Non-Invasive Characterisation of Age-Related Changes in Ascending Aortic Blood Pressure and Blood Flow

From Old Concept to Novel Approach

Audrey Indrawati (Sutanto) Adji (*MB MBiomedE*)

A thesis of the Department of Biomedical Sciences, Faculty of Medicine and Health Sciences, Macquarie University, submitted in fulfilment of the requirements for the degree of Doctor of Philosophy.

Supervisors:

Professor Michael F. O'Rourke MD DSc

Professor Alberto P. Avolio BE PhD

January 2016

DEPARTMENT OF
BIOMEDICAL SCIENCES
Faculty of Medicine and Health Sciences

MACQUARIE UNIVERSITY

Declaration of originality

I hereby declare that the work presented in this thesis has not been submitted for a higher degree to any other university or institution. To the best of my knowledge this submission contains no material previously published or written by another person, except where due reference is stated otherwise. Any contribution made to the research by others is explicitly acknowledged.

Audrey Indrawati (Sutanto) Adji

Department of Biomedical Sciences
Faculty of Medicine and Health Sciences
Macquarie University

14 January 2016

Declaration of contributions

Chapter 5

Data on central aortic pressure from SphygmoCor and left ventricular outflow tract from Doppler ultrasound have been provided by Prof Thomas Weber from Klinikum Wels, Austria. Data on carotid pressure from PulsePen and ascending aortic flow velocity from cardiac magnetic resonance have been provided by Prof Elie Mousseaux, Drs Nadjia Kachenoura and Emilie Bollache from Cardiovascular Imaging Department, Hôpital Européen Georges Pompidou, AP-HP, Paris, France. Prof Mousseaux, Drs Kachenoura and Bollache also provided constructive input and feedback in the manuscript writing.

Chapter 6

The work on cerebral pressure, flow and impedance is a result of collaborative work with recent PhD graduate Dr Mi Ok Kim. Data analysed in this project have been provided by Prof Marek Czosnyka and Prof John Pickard from Neurosurgical Unit, Cambridge University; Prof Per Eide from Neurosurgery Unit, Oslo Hospital. Data in normal subjects have been provided by Dr Yan Li and Prof Jiguang Wang from Ruijin Hospital, Shanghai, and volunteers from Macquarie University.

Chapter 7

This chapter contains all my related publications in the field of aging and arterial stiffness. Contributions of collaborators will be detailed in the specific sections.

Acknowledgements

This PhD thesis is the culmination of 8 years of hard work and dedication. It involved many stressful occasions, where I thought I could not go any further; yet with encouragement of my family and friends, I could cross the finish line. It would not have been completed without continuous support of many people. While I am not able to thank every single person in this thesis, I would like to acknowledge a few important people here.

Firstly, thanks to my supervisor and life-long mentor, Michael O'Rourke. I would not be where I am right now without your continuous support and guidance. You have taught me a lot more that I can write here, academically and beyond, and I will be forever grateful. Your endless energy and passion for research is incredible, and I am fortunate to be taught by you and working by your side for the last 15 years, hopefully for many years ahead.

To my other teacher, Albert Avolio, thank you. I am grateful that you introduced me to Michael; it was a life-changing experience and opportunity. Your "no-nonsense" attitude always encourages me not to give up trying and to keep going. You are always supportive to all of your students, and I am blessed to be one of your students (twice). I will be forever thankful to know you personally.

To my fellow past- and present students at the Department of Biomedical Sciences (formerly ASAM); although I do not see every one of you often enough, you have touched my life in a way throughout my study period, in a way that cannot be expressed in words. In particular to Isabella Tan and Mi Ok Kim; we have started this journey together, of studying while looking after our children, and I look forward to three of us finishing our PhD.

