Vascular Function and Structure in the Rat Aorta

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By

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To
My parents
My best friends

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All errors and limitations remaining in this book are mine alone.

Keith Ng
Macquarie University
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PREFACE

Arterial stiffness is a strong predictor of cardiovascular events. Arterial stiffness increases with age and in the presence of cardiovascular disease risk factors, such as hypertension, aortic calcification and chronic kidney disease (CKD). Large arteries stiffen with increased distending pressure and/or pathological changes in arterial wall properties. This study aimed to characterise the structure and function of large arteries under the effect of hypertension, calcification, CKD and therapy by angiotensin-converting enzyme (ACE) inhibitor (perindopril). The investigation was conducted in rat models using two high fidelity pressure sensors for measuring aortic haemodynamic parameters and pulse wave velocity (PWV) as a surrogate measure of arterial stiffness. The aorta was pressure perfused and fixed for histomorphometry and quantification of aortic calcium content. Findings indicate that for all rat strains, aortic segmental PWV increased with mean arterial blood pressure (MAP). Isobaric PWV for the whole aortic trunk and thoracic PWV (tPWV) were higher in spontaneously hypertensive rats (SHR) and in vitamin D3 and nicotine treated rats (VDN), compared with their controls. Wistar Kyoto rats (WKY) and SHR showed similar abdominal PWV (aPWV), whereas aPWV of VDN was significantly higher. Similarly, the Lewis polycystic kidney disease rats (LPK) also showed greater aortic PWV compared with Lewis rats. The increased PWV in SHR, VDN and LPK was associated with greater aortic calcification, greater aortic medial cross-sectional area (MCSA), lower elastic modulus-to-wall stress ratio (EM/WS), increased aortic wall thickness, reduced smooth muscle cell area, and decreased elastin density, with no statistical difference in collagen fibre density. Arterial stiffness was also associated with marked differences in the pressure sensitivity of PWV (determined from the incremental slopes of the PWV-MAP curves) in the thoracic and abdominal aortic segments of rats with induced calcification. When treated with ACE inhibitor at 6-10 weeks of age (SHR) and chronically from 6 weeks of age (LPK), the aortic PWV-MAP curve of both strains regressed downward (towards the MAP axis) and to the left, almost overlapping with their controls. ACE inhibition significantly reversed structural changes and aortic calcification in the thoracic segment in the SHR and LPK. This study characterises pressure-dependent PWV associated with modified wall properties and

explores possible pharmacological intervention on aortic stiffness independent of blood pressure with ACE inhibition. Pressure dependency of PWV can potentially be a better discriminator of underlying mechanisms than simple comparison of isobaric stiffness parameters.

LIST OF ACRONYMS

ACE	Angiotensin-converting enzyme
Aix	augmentation index
aPWV	abdominal pulse wave velocity
ARB	Angiotensin II type 1 receptor blocker
C	compliance
CCB	calcium channel blocker
CKD	chronic kidney disease
CO	cardiac output
d	vessel diameter
D	distensibility
DBP	diastolic blood pressure
EM	elastic modulus
ECM	extra-cellular matrix
E_{inc}	incremental elastic modulus
EM	elastic modulus
ENU	elastic non-uniformity
ESRD	end stage renal disease
h	wall thickness
HR	heart rate
L-NMMA	N^G-monomethyl-L-arginine
LPK	Lewis polycystic kidney disease rat
MAP	mean aortic blood pressure
MCSA	medial cross-sectional area
MMP	matrix metalloproteinase
NOS	nitric oxide synthase
P	distending pressure
PP	pulse pressure
PPA	pulse pressure amplification
PWV	pulse wave velocity
PWV_s	pulse wave velocity sensitivity
MRI	magnetic resonance imageing
NO	nitric oxide
r	lumen radius
R	resistance
RAAS	renin-angiotensin-aldosterone system

REASON	pREterax in regression of Arterial Stiffness in a controlled double-bliNd study
SBP	systolic blood pressure
SHEP	Systolic Hypertension in the Elderly
SHR	spontaneously hypertensive rats
T	tension
tPWV	thoracic pulse wave velocity
VDN	hypervitaminosis D3 and nicotine
VSMC	vascular smooth muscle cells
WKY	Wistar Kyoto rats
wPWV	whole aortic pulse wave velocity
WS	wall stress
ADMA	asymmetrical dimethylarginine
P	blood density
σ	wall stress
ε	wall strain

