Thus, future studies are required to accurately determine the R_p value at the bifurcation using in-vivo methods.

There are some limitations that should be considered when interpreting the results of this study. First, for simplicity and consistency, a single value of $\tau = 1.3$ was used for all vascular beds. Although this produced acceptable waveforms in all arteries, using $\tau = 0.5$ in just the arm vascular beds (with $\tau = 1.3$ in all other beds) produced arm waveforms that were closer to those obtained in vivo compared to the baseline model (Figure 4.4); however, using $\tau = 0.5$ in all vascular beds abolished the early systolic peak and negative augmentation in the ascending aortic pressure waveform. Thus, future studies could investigate methods for estimating C_{bed} of individual vascular beds more precisely. Second, directly obtaining the ascending aortic pressure waveform was beyond the scope of this study; hence, it had to be estimated using a transfer function applied to the carotid pressure waveform, which could potentially reduce the accuracy of the in vivo systolic and pulse pressure values obtained for the ascending aorta. Although the resulting ascending aortic pulse pressure was lower than that calculated in our cohort, the value obtained was within the normal range compared to literature data (145). Finally, the small sample size ($n=7$) of the validation cohort in this study should be acknowledged. This could explain why the ascending aortic pressures of the cohort were not in the range of the model. Nevertheless, all other pressure and velocity values were within the range of the model, indicating that the sample size was sufficient to show that model is representative of an average healthy young adult.

In conclusion, this study has shown that the YoungAdult systemic arterial network model incorporating more accurate arterial wave speeds, impedance-preserving taper, and well-matched junctions exhibits reflected waves that predominantly arise at the level of the vascular beds and arrive in the ascending aorta during the diastolic period. These physiological features produce waveform features that are typical of a healthy young adult, including an early systolic peak, negative augmentation, and a diastolic hump in the ascending aorta, as well as triphasic velocity profiles in peripheral arteries. Our model provides novel insights into the ‘fine-tuning’ of arterial network properties, and it can be used as a baseline in future studies of cardiovascular ageing and disease.

Chapter 5: Centroid method for estimating return time

This chapter introduces a novel centroid method for estimating the return time of reflected waves. Unlike previous methods, this new approach takes into account the distributed nature of wave reflection. This chapter presents a computational validation of the accuracy of the centroid method against a ground truth enabled by the YoungAdult model described in Chapter 4 and assesses its sensitivity to diastolic and systolic return times using animal experiments. This chapter has been accepted for publication as a peer-reviewed article titled “Novel centroid method for robust evaluation of return time of reflected waves in the systemic arterial network” in IEEE Transactions on Biomedical Engineering.

5.1 Introduction

As the left ventricle starts ejecting, it generates a forward-travelling pressure wave that is reflected at various sites of impedance mismatch in the vasculature. The resulting multitude of backward waves return to the ventricle throughout the cardiac cycle (238)—at different times (depending on the wave propagation speed and the distance from various reflection sites) and with different magnitudes (depending on the degree of reflection). The return time of these waves to the ventricle—whether during systole or diastole—is of importance because they predominantly exert a pressure-increasing effect (141). In youth, the backward waves are thought to return predominantly during diastole and cause diastolic augmentation of the ascending aortic pressure waveform, which supports coronary perfusion pressure (45, 181, 190). As arteries stiffen (e.g., with age), it is thought that backward waves return earlier, shifting the pressure augmentation from diastole to systole and increasing systolic pressure and left ventricular afterload (45, 181, 190). If left uncontrolled, increases in afterload can lead to left

ventricular hypertrophy, which increases the risk of congestive heart failure (133). Thus, the change in return time of backward waves with vascular ageing not only helps explain the physiological changes observed in the central pressure waveform, but is also considered a critical aspect of pulsatile ventricular load with potential clinical value (39).

Although there are numerous backward waves of different magnitudes that return at different times because of the distributed nature of wave reflection, it is generally not possible to distinguish individual waves in vivo; therefore, a composite or ensemble “backward pressure waveform” composed of many individual backward waves is used to estimate the “bulk” return time. The most widely used method for estimating return time is the inflection point method (154). The inflection point is a feature commonly visible in the systolic portion of central arterial blood pressure waveforms where the pressure temporarily plateaus and rises again. The inflection point is thought to indicate the time when the backward wave arrives and begins to augment pressure. A meta-analysis by Baksi et al. found that return times estimated by this method decreased with age but were within systole throughout the lifespan (12). This may seem inconsistent with the traditional view that backward waves return predominantly in diastole in youth, although it should be recognised that the inflection point only indicates the onset of the backward wave, not the timing of return of the bulk of the backward wave. In fact, the inflection point is calculated in such a way that it can never occur during diastole. Moreover, while wave reflection does give rise to the inflection point, it is also affected by factors independent of wave reflection such as ventricular outflow patterns (111). Thus, it may not provide an accurate representation of return time, which has indeed been the conclusion of several studies (38, 94, 100, 177).

To improve the accuracy of estimated return time, other methods have been developed that involve extracting forward and backward pressure waveforms from the central pressure waveform using either frequency-domain (286) or time-domain methods (203). Two such methods include the zero crossing (239) and foot methods (266, 281), with both providing the same trend of decreasing return time with age as the inflection point method. However, both methods also produce return times within systole (239, 266), and again tend to quantify the onset of the reflected wave rather than the timing of its bulk pressure effect. Importantly, however, the ability of existing methods for estimating bulk return time have not yet been rigorously evaluated, in part because there is no ‘ground truth’ for such an evaluation.

A key limitation of existing methods is that they rely on finding a single point on the waveform to estimate return time. This runs fundamentally counter to the composite nature of the backward pressure waveform (i.e., there is no ‘single’ backward wave). Hence, taking the entire backward pressure waveform into account rather than a single point could better represent its composite nature, and provide clarity in the controversies about how return time changes with age. This study proposes a novel “centroid method”, in which the centroid of the entire backward pressure waveform is used to estimate an effective or ‘bulk’ return time of the backward wave ensemble.

The first aim of this study was therefore to rigorously investigate which method of estimating return time—centroid, zero crossing, inflection point, or foot method—provides the most accurate estimate of the bulk return time. Accuracy was evaluated by comparison with a ground truth return time (GTRT) obtained via a linear wave tracking algorithm applied in a one-dimensional model of the systemic arterial network. It was hypothesized that the centroid method would provide a better estimate of return time than the other methods because it takes

the composite nature of the backward pressure waveform into account. The second aim was to investigate the sensitivity of all methods to changes in return time, during both diastole and systole. Towards this, an experimental study in sheep was conducted where an artificially generated backward-travelling pressure pulse was introduced using an intra-aortic balloon pump. These pulses arrived at the ascending aorta at precisely controlled times in systole and diastole, hence changing the bulk return time. It was hypothesized that only the centroid method, which accounts for the entire backward pressure waveform, would be sensitive to changes in wave reflection profile during both systole and diastole, because the other methods are based on single-point features found only in systole.

5.2 Methods

5.2.1 Wave Separation

The relationship between pressure and flow waves is described by the ‘water hammer’ equation (203, 264):

$$\begin{aligned} dP_f &= Z_c dQ_f \\ dP_b &= -Z_c dQ_b \end{aligned} \tag{Equation 5.1}$$

where dP and dQ are wave-related changes in pressure and flow, respectively, Z_c is characteristic impedance, and the subscripts indicate direction of travel (subscript ‘ f ’ is forward and ‘ b ’ is backward). Equation 5.1 indicates that forward waves cause pressure and flow to change in the same direction, while backward waves cause opposite changes. Thus, in the absence of wave reflection, the pressure waveform will be identical to the flow waveform (but scaled by characteristic impedance); therefore, wave reflection is entirely responsible for the difference between the waveforms observed in vivo.

Using Equation 5.1, the pressure waveform can be separated into forward (from the heart) and backward (towards the heart) pressure waveforms using the method proposed by Westerhof et al. (286), which requires the measurement of both pressure and flow waveforms:

$$P_f = \frac{1}{2}(P_m + Z_c Q_m)$$

$$P_b = \frac{1}{2}(P_m - Z_c Q_m)$$

(Equation 5.2)

where the subscript ‘*m*’ refers to the measured waveform and Z_c is calculated as the average value of the modulus of the 4th to 11th harmonic of the input impedance (239), which is the ratio of the Fourier transformed pressure and flow waveforms (286).

It is important to note that backward waves are re-reflected at the closed aortic valve during diastole and at the ventricle during systole when the aortic valve is open (17, 86, 176, 206). Thus, the forward pressure waveform (P_f) comprises both waves that are produced by active ventricular contraction ($P_{f,in}$) and waves arising from re-reflection of backward waves. $P_{f,in}$ may therefore be considered the pressure that would exist in the absence of wave reflection, or the ventricular ‘input’ pressure to the arterial network; the best approximation of this is the flow waveform scaled by characteristic impedance ($Z_c \times Q_m$).

5.2.2 Methods of Estimating Return time

The zero crossing (239), inflection (158), and foot methods (281) have been described in detail elsewhere. Here a brief description of each method is provided and its implementation in the present study. The inflection point method only requires the pressure waveform, while the zero crossing and foot methods require both pressure and (measured or synthesized) flow waveforms because they involve wave separation analysis.

5.2.2.1 Inflection Point

The dicrotic notch was first determined as the peak of the second derivative of the pressure waveform with the highest relative height (determined using 'findpeaks' function of MATLAB) after the maximum pressure (Figure 5.1a). The foot of the pressure waveform was found using the intersecting tangents method (47). The inflection point was then identified as the second derivative peak between the foot and dicrotic notch (239). The time difference between the foot and the inflection point was taken as the estimate of return time (Figure 5.1a).

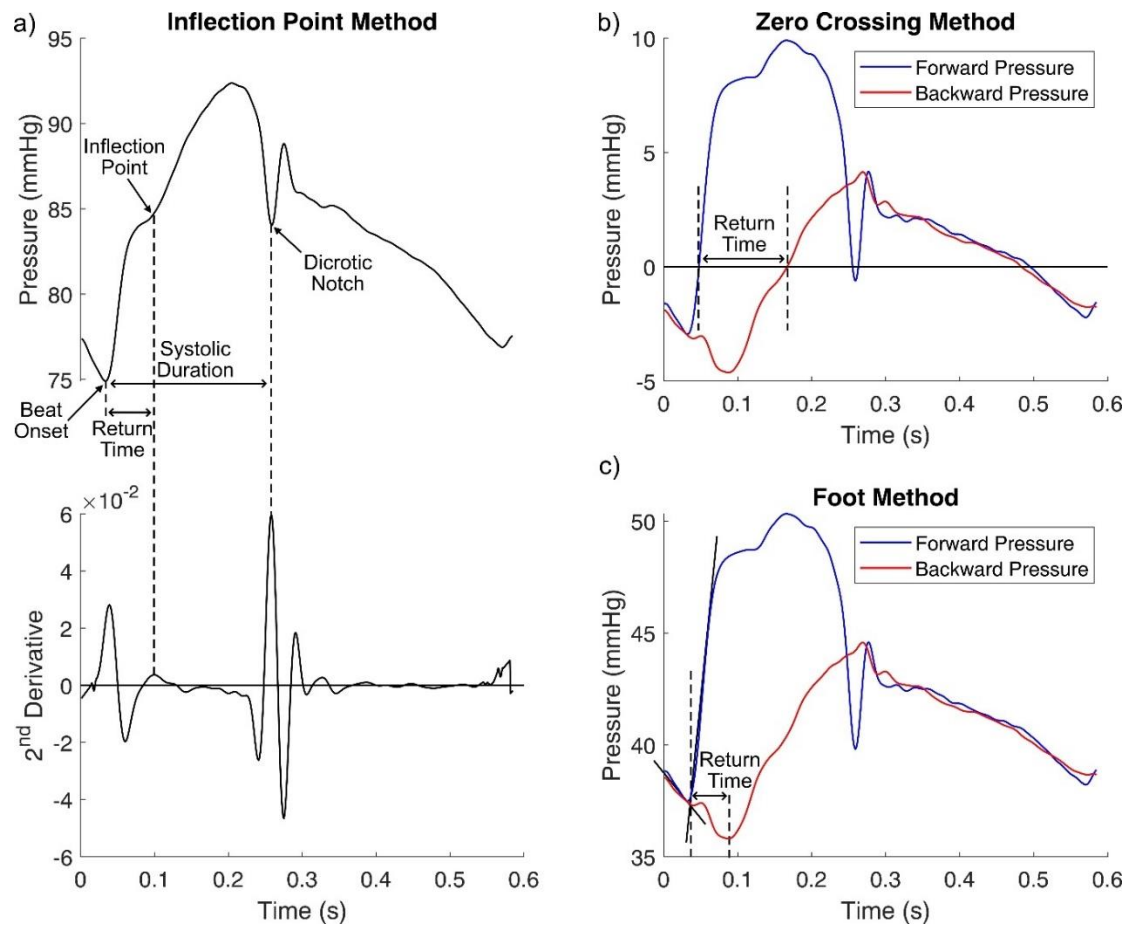


Figure 5.1: ESTIMATING RETURN TIME. Estimation of backward wave return time via the (a) inflection point, (b) zero crossing, and (c) foot methods.

5.2.2.2 Zero Crossing

As described by Segers et al, the pressure waveform was offset to zero mean and then separated into forward and backward pressure waveforms using wave separation in the frequency domain (239). The time difference between the zero crossings of the backward and forward pressure waveforms was taken as the estimate of return time (Figure 5.1b).

5.2.2.3 Foot Method

The pressure waveform was decomposed into forward and backward pressure waveforms using wave separation. The foot of the forward and backward pressure waveforms was found using the intersecting tangents method (281). However, in instances where the backward pressure waveform did not have a monotonic upstroke, the foot was instead taken as the minimum point of the backward pressure waveform. The time difference between the foot of the backward and forward pressure waveforms was taken as the estimate of return time (Figure 5.1c).

5.2.3 Centroid Method

The zero crossing and foot methods estimate return time using the backward pressure waveform (P_b) relative to a feature of P_f ; however, as mentioned earlier, P_f is influenced by re-reflections of the backward wave at the ventricle. To represent return time in terms of the actual pressure effect of backward waves, the centroid method therefore uses $P_{f,in}$, the ‘input’ pressure to the arterial network without the influence of wave reflection ($Z_c \times Q_m$), instead of P_f . The centroid method estimates the bulk return time of backward waves as follows:

1. Offset the P_b waveform so that it has a minimum value of zero.

2. Calculate the time axis centroid of the P_b waveform from its foot in the 1st beat (i.e., at which P_b starts to rise) to that in the 2nd beat, and that of the $P_{f,in}$ waveform from its foot to the dicrotic notch of the total pressure waveform. The diastolic part of the $P_{f,in}$ waveform (i.e., after the dicrotic notch) is ignored to prevent potentially noisy signals during diastole (when there is no flow) from interfering with the centroid calculation.
3. The difference in these times is equal to 'return time'.
4. 'Arrival time', defined as the absolute time at which the bulk reflected wave arrives at the ventricle after the onset of the pressure upstroke, is numerically equal to return time (shown as black arrows in Figure 5.2).

The foot of the P_b waveform for one cardiac cycle is determined in the same manner as the foot method, and that of $P_{f,in}$ is determined using the intersecting tangents method. Minimum pressure is subtracted from P_b to better elucidate the influence of the shape of the waveform on its centroid. This is necessary because in the limit that the minimum pressure is very high, the time-axis centroid will always be in the middle of the waveform, regardless of its shape. The time-axis centroids ($\bar{t}$) of P_b and $P_{f,in}$ are determined using the following formula:

$$\bar{t} = \frac{\int_a^b tP(t)dt}{\int_a^b P(t)dt} \quad (\text{Equation 5.3})$$

where $P(t)$ is the pressure waveform (either P_b or $P_{f,in}$) and t is time. In the case of P_b , a and b refer to the timing of its foot in the 1st beat to that in the 2nd beat, respectively, and in the case of $P_{f,in}$, they refer to the timing of its foot and the dicrotic notch of the total pressure waveform, respectively (as described above). The difference between the time-axis centroids of P_b and $P_{f,in}$ is taken as the estimate of return time by the centroid method (Figure 5.2).

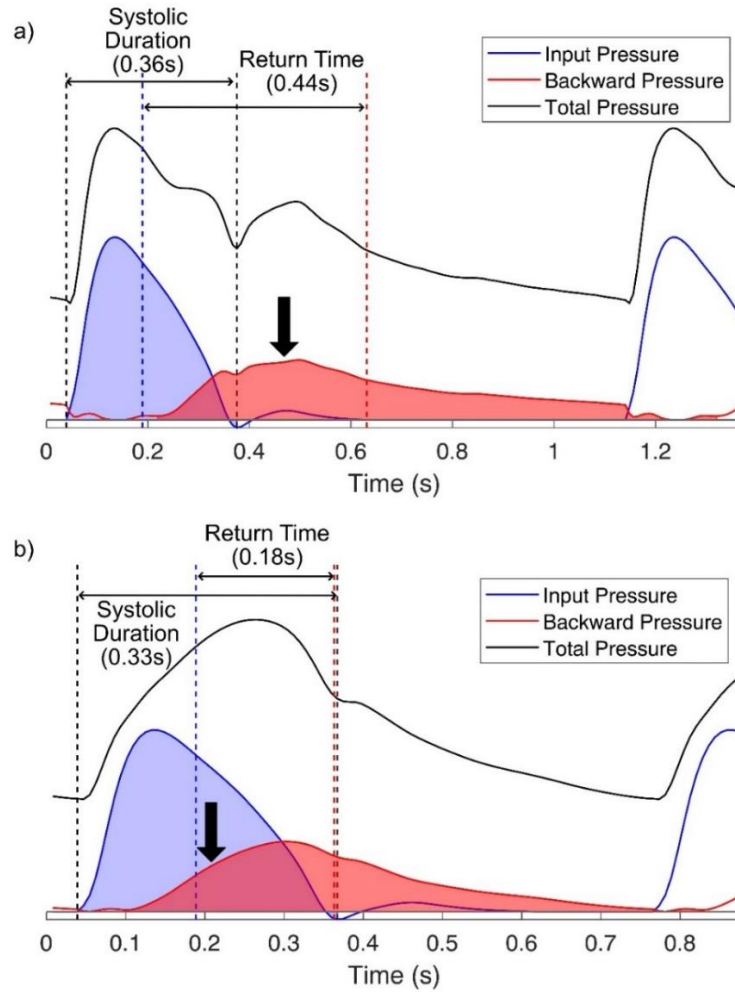


Figure 5.2: DESCRIPTION OF THE CENTROID METHOD. The area under the backward pressure waveform (red solid line) from its foot in the 1st beat to that in the 2nd beat is used to calculate its centroid (red dashed line). The area under the input pressure waveform (blue solid line) from its foot to the dicrotic notch (black dashed line) of the total pressure waveform (black solid line) is used to calculate its centroid (red dashed line). The difference between the two centroids is taken as the return time by the centroid method. The time difference between beat onset of the total pressure waveform (black dashed line) and the dicrotic notch (black dashed line) is taken as the systolic duration. The black arrow denotes the return time relative to beat onset and thus represents when the “bulk” of the backward pressure waveform arrives. Here, two examples are shown: a) return time is greater than systolic duration and thus the “bulk” backward pressure waveform predominantly returns during diastole; b) return time is less than systolic duration and thus the “bulk” backward pressure waveform predominantly occurs during systole. Note: Pressure waveforms from the carotid artery of an 18-year-old (a) and 57-year old (b) participant were taken the ACCTIII dataset (145) courtesy of Prof Carmel McEniery, Cambridge University, and the flow waveforms were an average representative aortic waveform scaled to beat onset and dicrotic notch of the pressure waveforms (165).

5.2.4 Linear Model

To assess the accuracy of these methods using a GTRT, every individual backward wave arriving at the ventricle must be tracked; this can only be achieved through computational methods. Chapter 4 described the development and validation of a non-linear one-dimensional model of the systemic arterial circulation of a young adult—the ‘YoungAdult’ model. In brief, a two-chamber heart model served as the input to the systemic arterial circulation, and distal arteries were terminated with 3-element windkessels representing vascular beds. Since all bifurcations in the arterial tree are thought to be relatively well-matched, with a reflection coefficient (Γ_p) of 0 in the forward direction (199), this was replicated in the YoungAdult model using an optimization algorithm described in Section 4.2.3.2.

A linear wave tracking algorithm can enable tracking of every individual backward wave (5, 275), but it requires a linear model. Thus, the following modifications were made to the YoungAdult model to linearize it. The wave tracking algorithm requires a simple bifurcating arterial tree; however, the cerebral arterial tree is looping in nature due to the circle of Willis. Hence, the cerebral arteries were replaced with a terminal windkessel to represent the cerebral vascular bed. Furthermore, the ventricle, arterial taper, and terminal windkessels were represented in a simplified form. First, the ventricle and aortic valve were assumed to be perfect reflectors of backward waves during systole and diastole, respectively. In reality, the value of Γ_p may change throughout the cardiac cycle; however, its precise value has not yet been determined but is thought to be close to 1 (17). Hence, the ventricle and aortic valve were removed and a constant value of $\Gamma_p = 1$ was imposed at the proximal end of the aorta. Second, tapered arteries (where employed) were discretized into 10 uniform segments of equal length, with successively decreasing area based on the degree of taper. Thus, there was a non-zero Γ_p at the junctions of successive segments, which represented the reflection properties of tapered vessels. Note that

this only applied to distal branches of the internal and external carotid arteries, as there is no continuous taper in other arteries of the YoungAdult model (119). The resulting discrete tapering was close to continuous, with discrete steps that were 4.6 ± 3.8 mm in length and discrete area reductions of $2.5 \pm 1.7\%$.