Last, but not least, to my family. Thanks to my parents, by allowing me to embark in an unknown journey away from home. To my husband, Reza; it is a blessing that I have been with you more than half of my life. Thank you for all your (quiet) support and encouragements. Even though our lives are far from perfect, I am always fortunate to be able to go home and to know someone is there for me. To my children, Patrick and Jonathan; I hope I have showed you that education is very important in life, and for both of you to continue learning in life. The sky is your limit. This thesis is dedicated to both of you.

Publications

List of publications relevant to this thesis

(* publications that appeared or submitted during the PhD candidature)

Journal publications

1. **Adji A**, O'Rourke MF. Determination of central aortic systolic and pulse pressure from the radial artery pressure waveform. *Blood Pressure Monitoring* 2004;9:115-121.
2. Hirata K, Vlachopoulos C, **Adji A**, O'Rourke MF. Benefits from angiotensin-converting enzyme inhibitor "beyond blood pressure lowering": beyond blood pressure or beyond the brachial artery? *Journal of Hypertension* 2005;23:551-556. Erratum *Journal of Hypertension* 2005;23:905-906.
3. Hirata K, **Adji A**, Vlachopoulos C, O'Rourke MF. Sildenafil improves cardiac performance in heart failure patients. *American Journal of Cardiology* 2005;96:1436-1440.
4. **Adji A**, Hirata K, O'Rourke MF. Clinical use of indices determined non-invasively from the radial and carotid pressure waveforms. *Blood Pressure Monitoring* 2006;11:215-221.
5. **Adji A**, Hirata K, Hoegler S, O'Rourke MF. Non-invasive pulse waveform analysis in clinical trials: similarity of two methods for calculating aortic systolic pressure. *American Journal of Hypertension* 2007;20:917-922.
6. ***** O'Rourke MF, **Adji A**. Basis for use of central blood pressure measurement in office clinical practice". *Journal of the American Society of Hypertension* 2008;2:28-38.
7. ***** Weber T, Ammer M, Rammer M, **Adji A**, O'Rourke MF, Wassertheurer S, Rosenkranz S, Eber B. Non-invasive determination of carotid-femoral pulse wave velocity depends critically on assessment of travel distance – a comparison with invasive measurement. *Journal of Hypertension* 2009;27:1624-1630.
8. ***** O'Rourke MF, **Adji A**. Clinical use of applanation tonometry: Hope remains in Pandora's box. *Journal of Hypertension* 2010;28:229-233.
9. ***** Namasivayam M, **Adji A**, O'Rourke MF. Aortic augmentation index and aging: mathematical resolution of a physiological dilemma? *Hypertension* 2010;56:e9-10.
10. *** Adji A**, O'Rourke MF, Namasivayam M. Arterial stiffness, its assessment, prognostic value, and implications for treatment. *American Journal of Hypertension* 2011;24:5-17.
11. ***** O'Rourke MF, **Adji A**, Namasivayam M, Mok J. Arterial aging: a review of the pathophysiology and potential for pharmacological intervention. *Drugs and Aging* 2011;28:779-795.
12. ***** Namasivayam M, **Adji A**, O'Rourke MF. Influence of aortic pressure wave components determined non-invasively on myocardial oxygen demand in men and women. *Hypertension* 2011;57:193-200.
13. *** Adji A**, O'Rourke MF. Brachial artery tonometry and the Popeye phenomenon: explanation of anomalies in generating central from upper limb pressure waveforms. *Journal of Hypertension* 2012;30:1540-1551.
14. ***** O'Rourke MF, **Adji A**. Noninvasive studies of central aortic pressure. *Current Hypertension Report* 2012;14:8-20.
15. ***** O'Rourke MF, **Adji A**. Guidelines on Guidelines: Focus on isolated systolic hypertension in youth. *Journal of Hypertension* 2013;31:649-654.
16. ***** O'Rourke MF, **Adji A**. Non-invasive generation of the aortic from radial pressure waveform using applanation tonometry, brachial cuff calibration, and generalized transfer function. *American Journal of Hypertension* 2014;27:143-145.