CHAPTER ONE

INTRODUCTION

Prospective studies such as the Framingham Heart Study have confirmed the relationship between arterial stiffness and cardiovascular disease (5). The multitude of reasons for the association between increased arterial stiffness and cardiovascular disease are not fully understood, although epidemiological studies have shown that arterial stiffness gives rise to elevated systolic (6) and pulse pressure (7-13). In large populations, antihypertensive therapy frequently achieves adequate diastolic blood pressure (DBP) control (≤90 mm Hg), but treating systolic blood pressure (SBP) to goal (<140 mmHg for uncomplicated hypertensives and <130 mmHg for hypertensives with diabetes mellitus or chronic renal failure) is still difficult to achieve (14). This focus on SBP control has resulted in increased interest in the role of arterial stiffness and wave reflections in the mechanism of hypertension and hence cardiovascular risk (15-17). This book aims to characterise hypertension not only in terms of increase in peripheral resistance but also by incorporating the pathological effects of loss of distensibility of large arteries.

The arterial system serves two functions: one as a conduit to deliver blood from the left ventricle to capillaries and end organs, and one as a cushion to buffer pulsations generated by the heart so that blood flowing through capillaries is essentially continuous. The efficiency of the arterial system is measured by the extent to which the system discharges these functions. While an unobstructed artery generally can deliver an adequate quantity of blood to the end organs, it can fall short on its cushioning function, especially in the ageing population or in the presence of other cardiovascular risk factors such as hypertension. This impairment in vascular function can be explained by the loss of distensibility and the effect is greatest in the aorta as compared with muscular peripheral arteries (18, 19). As the aorta ages and stiffens, as will be discussed in greater detail in this book, aortic pulse wave velocity markedly increases with progressive arterial wall remodelling, ultimately leading to an increase in cardiovascular morbidity and mortality.

The two functions served by the arterial system can be simply illustrated with a Windkessel model. While the Windkessel model has been extensively used by cardiovascular physiologists in the investigation of vascular function, the classic work of McDonald, Womersley, Taylor and then later Safar and O'Rourke has shown that this simplistic model in fact has limitations and could potentially lead to misinterpretation of arterial pressure. One of the criticisms is that the Windkessel concept models the arterial system with a separate chamber to dampen flow pulsations and a distal conduit to pass on a steady stream. Thus the model cannot address the substantial issue of pressure wave travel and reflection due to the fact that the cushioning and conduit functions of the arterial system are in fact combined (20). Corresponding to the vascular events (wave travel and reflection) which the Windkessel model cannot describe, a transmission line model that represents the cushioning and conduit functions of the artery system was introduced (21, 22). This model is superior to the Windkessel model since it exploits another aspect of cardiovascular efficiency – the wave propagation phenomenon. In ideal conditions, with normal ventricular rate and ejection period, the design of the circulatory system should locate reflection sites at a distance (23), such that consequent interactions of the reflected waves would not augment systole blood pressure. Instead, reflected pressure should be added to diastole only (24, 25). Factors determining the efficiency of the arterial system in discharging such interaction rely greatly on its distensibility, particularly in the proximal aorta. This is intuitive, as for any wave that travels in a solid medium, the stiffer the path, the higher the velocity. The differentiating ability of PWV as a surrogate indicator of stiffness in this book is based on this natural physical phenomenon. PWV is inherently an arterial property, measuring a local stiffness of a segment between the sensors. In fact, one of the interesting results in this book is that the non-uniformity of the aorta given by the difference in stiffness between abdominal and thoracic segments is associated with an amplification phenomenon. Hence, this amplification phenomenon has also been used as an index for characterising aortic stiffness.

In an optimally distensible arterial system, such as occurs in youth, the elasticity of arteries is perfectly adapted to this requirement. However, this optimality is progressively lost with age (26). Any change affecting the structure of the aorta would inevitably alter its function. Therefore, understanding these changes is of great importance in terms of the effect on arterial blood pressure and associated cardiovascular sequelae.