Finally, to account for the terminal windkessels, they were initially replaced with fractal arterial networks at every terminal vessel to represent the microvasculature. However, this increased the computation time exponentially. To improve efficiency, a Γ_p value was used at the distal end of the terminal vessels instead of the fractal network, which was calculated using the characteristic impedance of the terminal vessel (Z_{tv}) and the vascular bed resistance (R_{vb}):

$$\Gamma_p = \frac{R_{vb} - Z_{tv}}{R_{vb} + Z_{tv}} \quad (\text{Equation 5.4})$$

This did not significantly affect the results compared to the fractal network but dramatically improved the computation time (data not shown). This linearized form of the YoungAdult model is henceforth referred to as the LinearYoungAdult model. Wave attenuation due to viscous damping and the non-linearity introduced by the pressure-dependence of vessel wave speed were not accounted for by the linear wave tracking algorithm. The focus of this study is instead on the effect of complex arterial geometry on wave propagation.

5.2.5 Linear Wave Tracking

To start the linear wave tracking algorithm using the LinearYoungAdult model, the heart model was removed and a forward-travelling impulse of amplitude 1 at time 0 was instead applied at the proximal end of the ascending aorta. The time taken for this impulse to ‘traverse’ the parent vessel was calculated by dividing the length of the vessel by its wave speed. At the distal end of the parent vessel where it bifurcated into two daughter vessels, the incident wave produced

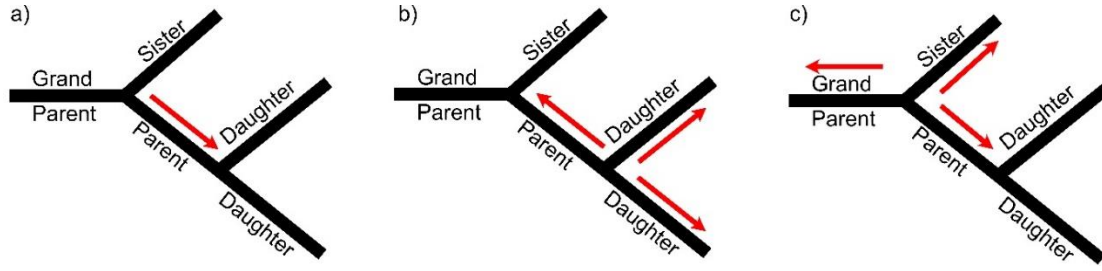


Figure 5.3: LINEAR WAVE TRACKING. Diagrammatic representation of the 1-dimensional model defining parent, daughter, grandparent, and sister vessel terminology. A wave travelling in the parent vessel (a) will be transmitted into the two daughter vessels and reflected back into the parent vessel at its distal end (b). The backward wave in the parent will then be transmitted into the grandparent and sister vessels and reflected back into the parent vessel at its proximal end (c).

three waves: a backward wave traversing backwards through the parent vessel and a transmitted wave entering each of the daughter vessels. The ratio of backward to incident wave amplitudes was calculated via Γ_p :

$$\Gamma_p = \frac{\frac{A_0}{c_0} - \frac{A_1}{c_1} - \frac{A_2}{c_2}}{\frac{A_0}{c_0} + \frac{A_1}{c_1} + \frac{A_2}{c_2}} \quad (\text{Equation 5.5})$$

where A is reference vessel area, c is reference wave speed, the subscript 0 refers to parent vessel and subscripts 1 and 2 to the two daughter vessels, and 'reference' values refer to initial values (i.e., at a pressure of 80 mmHg) used in the non-linear model. The ratio of transmitted to incident wave amplitudes (i.e., the transmission coefficient T_p) was equal in both daughter vessels and was calculated using the relationship $T_p = 1 + \Gamma_p$. A backward wave traversing through a parent vessel will be reflected into the parent vessel at its proximal end and transmitted into the 'grandparent' and 'sister' vessels (Figure 5.3). The Γ_p value at the proximal end of the parent vessel was again calculated using Equation 5.5, where subscript 0 now refers to the parent vessel and the subscripts 1 and 2 now refer to the grandparent and sister vessels. In this manner, the Γ_p values at the proximal and distal ends of every vessel were calculated, which helped determine the amplitudes of the waves as they propagated through the network.

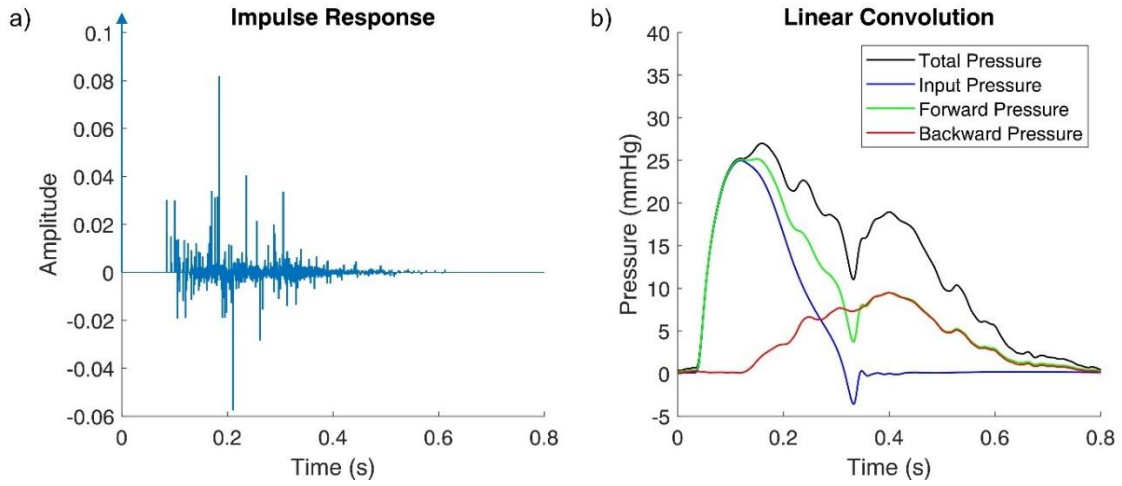


Figure 5.4: IMPULSE RESPONSE AND LINEAR CONVOLUTION. a) The impulse response indicating the timing and amplitude of all waves at the proximal end of the aorta obtained using the linear wave tracking algorithm. The arrow denotes the input impulse of amplitude 1 at time 0. b) The pressure waveform (including the backward and forward pressure waveforms) obtained by convolving the impulse response with an input pressure waveform (shown in blue).

In this manner, the timing and amplitude of every wave above an amplitude threshold (both forward and backward, see below) at the ascending aorta was kept track of, which was visualized by an impulse response (Figure 5.4a). Waves with positive and negative amplitudes exert a pressure-increasing (compression) and pressure-decreasing (decompression) effect, respectively. Finally, the amplitude-weighted mean time at which all backward waves (including both compression and decompression) returned to the inlet (within one cardiac cycle of 0.8 s) was taken as the GTRT.

5.2.6 Waveform Generation

To compare the various methods of estimating return time against GTRT, they need to be applied to waveforms from the linear wave tracking algorithm. Towards this, the ascending aortic flow waveform from the YoungAdult model was scaled by characteristic impedance (Z_c) to obtain $P_{f,in}$, where Z_c was obtained by applying frequency-domain methods to the ascending aortic pressure and flow waveform of the YoungAdult model (181). $P_{f,in}$ was then convolved

with the impulse response of the LinearYoungAdult model. The linear convolution of all forward and backward waves provided forward and backward pressure waveforms, respectively, which were then added to obtain the total pressure waveform (Figure 5.4b). Note that the pressure waveform is not as smooth as a measured waveform because the linear wave tracking algorithm does not account for attenuation of high frequency waves due to blood viscosity and wall viscoelasticity.

5.2.7 Amplitude Threshold

The amplitude threshold used for the linear wave tracking algorithm was determined by comparisons with the non-linear model. First, the cerebral arteries were excluded from the YoungAdult model to make it geometrically identical to the LinearYoungAdult model; the heart model and terminal windkessels were retained to maintain non-linearity. A previously described non-linear flow solver (175) was then applied to the YoungAdult model to obtain a pressure waveform at the ascending aorta. Comparison with the waveform obtained from the LinearYoungAdult model showed no further improvement in root mean square error below a threshold of 5.6×10^{-4} , and therefore this threshold was adopted throughout this study.

5.2.8 Virtual Cohort

To test the accuracy of the methods under a wide range of GTRT values, a virtual cohort was created using the LinearYoungAdult model by performing a parameter sweep of the following: Γ_p at every junction of the network, systemic vascular resistance, wave speed, and aortic taper. The same optimization algorithm used to match the junctions in the forward direction was used to change junction Γ_p values between -0.01 and 0.04 (120). Vascular resistance was varied between 0.5 and 1.5 mmHg·s·mL⁻¹ by multiplying the resistance of all vascular beds by a factor

to achieve the target systemic vascular resistance and modifying the distal Γ_p of terminal vessels accordingly (Equation 5.4). Wave speeds of all vessels in the model were multiplied by a factor between 0.5 and 3, resulting in aortic wave speeds covering a wide but physiological range of 2 to 14 $\text{m}\cdot\text{s}^{-1}$ (263). Finally, while the baseline LinearYoungAdult model had no taper in any segment, the area of the ascending aorta is known to increase with age up to $\sim 16 \text{ cm}^2$ (231). To assess the influence of aortic taper, increases in ascending aortic area were therefore simulated from 6 to 16 cm^2 , whilst keeping the area of the distal abdominal aorta constant and adjusting intervening aortic segments to achieve a linear taper (prior to discretization as described above). All combinations of junction Γ_p values (-0.01, 0, 0.01, 0.02, 0.03, and 0.04), vascular resistance (0.5, 0.75, 1, 1.25, and 1.5 $\text{mmHg}\cdot\text{s}\cdot\text{mL}^{-1}$), wave speed multiplier (0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.5, 2, 2.5, and 3), and aortic taper (ascending aorta area: 5.94, 7.62, 10, and 16 cm^2) were used to create a virtual cohort of $6 \times 5 \times 10 \times 4 = 1200$ individuals.

5.2.9 Experimental Model

Methods for estimating return time were also evaluated in experimental studies performed in sheep. The protocol was approved by the Animal Ethics Committee of the Murdoch Children's Research Institute and conformed to the guidelines of the National Health and Medical Research Council of Australia. This manuscript is compliant with the ARRIVE guidelines for reporting of animal research.

Ten castrated male Border-Leicester cross sheep aged 12-15 months were anesthetized with an intramuscular injection of xylazine (0.05 mg/kg) and ketamine (5 mg/kg) followed by isoflurane (3-4%) in O_2 delivered by mask. After intubation of the trachea, anaesthesia was maintained with a mixture of 1-3% isoflurane and nitrous oxide (10-20%) in oxygen-enriched air delivered via a ventilator (WATO EX-20Vet, Mindray, Shenzhen, China), and supplemented by an

intravenous infusion of ketamine (1-1.5 mg/kg/hr), midazolam (0.1-0.15 mg/kg/hr), and fentanyl (2-2.5 μ g/kg/hr) administered via a 7-Fr triple lumen catheter inserted into the right external jugular vein. Transcutaneous oxygen saturation (S_pO_2) was monitored continuously with a pulse-oximetry sensor applied to the ear. Through a neck incision, the right common carotid artery was cannulated with a 5-Fr micromanometer catheter (SPC-454D; Millar Instruments, Houston, TX, USA) that was passed into the aortic root to obtain high-fidelity pressure and a 7-Fr vascular sheath for initial blood pressure monitoring and arterial sampling for blood gas analysis (ABL 800, Radiometer, Copenhagen, Denmark), with ventilation adjusted to maintain arterial O_2 tension (P_{aO_2}) at 100-120 mmHg and CO_2 tension (P_{aCO_2}) at 35-40 mmHg. Central temperature was monitored via a nasal thermistor probe and maintained at 38-39°C with a combination of heating pad and towel covering.

With animals in a right lateral position, a left thoracotomy was performed in the third intercostal space and the 2nd to 4th ribs removed to increase exposure of the heart and great arteries. A fluid-filled catheter was inserted into the proximal portion of the aortic arch via a purse-string suture to measure mean central aortic blood pressure via a transducer calibrated against a water manometer before each study and referenced to atmospheric pressure at the level of the thoracic spine; this signal was used to calibrate the mean value of the high fidelity pressure from the micromanometer. A 24 mm transit-time flow probe (Transonic Systems Inc, Ithaca, NY, USA) was placed around the ascending aorta to obtain cardiac output (minus coronary blood flow). A second 5-Fr micromanometer catheter was inserted into the left ventricle via the carotid artery sheath, and its signal was used to define beat onset using previously described methods (171). Catheter, micromanometer, and flow probe signals were digitized at a sampling rate of 1 kHz using programmable acquisition software (Spike2, Cambridge Electronic Design, Cambridge, UK).

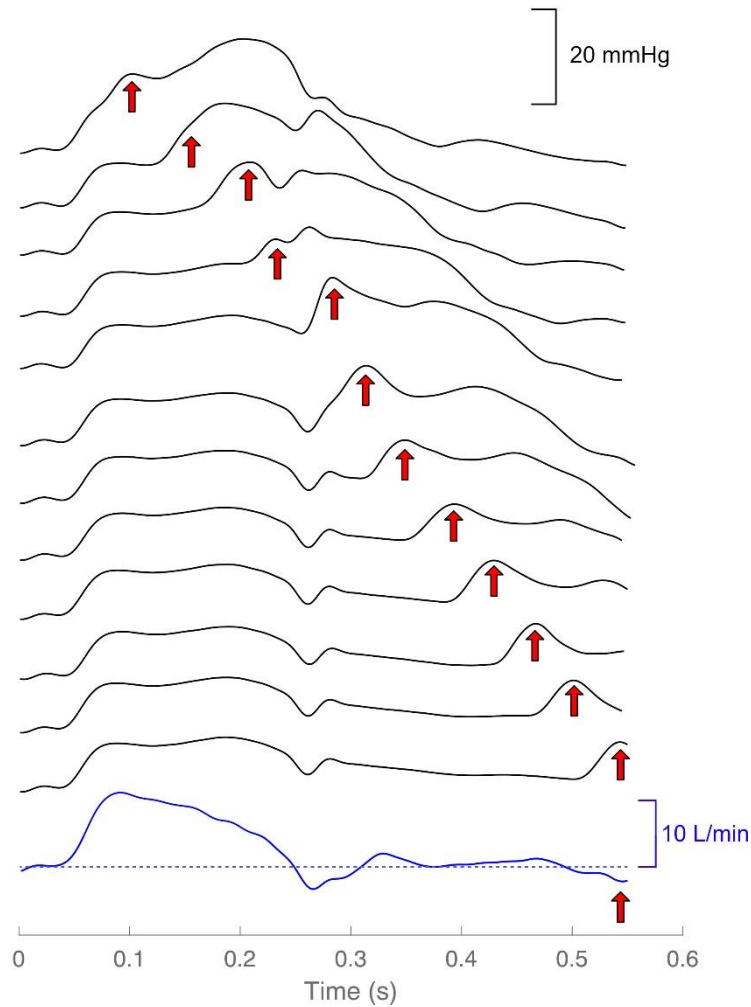


Figure 5.5: BALLOON-INDUCED PULSE. The balloon-induced pulse (BLIP) created by the inflation of the balloon catheter at various times from diastole (bottom) to systole (top) as observed in the pressure waveform (black) in the animal experiments. The red arrows indicate the location of the BLIP on each waveform. The flow waveform for the first diastolic BLIP is shown in blue.

Through an incision in the right groin, an intra-aortic balloon catheter (MEGA 8-Fr 50cc; Maquet Cardiovascular, Wayne, NJ, USA) was inserted via the right femoral artery and passed into the descending thoracic aorta. Using a custom-made triggering interface to precisely control its timing, the balloon catheter was initially inflated at end diastole. This generated a backward-running pulse that travelled towards the ascending aorta, producing a prominent brief pulse in the ascending aortic pressure waveform. The timing of the pulse was then altered in a stepwise

manner from end diastole to the start of systole (Figure 5.5). At each timestep, the balloon catheter was inflated once every 3 beats over approximately 30 beats.

5.2.10 Data Analysis

The time difference between the peak of the balloon-induced pulse ('BLIP') and the foot of the pressure waveform was called BLIP time. BLIP time was normalized to systolic duration (i.e., the time from the foot of the pressure waveform to the dicrotic notch), with the resulting quantity (BLIP Index) being less than 1 if occurring during systole and greater than 1 if occurring during diastole. Systolic duration was determined only once per animal when the BLIP arrived in late diastole because earlier arrival tended to obscure the dicrotic notch. The corresponding flow waveform was also used to calculate Z_c for a particular animal for consistency. Finally, as the BLIP time decreases, a decrease in the apparent "bulk" return time of backward waves is expected, given that the BLIP induces a backward wave. This was used to evaluate the sensitivity of the various methods for detecting changes in bulk backward wave return time during both systole and diastole.

To implement the centroid method using in vivo measurements, the flow waveform can be used as the input waveform and does not need to be scaled by characteristic impedance to obtain $P_{f,in}$; this is because the time-axis centroid is unaffected by amplitude scaling (271). Furthermore, in vivo recordings of the flow waveform contain low level noise and fluctuations during diastole, when there is no aortic outflow. Flow and pressure waveforms were therefore first aligned, and the centroid of the flow waveform was then obtained by considering only the region from its foot to the end of systole, marked by the dicrotic notch of the pressure waveform (Figure 5.2). (Note: Future studies should consider how to apply the centroid method in the setting of aortic regurgitation when there could be negative flow during diastole.)

5.2.11 Statistical Analysis

To analyse the results of the virtual cohort, linear regression was used to determine the coefficient of correlation (r) between GTRT and estimated return time of the various methods; the corresponding degree of agreement was quantified by the intraclass correlation coefficient (ICC). Additionally, Bland-Altman analysis was used to evaluate the difference between GTRT and the various methods; the method that provided the least overall difference and limits of agreement was judged as the one with the highest accuracy and precision respectively. When plotting return time against BLIP Index for the sheep experiments, the zero crossing, inflection point, and foot methods had two visually distinct datasets, with the breakpoint (the boundary between the two datasets) approximately at a BLIP Index of 1. Thus, segmented regression for all methods was performed to precisely determine a breakpoint and analyse the two datasets separately. For each animal experiment, the datapoints between 20% and 80% of the BLIP Index values were iteratively selected as the breakpoints and linear regression on the two datasets produced was performed. The datapoint that provided the lowest total error of the two resulting regressions was taken as the break point. The breakpoint analysis was not restricted to a narrow band around a BLIP Index of 1 to limit visual bias and due to the lack of a visually discernible breakpoint for the centroid method. The break point analysis was performed for all 10 animals individually; the break point, regression intercept and slope, correlation coefficient, and p-value of all animals for a particular method were averaged to obtain the overall values. A method with a significant coefficient of correlation for both systolic and diastolic slopes was robust, in the sense that the method is sensitive to pulses arriving in both systole and diastole. Data are reported as mean $\pm$ SD and a value of $p < 0.05$ was considered significant.

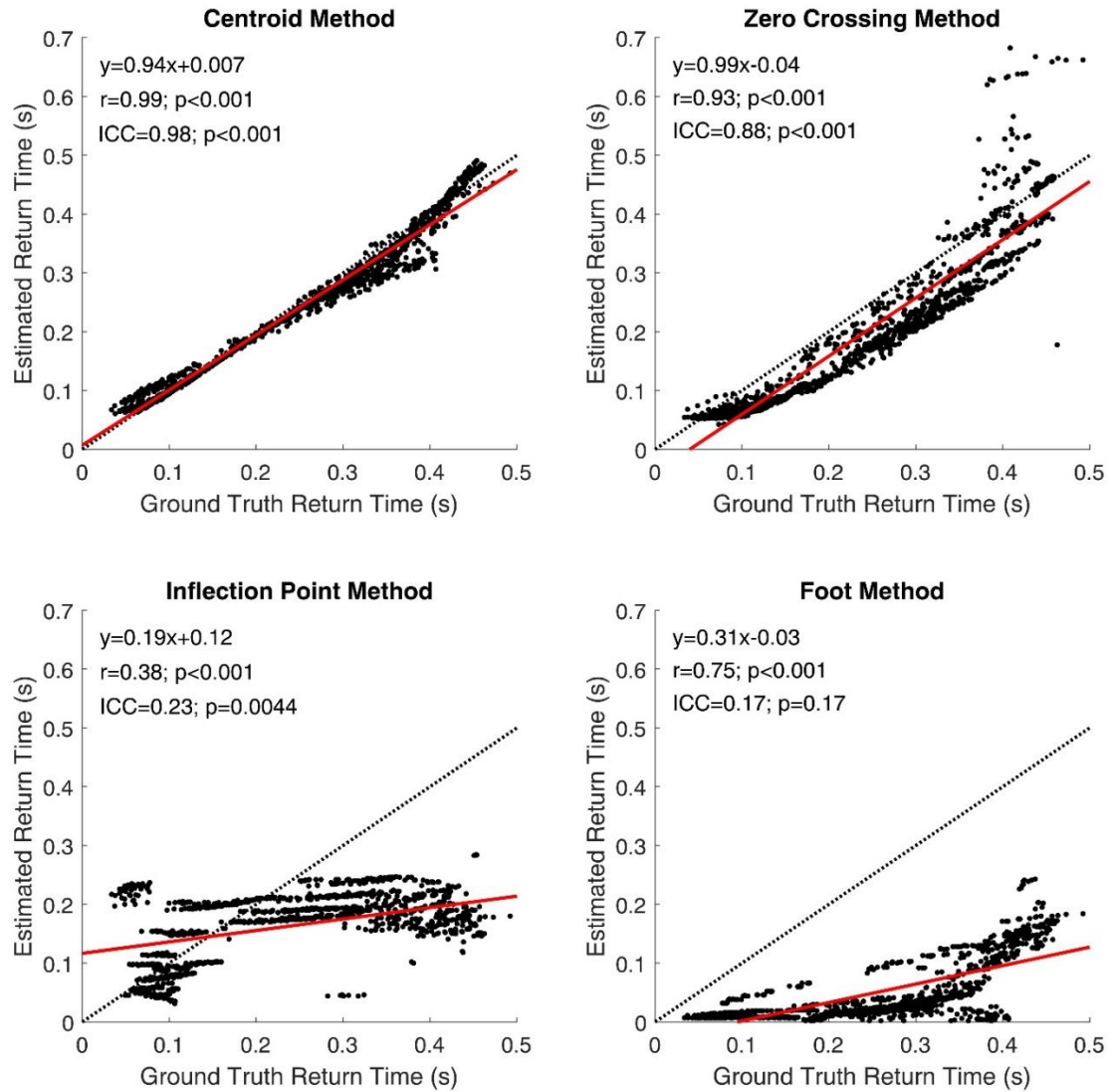


Figure 5.6: VIRTUAL COHORT ANALYSIS (LINEAR REGRESSION). Linear regression analysis of the various methods with the ground truth return time using data from the virtual cohort (black dots). r = correlation coefficient, ICC = intraclass correlation coefficient. The dotted line represents the line of identity ($y = x$) while the solid red line indicates the linear regression of the data.