17. ***** The Reference Values for Arterial Measurements Collaboration. Establishing reference values for central blood pressure and its amplification in a general healthy population and according to cardiovascular risk factors. *European Heart Journal* 2014;35:3122-3132.
18. ***** Kim MO, **Adji A**, O'Rourke MF, Avolio AP, Smielewski P, Pickard JD, Czosnyka M. Principles of cerebral hemodynamics when intracranial pressure is raised: lessons from the peripheral circulation. *Journal of Hypertension* 2015;33:1233-1241.
19. ***** Namasivayam M, **Adji A**, O'Rourke MF. Evaluating the hemodynamic basis of age-related central blood pressure change using aortic flow triangulation. *American Journal of Hypertension* 2015 (online 4 June, doi: 10.1093/ajh/hpv80).
20. * O'Rourke MF, **Adji A**, Namasivayam M. Interpreting blood pressure in younger adults. *Journal American College of Cardiology* 2015;66:329-330.
21. *** Adji A**, O'Rourke MF. Tracking of brachial and central systolic pressure over the entire life course. (ready for submission)
22. *** Adji A**, Kachenoura N, Bollache E, O'Rourke MF, Avolio AP, Mousseaux E. Magnetic resonance and applanation tonometry for non-invasive determination of left ventricular load and ventricular vascular coupling in the time and frequency domain. *Journal of Hypertension* 2015 (under review)
23. ***** Kim M, Li Y, Wei F, Wang J, O'Rourke MF, **Adji A**, Avolio AP. Cerebral vascular pulsations: implications for microvascular disease. *Journal American College of Cardiology* 2015 (under review)

Conference proceedings (In: Ang B (ed). *Acta Neurochirurgica Supplement: Intracranial Pressure and Brain Monitoring XV* 2016; series vol. 122**)**

24. ***** Kim MO, O'Rourke MF, Avolio AP, **Adji A**. Central pulsatile pressure and flow relationship in time and frequency domain to characterise hydraulic input to the brain and cerebral vascular impedance.
25. ***** Kim MO, **Adji A**, O'Rourke MF, Avolio AP, Smielewski P, Pickard JD, Czosnyka M. Change in pulsatile cerebral arterial pressure and flow waves as a therapeutic strategy.
26. ***** Kim MO, Eide PK, O'Rourke MF, Avolio AP, **Adji A**. Intracranial pressure waveforms are more closely related to central aortic than radial pressure waveforms: implications to pathophysiology and therapy.

Conference abstracts published in journals

27. *** Adji A**, O'Rourke MF, Avolio AP. Disparate effect of ageing in pressure and flow waveform: a modelling study. Hypertension 2009;53:1099 (poster presented at High Blood Pressure Research Council of Australia Meeting, Melbourne, Victoria 2008)
28. ***** Namasivayam N, **Adji A**, O'Rourke MF. Mechanisms for change in aortic augmentation with age. Hypertension 2009;53:1114 (poster presented at High Blood Pressure Research Council of Australia Meeting, Melbourne, Victoria 2008)
29. ***** Namasivayam N, **Adji A**, O'Rourke MF. Mechanisms for change in aortic augmentation with age (poster presented at Pulse of Asia Meeting, Daegu, South Korea 2009). Artery Research 2009;3:95.
30. *** Adji A**, O'Rourke MF, Avolio A. Modelling study of change in aortic pressure and flow waveforms with age. Heart, Lung and Circulation 2009;18S:S278 (poster presented at Cardiac Society of Australia and New Zealand Meeting, Sydney, NSW)
31. ***** Namasivayam M, **Adji A**, O'Rourke MF. Mechanisms of age-related blood pressure change in a cross-sectional cohort of 1888 cardiology outpatients. Heart, Lung and Circulation 2009;18S:S278 (presented orally at Cardiac Society of Australia and New Zealand Meeting, Sydney, NSW)
32. *** Adji A**, O'Rourke MF. Measurement of mean arm pressure for calculation of central aortic systolic and pulse pressure. Hypertension 2010;55:1494 (poster presented at the High Blood Pressure Research Council of Australia Meeting, Sydney, NSW)
33. *** Adji A**, Hoegler S, O'Rourke MF. Amplification of the pressure wave in human upper limb. Hypertension 2010;55:1493 (presented as oral communication at the High Blood Pressure Research Council of Australia Meeting, Sydney, NSW)