This book addresses this issue. First, a background section is outlined in which historical perspectives of arterial stiffness (Section 2.1) and arterial wall structure (Section 2.2) are explained. The discussion proceeds to the mechanical design of arteries of non-mammalian species from an evolutionary viewpoint (Section 2.3). Basic biophysical properties of large arteries under a distending pressure in physiological conditions are explained (Section 2.4). This is followed by acknowledging relevant preceding experimental investigations (Section 2.5) of the pressure-dependent (Section 2.6) aortic wall function and structure. Arterial stiffness is related to elevated blood pressure (Section 2.7) and the pathophysiological mechanisms associated are discussed (Section 2.8). This book uses rodent models to investigate arterial stiffness and their phenotypes are discussed (Section 2.9). Techniques for the quantification of arterial stiffness are discussed in Section 2.10. The rationale for studying ACE inhibition and its effect in the rat aorta is also discussed in relation to clinical situations with different drug therapies (Chapter 3).

Characterisation of large arterial function was conducted both *in vivo* and *ex vivo* in this work. Common methodologies used in all experiments are discussed in Chapter 4. Any techniques that were used only in a particular experiment are introduced separately in the respective methods section of the relevant chapter. Emphasis is given to theoretical details and experimental applications of parameters used in this book to characterise arterial stiffness. Various acronyms are used throughout this book and are defined on page VIII. PWV is used as a measure of vessel stiffness. PWV can be measured using various techniques. Since accurate measurement of PWV is crucial in characterising segmental vascular properties, it is necessary to measure two pressures with high fidelity transducers placed at a known distance apart to accurately determine the time delay between the recorded pressure waveforms. Other *in vivo* and *ex vivo* indices were also determined and are outlined in Chapter 4.

The overall hypothesis underlying the work reported in this book is that pressure-dependent large artery function alters with structural changes in wall properties. Chapters 5 to 8 investigate which changes would be brought about and how they could change PWV in the animal models. This is a significant research question as the large artery wall is a complex composite with different mechanical and chemical wall properties at different locations. Large arteries also behave differently in their response to vasoactive drugs and stimuli and when a systemic or pathological change is present in the physiological environment such as during ageing (16, 26-28), in hypertension (29, 30), CKD (31, 32), atherosclerosis (33)

or vascular calcification (34, 35). Conversely, large arteries also affect blood pressure. Large arteries become stiff with increased distending pressure such that the higher the blood pressure at the time of the measurement, the higher the measured arterial stiffness without any structural change in the wall properties of the vessel. This passive mechanical behaviour manifests itself differentially along the aorta. Hence, measurement of arterial properties at one site does not necessarily assist in the interpretation of changes at other sites. Chapter 5 investigates this phenomenon in the normotensive WKY, SHR and rats with aortic calcification (VDN). Chapter 6 targets the characterisation of large artery structure and function in the LPK, a rat model of chronic kidney disease. All of these complex confounding factors in the characterisation of large arteries need to be addressed for a better quantification of the effects of alterations in arterial mechanical properties of large arterial functions.

The next logical query arose: Is the stiffening of large arteries with age and with other cardiovascular risk factors an inevitable phenomenon or can it be modified by pharmacological interventions? This led on to the investigation of the effects of antihypertensive treatment (ACE inhibition) on rodent models of hypertension (Chapter 7) and chronic kidney disease (Chapter 8). The implication of this investigation is important as arterial stiffness is an independent predictor of cardiovascular disease and mortality in hypertension and chronic kidney disease. Arterial stiffness has been found to improve with antihypertensive treatment, independently of BP lowering (34-36). What could be the possible mechanism(s) involved in the preservation of large artery function in these diseases? Does the method by which treatment is administered (short/long-term, early/late in the development of hypertension) make a difference in treatment outcome? Experiments and results described in Chapters 7 and 8 aimed to provide answers, at least in part, to these questions.

Finally, a summary of the results and conclusions of this research (Chapter 9) and future directions (Chapter 10) are presented. It is argued by presenting findings from this work that assessing arterial stiffness as an independent risk factor for cardiovascular disease and therapy is useful, especially since direct pharmacological manipulation of arterial stiffness is possible. Therapeutic strategies that specifically target the large arteries could potentially better manage blood pressure in those individuals with increased or premature arterial stiffening.