5.3 Results

5.3.1 Virtual Cohort

Data from the virtual cohort showed that the centroid method was closest to the identity line ($y = x$; Figure 5.6) and had the highest correlation and degree of agreement with GTRT [$r = 0.98$ and $ICC = 0.98$ (both $p < 0.001$)]. The zero crossing method also had good agreement with GTRT

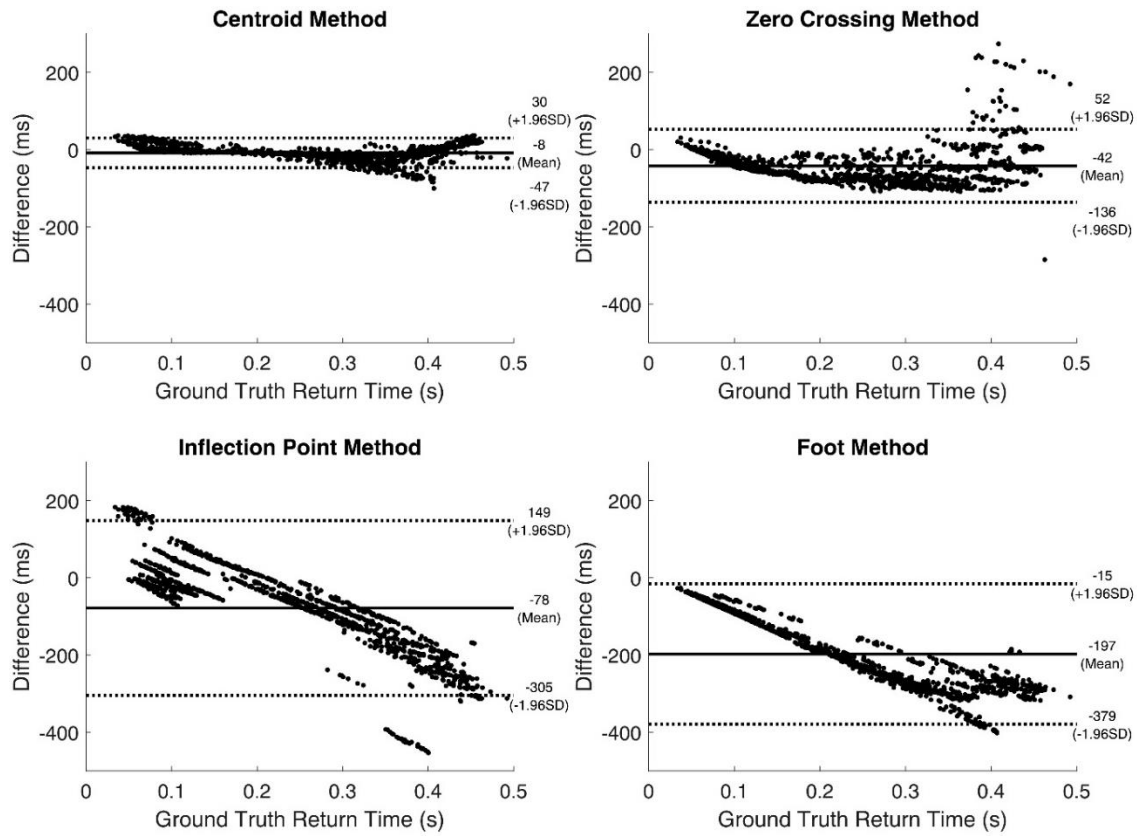


Figure 5.7: VIRTUAL COHORT ANALYSIS (BLAND-ALTMANN). Bland-Altman analysis of the return time methods indicating the difference between the return time and ground truth return time using data from the virtual cohort. The mean (solid line) $\pm 1.96 \times \text{SD}$ (dotted lines) of the differences are shown.

but (mostly) underestimated return time [$r = 0.93$ and $\text{ICC} = 0.88$ (both $p < 0.001$)]; it also had increased variability at larger GTRT values. Moreover, it performed better than the inflection point [$r = 0.38$ ($p < 0.001$) and $\text{ICC} = 0.23$ ($p = 0.0044$)] and foot methods [$r = 0.75$ ($p < 0.001$) and $\text{ICC} = 0.17$ ($p = 0.17$)]. Furthermore, the Bland-Altman plots, with GTRT as the reference, showed that the centroid method had the lowest bias (highest accuracy) and tightest limits of agreement (highest precision) compared to the zero crossing, inflection point, and foot methods; mean differences (limits of agreement) were -8 ms ($-47, 30$), -42 ms ($-136, 52$), -78 ms ($-305, 149$), and -197 ms ($-379, -15$), respectively (Figure 5.7).

Table 5.1: ANIMAL CHARACTERISTICS. Characteristics of sheep included in the animal experiment (n = 10). Data is presented as mean $\pm$ SD.

Characteristic	Units	Value
Weight	kg	35.3 $\pm$ 2.8
Heart Rate	beats/min	107 $\pm$ 12
Systolic Blood Pressure	mmHg	78 $\pm$ 9
Diastolic Blood Pressure	mmHg	63 $\pm$ 11
Cardiac Output	L/min	2.67 $\pm$ 0.86

5.3.2 Animal Experiments

Table 5.1 presents the characteristics of the sheep included in this study. The break points for the centroid, zero crossing, inflection point, and foot methods were at a BLIP Index of 0.83, 1.35, 1.09, and 0.78, respectively (Figure 5.8). The zero crossing and inflection methods showed significant correlation with BLIP Index < 1 [i.e., systolic arrival, $r = 0.95$ ($p < 0.001$) and $r = 0.9$ ($p = 0.0031$), respectively] but no significant correlation for BLIP Index > 1 [i.e., diastolic arrival, $r = -0.43$ ($p = 0.28$) and $r = -0.11$ ($p = 0.49$), respectively]. The correlation for the foot method did not reach significance during systole or diastole [$r = 0.83$ ($p = 0.064$) and $r = 0.13$ ($p = 0.34$), respectively]. Only the centroid method showed strong correlation with BLIP index during both systole ($r = 0.96$, $p = 0.016$) and diastole ($r = 0.84$, $p = 0.014$).

5.4 Discussion

In this study, a novel centroid method for estimating the return time of backward waves is proposed that uniquely takes the composite nature of the backward pressure waveform into account. Furthermore, a GTRT to rigorously test the accuracy of various methods of estimating return time is described. Using the GTRT, results from the virtual cohort showed that the

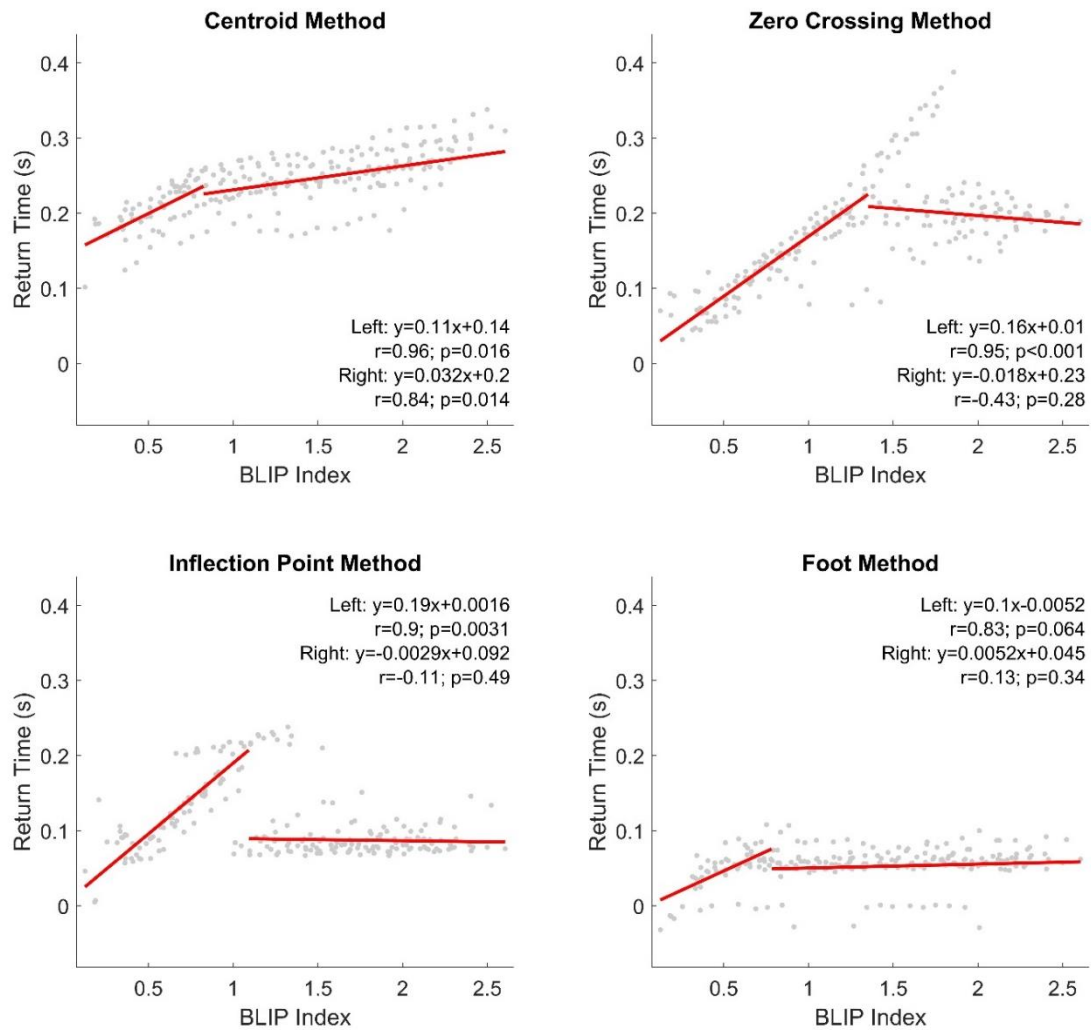


Figure 5.8: ANIMAL EXPERIMENT ANALYSIS. Segmented regression analysis of the return time methods with balloon-induced pulse (BLIP) Index using data from the animal experiments. The breakpoint divides the data into 'Left' and 'Right' datasets, whose regression equation and corresponding statistics are shown.

centroid method provided the most accurate and precise estimates of return time across a wide range of conditions compared to all other methods. Furthermore, sheep experiments showed that only the centroid method was sensitive to changes in both diastolic and systolic return times, with the other methods being sensitive only to systolic return times. The drawbacks of other methods are now discussed that explain their lower performance in this study and how the centroid method addresses them to provide more accurate and robust results.

The inflection point method is based on locating a fiducial point on the central pressure waveform that marks the point when backward waves begin to exert an influence on the pressure waveform. There are several limitations of this method that should be considered. First, the inflection point is found using the second derivative of the pressure waveform (239), making it highly susceptible to noise; furthermore, central pressure waveforms may not always have a distinct inflection point (193). Second, in reality many backward waves arise from distributed reflection and return throughout the cardiac cycle; hence, finding a single point marking their return runs counter to their physiological behaviour. Third, it has been shown that the inflection point is not a true marker of the return of backward waves because it is also influenced by factors such as ventricular outflow patterns (111), ejection duration (243), and heart rate (290). Finally, the inflection point is always found in systole throughout life (12), which is inconsistent with the expected diastolic-to-systolic shift in return time with ageing (45, 181, 190).

These limitations explain why the inflection point method did not estimate return times beyond 0.3 s (which was the systolic duration) in the virtual cohort and exhibited a low correlation with GTRT. They also explain the results of the sheep experiments, where the breakpoint was found at a BLIP Index of 1.03 (which corresponded to the boundary between systole and diastole). With a systolic arrival of BLIP (BLIP Index < 1), the BLIP created a prominent inflection point, which the inflection point method “locked onto”. It thus gave a good correlation in this region and explains the high slope of the linear regression. With a diastolic arrival of BLIP (BLIP Index > 1), it just detected the natural inflection point of the pressure waveform during systole, which did not change with the timing of BLIP; thus, the inflection point method provided no correlation during diastole. The limitations of the inflection point method have led researchers to conclude that wave reflection metrics cannot be reliably obtained from the pressure waveform alone

(111, 237); they suggest that wave separation using both pressure and flow waveforms should be used instead (181, 283, 286).

Wave separation decomposes the pressure waveform into forward (travelling away from the heart) and backward (travelling towards the heart) pressure waveforms. The backward pressure waveform is produced entirely by wave reflection and is thus ideal for obtaining insights into the return time of backward waves. The foot method uses wave separation and estimates return time using the foot of the forward and backward pressure waveforms. This method shares some limitations with the inflection point method: 1) choosing a single point on the backward pressure waveform ignores its composite nature, and 2) the foot of the backward pressure waveform may not always be distinct, especially in case of noisy waveforms. The results of the virtual cohort suggest that an increase in GTRT did cause a slight increase in the timing of the foot of the backward pressure waveform, but not in a 1:1 manner (Figure 5.6), indicating the low accuracy of the foot method in estimating return time. The animal experiments showed that the foot method displayed marginal sensitivity to systolic arrival of BLIP, but it was insensitive to diastolic arrival. These findings are consistent with work by Torjesen et al., who showed that return times estimated by the foot method occur in systole over the entire adult age range (266).

The zero crossing method was introduced by Segers et al. and also uses wave separation (239). The results of the virtual cohort showed that this method provided good correlation with GTRT, although with some underestimation, but with variable error at large GTRT values. The animal experiments showed that, similar to the inflection point and foot methods, the zero crossing method was sensitive to changes in systolic arrival of BLIP, but not diastolic arrival. This was because it detected only the first zero crossing of the backward pressure waveform and was

therefore unaffected by backward waves that returned later. This method has only been applied in participants 35-55 years of age, and only systolic return times were found (239).

In contrast to existing methods, the centroid method proposed in this study accounts for the distributed nature of reflected waves and uses the entire backward pressure waveform rather than a single fiduciary point. Furthermore, since the centroid method accounts for the foot-to-foot area under the backward pressure waveform to determine its centroid, the exact location of the foot has little influence on the centroid, making it more robust than the foot method. This explains why it had a very high correlation with GTRT in the virtual cohort and was the only method that displayed good correlation with the BLIP timing across both systole and diastole in the animal experiments. The centroid method had a lower regression slope during systole compared to the inflection point and zero crossing methods. This is desirable in that the other methods “locked onto” the BLIP and were influenced entirely by the BLIP timing during systole, whereas the centroid return time was influenced by BLIP as well as other backward waves. These results indicate the greater robustness of the centroid method compared to other methods in representing bulk return time of reflected waves. The centroid method was also less sensitive to errors in the estimation of Z_c than the other methods. A 20% increase in Z_c caused a 7% decrease, 21% increase, and 11% increase in return time estimated by the centroid, zero crossing, and foot methods, respectively. There was no change in the return time estimated by the inflection point method with errors in Z_c because it does not require wave separation.

A major advance in this study was the description of a GTRT, which was obtained using linear wave tracking. This method has been previously used to explore the dynamics of wave propagation and reflection in the systemic arterial network (5, 275). The advantage of this approach is that it allows individual waves to be discretely tracked, which is necessary for

obtaining a GTRT. One limitation of GTRT is that it did not account for the dispersion of waves that occur in vivo. This non-linear effect has a smoothing effect on the waveforms, but accounting for this phenomenon would make it difficult to track discrete waves and therefore calculate a GTRT.

Given the low sensitivity of the inflection point method to changes in return time, it can be hypothesized that it is less sensitive to the reflection magnitude as well (100). A similar centroid method could also be used to quantify reflection magnitude more accurately. A study by Alastruey et al. defined a wave intensity reflection index as the ratio of the centroids of the backward and forward compression waves (4). However, Mynard et al. found that non-linear effects cause amplification or attenuation of wave intensity, leading to errors in indices of wave reflection, and potentially to values beyond the theoretical limits of -1 to +1 under some conditions (161). They also found that reflection magnitude obtained by the ratio of the amplitudes of the forward and backward pressure waveforms obtained by wave separation (the current gold standard) was more accurate and unaffected by non-linearity (161). However, the traditional approach for calculating reflection magnitude (as the ratio of the amplitudes of the backward and forward pressure waveforms) in theory suffers from the same drawback as the existing return time methods, in that differing reflection patterns could result in the same reflection magnitude and the distributed nature of wave reflection is not accounted for. Thus, future studies could investigate the ratio of the pressure-axis centroids of the backward pressure waveform and input pressure as an index of reflection magnitude. Finally, techniques that in some way quantify the combined impact of both reflection magnitude and timing would be desirable, such as the approach proposed by Chirinos and Sweitzer (46), where wasted ventricular effort due to wave reflection was quantified as the area under the pressure curve minus the area under $P_{f,in}$ (that is, the systolic pressure-area related to wave reflection).

In conclusion, this study has presented a novel centroid method for estimating the bulk return time of backward waves and have shown its greater accuracy, precision and robustness compared to current methods using virtual and animal experiments. This method is therefore likely to provide accurate insights into changes in wave reflection timing that occur in settings such as childhood growth, adult ageing, and disease conditions.

Chapter 6: Central arterial return time of reflected waves in children and adults

This chapter investigates the shift in return time of reflected waves with increasing age using the novel centroid method introduced in Chapter 5 compared to other commonly used methods: zero crossing, inflection point, and foot methods. It also sheds light onto the factors underlying the shift in return time.

6.1 Introduction

Multiple studies have proposed that reflected waves in the systemic arterial circulation return to the heart primarily during diastole in young adulthood, causing a pressure augmentation referred to as the 'diastolic hump' (45, 181, 190). These waves are thought to arrive earlier during systole with ageing, shifting the diastolic hump to systole and causing an augmentation of systolic blood pressure. Due to these qualitative changes in the central arterial pressure waveform, it is widely thought that the time taken for reflected waves to return to the left ventricle ('return time') shifts from diastole to systole with ageing (45, 181, 190). A systolic return time increases left ventricular (LV) afterload while a diastolic return time promotes coronary perfusion (45, 181, 190); hence, return time is thought to be an important marker of cardiac health. Return time has indeed been shown to decrease with ageing (12, 239, 266) using the inflection point, foot, and zero crossing methods. However, the inflection point method (12) and zero crossing method (239) indicate that return times are always in systole. Similarly, in a study by Torjesen et al (266), the upper limit of return time by the foot method (estimated as mean + 2 × SD) was 257 ms; although systolic duration was not reported for the foot method, this is below even the lower end of a normal systolic duration of 270 ms (13). These findings do not provide evidence against the notion of a diastolic-to-systolic shift in return time with ageing

because these methods determine only the start of the reflected wave, whereas there could still be a shift in the bulk of the waveform.

There is still a notable dissonance between the most widely accepted haemodynamic paradigm (involving a diastolic-to-systolic shift in return time with ageing) and the data obtained from cohort studies using previously available methods for the estimation of return time. Importantly, results from Chapter 5 indicated that existing methods were generally unable to detect diastolic return times due to intrinsic limitations. However, it was shown that a novel centroid method was able to detect both systolic and diastolic return times in animal experiments, and it provided more accurate estimates of return time than current methods when compared with a model-based ground truth. Thus, the centroid method is well suited to quantitatively investigate the prevailing haemodynamic paradigm over the human life course.

An important question within such an investigation relates to whether a dichotomous view of return time (diastolic return times being considered ‘good’ for the ventricle and systolic return times ‘bad’) is too simplistic. For example, in the context of the right heart and pulmonary arterial wave reflection, Fukumitsu et al. investigated patients with pulmonary hypertension and found that those with mid-systolic return times had significantly larger right ventricular hypertrophy than those with diastolic or late-systolic return times (73). This suggests that in addition to diastolic return times, late-systolic return times could also be benign. Thus, investigating the shift in return time from diastole to late-, mid- and early-systole with ageing might provide more granular information on cardiac health than just the diastolic-to-systolic shift.

The decrease in return time with increasing age is thought to occur due to vascular ageing, which involves “deterioration in vascular structure and function over time” (50). Associated stiffening of arteries causes the reflected waves to travel faster and return earlier (263). Thus, in addition to serving as an indicator of arterial contributions to ventricular afterload, return time is also likely to be an important marker of arterial health per se. In addition, there is evidence that the process of vascular ageing begins in childhood and is accelerated by cardiovascular risk factors such as obesity, diabetes, and hypertension (55, 106). Identifying the emergence of early vascular ageing in childhood may therefore aid in identifying individuals who require targeted preventive intervention. However, the inflection point, foot, and zero-crossing methods have only been applied in adults (>18 years). Establishing reference values of return time in a healthy population including both adults and children will not only provide important information about how return time changes with age, but also enable assessment of whether vascular ageing is normal or accelerated. While reference values for some methods over limited age ranges have been published (96, 239), those derived from the more accurate centroid method have not yet been established.

A decrease in return time with adult ageing is thought to occur because of the progressive increase in pulse wave velocity (PWV) of central arteries (263). In children, however, Hidvegi et al. found that return time measured by the Arteriograph device increased with childhood growth between the ages of 3 and 12 years, without corresponding changes in PWV (96). The increase in return time was instead related to the increase in height, with increasing wave transit distance increasing the return time. Thus, it is likely that two distinct periods—childhood growth and adult ageing—exhibit different trends in return time, with different mechanisms (somatic growth vs arterial stiffening) underlying the changes. However, the accuracy of return time from the Arteriograph device is uncertain given that questions that have been raised about its working

principle (267). Hence, questions remain regarding the degree to which return time changes during childhood and the associated mechanisms.