34. *** Adji A**, O'Rourke MF, Avolio A, Weber T. Estimation of aortic flow from derived aortic pressure waveforms: a modelling study. Hypertension 2010;55:1493 (poster presented at the High Blood Pressure Research Council of Australia Meeting, Sydney, NSW)
35. *** Adji A**, Hoegler S, O'Rourke MF. Calibration of central pressures: a flaw in applanation tonometry? J Hypertens 2010;28:e37 (presented as oral communication at the European Society of Hypertension, Oslo, Norway)
36. *** Adji A**, Namasivayam M, O'Rourke MF, Avolio A, Weber T. Generation of aortic flow velocity from derived aortic pressure waveforms. Heart, Lung, Circulation 2010; 19S:S217 (presented as poster for the Cardiac Society of Australia and New Zealand, Adelaide, SA).
37. *** Adji A**, O'Rourke MF. Calibration of carotid central pressure: a flaw in brachial applanation tonometry? Heart, Lung, Circulation 2011;20S:S12 (presented as poster at the Cardiac Society of Australia and New Zealand 2011 Meeting, Perth, WA).
38. *** Adji A**, Kim M, O'Rourke MF, Avolio AP, Eide PK. Relationship between central pulsatile aortic and intracranial pressure in humans. Hypertension 2012;60:502 (presented as oral communication at the High Blood Pressure Research Council of Australia 2011 Meeting, Perth, WA).
39. *** Adji A**, Kim M, O'Rourke MF, Avolio AP. Relationship between central pulsatile aortic pressure and middle cerebral artery flow waveforms in normal young adults. Hypertension 2012;60:497 (presented as poster at the High Blood Pressure Research Council of Australia 2011 Meeting, Perth, WA).
40. *** Adji A**, Kim M, O'Rourke MF, Avolio AP, Eide PK. Relationship between central pulsatile aortic and intracranial pressure in humans. J Hypertens 2012;30 (suppl A):e110 (presented as oral communication at the European Society of Hypertension Meeting, London, UK).
41. ***** Kim M, **Adji A**, Li Y, Wei F, Wang J, O'Rourke M, Avolio A. Pulsatile pressure/ flow relations in human cerebral arteries, described in time and frequency domain as vascular impedance. J Hypertens 2012;30:e102 (presented for poster at the International Society of Hypertension 2012 Meeting, Sydney, NSW).
42. ***** Kim M, **Adji A**, Li Y, Wei F, Wang J, O'Rourke M, Avolio A. The vis-a-tergo for cerebral perfusion: role of the left ventricle and systemic arteries and implications for therapy in stroke. J Hypertens 2012;30:e102 (presented for poster at the International Society of Hypertension 2012 Meeting, Sydney, NSW)
43. *** Adji A**, O'Rourke M, Avolio A, Weber T. Estimation of aortic flow velocity from derived aortic pressure waveforms. J Hypertens 2012;30:e155 (presented for poster at the International Society of Hypertension 2012 Meeting, Sydney, NSW and **won 2nd prize in Best Poster Presentation** at the concurrent Pulse of Asia Meeting).
44. ***** Kim MO, **Adji A**, Li Y, Wei FF, Wang JG, O'Rourke MF, Avolio AP. Pulsatility of pressure and flow waveforms in cerebral arteries: origin and significance. Circulation 2012;126 (suppl): A17734 (presented as oral communication at the American Heart Association 2012 Meeting, Los Angeles, US).
45. ***** O'Rourke M, **Adji A**, Kachenoura N, Bollache E, Mousseaux E, Avolio A. Effects of Aging on Ascending Aortic Flow Waveform. Pulse 2013;1:44-45 (presented as moderated poster at the Pulse of Asia meeting, April 2013, Seoul, South Korea and **won 1st prize in Best Moderated Poster Presentation**).
46. *** Adji A**, Kachenoura N, Bollache E, Avolio AP, O'Rourke MF, Mousseaux E. Effect of aging on ascending aortic flow measured by non-invasive MRI. Hypertension 2014;63:e143. (presented as poster at HBPRCA 2013 meeting, Melbourne, VIC)
47. ***** Kachenoura N, Bollache E, **Adji A**, Avolio AP, O'Rourke MF, Mousseaux E. Non-invasive determination of ascending aortic impedance. Hypertension 2014;63:e143.-144. (presented as poster at HBPRCA 2013 meeting, Melbourne, VIC)
48. *** Adji A**, O'Rourke MF, Avolio AP. Tracking of aortic systolic pressure over the entire left course. Hypertension 2014;63:e144 (presented as poster at HBPRCA 2013 meeting, Melbourne, VIC).
49. ***** Namasivayam M, **Adji A**, O'Rourke MF. Delineating the mechanisms of age related pulsatile blood pressure change. J Am Coll Cardiol 2014;63(Suppl A):A358 (presented as poster at the ACC Meeting 2014).
50. ***** O'Rourke MF, **Adji A**, Avolio AP. Tracking of central aortic systolic blood pressure over the entire life course. J Am Coll Cardiol 2014;63(Suppl A):A513 (presented as poster at the ACC Meeting 2014).
51. *** Adji A**, Kachenoura N, Bollache E, Avolio AP, O'Rourke MF, Mousseaux E. Cardiac magnetic resonance and applanation tonometry for non-invasive determination of ascending aortic flow, pressure and impedance and their changes with aging. J Hypertens 2014;32(e-Suppl 1):e444 (presented as poster presentation at ESH 2014 meeting, Athens, Greece).
52. *** Adji A**, O'Rourke MF, Avolio A. Tracking of central and upper limb systolic pressure over the normal human lifespan. Circulation 2014;130:A12363 (presented as poster presentation at the AHA Scientific Meeting, November 2014, Chicago, IL, USA).