CHAPTER TWO

ARTERIAL FUNCTION AND STRUCTURE

2.1 Historical perspectives

The arterial pulse has been an important feature in clinical examination in ancient Chinese, Indian, and Greek medicine (37). Diagnosis involved the patient being placed on a cushion, with the physician placing his index, ring and middle fingers at three sites of the wrist to elicit the superficial and deep pulses. The working principle was that each organ palpated at particular "normal" pulse amplitude and rate, and these pulses prevailed themselves at different seasons. If a particular pulse appeared at the wrong place or in the wrong season, a serious disequilibrium of the system (or a disease) was indicated. The physician also studied the patient's features and complexion and, sometimes, they inspected the urine and faeces for a more complete diagnosis. However, the patient's pulse was all that was required, and the physician did not necessarily need to interrogate the patient, collect medical history or symptoms as the entire prognosis would have been available through feeling the texture of the pulse. Chinese sphygmology was a carefully guarded secret. Pulse diagnosis was extremely difficult to learn and even if they could, few physicians were willing to devote 5-10 years of supervision under an experienced master to master the technique (38).

As in Chinese medicine, the art of feeling the pulse was also highly developed amongst ancient Hindu physicians (37). The pulse was felt at the wrist, on the right side in males and on the left side in females. The various pulses were likened to the motions of animals such as the serpent, the frog, the swan, and the peacock. Diseases were attributed to the eccentricity of the three humours, namely air, bile, and phlegm, which were duly reflected in the pulse.

It was not until Hippocrates and other Greek physicians that a scientific basis of the pulse was founded. Various features of the pulse were recognised and named in the fourth century BC (39). The arteries were thought to dilate actively, thus drawing in vital spirits from the airway.

Herophilos later described a relation between the heart and the arteries and invented the first sphygmograph that could measure the number of pulses in the time domain. Erasistratos was the first to note a delay in the travel of the pulse from central to peripheral, but he did not measure the delay or relate it to the stiffness of the arterial path travelled by the pulse. Galen (AD 130-200) later discovered the relationship among the heart, arteries, and veins and he was the first to point out that the arteries contained blood, not air. Galen's approach dominated medicine for over 14 centuries (40).

The beginning of modern cardiovascular medicine was in the sixteenth century. William Harvey (1578-1657) proved the circulation of blood and noted for the first time that the pulse was a consequence of cardiac contraction (40, 41). Harvey's attempt to explain a physical phenomenon from a modern scientific approach rather than from "natural philosophy" might have been influenced by his contemporary Galileo Galilei (1564-1642). Harvey's work laid the foundation for the physiological understanding of the mechanism of the arterial pulse and later its clinical applications. The implication was highly significant. The pulse was established as a manifestation of cardiac contraction and thus would be altered by abnormalities in the function of the heart and blood vessels.

Reverend Stephen Hales (1677-1761) was the first to use experimental animals to study the circulatory system (42, 43). Hales formulated the concept of peripheral resistance by demonstrating in a simple yet elegant experiment that greater resistance to flow resides in the smaller blood vessels. Hales also conceptualised the elastic arterial system as the air-filled chamber of the contemporary fire engine, which later translated into German as "Windkessel", and this word has been used since. The Windkessel model describes the conduit and cushioning function of the arteries and has been widely used to model the circulatory system, despite being simplistic and limited (44).

The inability of the Windkessel model to address the substantial issue of pressure wave propagation led to the establishment of the wave transmission model in the nineteenth century. Thomas Young (1773-1829) investigated and established the relationship between the elasticity of the artery and the speed of propagation of the arterial pulse (45, 46). In 1828, Jean Poiseuille (1797-1869) measured blood pressure with a mercury-filled column and determined the factors responsible for resistance to flow in tubes of capillary dimensions. This was further developed into a series of sphygmographs by Étienne-Jules Marey (1830-1904) (47). Frederick Akbar Mohamed later established the foundation of pulse wave analysis.