In this study, central pressure waveforms from cross-sectional studies covering almost the entire lifespan were analysed to characterise return times in both children and adults. Aim 1 of this study was to ascertain whether the centroid method showed evidence of a shift in return time from diastole to late-, mid- and early systole across the life course (compared with the zero crossing, inflection point, and foot methods). Aim 2 was to establish reference values for return time estimated by the centroid method for males and females, which are known to be different (138, 239). Aim 3 was to determine the relative influence of various factors such as age, sex, height, and PWV on return time during childhood growth and adult ageing.

6.2 Methods

6.2.1 Cohort Studies

This was a retrospective study of three datasets obtained from previously completed cross-sectional cohort studies, the details of which are provided below. All included studies involved measurement of carotid pressure waveforms of healthy participants collected over ~10 seconds via applanation tonometry, along with the following information: age, sex, height, and carotid-femoral PWV (cfPWV). cfPWV is considered the most reliable index of central arterial stiffness and provides the average PWV along the entire length of the aorta (277). Participants were aged between 4 and 92 years and there was an approximately equal distribution of participants across the entire age range, except between 4 and 18 years. Table 6.1 provides a brief overview of each dataset, with the subsequent sections describing each dataset in detail. All studies were approved by the relevant ethics committees, and participants provided written informed

Table 6.1: DATASET OVERVIEW. Overview of datasets from cohort studies included in this study

Dataset Name	Country	Subjects (n)	Age Range (Years)
Barwon Infant Study (BIS)	Australia	594	4-5
Anglo-Cardiff Collaborative Trial (ACCTIII)	United Kingdom	3743	18-92
Asklepios	Belgium	2404	35-55

consent for their participation and for their data to be used in future studies. Utilization and analysis of these datasets was also approved by the Ethics Committee of the Royal Children's Hospital, Victoria, Australia.

6.2.1.1 Barwon Infant Study (BIS)

The detailed description of this dataset is given in Vuillermin et al (272). The Barwon Infant Study (BIS) study enrolled infants at birth by recruiting pregnant women at <28 weeks of gestation from the Barwon region of south-west Victoria, Australia. When the infants reached 4 years of age, a SphygmoCor XCEL (AtCor Medical, Sydney, Australia) was used to simultaneously record the pressure waveforms of the common carotid (via a tonometer) and femoral artery (via a cuff). Wave transit time between the two locations was automatically determined by the device. The distance between the suprasternal notch and the carotid measurement site was subtracted from the distance between the suprasternal notch and the femoral measurement site, which was then divided by the wave transit time to obtain cfPWV.

6.2.1.2 Anglo-Cardiff Collaborative Trial (ACCTIII)

The detailed description of this dataset is given in McEniery et al (145). The Anglo-Cardiff Collaborative Trial (ACCTIII) study included healthy participants selected at random from local general practice lists and open-access data from Cardiovascular Risk Assessment Clinics across East Anglia and Wales. A high-fidelity tonometer (SPC-301, Millar Instruments, Houston, Texas) was used to obtain pressure waveforms from the common carotid artery via applanation. cfPWV

was measured using the same device by sequentially recording the pressure waveforms of the common carotid and femoral arteries. Wave transit time was calculated using a SphygmoCor device (Sphygmocor BPAS-1; PWV Medical, Sydney, Australia) by taking the R wave of a simultaneously recorded electrocardiogram (ECG) as a reference. Direct surface distance between the two locations was measured and divided by the wave transit time to determine cfPWV (289).

6.2.1.3 Asklepios

The detailed description of this dataset is given in Rietzschel et al. (226) and Segers et al (239). The Asklepios study recruited a representative cohort of healthy volunteers from local general practice lists across two communities in Belgium. Carotid arterial pressure waveforms were obtained by a high-fidelity tonometer (SPT-301, Millar Instruments, Houston, Texas). cfPWV was measured by sequentially recording the common carotid and femoral velocity waveforms using Doppler ultrasonography (VIVID 7; GE Vingmed Ultrasound, Horten, Norway). Wave transit time was calculated as the time difference between the visually identified upstroke of the velocity waveform at each location by taking the start of the QRS complex of the simultaneously recorded ECG as a reference. The distance between the suprasternal notch and the carotid measurement site was subtracted from the distance between the suprasternal notch and the femoral measurement site, which was then divided by the wave transit time to obtain cfPWV (239).

6.2.2 Data Processing

Carotid arterial pressure waveforms for each participant were averaged across multiple beats over ~10 seconds. If a participant had multiple tonometry recordings, an ensemble average was taken across all recordings. The pressure waveforms were not calibrated to the measured mean

and diastolic blood pressure of the brachial artery because return time is only affected by the shape of the waveform, not its absolute values. All waveforms were visually inspected for adequate quality; in particular, approximately 2% of waveforms without a distinct dicrotic notch or those of poor quality were excluded because their systolic duration could not be accurately determined. Systolic duration was taken as the time difference between the foot of ascending portion of the pressure waveform and its dicrotic notch, which were determined using methods described in Section 5.2.2.1.

Four methods of estimating return time—centroid, zero crossing, inflection point, and foot—were applied to each of the averaged pressure waveforms. The methodological details of each method are provided in Sections 5.2.2 (zero crossing, inflection point, and foot methods) and 5.2.3 (centroid method). The inflection point method required just the pressure waveform, while the other methods additionally required a flow waveform to enable wave separation (Section 5.2.1). While the Asklepios dataset measured flow waveforms via ultrasound, such data was not available for the ACCTIII and BIS datasets. Wave separation is commonly performed using a pressure waveform alone, by employing a synthesised (279) or representative (244) flow waveform. For consistency, in this study a representative flow waveform was used for all datasets (165). As shown in Figure 5.2, the foot of the flow waveform was first aligned with that of the pressure waveform, and then the flow waveform was scaled such that its minimum was aligned with the dicrotic notch of the pressure waveform (Figure 5.2). Mynard et al. found this method to be a suitable alternative to a measured flow waveform in children and adolescents (165), as well as in adults with a history of congenital heart disease (publication in preparation). Return times were divided by the corresponding systolic duration to generate a Return Time Index (RTI), where $RTI \geq 1$ and $RTI < 1$ indicate diastolic and systolic return times, respectively. Furthermore, late-, mid- and early-systolic return times were defined as $0.66 \leq RTI < 1$, $0.33 \leq RTI < 0.66$, and $0 \leq RTI < 0.33$, respectively (73).

6.2.3 Statistical Analysis

To investigate differences in return time across the available age range, the BIS, ACCTIII and Asklepios RTI from each method were pooled and then grouped by ages 4–5, 18–20, 20–30, 30–40, 40–50, 50–60, 60–70, 70–80, and 80–92 years with no overlapping datapoints among the groups. The first two groups were used to compare children (4–5 years) and young adults (18–20 years) and investigate changes in return time with childhood growth. The percentage of diastolic, and late-, mid-, and early-systolic return times in each age group were determined for each method. To investigate the physiological basis for an age-dependence of diastolic vs systolic return times by the centroid method, the height and cfPWV of participants with $RTI \geq 1$ and $RTI < 1$ were compared for each age group using a two-sample student t-test. A more granular comparison using late-, mid- and early-systolic return times was not possible due to inadequate sample sizes for each return time in most age groups. To ascertain whether there were significant differences in return time between successive age groups, one-way analysis of variance (ANOVA) with a Bonferroni correction for multiple comparisons was used to test differences among the groups. Reference values for return times via the centroid method were determined for males and females by performing linear quantile regression on the pooled ACCTIII and Asklepios return time data to obtain the 10th, 25th, 50th, 75th, and 90th percentile values for return time during adult ageing. Due to the lack of data between 5 and 18 years, the percentiles for the BIS dataset were presented separately to the quantile regression.

To investigate the physiological basis of differences in RTI between young children and young adults, univariate analysis was first performed to determine which variables (out of height, weight, heart rate, cfPWV) had a significant correlation with age. These variables, along with age, were included as independent variables in a stepwise linear regression model, with RTI data for childhood growth from children (4–5 years; BIS dataset) and young adults (18–20 years;

ACCTIII dataset) as the dependent variable. The coefficients for each independent variable (b_i), except sex and interaction terms, were standardized using Equation 6.1.

$$b_i = \frac{S_{X_i}}{S_Y} \quad (\text{Equation 6.1})$$

where S_Y is the standard deviation (SD) of RTI and S_{X_i} is the SD of the corresponding independent variable. The same analysis was used to determine the factors underlying changes in RTI with adult ageing by pooling the ACCTIII and Asklepios datasets (18-93 years). Participants in the 18-20 year range were used for both the childhood growth and adult ageing models

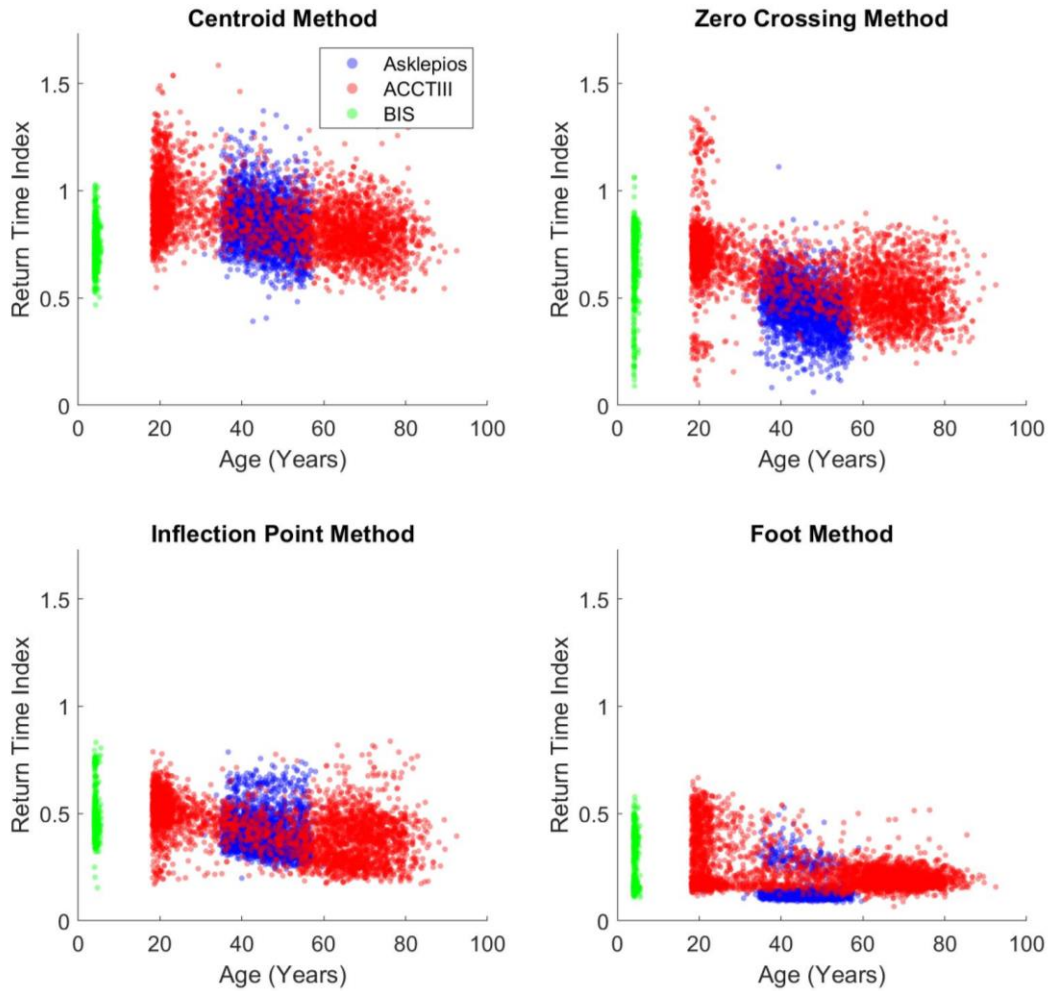


Figure 6.1: SCATTER PLOTS OF DATASETS. Scatter plots of the Return Time Index of the pooled BIS (green), ACCTIII (red), and Asklepios (blue) datasets estimated using the centroid, zero crossing, inflection point, and foot methods.

because of the lack of data between 5-18 years for the childhood growth group. Data are reported as mean $\pm$ SD and a value of $p < 0.05$ was considered significant.

6.3 Results

Figure 6.1 shows the RTI of all data when evaluated via the four methods. The inflection point and foot methods did not reveal any diastolic return times (i.e., with $RTI \geq 1$); although a small number of diastolic return times were found with the zero crossing method in young adults, these visually appeared to be outliers. Only the centroid method had a clear proportion of

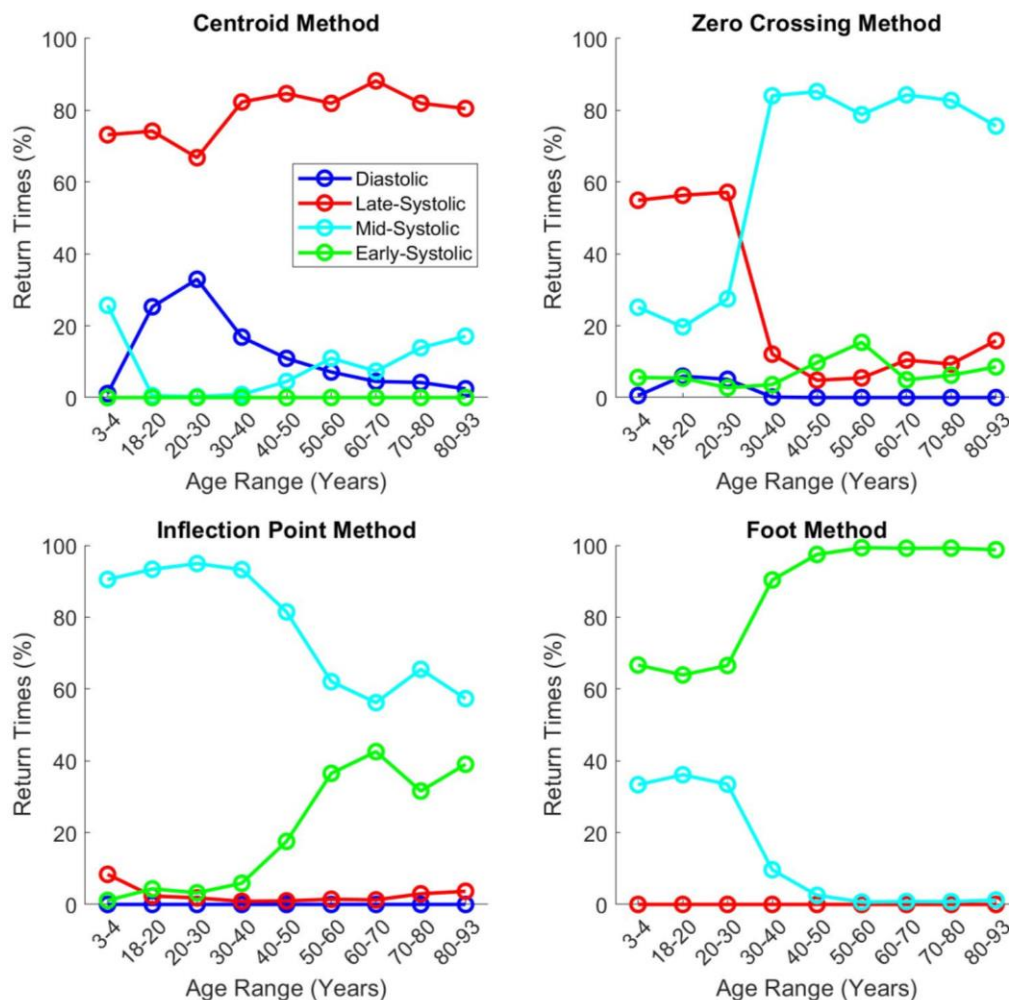


Figure 6.2: RETURN TIME RELATIVE TO CARDIAC CYCLE. The percentage of diastolic, and late-, mid- and early-systolic return times across each age group for each method.

diastolic return times during adulthood. However, almost all (98.8%) the young children (4-5 years) had systolic return times ($RTI < 1$).

These observations were further analysed in Figure 6.2, which shows the percentage of diastolic, and late-, mid- and early-systolic return times in each age group for all methods. Return time by the centroid method occurred mainly during late- and mid-systole in young children; it was substantially higher in young adults and reached a peak at 20-30 years, occurring during diastole in approximately one third of the population and late-systole in the remaining two thirds. Thereafter, return time decreased with increasing age, with the proportion of diastolic return time decreasing and mid-systolic return times increasing. The proportion of late-systolic return times was relatively constant across all age groups and there were no early-systolic return times.

Table 6.2: COMPARING DIASTOLIC AND SYSTOLIC RETURN TIMES. Two-sample t-test comparison of height, and carotid-femoral pulse wave velocity (cfPWV) of participants with return time index ($RTI \geq 1$ (diastolic return time) and $RTI < 1$ (systolic return time) using the centroid method in each group. The 4-5 and 80-93 age groups are not shown due to insufficient participants with $RTI \geq 1$ in these groups. The p-values refer to the height or cfPWV differences between $RTI < 1$ and $RTI \geq 1$.

Age Group (years)	RTI < 1 (%)	RTI ≥ 1 (%)	Height (cm)			cfPWV ($m \cdot s^{-1}$)		
			RTI < 1	RTI ≥ 1	p-value	RTI < 1	RTI ≥ 1	p-value
18-20	412 (75%)	139 (25%)	168 $\pm$ 9	176 $\pm$ 8	<0.001	6.3 $\pm$ 0.8	6.3 $\pm$ 0.9	0.870
20-30	514 (67%)	251 (33%)	170 $\pm$ 9	176 $\pm$ 9	<0.001	6.4 $\pm$ 0.1	6.3 $\pm$ 0.9	0.475
30-40	574 (83%)	117 (17%)	170 $\pm$ 10	176 $\pm$ 9	<0.001	6.4 $\pm$ 1.2	6.2 $\pm$ 1.2	0.065
40-50	1253 (89%)	154 (11%)	168 $\pm$ 9	176 $\pm$ 7	<0.001	6.7 $\pm$ 1.3	6.2 $\pm$ 1.1	<0.001
50-60	954 (93%)	74 (7%)	167 $\pm$ 9	173 $\pm$ 14	<0.001	7.6 $\pm$ 1.7	6.9 $\pm$ 1.4	<0.001
60-70	820 (95%)	39 (5%)	167 $\pm$ 9	173 $\pm$ 9	<0.001	8.6 $\pm$ 1.4	8.9 $\pm$ 1.2	0.340
70-80	611 (96%)	26 (4%)	166 $\pm$ 9	172 $\pm$ 8	0.005	9.4 $\pm$ 1.7	8.9 $\pm$ 1.8	0.137

The overall proportion of diastolic return times across all age groups in the zero crossing method was 91% less than that of the centroid method; furthermore, there was an increase in early- and mid-systolic return times with increasing age, along with a decrease in late-systolic return times. The inflection point and foot methods had no diastolic return times and a very small percentage of late-systolic return times (overall 2.1% and 0%, respectively); there was an increase in early-systolic return times for these methods with increasing age. Interestingly, the majority of return times from the centroid, inflection point, and foot methods were late-systolic, mid-systolic, and early-systolic, respectively across most age groups; whereas the zero crossing method had predominantly late-systolic return times until 30 years and mid-systolic return times thereafter.

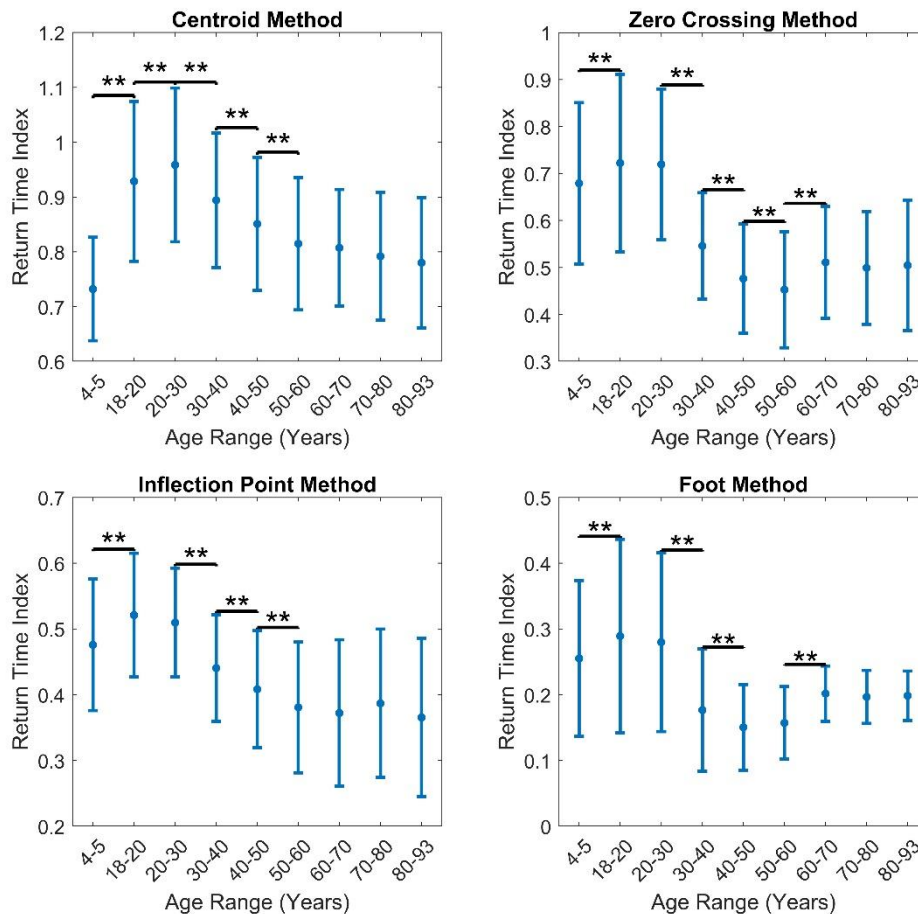


Figure 6.3: DIFFERENCES IN RETURN TIME INDEX ACROSS AGE GROUPS. Analysis of variance performed on RTI data across the different age groups for each method. ** = $p < 0.001$. Note that age groups have been plotted on an equidistant scale to aid in visualization. The error bars depict the standard deviation.

Table 6.2 shows the differences in height and cfPWV of participants with diastolic vs systolic return times using the centroid method in each age group. Height was greater in participants with diastolic than those with systolic return times across all age groups (all $p < 0.001$). On the other hand, cfPWV was lower in those with diastolic compared with systolic return times in the 40–50 and 50–60-year groups (both $p < 0.001$), although the same trend (approaching significance, $p = 0.065$) was also observed in the 30–40-year group. The 4–5 and 80–93-year groups had insufficient participants with diastolic return times to perform a statistical comparison.

Figure 6.3 shows comparisons of RTI in different age groups with ANOVA. All methods showed a significant increase in RTI with childhood growth (3–4 vs 18–20-year groups). With adult ageing, all methods showed significant decreases in RTI up to 60 years. Interestingly, the zero crossing and foot methods indicated an unexpected increase in RTI between the 5th and 6th decades, which was not found with the centroid method.

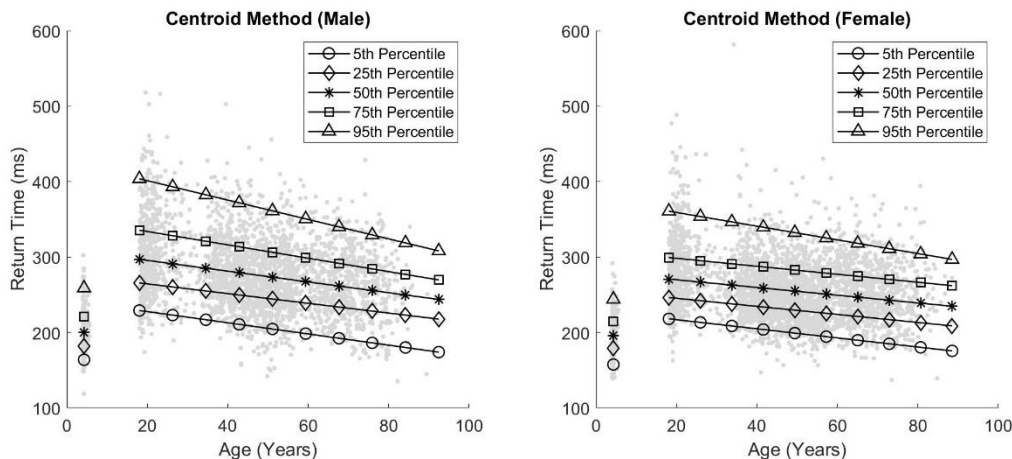


Figure 6.4: QUANTILE REGRESSION OF THE CENTROID METHOD. Quantile regression performed on the return time estimated by the centroid method showing the 5th, 25th, 50th, 75th, and 95th percentile values for males (left) and females (right) across the lifespan.

Table 6.3: REGRESSION EQUATIONS FOR REFERENCE VALUES. Regression equations of 5th, 25th, 50th, 75th, and 95th percentiles of reference values of return time estimated by the centroid method for males and females between 18 and 93 years of age. y = return time (ms) and x = age (years).

Percentile	Male	Female
95 th	$y = -1.28x + 427$	$y = -0.907x + 377$
75 th	$y = -0.887x + 352$	$y = -0.529x + 309$
50 th	$y = -0.715x + 310$	$y = -0.512x + 280$
25 th	$y = -0.645x + 277$	$y = -0.534x + 256$
5 th	$y = -0.742x + 243$	$y = -0.604x + 299$

Figure 6.4 shows results of the quantile regression (5th, 25th, 50th, 75th, and 95th percentiles) for return time estimated by the centroid method for male and female adults (18-93 years) in the ACCTIII and Asklepios datasets, along with separate percentile data for children (4-5 years) in the BIS dataset (also separated by sex). Table 6.3 displays the regression equations for each percentile for male and female adults.

Table 6.4 shows the results of the univariate analysis with height, cfPWV, heart rate, and weight as the independent variables and age as the dependent variable. Only height and cfPWV had significant correlations with age. Thus, these were used as independent variables in the stepwise regression models (along with age and sex).

Table 6.4: UNIVARIATE CORRELATES WITH AGE. Univariate analysis to determine variables with a significant correlation with age.

Variable	Correlation Coefficient	p-value
Height	-0.201	<0.001
cfPWV	0.595	<0.001
Heart Rate	-0.002	0.862
Weight	0.012	0.345

Stepwise regression results for the correlates of RTI via the centroid method during childhood growth and adult ageing are shown in Table 6.5. When considering the childhood and young adult groups (here termed ‘childhood growth’), height and sex were significantly associated with RTI, with height having the largest effect; cfPWV had no effect on RTI but the effect of age remained significant. There was also a small interaction term involving female sex and height. During adult ageing, height, cfPWV, and sex were significantly associated with RTI, with cfPWV having the largest effect. RTI was not directly associated with age in the multivariable model; however, there were significant but very small age-cfPWV, age-height, and cfPWV-sex (female) interaction terms. It is interesting to note that there was a positive association of female sex with higher RTI during childhood growth, but a negative association during adulthood.

6.4 Discussion

This study demonstrates that return time of reflected waves as assessed by the centroid method was higher among young adults compared to young children and decreased with increasing adult age. The proportion of diastolic return times also followed the same pattern, and they were more likely in taller individuals, and in those with lower cfPWV during mid-life. The observed differences in return time with age were primarily explained by height differences

Table 6.5: STEPWISE REGRESSION CORRELATES WITH RETURN TIME. Stepwise regression results of the correlates of return time index during childhood growth and adult ageing. Coefficients are standardized except for sex (categorical variable) or interaction terms, as indicated with †. cfPWV = carotid-femoral pulse wave velocity.

Correlate of RTI	Childhood Growth (4-20 years)		Adult Ageing (18-93 years)	
	Coefficient	p-value	Coefficient	p-value
Age (years)	0.35	0.008	0.10	0.64
Height (cm)	0.40	0.001	0.24	<0.001
cfPWV ($\text{m}\cdot\text{s}^{-1}$)	-	-	-0.43	<0.001
Sex (Female)	0.090 [†]	0.009	-0.11 [†]	<0.001
Height:Sex (Female)	$-9.8\times 10^{-4\ddagger}$	<0.001	-	-
Age:Height	-	-	$-3.0\times 10^{-5\ddagger}$	0.001
Age:cfPWV	-	-	$3.2\times 10^{-4\ddagger}$	<0.001
cfPWV:Sex (Female)	-	-	$5.1\times 10^{-3\ddagger}$	0.006
Overall R ²	0.445	<0.001	0.308	<0.001

when comparing children and young adults, whereas cfPWV had the largest effect during adult ageing.

The well-established paradigm of a diastolic-to-systolic shift in return time with ageing is thought to explain the physiological changes in the central pressure waveform observed with ageing (45, 181, 190). While even the highest proportion of diastolic return times with the centroid method was only 33% in the 20-30 year group in this study, late-systolic return times remained relatively constant with increasing age and formed the largest proportion across all age groups (mean: $80 \pm 7\%$). However, there was a decrease in diastolic return times and an increase in mid-systolic return times with age. Importantly, diastolic return times were found at all age groups, including the 80-93 year group. These findings suggest that two important modifications to the diastolic-to-systolic shift paradigm should be considered. First, return times span a range of values at all

ages and diastolic return times are not only found in young adults and systolic return times only in older adults. Second, return times in young adults are predominantly in the late-systolic to diastolic range; return times decrease with age and cause a shift in return times primarily towards the late-to-mid-systolic range. This also helps explain the relatively constant proportion of late-systolic return times across all age groups.

The cardioprotective and cardiopathic effects of diastolic and systolic return times, respectively, have been theorized; systolic return times are thought to increase left ventricular afterload and thus put additional stress on the heart (45, 181, 190). However, it is important to distinguish between late-, mid-, and early-systolic return times. Chirinos et al. found that peak myocardial stress occurred only in early-systole and that return time (estimated by the inflection point method) was not predictive of peak stress (44). They also found evidence of a mid-systolic shift where myocardial stress was lower in late-systole compared to early-systole for a given pressure due to the increasing wall thickness that occurs with contraction. This suggests that peak myocardial stress may not be impacted by wave reflection, which exerts pressure effects on the ventricle primarily during the later part of systole. Their results also suggest that only an early-systolic return time would affect peak myocardial stress, which is of interest because the present study found no early-systolic return times in any age group of healthy participants using the centroid method.

Although a mid-systolic return time may not affect peak myocardial stress, this is likely to have an impact on overall load faced by the ventricle (and hence its energy consumption). Gillebert et al. showed that a mid-to-late-systolic load caused diastolic dysfunction and was associated with left ventricular hypertrophy (81). Furthermore, Fukumitsu et al. found increased right ventricular hypertrophy among patients with mid-systolic return times in the pulmonary

network compared to those with diastolic or late-systolic return times (73). Thus, future studies should investigate the relationship between return time in the systemic network (diastolic and late-, mid, and early-systolic) and other metrics of cardiovascular health such as blood pressure, ejection fraction, etc, to better understand the influence of return time on the cardiovascular system.

Height has been shown to have an important influence on cardiovascular health, with shorter height being associated with higher blood pressure (29, 52, 62, 105, 121, 126) and higher cardiovascular risk (93, 109, 143, 295). Smulyan et al. suggested that shorter height necessarily implies a shorter path length and thus earlier return time and increased systolic pressure (250); this increases left ventricular afterload that increases cardiovascular risk. While Smulyan et al. did find a higher return time in taller individuals, all return times were during systole for that study (which employed the inflection point method); thus, this does not explain the increase in blood pressure in the expected sense (as return time goes from diastole to systole with ageing). The findings of the present study shed more light on these associations and show that a shorter height tends to promote earlier return times by the centroid method and diastolic return times are more common in taller individuals. However, as discussed above, an early-to-mid-systolic return time is likely to have a greater influence on systolic pressure than a late-systolic one. Thus, more work is required to investigate the relationship between height and more granular return times (diastolic, and late-, mid-, and early-systolic), in addition to the influence of these return times on systolic blood pressure and ventricular loading sequence.

The influence of height on return time also helps explain the haemodynamics observed in children. During childhood growth, cfPWV is relatively constant (or increasing only to a minor extent) while height is increasing substantially, thus leading to increasing return time (96).

Indeed, height was found to be the dominant factor associated with the increase in return time from early childhood (4-5 years) to young adulthood (18-20 years). Interestingly, young children had predominantly mid-to-late-systolic return times, similar to older adults. This is in line with previous studies showing similar pressure waveforms in children and elderly patients since similar return times can be expected to have similar effects on pressure waveforms (79, 246). The current study also suggests that lower return times among children is primarily due to their smaller height but among adults due to increased cfPWV with ageing, as previously postulated (181). It is worth noting that there can also be reduction in height with adult ageing, along with an increase in vessel length due to increased tortuosity (278); however, the increase in vessel length with adult ageing might not be to the same extent as that seen with childhood growth. The relative effects of these opposing factors on return time during adult ageing should be investigated in future studies.

There are certain limitations of this study that should be considered. First, all datasets were cross-sectional in nature; stronger conclusions could be derived from longitudinal datasets. Nevertheless, this study lays important groundwork regarding the changes in return time with ageing and suggests the mechanisms responsible for these changes, which can inform future studies. Second, there were no participants between 5 and 18 years of age and there was missing cfPWV data in the BIS dataset (17%), which could affect the regression results during childhood growth. Regardless, the lack of a relationship between cfPWV and return time during childhood growth, but a strong relationship between return time and height found in this study has been confirmed in previous studies (96). The reason why female sex was associated with a higher RTI than male sex during childhood growth but a lower RTI during adult ageing is hard to explain given that most studies found lower return times for women across both childhood growth (96) and adult ageing (154, 239).

In conclusion, the paradigm of a diastolic-to-systolic shift in reflected wave return time with ageing has dominated for decades, despite the absence of any quantitative methods that clearly indicate diastolic return times in young adults. Although this has led to controversy in the field (12), this likely arose from a mismatch between what the prevailing paradigm envisaged (the 'main weight' of wave reflection occurring in diastole) versus what the available methods were quantifying (the early onset of the reflected wave). The present study employing the centroid method developed in Chapter 5 (which better represents the location of the 'main weight' of the reflected wave) uncovered evidence of a predominance of late-systolic and early diastolic return time in young adults, with lower return times evident in children and with adult ageing. Based on this evidence, a modification to the 'diastolic-to-systolic shift' paradigm is proposed, i.e., that return times shift from late-systole/diastole to mid-/late-systole with normal adult ageing. Return time potentially offers valuable insights into vascular health and its impact on ventricular afterload that are not captured by traditional metrics such as blood pressure and cfPWV. This potential should be explored in future studies that investigate return time by the centroid method as a marker of cardiovascular risk.

Chapter 7: Discussion

7.1 Overview

The broad aim of this thesis was to investigate the effect of wave reflection on haemodynamics in the microvasculature and central arteries. Towards this, Chapter 2 first described the theory underpinning wave reflection and introduced 1D models that are best suited to investigate the precise impact of wave reflection on proximal and distal haemodynamics. To investigate the effect of wave reflection on the microvasculature, Chapter 3 used transmission line theory and a fractal 1D model to show that decreased wave reflection at junctions within a conduit arterial network promotes pressure transmission but impedes hydraulic energy transmission to the microvasculature. It also provided strong basis for the contention that decreased arterial compliance is primarily responsible for the increase in both large artery *and* microvascular pulse pressure that occurs with ageing. To investigate the effect of wave reflection on central arteries in young adults, an anatomically and physiologically representative model was required. Thus, Chapter 4 introduced a 1D model ('YoungAdult') of the systemic arterial network that better represented the physiology of a healthy young adult, compared with previous models, by optimizing the wave speed, arterial taper, and vascular bed compliance. Chapter 5 presented a novel centroid method for estimating the return time of reflected waves and used the YoungAdult model to show its superior accuracy and robustness compared to previous methods. Based on experimental studies employing an intra-aortic balloon pump to generate backward waves at different times in the cardiac cycle, it was also demonstrated that only the centroid method was sensitive to diastolic to systolic return times. Finally in Chapter 6, carotid pressure waveforms from several large datasets, covering most of the human lifespan were used to evaluate a long-standing but controversial paradigm regarding the age-dependent diastolic-to-systolic shift in return time. Based on results from the centroid method, an important

modification to this paradigm was proposed: return times are predominantly in the mid-to-late systolic range in young children, the late-systolic-to-diastolic range in young adults, and they decrease with progressing age towards the mid-to-late-systolic range in older adults.

7.2 Wave Reflection in Conduit Arteries

Whilst Chapter 3 clarified the roles that wave reflection and arterial compliance play in modulating microvascular pressure, exactly how wave reflection in conduit arteries changes with ageing, and consequently, how wave reflection modulates microvascular pressure with increasing age, requires further study. Mitchell et al. (153) proposed that due to the known difference in stiffness of elastic and muscular arteries (27, 129, 300), there was a major reflection site at the boundary between the two in youth; furthermore, they proposed that reflection at this site decreases as the elastic arteries get preferentially stiffer with ageing. However, whether such a reflection site exists at this elastic-muscular interface in youth remains unclear. Chapter 4 provided indirect evidence against the existence of such a reflection site, as it was found that the arterial tree needed to be exquisitely well-matched (including in the vicinity of elastic-muscular transition zones) for the YoungAdult model to reproduce an ascending aortic pressure waveform with features typically found in young adults. Papageorgiou et al. measured the area ratios of various junctions of the arterial tree (including both elastic and muscular arteries) and theorized minimal wave reflection throughout the tree (199). It should be noted that this conclusion was based on assuming a simple power relationship between area and wave speed to determine the reflection coefficient at a junction, which Chapter 4 has shown to be inaccurate. Moreover, Papageorgiou et al. did not specify the age associated with the area ratios measured, just that they were of healthy participants (199). Thus, future studies should precisely calculate the reflection coefficient at various junctions along the systemic arterial tree at various ages, with a focus on the elastic-muscular arterial transition zones. For simplicity, these could

be performed by a similar indirect area ratio method employed by Papageorgiou et al. (199) but using the improved relationship between area and wave speed introduced in Chapter 4. Another method could involve direct in vitro measurements similar to Greenwald et al (82). This would help elucidate the true impact of wave reflection on microvascular pressure with ageing.

7.3 Improvements in Modelling Approaches

Chapter 4 introduced key modifications to a 1D model that were necessary to achieve characteristic features of central and peripheral haemodynamics of a healthy young adult. This YoungAdult model provided insight into key design features that appear to be required to obtain these waveforms. In addition, the model will serve as a useful baseline to investigate haemodynamic changes that occur with ageing and/or disease. Furthermore, although the changes in systemic vascular resistance and in large artery compliance with ageing are well-established (146), those in vascular bed compliance (C_{bed}) are less known. This is because, as shown in Chapter 4, current methods of estimating arterial compliance are more sensitive to large artery compliance than C_{bed} , which has a profound impact on peripheral pressure and flow. In the context of model parameterisation, in Chapter 4 it was suggested that since the triphasic nature of peripheral velocity waveforms is primarily determined by C_{bed} , this value can be adjusted to match the velocity waveforms observed in peripheral arteries in vivo. Whether this model-based approach may be an effective means for characterising how C_{bed} requires further study, but if so, could be valuable to study changes in vascular bed compliance with age or in the context of microvascular disease.

7.4 Effective Reflection Distance

Chapter 5 presented a novel centroid method of estimating return time that better represented the return of ‘bulk’ reflected waves than previous methods. Instead of investigating the utility of return time itself, many previous studies instead used return time mainly to estimate an “effective” reflection distance (ERD), which is thought to be the primary reflection site in the arterial tree; from the perspective of the ascending aorta, this is usually considered to be located in the vicinity of the aortoiliac bifurcation (128). ERD is calculated by multiplying the carotid-femoral PWV (cfPWV) and $0.5 \times$ return time (158); a factor of 0.5 is included because return time is the time taken for the wave to travel from the heart to the reflection site and back, while ERD is the distance from the heart to this effective reflection site. Using the inflection point method to estimate return time, several studies found that ERD increased with ageing, suggesting that the primary reflection site was moving distally, thus causing an increase in the pressure of distal organs (154, 259). However, Phan et al. (207) measured return time using a single-tube model with a complex load (18, 33) and found a decrease in ERD with ageing, suggesting that reflected waves return earlier to the heart with ageing, in line with the diastolic-to-systolic shift in return time that seems to be apparent from qualitative assessment of waveform morphology. These differences in findings can likely be attributed to the difference in methods of estimating return time. The issues associated with both the inflection point method (38, 100, 111) and the single-tube model are well-established (166). Nevertheless, not only is there little evidence of clinical utility for ERD, but the physical meaning of ERD is complicated. Davies et al. found that ERD measured at two separate points along the aorta did not differ significantly, indicating the lack of a physically meaningful ERD (53). They reasoned that an apparent ERD is caused by repeated reflections along with wave attenuation that limit reflected waves from distal sites from being observed in proximal measurement sites—an effect termed “horizon effect” by Davies et al (53). For these reasons, it is suggested that quantifying return time is preferable to quantifying ERD in studies of wave reflection.

7.5 Horizon Effect

This existence of a horizon effect may seem to conflict with the conclusion in Chapter 4 that the major site of wave reflection in a healthy arterial tree was in the vicinity of vascular beds, as has been suggested by a number of physiological studies (185, 286). Importantly, van den Bos et al. found that vasodilators, which reduced wave reflection at vascular beds, caused prominent changes in ascending aortic pressure waveforms (269). While this seemingly contradicts the horizon effect, it is important to note that higher frequency waves undergo more attenuation than lower frequency ones. Furthermore, the horizon effect does not totally block backward waves since there is non-zero transmission of waves in the backward direction. Although not specifically investigated in this thesis, it is proposed that lower frequency reflected waves do indeed tend to reach the ascending aorta and affect local haemodynamics, whereas higher frequency waves (such as are apparent in wave intensity analysis) are strongly affected by the horizon effect. Indeed, inspection of the frequency-dependent 'global' reflection coefficient shows that lower frequencies are strongly reflected by the arterial network when measured at the ascending aorta, whereas very little reflection of higher frequencies is detectable (286).

7.6 Return Time in Pulmonary Circulation

While this thesis focused on the left ventricle and systemic arteries, return time also has relevance to the pulmonary arteries and right ventricle. Fukumitsu et al. showed that a proximal obstruction in the pulmonary arteries of patients with pulmonary hypertension caused an earlier return time compared to a distal obstruction (74); there were no differences in resistance, compliance, or characteristic impedance values between the two groups. Strikingly, in this context, return time was related to right ventricular mass, ejection fraction, and volume. This study employed a new heuristic method of estimating return time as the difference between

the time of the peak of the reflected pressure waveform and the onset of the pressure waveform. This method has not been widely used, and the accuracy and validity of this method has not been established, which should be considered when interpreting their results.

7.7 Return Time as an Indicator of Ventricular Load

Whether pulmonary arterial reflected waves return during diastole or early-, mid- or late-systole was also shown to be important in another study by Fukumitsu et al. Under similar resistance conditions of the pulmonary arterial tree, a mid-systolic return time at the right ventricle (RV) was associated with more severe RV hypertrophy than a late-systolic or diastolic return time (73). The findings by Fukumitsu et al. indicate that return time could serve as a risk factor for RV hypertrophy (73, 74). Furthermore, using an intra-aortic balloon pump catheter to generate backward waves at precise times in the cardiac cycle (similar to the experiments performed in Chapter 5 of this thesis), Gillebert et al. showed that a mid-to-late-systolic load caused diastolic dysfunction (81). Another study clarified further that a mid-systolic load was associated with diastolic dysfunction, whereas a late-systolic load was not (302). This is consistent with the findings of Chirinos et al. who showed that mid-systole was a critical time when there is a downward shift in the pressure-stress relationship of the LV, which protects cardiomyocytes from the effects of wave reflection that arrives towards the end of systole (44). This suggests that wave reflection returning during mid-systole (as occurs in older adults) could disrupt this protective shift and contribute to dysfunction. Chirinos et al. also found that late-systolic hypertension (defined as the ratio of late-systolic to mid- and early-systolic pressure-time integrals of the aortic pressure waveform) was predictive of heart failure independent of blood pressure and even after adjusting for traditional risk factors of heart failure (42). While the precise cause underlying late-systolic hypertension would have to be confirmed in future

studies, it can be hypothesized that late-systolic hypertension could be caused by mid-systolic return times, which could disrupt the protective shift and increase the risk of heart failure.