He described normal levels of blood pressure and the effect of high blood pressure on the radial pressure waveform, and used the waveform to chart the natural history of essential hypertension even before the invention of the sphygmomanometer. He also described the effects of arterial degeneration with ageing on the arterial pulse (48, 49), which was then used in the life insurance studies of the late nineteenth century (50).

Mohamed's sphygmogram was succeeded by the introduction and acceptance of the sphygmomanometer of Scipione Riva-Rocci (1896) (51) and Nicolai Korotkoff (1905) (52). Although the sphygmomanometer enabled pressure to be recorded reasonably accurately, quickly and noninvasively, the sphygmomanometer disoriented the biological significance in the pulse wave shape by giving only a simplistic notion of two extremes of pressure waveform. Nevertheless, these two figures, systolic and diastolic pressures, were still of great importance as the former is a manifestation of left ventricular ejection and the latter a manifestation of the arteriolar tone (peripheral resistance). The sphygmomanometer has been widely used in clinical settings despite its limitation in predicting the central blood pressure (45).

While Mohamed was the first to note the difference between pressure waves in central and peripheral arteries, Donald McDonald and John Womersley were responsible for quantifying and explaining this phenomenon based on wave reflection (46, 53, 54). They also introduced the use of transfer functions between pressure and flow to characterise the properties of vascular beds in the frequency domain, using the technique of Fourier analysis developed by Frank (55). Bramwell and Hill described cardiac function in relation to hydraulic load and more importantly showed that arterial stiffness was an important component in the determination of cardiac load (56). These classic works of McDonald, Womersley, Taylor and their followers have informed the conceptual background and the rationale of research work in this book.

2.2 Large artery wall structure

Arterial tissue can be mechanically described in terms of a long-range elastic element (elastin) arranged in parallel with a system of continuous collagen fibres that set a limit on extension. There are three recognisable layers in an artery: tunica intima, tunica media and tunica adventitia (Figure 2.1).

2.2.1 Tunica intima

The tunica intima is defined as the endothelial cells and subendothelial area on the luminal side of the inter elastic lamina. These endothelial cells are able to produce elastin *in vitro*, thus contributing to the formation of the inter elastic lamina (57-59). The subendothelial area contains cellular matrix in lower order animals and a population of smooth muscle cell in higher order animals such as humans (60). This layer is particularly important in atherosclerosis (61) but plays no role in the mechanical properties of the normal conducting vessel.

2.2.2 Tunica media

The next layer of the arterial wall is the tunica media, which consists of smooth muscle cells and elastic. Elastin is arranged in fenestrated sheets (lamellae) with collagen fibres, extracellular matrix and smooth muscle cells in between layers. Inter-lamellae elastin connects to the lamellae and smooth muscle cells forming a three-dimensional continuous network (62). Elastin fibres, with high distensibility but low tensile strength, function primarily as an elastic reservoir by distributing stress evenly across the vessel wall and on to collagen fibres, with high tensile strength but low distensibility, at high pressure. Interestingly, the number of elastin lamellae does not change after birth, suggesting that a loss of elastin, such as in the case of elastin fragmentation or degeneration, would translate into a permanent loss of the reservoir function. Elimination of smooth muscle function or disruption of the morphological organisation has also been found to show remarkable alterations which could cause functional impairments and vascular disorders (63-65). Given the unique vascular network, the media layer is a prominent site for aortic calcification, a phenomenon in which deposition of calcium particles obstructs and/or fragments the elastin lamellae. Aortic calcification is studied extensively in this book.

2.2.3 Tunica adventitia

The outermost layer of the vessel wall is the tunica adventitia. The tunica adventitia is defined as the area outside of the external elastic lamina and consists of a collagen-rich extracellular matrix (66). In this layer lie the vasa vasorum, small vessels that supply nutrients and oxygen to the vessel wall. The tunica adventitia is susceptible to vascular inflammation as it is the outermost protective layer and can act as an injury-sensing device for

the vessel wall. An elegant study by Hu *et al.* showed that resident progenitor cells populate within the adventitia layer contributing to atherosclerosis of vein grafts in ApoE-deficient mice (67, 68).