Based on the above discussion, return time appears to exert a strong influence on the heart and shows promise as a novel metric of ventricular afterload and as a risk factor for RV and LV hypertrophy, and heart failure. Towards this, additional data is required to establish return time as a predictor of cardiovascular events and mortality that is independent of traditional measures such as blood pressure (59, 211) and cfPWV (89, 104, 242). Furthermore, clinically-actionable threshold values for return time need to be established based on quantified risk for cardiac dysfunction. Another goal of future translation-focused research would be to investigate how pharmacological agents affect return time, and hence whether return time as a risk factor could be established as both important and modifiable. Towards this, one study has shown that return time at the RV increased after treatment for pulmonary arterial hypertension, which was also correlated with a decrease in RV hypertrophy (73). Another study found an increase in return time at the LV with anti-hypertensive treatment (91). Similar studies are required over large populations with diverse cardiovascular diseases to shed light on the effectiveness of return time as a measure of treatment effectiveness. In addition to these, randomised controlled trials (RCT) would be necessary to understand whether there is a clear benefit to modifying return time such as reducing RV/LV hypertrophy or reducing risk of heart failure. Finally, in addition to return time, reflection magnitude has been shown to predict all-cause mortality (40, 298). Reflection magnitude was also found to influence mid-to-late-systolic myocardial stress (43). Thus, reflection magnitude can be combined with return time to provide important information on cardiac health.

7.8 Clinical Adoption of Return Time

A number of key barriers exist to the widespread adoption of reflection magnitude and return time in the routine clinical setting, for example, as an adjunct to measurement of blood pressure. First, there is considerable heterogeneity in methodology used by studies to estimate both of these quantities, with known limitations of many of the methods, which reduces the confidence in applying these methods in clinical settings. Although there is consensus that reflection magnitude (obtained from wave separation) is the gold-standard, many studies continue to use quantities such as augmentation index to quantify reflection magnitude. However, the availability of pressure-only wave separation techniques (165, 279) now means that wave separation can be widely performed without the need for ultrasound or magnetic resonance imaging. Regarding return time, the limitations of the inflection point method are well-established (38, 94, 100, 177). Even though the single-tube method is implicitly considered by some to be a gold-standard method (207), it is now widely considered to be a poor representation of the arterial system (282, 287). Heuristic methods have also been introduced by Segers et al. (239) and Fukumitsu et al. (74); however, these do not account for the distributed nature of wave reflection in real arterial tree. Moreover, each method provides a different absolute value of return time, with no ground truth to assess the accuracy of these methods. Chapter 5 introduced a novel ground truth return time, which has enabled a direct comparison of the accuracy of different methods. This is a significant advance to previous studies and will inspire confidence among clinicians by ensuring the accuracy of a method, which can promote the adoption of measuring return time with a standardised technique. The results presented in this thesis provide a strong rationale for adopting the centroid method as the standard method for quantifying return time of reflected waves.

Another barrier to the widespread clinical adoption of wave reflection indices is the requirement of specialized equipment and user training to obtain the central pressure waveform, for example, using applanation tonometry and custom software to extract the return time from the waveform. Blood pressure is currently measured using automated oscillometric devices that require little input from clinicians. Similarly, a number of existing commercial arm cuff devices, such as the SphygmoCor XCEL PWA (AtCor Medical), Mobil-O-Graph (IEM), WatchBP (MicroLife) and BP+ (Uscom), measure the brachial pressure waveform via cuff volume plethysmography (in addition to a standard oscillometric blood pressure measurement). This is (or can be) converted to a central pressure waveform via a transfer function. Wave reflection indices are then automatically extracted from the central waveform via a pressure-only wave separation (279). It is worth noting that cuff volume plethysmography captures lesser high-frequency details of the pressure waveform compared to applanation tonometry. Owing to this, the centroid method is in fact well-suited to volume plethysmography because it uses the entire waveform to calculate return time and is therefore relatively independent of high-frequency components of the waveform, unlike current methods like the inflection point or foot methods. Thus, such devices could readily incorporate calculation of return time via the centroid method via a simple software upgrade, which would facilitate its widespread use in both research and clinical settings.

7.9 Conclusion

In conclusion, this thesis has contributed major insights into areas of controversy in the haemodynamics field regarding the physiology and quantification of systemic arterial wave reflection. These include insights into the effect of wave reflection on both central and peripheral haemodynamics, the structural components of the arterial network that give rise to wave reflection, and the impact of normal ageing on wave reflection. Taken together, this thesis

provides solid footing for future studies to further explore the potential clinical value of wave reflection indices to improve diagnosis and treatment of cardiovascular disease.

Appendices

Appendix A: Appendices for Chapter 3

Appendix A.1: Derivation of $T_p = 1 + \Gamma_p$

This section provides a brief derivation of the relationship between pressure transmission and reflection coefficients (a similar derivation was presented by Parker (202)). Consider two vessels (1 and 2) with different characteristic impedances (Z_1 and Z_2) connected at a junction (Figure A.1); the initial pressure (P) and flow (Q) in both vessels are P_1, Q_1 and P_2, Q_2 . As a wave propagates forward in vessel 1, it produces changes in pressure (dP_{1+}) and flow (dQ_{1+}) respectively. When the wave encounters the impedance mismatch at the junction, the reflected wave (dP_{1-}, dQ_{1-}) will propagate back into vessel 1 and the transmitted wave (dP_{2+}, dQ_{2+}) will propagate into vessel 2. The plus and minus signs denote forward and backward travelling waves, respectively.

Assuming conservation of mass ($Q_1 = Q_2$) and continuity of pressure ($P_1 = P_2$), Equations A.1 and A.2 are obtained.

$$P_1 + dP_{1+} + dP_{1-} = P_2 + dP_{2+} \quad (\text{Equation A.1})$$

$$Q_1 + dQ_{1+} + dQ_{1-} = Q_2 + dQ_{2+} \quad (\text{Equation A.2})$$

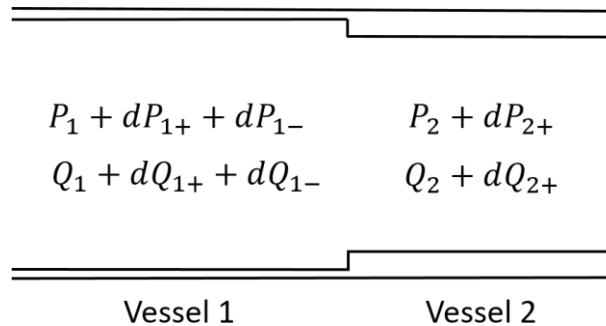


Figure A.1: EFFECT OF IMPEDANCE MISMATCH ON PRESSURE AND FLOW. Pressure and flow values proximal and distal to an impedance mismatch after wave reflection.

Substituting the water hammer equation ($dP_{\pm} = \pm Z_c dQ_{\pm}$) into Equation A.2 and simultaneously solving Equations A.1 and A.2 results in expressions for the reflection (Γ_p) and transmission coefficients (T_p) of pressure:

$$\Gamma_p = \frac{dP_{1-}}{dP_{1+}} = \frac{Z_2 - Z_1}{Z_2 + Z_1} \quad (\text{Equation A.3})$$

$$T_p = \frac{dP_{2+}}{dP_{1+}} = \frac{2Z_2}{Z_2 + Z_1} \quad (\text{Equation A.4})$$

From Equations A.3 and A.4, it can be shown that $T_p = 1 + \Gamma_p$.

Appendix A.2: Determining the Value of γ_c

The fractal exponent (ξ) and area asymmetry ratio (γ_A) are defined by Equations 3.1 and 3.2.

Equation 3.1 can also be written as Equation A.5 based on the area of a circle ($A = \pi r^2$). A_1 (Equation A.6) and A_2 (Equation A.7) can then be determined using prescribed values of A_0 , ξ , γ_A , and Equation 3.2.

$$A_0^{\xi/2} = A_1^{\xi/2} + A_2^{\xi/2} \quad (\text{Equation A.5})$$

$$A_1 = \gamma_A \cdot A_0 \left(1 + \gamma_A^{\xi/2}\right)^{-2/\xi} = \gamma_A A_0 \cdot \alpha \quad (\text{Equation A.6})$$

$$A_2 = A_0 \left(1 + \gamma_A^{\xi/2}\right)^{-2/\xi} = A_0 \cdot \alpha \quad (\text{Equation A.7})$$

where $\alpha = \left(1 + \gamma_A^{\xi/2}\right)^{-2/\xi}$. Similarly, using Equations 3.3 and 3.4, c_1 (Equation A.8) and c_2

(Equation A.9) can be determined in terms of c_0 , γ_A and γ_c for a desired value of R .

$$c_1 = \frac{c_0}{\gamma_c} \left[\frac{1 + \Gamma_p}{1 - \Gamma_p} \cdot \frac{\gamma_A \gamma_c + 1}{\left(1 + \gamma_A^{\xi/2}\right)^{2/\xi}} \right] \quad (\text{Equation A.8})$$

$$c_2 = c_0 \left[\frac{1 + \Gamma_p}{1 - \Gamma_p} \cdot \frac{\gamma_A \gamma_c + 1}{\left(1 + \gamma_A^{\xi/2}\right)^{2/\xi}} \right] \quad (\text{Equation A.9})$$

Here there are 3 unknowns— c_1 , c_2 , and γ_c —but only 2 equations (Equation A.8 and A.9). To determine the value of γ_c , a third equation is needed. Thus, a non-linear inverse relationship between area and wave speed is imposed (Equation A.10), which is reasonable given that larger arteries have a lower wave speed.

$$c = A^{-B} \quad (\text{Equation A.10})$$

where B is an additional unknown to be determined. Hence, there are 4 unknowns— c_1 , c_2 , γ_c , and B —and 4 equations (Equation A.8 and A.9, and re-writing Equation A.10 in terms of c_1 and c_2 yields 2 additional equations). Equation A.11 is obtained by substituting these equations into Equation 3.4.

$$\alpha^{(1+B)}(\gamma_A^{(1+B)} + 1) = \frac{1 - \Gamma_p}{1 + \Gamma_p} \quad (\text{Equation A.11})$$

For a given value of Γ_p , the value of B can be determined using the `fminsearch` function in MATLAB because an analytical solution for Equation A.11 in terms of B is not possible. Finally, substituting Equations A.6, A.7, A.8, and A.9 into Equation A.10 in terms of c_1 and c_2 , Equation A.12 is obtained.

$$\gamma_c = \gamma_A^B \quad (\text{Equation A.12})$$

In this manner, the value of γ_c can be set based on given values of γ_A , ξ , and R .

Appendix A.3: Elastance Heart Model

A left-heart model was used in the simulations, as shown in Figure A.2; it comprised the left atrium and ventricle, mitral and aortic valves, a pulmonary venous resistance ($R_{PV} = 0.05 \text{ mmHg}\cdot\text{s}\cdot\text{mL}^{-1}$), and a constant pulmonary venous pressure ($P_{PV} = 10.8 \text{ mmHg}$). The left atrium and ventricle were modelled as time varying elastance chambers (E_{LA} and E_{LV} , respectively) with source resistance (R_{LA} and R_{LV} , respectively), as described by Mynard (162). Heart rate was set to 75 beats per minute.

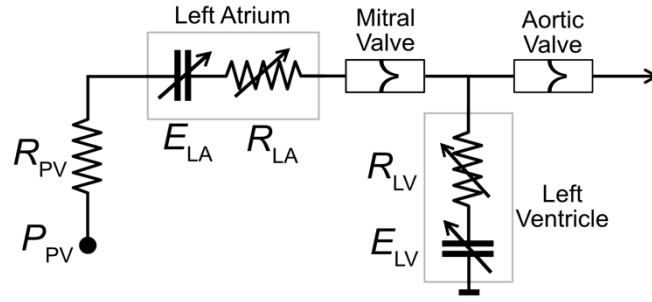


Figure A.2: SCHEMATIC DIAGRAM OF THE LEFT-HEART MODEL

E_{LA} and E_{LV} are defined by two Hill functions using the following parameters: E_{max} , E_{min} , τ_1 , τ_2 , m_1 , m_2 , $V_{p=0}$, and $V_{t=0}$; R_{LA} and R_{LV} are related to E_{LA} and E_{LV} , respectively, via K_s (see (162) and (164) for further details). The values of these parameters for this study are given in Table A.1.

Table A.1: PARAMETER VALUES FOR THE LEFT-HEART MODEL

Parameter	Symbol	Units	Left Atrium	Left Ventricle
Maximal elastance	E_{max}	mmHg·mL ⁻¹	0.13	2.8
Minimal elastance	E_{min}	mmHg·mL ⁻¹	.09	0.07
Systolic time constant	τ_1	s	0.042	0.215
Diastolic time constant	τ_2	s	0.138	0.362
Contraction rate constant	m_1	-	1.99	1.32
Relaxation rate constant	m_2	-	11.2	21.9
Residual volume	$V_{p=0}$	mL	3.0	10.0
Initial volume	$V_{t=0}$	mL	71.0	136.0
Source resistance coefficient	K_s	x 10 ⁻⁴ s·mL ⁻¹	2.5	5.0
Onset of contraction	-	s	0.65	0.0

The pressure-flow relationship of the mitral and aortic valves (with annulus area A_{ann}) was described by the Bernoulli equation, and the opening/closing dynamics were governed by the rate coefficients K_{vo} , K_{vc} (Table A.2) (164).

Table A.2: PARAMETER VALUES FOR THE MITRAL AND AORTIC VALVE MODELS

Parameter	Symbol	Units	Mitral Valve	Aortic Valve
Opening pressure coefficient	K_{vo}	-	0.02	0.02
Closure pressure coefficient	K_{vc}	-	0.04	0.02
Annular area	A_{ann}	cm ²	5.1	4.9

Appendix A.4: Proximal Stiffening

This appendix describes the process of how proximal stiffening was achieved while maintaining the prescribed reflection coefficients, taking the $R = -0.01$ fractal tree for illustration purposes. With the distal stiffening approach, the wave speed of the smallest vessel (c_{sv}) of the $\Gamma_p = -0.01$ fractal tree was $28.4 \text{ m}\cdot\text{s}^{-1}$ while that of $R = 0.04$ was $106.8 \text{ m}\cdot\text{s}^{-1}$. Thus, to make these two values equal, the c_{sv} of the $R = -0.01$ fractal tree was multiplied by a factor (f), where $f = \frac{106.8}{28.4} = 3.76$. In addition, to maintain the same R value throughout the fractal tree, the wave speed of every vessel was multiplied by this same factor, since the factors cancel out (Equation A.13).

$$R = \frac{\frac{A_0}{fc_0} - \frac{A_1}{fc_1} - \frac{A_2}{fc_2}}{\frac{A_0}{fc_0} + \frac{A_1}{fc_1} + \frac{A_2}{fc_2}} = \frac{\frac{A_0}{c_0} - \frac{A_1}{c_1} - \frac{A_2}{c_2}}{\frac{A_0}{c_0} + \frac{A_1}{c_1} + \frac{A_2}{c_2}} \quad (\text{Equation A.13})$$

The same process was applied for $R = 0, 0.01, 0.02$, and 0.03 fractal trees to achieve progressive proximal stiffening.

Appendix A.5: Model Equations

Blood flow in the fractal tree model was simulated by solving the one-dimensional form of the Navier-Stokes equations, which express conservation of mass and momentum (Equations A.14 and A.15).

$$\frac{\partial A(t)}{\partial t} + \frac{\partial A(t)u(t)}{\partial x} = 0 \quad (\text{Equation A.14})$$

$$\frac{\partial u(t)}{\partial t} + u(t) \frac{\partial u(t)}{\partial x} + \frac{1}{\rho} \frac{\partial p(t)}{\partial x} = \frac{-\xi \pi \mu u(t)}{\rho A(t)} \quad (\text{Equation A.15})$$

where $A(t)$ = lumen area, $u(t)$ = velocity, $p(t)$ = pressure, ρ = blood density (1.06 g/cm³), and μ = blood viscosity (0.025 poise); the viscous friction term (ξ) was estimated based on the approximate velocity profile method described by Bessems et al. (19). The relation between pressure and area was given by a non-linear viscoelastic wall law (Equation A.16) (175).

$$p = \frac{2\rho c_0^2}{b} \left[\left(\frac{A}{A_0} \right)^{b/2} - 1 \right] + \frac{\Gamma}{A\sqrt{A}} \frac{\partial A}{\partial t} + P_0 \quad (\text{Equation A.16})$$

where c_0 = reference wave speed, A_0 = reference lumen area, P_0 = reference pressure, Γ = coefficient of wall viscosity (with values given by $\Gamma = 100 + 200/D_0$, where D_0 is reference diameter), and b is given by Equation A.17.

$$b = \frac{2\rho c_0^2}{(P_0 - P_{collapse})} \quad (\text{Equation A.17})$$

where $P_{collapse}$ is a nominal collapse pressure (-10 mmHg). Continuity of total pressure was assumed at all vessel junctions, and these equations were solved using methods described previously (169, 175).

Appendix B: Appendices for Chapter 4

Appendix B.1: Improved Wave Speed Relationship

Wave speed values from the literature used to guide development of area- and transition distance index-dependent wave speed relation used in the YoungAdult model. Segment numbers refer to Figure 4.2, and area and transition distance index refer to model-based values. Average wave speeds are the final values used to develop the wave speed relation.

Table B.1: WAVE SPEED VALUES FROM LITERATURE. Reference wave speeds for various arteries from literature along with area and transition distance index values taken from the model.

Segment Number	Vessel Name	Area (cm ²)	Transition Distance Index	Wave Speed (reference) (cm·s ⁻¹)	Average Wave Speed (cm·s ⁻¹)
2	Ascending Aorta	5.94	0.022	357 (218) [§] 374(205) [§] 364 (225) [§] 370 (117) [¶]	366
6	Right Common Carotid Artery	0.40	0.447	458 (215) [#] 426 (108) [#] 485 (63) [#] 397 (149) [#] 424 (205) [§]	438
32	Aortic Arch II	4.69	0.154	390 (95) [¶] 420 (124) [¶]	405
38	Descending Thoracic Aorta I	4.00	0.240	362 (218) [§] 440 (205) [§] 410 (225) [§] 459 (117) [§] 430 (95) [¶] 490 (124) [¶]	432
46	Left Axillary Artery II	0.39	0.945	481 (21) [#]	481
48	Left Brachial Artery I	0.37	1	801 (21) [#]	801
54	Left Brachial Artery IV	0.14	2.261	904 (235) [#] 991 (56) [#] 1107 (21) [#]	1001
57	Left Radial Artery II	0.04	3.13	1069 (80) [#] 1007 [*]	1038
62	Descending Thoracic Aorta II	2.68	0.355	424 (83) [§] 467 (117) [§] 405 (117) [¶]	439

				360 (58) [¶]	
				446 (230) [¶]	
				570 (128) [†]	
				480 (117) [¶]	
				440 (95) [¶]	
				360 (58) [¶]	
				480 (58) [¶]	
				514 (230) [¶]	
73	Abdominal Aorta IV	1.40	0.744	470 (117) [¶]	476
				450 (95) [¶]	
				510 (124) [¶]	
				430 (58) [¶]	
76	Left Common Iliac Artery	1.31	1	880 (128) [†]	880
				926 (268) [#]	
80	Left Femoral Artery I	0.42	1.449	1029 (28) [#]	905
				709 (214) [#]	
				957 (56) [#]	
94	Left Popliteal Artery I	0.22	2.154	916 (215) [#]	916

[§]Calculated via reported distensibility measured using magnetic resonance imaging (MRI) and

$c = \sqrt{(1/\rho D)}$, where c is wave speed, ρ is density, and D is distensibility.

[¶]Calculated via the transit time between two sections a known distance apart using MRI.

[#]Calculated via reported distensibility measured using ultrasonography using $c = \sqrt{(1/\rho D)}$.

*Calculated using transit time from the validation portion of this study using applanation tonometry and electrocardiography. Arrival time to the distal end of the brachial and radial arteries was calculated as the time difference between the peak of the QRS complex of the electrocardiogram and upstroke of the pressure waveform obtained using applanation tonometry. The transit time was taken as the difference between the arrival times of the distal ends of the radial and brachial arteries. Finally, the radial wave speed was estimated by measuring the distance between the tonometry sites.

[†]Calculated via the transit time between two sections a known distance apart using simultaneous invasive micromanometer measurements.

Note 1: The vessel names and segment numbers correspond to the vessel names in Appendix B.4.

Appendix B.2: Model Formulation

Governing Equations

The equations governing haemodynamics in the YoungAdult model were the 1D Navier-Stokes equations derived from the laws of conservation of mass and momentum (245, 257).

$$\frac{\partial A}{\partial t} + \frac{\partial Au}{\partial x} = 0 \quad (\text{Equation B.1})$$

$$\frac{\partial u}{\partial t} + u \frac{\partial u}{\partial x} + \frac{1}{\rho} \frac{\partial P}{\partial x} = f \quad (\text{Equation B.2})$$

where, A is area, u is velocity, P is pressure, ρ is blood density (1.06 g/cm³), $f = -\xi\pi\mu u/A$, where ξ was calculated using the model described by Bessems, Rutten (19). Additionally, a wall law was implemented that governed the relationship between pressure and area

$$P - P_{ext} = \frac{2\rho c_0^2}{b} \left[\left(\frac{A}{A_0} \right)^{\frac{b}{2}} - 1 \right] + \frac{\Gamma}{A\sqrt{A}} \frac{\partial A}{\partial t} + P_0 \quad (\text{Equation B.3})$$

$$b = \frac{2\rho c_0^2}{P_0 - P_{collapse}} \quad (\text{Equation B.4})$$

$$\Gamma = \frac{b_1}{D} + b_0 \quad (\text{Equation B.5})$$

where P_{ext} is external pressure (assumed to be 0), $P_{collapse}$ is a nominal pressure at which $A \rightarrow 0$ (taken as -10 mmHg (127)), P_0 is a reference pressure (taken to be 80 mmHg), c_0 is the wave speed at P_0 , A_0 is the area at P_0 , Γ is a coefficient of wall viscosity, D is vessel diameter, $b_1 = 100 \text{ g}\cdot\text{cm}\cdot\text{s}^{-1}$, and $b_0 = 400 \text{ g}\cdot\text{s}^{-1}$ (175).

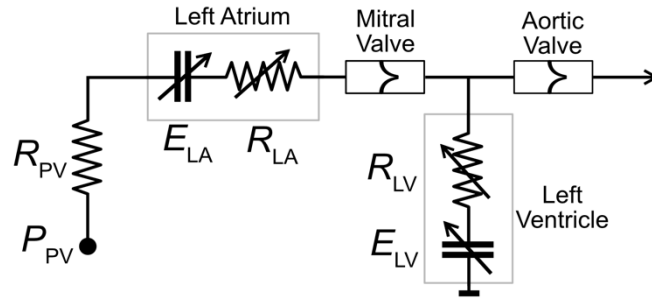


Figure B.1: SCHEMATIC DIAGRAM OF THE LEFT-HEART MODEL

Two-Chamber Elastance Heart Model

The two-chamber left-heart model shown in Figure B1 was used in all presented simulations; it comprised the left atrium and ventricle, mitral and aortic valves, a pulmonary venous resistance ($R_{PV} = 0.05 \text{ mmHg}\cdot\text{s}\cdot\text{mL}^{-1}$), and a constant pulmonary venous pressure ($P_{PV} = 10.8 \text{ mmHg}$). The left atrium and ventricle were modelled as time varying elastance chambers (E_{LA} and E_{LV} , respectively) with source resistance (R_{LA} and R_{LV} , respectively), as described in Mynard (162). Heart rate was set to 75 beats per minute. E_{LA} and E_{LV} are defined by two Hill functions using the following parameters: E_{max} , E_{min} , τ_1 , τ_2 , m_1 , m_2 , $V_{p=0}$, and $V_{t=0}$; R_{LA} and R_{LV} are related to E_{LA} and E_{LV} , respectively, via a source resistance coefficient K_s (see Mynard (162) for further

Table B.1: PARAMETER VALUES FOR THE LEFT-HEART MODEL

Parameter	Symbol	Units	Left Atrium	Left Ventricle
Maximal elastance	E_{max}	$\text{mmHg}\cdot\text{mL}^{-1}$	0.13	2.48
Minimal elastance	E_{min}	$\text{mmHg}\cdot\text{mL}^{-1}$	0.09	0.07
Systolic time constant	τ_1	s	0.053	0.269
Diastolic time constant	τ_2	s	0.172	0.452
Contraction rate constant	m_1	-	1.99	1.32
Relaxation rate constant	m_2	-	11.2	21.9
Residual volume	$V_{p=0}$	mL	3.0	10.0
Initial volume	$V_{t=0}$	mL	15.8	158.0
Source resistance coefficient	K_s	$\times 10^{-4} \text{ s}\cdot\text{mL}^{-1}$	2.5	5.0
Onset of contraction	-	s	0.8125	0.0

Table B.2: PARAMETER VALUES FOR THE MITRAL AND AORTIC VALVE MODELS

Parameter	Symbol	Units	Mitral Valve	Aortic Valve
Opening pressure coefficient	K_{vo}	-	0.02	0.02
Closure pressure coefficient	K_{vc}	-	0.04	0.02
Annular area	A_{ann}	cm ²	5.1	4.9

details). The values of these parameters for this study are given in Table B.1. The pressure-flow relationship of the mitral and aortic valves (with annulus area A_{ann}) was described by the Bernoulli equation, and the opening/closing dynamics were governed by the valve opening and valve closing rate coefficients K_{vo} , K_{vc} (Table B.2) (164).

Vascular Bed Model

All terminal 1D arteries were connected to 3-element windkessel compartments, which included 2 resistance elements—characteristic impedance of the terminal 1D artery (Z_{art}) and peripheral resistance of the vascular bed (R_{bed})—and 1 capacitor element (C_{bed}) that represents the compliance of the vascular bed (Figure B.2). The venous system is represented as a constant outlet pressure (P_{∞}) of 5 mmHg. Z_{art} was matched to the characteristic impedance of the 1D

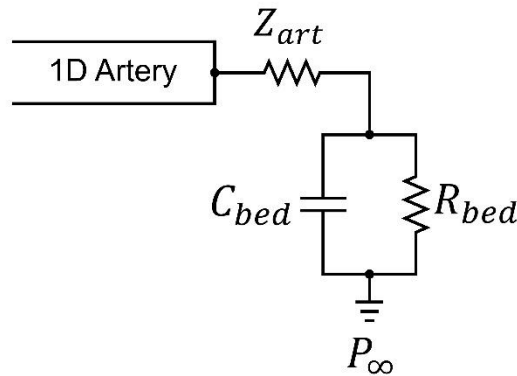


Figure B.2: WINDKESSEL MODEL. Schematic diagram of a 1D artery terminating in a vascular bed.

artery to prevent non-physiological reflection of higher frequency wave components (6, 256). For more detail, please refer to Mynard (162).

Appendix B.3: Windkessel Compliance

This appendix investigates whether the 2-element windkessel pulse pressure method (255) to estimate total arterial compliance (TAC_{wk}) was sensitive to both conduit arterial (C_{art}) and vascular bed compliance (C_{bed}). Towards this, two experiments were performed using the YoungAdult model: (Exp1) keeping C_{bed} of all beds constant and progressively decreasing C_{art} by multiplying the wave speed of every vessel by a factor (thus maintaining the junction matching); and (Exp2) keeping C_{art} constant and progressively increasing C_{bed} of all beds by the same factor. For each scenario, the total compliance of every vessel and vascular bed in the YoungAdult model (TAC_m) was calculated, which is precisely known, and compared it to the corresponding TAC_{wk} using the aortic pressure and flow waveforms produced by the model.

As seen in Figure B.3a, when only C_{art} was decreased but C_{bed} was kept constant (Exp1), the aortic pulse pressure increased with a decrease in C_{art} (and consequently, a decrease in TAC_m), with a range of 17–65 mmHg. There was also a good correlation between TAC_{wk} and TAC_m when only C_{art} was decreased but C_{bed} was kept constant; a 56% reduction in TAC_m corresponded to a 76% reduction in TAC_{wk} (Figure B.3b). On the other hand, while there was a significant change in the shape of the aortic pressure waveform with an increase in C_{bed} (and consequently, an increase in TAC_m) but constant C_{art} (Exp2), there was not much change in its pulse pressure, with a range of only 24–26 mmHg (Figure B.3c). There was also very little change in TAC_{wk} with increasing TAC_m ; even an increase in TAC_m by 153% corresponded to only a 1.6% increase in TAC_{wk} (Figure B.3d). These results suggest that while TAC_{wk} is sensitive to

C_{art} , it is insensitive to C_{bed} . This is because TAC_{wk} is entirely dependent on the aortic pulse pressure, which is affected mostly by C_{art} but not significantly by C_{bed} .

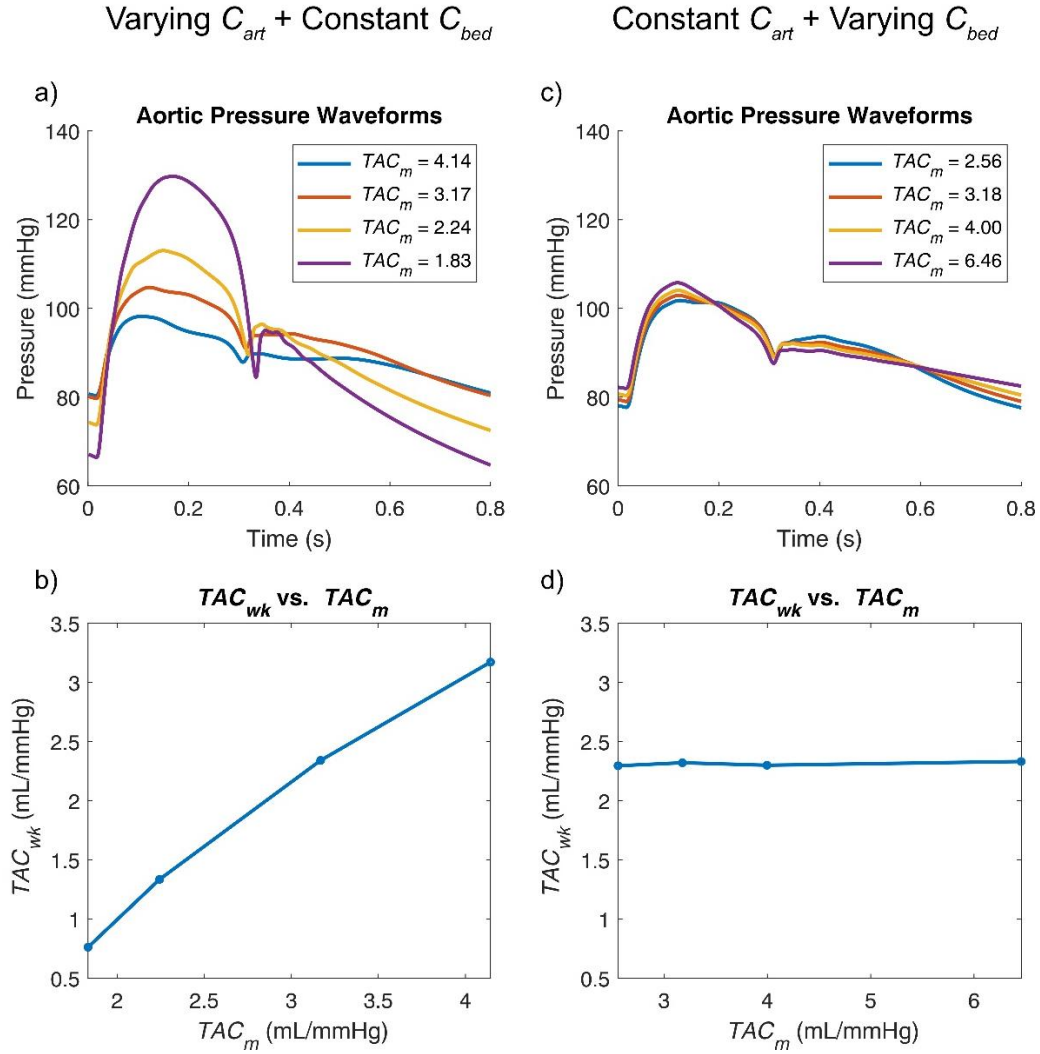


Figure B.3: VASCULAR BED COMPLIANCE VS ARTERIAL COMPLIANCE. a) Aortic pressure waveforms obtained by keeping vascular bed compliance (C_{bed}) constant but changing arterial compliance (C_{art}). b) Corresponding values of total arterial compliance obtained using the windkessel pulse pressure method (TAC_{wk}) vs. that of the YoungAdult model (TAC_m). c) Aortic pressure waveforms obtained by keeping C_{art} constant and changing C_{bed} . d) Corresponding values of TAC_{wk} vs. TAC_m .

Appendix B.4: Parameters and Connectivity of the One-Dimensional Segments

Note 1: In the connectivity table, items labelled with "VB" refer to specified vascular beds in Appendix B.5.

Note 2: Segments with [xN] in the segment name indicate that N identical vessels are included with the same parameters and connectivity.

	Segment Name	Segment Abbreviation	Length (cm)	Transition Distance Index	Inlet A_0 (cm ²)	Outlet A_0 (cm ²)	Inlet C_0 (cm·s ⁻¹)	Outlet C_0 (cm·s ⁻¹)	Inlet Segment	Outlet Segment/s
Systemic Arteries										
1	Left Ventricular Outflow Tract	LVot	1.0	0.000	5.940	5.940	369.0	369.0	Left Ventricle	AorticValve, AscAo
2	Ascending Aorta	AscAo	4.0	0.022	5.940	5.940	369.0	369.0	LVot	AoArc(I), BCA
3	Aortic Arch I	AoArc(I)	2.0	0.110	4.964	4.964	375.3	375.3	AscAo	AoArc(II), LCA
4	Brachiocephalic Artery	BCA	3.4	0.110	1.223	1.223	426.1	426.1	AscAo	RCA, RSub(I)
5	Right Subclavian Artery I	RSub(I)	3.4	0.435	0.888	0.888	438.9	438.9	BCA	RVert, RIntTh, RSub(II)
6	Right Common Carotid Artery	RCA	9.4	0.447	0.398	0.398	470.5	470.5	BCA	RICA, RECA(I)
7	Right Vertebral Artery	RVert	14.9	0.628	0.056	0.056	555.1	555.1	RSub(I)	Bas(II)
8	Right Internal Thoracic Artery	RIntTh	8.0	0.260	0.170	0.170	505.2	505.2	RSub(I)	VB:Chest
9	Right Subclavian Artery II	RSub(II)	2.5	0.611	0.711	0.711	448.2	448.2	RSub(I)	RThyrc, RAxil(I)

10	Right Thyrocervical Artery	RThyrc	5.0	0.741	0.253	0.253	490.9	490.9	RSub(II)	VB:RShoulder
11	Right Axillary Artery I	RAxil(I)	3.8	0.741	0.496	0.496	463.6	463.6	RSub(II)	RSubsc, RAxil(II)
12	Right Subscapular Artery etc [x4]	RSubsc	4.0	0.938	0.038	0.038	588.4	588.4	RAxil(I)	VB:RShoulder
13	Right Axillary Artery II	RAxil(II)	1.2	0.938	0.396	0.396	486.7	486.7	RAxil(I)	RHCA, RBrach(I)
14	Right Humeral Circumflex Artery [x2]	RHCA	4.8	1.000	0.170	0.170	898.4	898.4	RAxil(II)	VB:RUpArm
15	Right Brachial Artery I	RBrach(I)	5.1	1.000	0.377	0.377	865.6	865.6	RAxil(II)	RDpBrach, RBrach(II)
16	Right Deep Brachial Artery	RDpBrach	6.2	1.264	0.047	0.047	1014.3	1014.3	RBrach(I)	VB:RUpArm
17	Right Brachial Artery II	RBrach(II)	5.2	1.264	0.361	0.361	926.2	926.2	RBrach(I)	RUlnCol, RBrach(III)
18	Right Ulnar Collateral Artery [x2]	RUlnCol	15.0	1.534	0.079	0.079	992.2	992.2	RBrach(II)	VB:RUpArm
19	Right Brachial Artery III	RBrach(III)	17.2	1.534	0.219	0.219	948.3	948.3	RBrach(II)	RMuscBrach, RBrach(IV)
20	Right Muscular Brachial Artery [x2]	RMuscBrach	5.1	2.425	0.045	0.045	1018.0	1018.0	RBrach(III)	VB:RUpArm
21	Right Brachial Artery IV	RBrach(IV)	7.2	2.425	0.137	0.137	969.1	969.1	RBrach(III)	RRad, RUlnar(I)
22	Right Radial Artery I	RRad(I)	11.7	2.798	0.068	0.068	999.9	999.9	RBrach(IV)	VB:RLowArm
23	Right Radial Branch [x3]	RRadBranch	1.0	3.404	0.010	0.010	1089.4	1089.4	LRad(I)	VB:RLowArm
24	Right Radial Artery II	RRad(II)	11.7	3.404	0.041	0.041	1023.1	1023.1	LRad(I)	VB:RLowArm
25	Right Ulnar Artery I	RUlnar(I)	6.7	2.798	0.073	0.073	996.6	996.6	RBrach(IV)	RInter, RUlnar(II)

26	Right Interosseous Artery	RInter	7.9	3.145	0.028	0.028	1041.3	1041.3	RUlnar(I)	VB:RLowArm
27	Right Ulnar Artery II	RUlnar(II)	17.1	3.145	0.048	0.048	1015.9	1015.9	RUlnar(I)	VB:RLowArm
28	Right Internal Carotid Artery I	RICA(I)	8.9	0.947	0.280	0.280	504.8	504.8	RCA	RICASin, ROph
29	Right Internal Carotid Artery Branch	RICABranch	2.0	1.420	0.047	0.047	1015.2	1015.2	RICA(I)	VB:Face/Neck
30	Right Internal Carotid Artery II	RICA(II)	8.9	1.420	0.136	0.136	968.1	968.1	RICA(I)	VB:Face/Neck
31	Right External Carotid Artery	RECA	4.1	0.947	0.154	0.154	529.7	529.7	RCA	RECA(II), RSupThy
32	Aortic Arch II	AoArc(II)	3.9	0.154	4.694	4.694	377.3	377.3	AoArc(I)	DTA(I), LSub(I)
33	Left Common Carotid Artery	LCA	13.9	0.320	0.372	0.372	472.9	472.9	AoArc(I)	LICA, LECA(I)
34	Left Internal Carotid Artery I	LICA(I)	8.9	0.954	0.267	0.267	511.7	511.7	LCA	LIntCarSin, LOph
35	Left Internal Carotid Artery Branch	LICABranch	2.0	1.361	0.044	0.044	1017.6	1017.6	LICA(I)	VB:Face/Neck
36	Left Internal Carotid Artery II	LICA(II)	8.9	1.361	0.127	0.127	970.7	970.7	LICA(I)	VB:Face/Neck
37	Left External Carotid Artery	LECA	4.1	0.954	0.143	0.143	537.8	537.8	LCA	LExtCar(II), LSupThy
38	Descending Thoracic Aorta I	DTA(I)	5.2	0.240	3.995	3.995	383.1	383.1	AoArc(II)	Interc, DTA(II)
39	Left Subclavian Artery I	LSub(I)	3.4	0.500	0.884	0.884	439.3	439.3	AoArc(II)	LVert, LIntTh, LSub(II)
40	Left Vertebral Artery	LVert	14.8	0.653	0.063	0.063	549.8	549.8	LSub(I)	Bas(II)
41	Left Internal Thoracic Artery	LIntTh	8.0	0.315	0.162	0.162	507.5	507.5	LSub(I)	VB:Chest

42	Left Subclavian Artery II	LSub(II)	2.5	0.656	0.708	0.708	448.7	448.7	LSub(I)	LThyrc, LAxil(I)
43	Left Thyrocervical Artery	LThyrc	5.0	0.771	0.252	0.252	491.6	491.6	LSub(II)	VB:LShoulder
44	Left Axillary Artery I	LAxil(I)	3.8	0.771	0.494	0.494	464.3	464.3	LSub(II)	LSubsc, LAxil(II)
45	Left Subscapular Artery etc [x4]	LSubsc	4.0	0.945	0.038	0.038	591.3	591.3	RAxil(I)	VB:LShoulder
46	Left Axillary Artery II	LAxil(II)	1.2	0.945	0.397	0.397	489.7	489.7	RAxil(I)	LHCA, LBrach(I)
47	Left Humeral Circumflex Artery [x2]	LHCA	4.8	1.000	0.170	0.170	898.6	898.6	RAxil(II)	VB:LUpArm
48	Left Brachial Artery I	LBrach(I)	5.1	1.000	0.374	0.374	865.9	865.9	RAxil(II)	LDpBrach, LBrach(II)
49	Left Deep Brachial Artery	LDpBrach	6.2	1.234	0.046	0.046	1014.3	1014.3	RBrach(I)	VB:LUpArm
50	Left Brachial Artery II	LBrach(II)	5.2	1.234	0.358	0.358	926.2	926.2	RBrach(I)	LUInCol, LBrach(III)
51	Left Ulnar Collateral Artery [x2]	LUInCol	15.0	1.472	0.078	0.078	992.4	992.4	RBrach(II)	VB:LUpArm
52	Left Brachial Artery III	LBrach(III)	17.2	1.472	0.217	0.217	948.5	948.5	RBrach(II)	LMuscBrach, LBrach(IV)
53	Left Muscular Brachial Artery [x2]	LMuscBrach	5.1	2.261	0.045	0.045	1018.3	1018.3	RBrach(III)	VB:LUpArm
54	Left Brachial Artery IV	LBrach(IV)	7.2	2.261	0.136	0.136	969.3	969.3	RBrach(III)	LLad, LUInar(I)
55	Left Radial Artery I	LRad(I)	11.7	2.592	0.067	0.067	1000.1	1000.1	RBrach(IV)	VB:LLowArm
56	Left Radial Artery Branch	LRadBranch	1.0	3.128	0.010	0.010	1089.8	1089.8	LRad(I)	VB:LLowArm
57	Left Radial Artery II	LRad(II)	11.7	3.128	0.041	0.041	1023.4	1023.4	LRad(I)	VB:LLowArm

58	Left Ulnar Artery I	LUlnar(I)	6.7	2.592	0.073	0.073	996.8	996.8	RBrach(IV)	LInter, LUlnar(II)
59	Left Interosseous Artery	LInter	7.9	2.899	0.027	0.027	1041.6	1041.6	RUlnar(I)	VB:LLowArm
60	Left Ulnar Artery II	LUlnar(II)	17.1	2.899	0.047	0.047	1016.2	1016.2	RUlnar(I)	VB:LLowArm
61	Intercostal Arteries etc [x35]	Interc	8.0	0.355	0.058	0.058	552.2	552.2	DTA(I)	VB:Chest
62	Descending Thoracic Aorta II	DTA(II)	10.4	0.355	2.678	2.678	397.6	397.6	DTA(I)	AbdAo(I), Cel
63	Abdominal Aorta I	AbdAo(I)	5.3	0.584	2.309	2.309	403.7	403.7	DTA(II)	SupMes, AbdAo(II)
64	Celiac Artery	Cel	2.0	0.584	0.471	0.471	464.3	464.3	DTA(II)	Hep, Spl, Gas
65	Hepatic Artery	Hep	6.6	0.628	0.162	0.162	508.4	508.4	Cel	VB:Liver
66	Splenic Artery	Spl	6.3	0.628	0.113	0.113	524.1	524.1	Cel	VB:Spleen
67	Gastric Artery	Gas	7.1	0.628	0.237	0.237	492.6	492.6	Cel	VB:Stomach
68	Superior Mensenteric Artery	SupMes	5.9	0.700	0.561	0.561	458.3	458.3	AbdAo(I)	VB:Intestines
69	Abdominal Aorta II	AbdAo(II)	1.0	0.700	1.855	1.855	412.6	412.6	AbdAo(I)	LRenal, AbdAo(III)
70	Left Renal Artery	LRenal	3.2	0.722	0.287	0.287	485.5	485.5	AbdAo(II)	VB:LKidney
71	Abdominal Aorta III	AbdAo(III)	1.0	0.722	1.631	1.631	417.6	417.6	AbdAo(II)	RRenal, AbdAo(IV)
72	Right Renal Artery	RRenal	3.2	0.744	0.290	0.290	485.4	485.4	AbdAo(III)	VB:RKidney
73	Abdominal Aorta IV	AbdAo(IV)	10.6	0.744	1.402	1.402	423.6	423.6	AbdAo(III)	InfMes, AbdAo(V)
74	Inferior Mesenteric Artery	InfMes	5.0	0.978	0.073	0.073	626.8	626.8	AbdAo(IV)	VB:Intestines