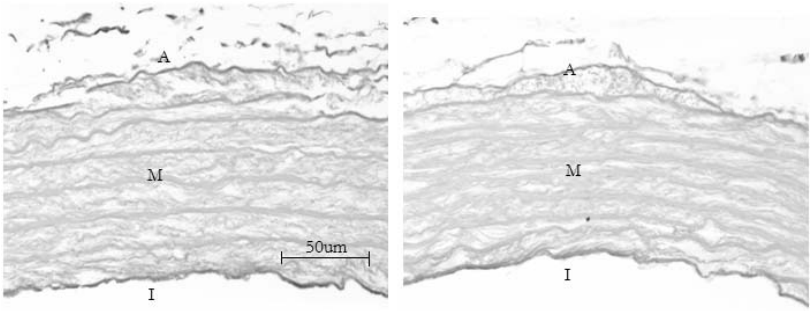

Figure 2.1 An example of photomicrographs of cross sections of a WKY rat thoracic (left) and abdominal (right) aorta. Fixation was done while distending at 110mmHg and stained with Shitaka's Orcein stain. The architecture is essentially the same. The abdominal aortic media is narrower than in the thoracic segment. The difference in thickness corresponds to the difference in diameter. Adventitial (A), media (M) and intima (I) layers are shown.

2.2.3 Intrinsic differences in segmental aortic structure

It is well known that the arterial wall structure varies with increasing distance from the heart. These inherent differences in the organisation and content subject the arterial wall to different compliance and integrity of the aorta. This difference in compliance and integrity is related to aortic disease as shown by several classic studies on the thoracic and abdominal aortas of man and other mammalian species (69). The human aorta consists of between 80 to 32 lamellae from the ascending to the midinfrarenal aorta (Figure 2.2a) (70). Similarly, collagen content also decreases from the proximal to the distal aorta (Figure 2.2b), although no difference was found between the suprarenal and midinfrarenal segments (70). The contribution of elastin and collagen to the function and structural integrity of the aorta has been investigated by Dobrin (71). Since the mean arterial pressure is essentially constant throughout the length of the aorta, degradation of the elastin network, as in arterial calcification and chronic kidney disease, could significantly impair the viscoelasticity properties of the wall. Comparing both the thoracic and abdominal aorta, the latter will be affected to a greater extent as more force is applied per gram of elastin in this segment. Collagen, on the other hand, provides tensile strength;

acute loss of collagen compromises wall integrity and could give rise to rupture even without dilatation. Morphologically, the aorta also shows different intimal, medial and adventitial thicknesses along its length. There is a progressive thinning of the tunica media and a progressive increase of intimal and adventitial thickness in the distal aorta towards the heart. What is not known, however, is how the difference in segmental structure affects PWV measurements and the phenomenon of pulse amplification. Collectively, these differences are likely to affect function and structure of the aorta, and may explain physiological phenomena, such as pressure amplification and predisposition to arterial calcification.

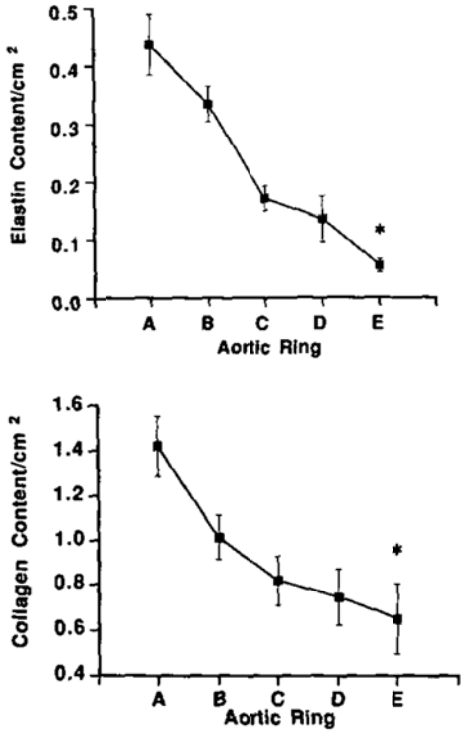

Figure 2.2 Collagen (left) and elastin (right) content (mean±SD) in the ascending (A), descending (B) thoracic aorta and abdominal supraceliac (C), suprarenal (D), and midinfrarenal (E) aorta. Both Collagen and elastin decrease progressively along the aortic trunk. (70)