75	Abdominal Aorta V	AbdAo(V)	1.0	0.978	1.600	1.600	501.4	501.4	AbdAo(IV)	LCmIliac, RCmIliac
76	Left Common Iliac Artery	LCmIliac	5.9	1.000	1.304	1.304	817.2	817.2	AbdAo(V)	LExIliac, LInIliac
77	Right Common Iliac Artery	RCmIliac	5.9	1.000	1.304	1.304	817.2	817.2	AbdAo(V)	RExIliac, RInIliac
78	Left External Iliac Artery	LExIliac	14.5	1.130	1.125	1.125	878.7	878.7	LCmIliac	LFem(I), LDpFem(I)
79	Left Internal Iliac Artery	LInIliac	5.0	1.130	0.294	0.294	931.6	931.6	LCmIliac	VB: Pelvis
80	Left Femoral Artery I	LFem(I)	6.4	1.449	0.425	0.425	920.9	920.9	LExIliac	LMuscFem(I), LFem(II)
81	Left Muscular Femoral Artery I	LMuscFem(I)	1.0	1.590	0.063	0.063	1002.6	1002.6	LFem(I)	VB: LU pLeg
82	Left Femoral Artery II	LFem(II)	6.4	1.590	0.370	0.370	926.9	926.9	LFem(I)	LMuscFem(II), LFem(III)
83	Left Muscular Femoral Artery II	LMuscFem(II)	1.0	1.731	0.055	0.055	1009.0	1009.0	LFem(II)	VB: LU pLeg
84	Left Femoral Artery III	LFem(III)	6.4	1.731	0.321	0.321	932.9	932.9	LFem(II)	LMuscFem(III), LFem(IV)
85	Left Muscular Femoral Artery III	LMuscFem(III)	1.0	1.872	0.048	0.048	1015.3	1015.3	LFem(III)	VB: LU pLeg
86	Left Femoral Artery IV	LFem(IV)	6.4	1.872	0.279	0.279	938.8	938.8	LFem(III)	LMuscFem(IV), LFem(V)
87	Left Muscular Femoral Artery IV	LMuscFem(IV)	1.0	2.013	0.042	0.042	1021.6	1021.6	LFem(IV)	VB: LU pLeg
88	Left Femoral Artery V	LFem(V)	6.4	2.013	0.242	0.242	944.8	944.8	LFem(IV)	LPop(I), LDescGen
89	Left Deep Femoral Artery I	LDpFem(I)	1.5	1.449	0.737	0.737	899.1	899.1	LExIliac	LMedCxFem, LLatCxFem, LDpFem(II)

90	Left Medial Circumflex Femoral Artery	LMedCxFem	4.5	1.482	0.120	0.120	973.5	973.5	LDpFem(I)	VB:LUpLeg
91	Left Lateral Circumflex Femoral Artery	LLatCxFem	3.6	1.482	0.214	0.214	949.1	949.1	LDpFem(I)	VB:LUpLeg
92	Left Deep Femoral Artery II	LDpFem(II)	11.1	1.482	0.433	0.433	920.3	920.3	LDpFem(I)	VB:LUpLeg
93	Left Descending Genicular Artery	LDescGen	8.2	2.154	0.023	0.023	1049.7	1049.7	LFem(V)	VB:LLowLeg
94	Left Popliteal Artery I	LPop(I)	4.5	2.154	0.223	0.223	948.4	948.4	LFem(V)	LMedSupGen, LLatSupGen, LPop(II)
95	Left Medial Superior Genicular Artery	LMedSupGen	3.5	2.253	0.013	0.013	1075.4	1075.4	LPop(I)	VB:LLowLeg
96	Left Lateral Superior Genicular Artery	LLatSupGen	3.5	2.253	0.014	0.014	1072.8	1072.8	LPop(I)	VB:LLowLeg
97	Left Popliteal Artery II	LPop(II)	2.0	2.253	0.199	0.199	953.2	953.2	LPop(I)	LMidGenSural, LPop(III)
98	Left Middle Genicular and Sural Arteries	LMidGenSural	2.3	2.297	0.011	0.011	1083.8	1083.8	LPop(II)	VB:LLowLeg
99	Left Popliteal Artery III	LPop(III)	2.0	2.297	0.190	0.190	955.2	955.2	LPop(II)	LMedInfGen, LLatInfGen, LPop(IV)
100	Left Medial Inferior Genicular Artery	LMedInfGen	5.2	2.341	0.011	0.011	1085.6	1085.6	LPop(III)	VB:LLowLeg
101	Left Lateral Inferior Genicular Artery	LLatInfGen	4.0	2.341	0.011	0.011	1085.6	1085.6	LPop(III)	VB:LLowLeg
102	Left Popliteal Artery IV	LPop(IV)	3.7	2.341	0.171	0.171	959.6	959.6	LPop(III)	LATib(I), LTibPerTrunk
103	Left Anterior Tibial Artery I	LATib(I)	17.2	2.423	0.059	0.059	1006.0	1006.0	LPop(IV)	LATibPerf, LATib(II)

104	Left Anterior Tibial Perforator Artery	LATibPerf	3.1	2.802	0.013	0.013	1079.2	1079.2	LATib(I)	VB:LLowLeg
105	Left Anterior Tibial Artery II	LATib(II)	17.2	2.802	0.048	0.048	1015.6	1015.6	LATib(I)	VB:LLowLeg
106	Left Tibial Peroneal Trunk	LTibPerTrunk	3.0	2.423	0.117	0.117	976.0	976.0	LPop(IV)	LPTib(I), LPeron(I)
107	Left Peroneal Artery I	LPeron(I)	16.1	2.490	0.037	0.037	1027.6	1027.6	LTibPerTrunk	LPeronPerf, LPeron(II)
108	Left Peroneal Perforating Artery	LPeronPerf	2.5	2.844	0.007	0.007	1106.2	1106.2	LPeron(I)	VB:LLowLeg
109	Left Peroneal Artery II	LPeron(II)	16.1	2.844	0.030	0.030	1036.8	1036.8	LPeron(I)	VB:LLowLeg
110	Left Posterior Tibial Artery I	LPTib(I)	16.1	2.490	0.083	0.083	991.0	991.0	LTibPerTrunk	LPTibPerf, LPTib(II)
111	Left Posterior Tibial Perforating Artery	LPTibPerf	3.0	2.844	0.017	0.017	1064.5	1064.5	LPTib(I)	VB:LLowLeg
112	Left Posterior Tibial Artery II	LPTib(II)	16.1	2.844	0.068	0.068	1000.0	1000.0	LPTib(I)	VB:LLowLeg
113	Right External Iliac Artery	RExlliac	14.5	1.130	1.125	1.125	878.7	878.7	RCmlliac	RFem(I), RDpFem(I)
114	Right Internal Iliac Artery	RInlliac	5.0	1.130	0.294	0.294	931.6	931.6	RCmlliac	VB:Pelvis
115	Right Femoral Artery I	RFem(I)	6.4	1.449	0.425	0.425	920.9	920.9	RExlliac	RMuscFem(I), RFem(II)
116	Right Muscular Femoral Artery I	RMuscFem(I)	1.0	1.590	0.063	0.063	1002.6	1002.6	RFem(I)	VB:RUUpLeg
117	Right Femoral Artery II	RFem(II)	6.4	1.590	0.370	0.370	926.9	926.9	RFem(I)	RMuscFem(II), RFem(III)
118	Right Muscular Femoral Artery II	RMuscFem(II)	1.0	1.731	0.055	0.055	1009.0	1009.0	RFem(II)	VB:RUUpLeg

119	Right Femoral Artery III	RFem(III)	6.4	1.731	0.321	0.321	932.9	932.9	RFem(II)	RMuscFem(III), RFem(IV)
120	Right Muscular Femoral Artery III	RMuscFem(III)	1.0	1.872	0.048	0.048	1015.3	1015.3	RFem(III)	VB:RUPLeg
121	Right Femoral Artery IV	RFem(IV)	6.4	1.872	0.279	0.279	938.8	938.8	RFem(III)	RMuscFem(IV), RFem(V)
122	Right Muscular Femoral Artery IV	RMuscFem(IV)	1.0	2.013	0.042	0.042	1021.6	1021.6	RFem(IV)	VB:RUPLeg
123	Right Femoral Artery V	RFem(V)	6.4	2.013	0.242	0.242	944.8	944.8	RFem(IV)	RPop(I), RDescGen
124	Right Deep Femoral Artery I	RDpFem(I)	1.5	1.449	0.737	0.737	899.1	899.1	RExIliac	RMedCxFem, RLatCxFem, RDpFem(II)
125	Right Medial Circumflex Femoral Artery	RMedCxFem	4.5	1.482	0.120	0.120	973.5	973.5	RDpFem(I)	VB:RUPLeg
126	Right Lateral Circumflex Femoral Artery	RLatCxFem	3.6	1.482	0.214	0.214	949.1	949.1	RDpFem(I)	VB:RUPLeg
127	Right Deep Femoral Artery II	RDpFem(II)	11.1	1.482	0.433	0.433	920.3	920.3	RDpFem(I)	VB:RUPLeg
128	Right Descending Genicular Artery	RDescGen	8.2	2.154	0.023	0.023	1049.7	1049.7	RFem(V)	VB:RLowLeg
129	Right Popliteal Artery I	RPop(I)	4.5	2.154	0.223	0.223	948.4	948.4	RFem(V)	RMedSupGen, RLatSupGen, RPop(II)
130	Right Medial Superior Genicular Artery	RMedSupGen	3.5	2.253	0.013	0.013	1075.4	1075.4	RPop(I)	VB:RLowLeg
131	Right Lateral Superior Genicular Artery	RLatSupGen	3.5	2.253	0.014	0.014	1072.8	1072.8	RPop(I)	VB:RLowLeg

132	Right Popliteal Artery II	RPop(II)	2.0	2.253	0.199	0.199	953.2	953.2	RPop(I)	RMidGenSural, RPop(III)
133	Right Middle Genicular and Sural Arteries	RMidGenSural	2.3	2.297	0.011	0.011	1083.8	1083.8	RPop(II)	VB:RLowLeg
134	Right Popliteal Artery III	RPop(III)	2.0	2.297	0.190	0.190	955.2	955.2	RPop(II)	RMedInfGen, RLatInfGen, RPop(IV)
135	Right Medial Inferior Genicular Artery	RMedInfGen	5.2	2.341	0.011	0.011	1085.6	1085.6	RPop(III)	VB:RLowLeg
136	Right Lateral Inferior Genicular Artery	RLatInfGen	4.0	2.341	0.011	0.011	1085.6	1085.6	RPop(III)	VB:RLowLeg
137	Right Popliteal Artery IV	RPop(IV)	3.7	2.341	0.171	0.171	959.6	959.6	RPop(III)	RATib(I), RTibPerTrunk
138	Right Anterior Tibial Artery I	RATib(I)	17.2	2.423	0.059	0.059	1006.0	1006.0	RPop(IV)	LATibPerf, LATib(II)
139	Right Anterior Tibial Perforator Artery	RATibPerf	3.1	2.802	0.013	0.013	1079.2	1079.2	RATib(I)	VB:RLowLeg
140	Right Anterior Tibial Artery II	RATib(II)	17.2	2.802	0.048	0.048	1015.6	1015.6	RATib(I)	VB:RLowLeg
141	Right Tibial Peroneal Trunk	RTibPerTrunk	3.0	2.423	0.117	0.117	976.0	976.0	RPop(IV)	RPTib(I), RPeron(I)
142	Right Peroneal Artery I	RPeron(I)	16.1	2.490	0.037	0.037	1027.6	1027.6	RTibPerTrunk	RPeronPerf, RPeron(II)
143	Right Peroneal Perforating Artery	RPeronPerf	2.5	2.844	0.007	0.007	1106.2	1106.2	RPeron(I)	VB:RLowLeg
144	Right Peroneal Artery II	RPeron(II)	16.1	2.844	0.030	0.030	1036.8	1036.8	RPeron(I)	VB:RLowLeg
145	Right Posterior Tibial Artery I	RPTib(I)	16.1	2.490	0.083	0.083	991.0	991.0	RTibPerTrunk	RPTibPerf, RPTib(II)
146	Right Posterior Tibial Perforating Artery	RPTibPerf	3.0	2.844	0.017	0.017	1064.5	1064.5	RPTib(I)	VB:RLowLeg

147	Right Posterior Tibial Artery II	RPTib(II)	16.1	2.844	0.068	0.068	1000.0	1000.0	RPTib(I)	VB:RLowLeg
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Head/Neck Arteries

148	Basilar Artery II	Bas(II)	2.0	1.309	0.126	0.113	974.3	979.4	RVert, LVert	RSupCer, LSupCer, Bas(I)
149	Right Superior Cerebellar Artery	RSupCer	1.0	1.407	0.025	0.017	1059.3	1081.0	Bas(II)	VB:Brain
150	Left Superior Cerebellar Artery	LSupCer	1.0	1.407	0.025	0.017	1059.3	1081.0	Bas(II)	VB:Brain
151	Basilar Artery I	Bas(I)	0.5	1.407	0.083	0.063	995.7	1009.9	Bas(II)	RPostCer(I), LPostCer(I)
152	Right Posterior Cerebral Artery I	RPostCer(I)	0.2	1.431	0.035	0.035	1041.0	1041.0	Bas(I)	RPostComm, RPostCer(II)
153	Left Posterior Cerebral Artery I	LPostCer(I)	0.2	1.431	0.035	0.035	1041.0	1041.0	Bas(I)	LPostComm, LPostCer(II)
154	Right Posterior Communicating Artery	RPostComm	0.4	1.441	0.014	0.014	1091.1	1091.1	RPostCer(I)	RDICAI
155	Left Posterior Communicating Artery	LPostComm	0.4	1.441	0.014	0.014	1091.1	1091.1	LPostCer(I)	LDICAI
156	Right Posterior Cerebral Artery II	RPostCer(II)	5.9	1.441	0.025	0.021	1058.8	1070.5	RPostCer(I)	VB:Brain
157	Left Posterior Cerebral Artery II	LPostCer(II)	5.9	1.441	0.025	0.021	1058.8	1070.5	LPostCer(I)	VB:Brain
158	Right Distal Internal Carotid Artery I	RDICA(I)	0.2	1.799	0.119	0.113	978.4	981.0	RICASin, RPostComm	RAntChor, RDICA(II)
159	Left Distal Internal Carotid Artery I	LDICA(I)	0.2	1.951	0.119	0.113	978.6	981.2	LIntCarSin, LPostComm	LAntChor, LDICA(II)
160	Right Anterior Cerebral Artery I	RAntCer(I)	1.2	1.819	0.039	0.035	1036.7	1041.9	RDICA(II)	RAntCer(II)

161	Left Anterior Cerebral Artery I	LAntCer(I)	1.2	1.971	0.039	0.035	1036.8	1042.0	LDICA(II)	AntComm, LAntCer(II)
162	Right Middle Cerebral Artery (M1)	RMCA(M1)	0.8	1.819	0.079	0.069	999.4	1006.4	RDICA(II)	RMCAsup(M2), RMCAinf(M2)
163	Right Superior Middle Cerebral Artery (M2)	RMCAsup(M2)	7.1	1.858	0.034	0.034	1042.9	1042.9	RMCA(M1)	VB:Brain
164	Right Inferior Middle Cerebral Artery (M2)	RMCAinf(M2)	7.0	1.858	0.034	0.034	1042.9	1042.9	RMCA(M1)	VB:Brain
165	Left Middle Cerebral Artery (M1)	LMCA(M1)	0.8	1.971	0.079	0.069	999.5	1006.6	LDICA(II)	LMCAsup(M2), LMCAinf(M2)
166	Left Superior Middle Cerebral Artery (M2)	LMCAsup(M2)	7.1	2.010	0.034	0.034	1043.1	1043.1	LMCA(M1)	VB:Brain
167	Left Inferior Middle Cerebral Artery (M2)	LMCAinf(M2)	7.0	2.010	0.034	0.034	1043.1	1043.1	LMCA(M1)	VB:Brain
168	Right Anterior Cerebral Artery II	RAntCer(II)	2.4	1.877	0.025	0.023	1059.4	1065.7	RAntCer(I), AntComm	VB:Brain
169	Anterior Communicating Artery	AntComm	0.2	2.029	0.012	0.012	1102.7	1102.7	LAntCer(I)	RAntCer(II)
170	Left Anterior Cerebral Artery II	LAntCer(II)	2.4	2.029	0.023	0.020	1065.9	1072.2	LAntCer(I)	VB:Brain
171	Right Internal Carotid Sinus	RICASin	1.1	1.745	0.132	0.109	973.3	983.0	RICA	RDICA I
172	Right Ophthalmic Artery	ROpth	1.1	1.745	0.007	0.007	1132.0	1132.0	RICA	VB:Face/Neck
173	Left Internal Carotid Sinus	LIntCarSin	1.1	1.897	0.124	0.102	976.9	986.6	LICA	LDICA I
174	Left Ophthalmic Artery	LOpth	1.1	1.897	0.007	0.007	1136.3	1136.3	LICA	VB:Face/Neck
175	Right External Carotid Artery II	RECA(II)	6.1	1.074	0.118	0.118	970.5	970.5	RECA(I)	RSupTemp, RMaxil
176	Right Superior Thyroid / Ascending	RSupThy	10.1	1.074	0.050	0.050	1014.6	1014.6	RECA(I)	VB:Face/Neck

	Pharyngeal / Lingual / Facial / Occipital Arteries									
177	Left External Carotid Artery II	LExtCar(II)	6.1	1.225	0.119	0.119	976.3	976.3	LECA(I)	LSupTemp, LMaxil
178	Left Superior Thyroid / Ascending Pharyngeal / Lingual / Facial / Occipital Arteries	LSupThy	10.1	1.225	0.036	0.036	1038.2	1038.2	LECA(I)	VB:Face/Neck
179	Right Superior Temporal Artery	RSupTemp	6.1	1.373	0.069	0.069	1005.2	1005.2	RECA(II)	RSupTempFront, RSupTempPari
180	Right Maxillary Artery	RMaxil	9.1	1.373	0.033	0.033	1044.8	1044.8	RECA(II)	VB:Face/Neck
181	Left Superior Temporal Artery	LSupTemp	6.1	1.525	0.069	0.069	1005.5	1005.5	LExtCar(II)	LSupTempFront, LSupTempPari
182	Left Maxillary Artery	LMaxil	9.1	1.525	0.033	0.033	1045.0	1045.0	LExtCar(II)	VB:Face/Neck
183	Right Superior Temporal Frontal Artery	RSupTempFront	10.0	1.672	0.034	0.034	1043.0	1043.0	RSupTemp	VB:Face/Neck
184	Right Superior Temporal Parietal Artery	RSupTempPari	10.1	1.672	0.034	0.034	1043.0	1043.0	RSupTemp	VB:Face/Neck
185	Left Superior Temporal Frontal Artery	LSupTempFront	10.0	1.824	0.034	0.034	1042.9	1042.9	LSupTemp	VB:Face/Neck
186	Left Superior Temporal Parietal Artery	LSupTempPari	10.1	1.824	0.034	0.034	1042.9	1042.9	LSupTemp	VB:Face/Neck
187	Right Anterior Choroidal Artery	RAntChor	3.6	1.809	0.016	0.012	1084.2	1100.6	RDICAI	VB:Brain

188	Right Distal Internal Carotid Artery II	RDICA(II)	0.2	1.809	0.105	0.105	985.1	985.1	RDICAI	RAntCer(I), RMCA(M1)
189	Left Anterior Choroidal Artery	LAntChor	3.6	1.961	0.016	0.012	1084.4	1100.7	LDICAI	VB:Brain
190	Left Distal Internal Carotid Artery II	LDICA(II)	0.2	1.961	0.105	0.105	985.3	985.3	LDICAI	LAntCer(I), LMCA(M1)

Appendix B.5: Resistance and Compliance of the Systemic Vascular Beds

Note 1: Resistances are pressure dependent. Values below refer to reference resistances, as described in the Mynard2015 model (175).

	Bed Name	Abbreviated Name	Resistance (mmHg·s·mL⁻¹)	Arterial Compliance (mL·mmHg⁻¹)
1	Brain	Brain	5.2	0.2477
2	Face/Neck	Face/Neck	15.8	0.0825
3	Right Shoulder	RShoulder	36.4	0.0357
4	Left Shoulder	LShoulder	35.2	0.0370
5	Right Upper Arm	RUpArm	39.8	0.0326
6	Right Lower Arm	RLowArm	77.8	0.0167
7	Left Upper Arm	LUpArm	39.8	0.0327
8	Left Lower Arm	LLowArm	77.6	0.0167
9	Chest	Chest	8.7	0.1496
10	Right Kidney	RKidney	6.1	0.2129
11	Left Kidney	LKidney	6.1	0.2129
12	Liver (arterial)	Liver	18.9	0.0686
13	Spleen	Spleen	21.4	0.0606
14	Stomach	Stomach	44.0	0.0296
15	Intestines	Intestines	8.2	0.1591
16	Pelvis	Pelvis	20.2	0.0642
17	Right Upper Leg	RUpLeg	24.0	0.0541
18	Left Upper Leg	LUpLeg	24.0	0.0541
19	Right Lower Leg	RLowLeg	35.6	0.0365
20	Left Lower Leg	LLowLeg	35.7	0.0365

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