Abstract

Background: The elucidation of mechanisms whereby arterial stiffness with increasing age alters the propagation of pressure (and flow ejection) waves generated by each heart beat is still evolving and sometimes debated. The research described in this thesis aims to better characterise the age-related changes in ascending aortic blood pressure and blood flow non-invasively.

Methods: This thesis investigates four key areas:- (i) measurement of aortic stiffness with pulse wave velocity; (ii) non-invasive central arterial pressure measurements; (iii) characterisation of age-related changes in central aortic pressure and flow with non-invasive methodology; (iv) relationship of cerebral arterial pressure and flow with central aortic pressure and flow.

Results: Findings of this investigation highlight the clinical importance of non-invasive measurement of central aortic pressure and aortic flow to determine ascending aortic impedance as a measure of cardiac load. The physical relationship between aortic pressure, flow and arterial impedance is quantified in terms of age-related changes. Changes in aortic flow pattern and means to derive aortic flow waveform from aortic pressure waveform non-invasively are compared with other methods. Results show that changes in the cardiac ejection pattern with age are better determined using magnetic resonance imaging compared to Doppler ultrasound techniques. Initial investigation of the effect of arterial stiffening, as occurs with age, shows that there is a relationship between the higher pressure pulsations from the heart and the damage in the brain due to the higher flow pulsations being transferred to the cerebral circulation.

Conclusion: This investigation confirmed the changes in central aortic blood pressure and flow ejection with aging. Derivation of the aortic flow pattern from central aortic pressure is feasible, through their relationship with aortic impedance. Increased pulsatility of arterial pressure and flow may cause damage to the microvasculature in the brain and may relate to the cognitive decline with aging and disease.

Table of Contents

List of Figures

List of Tables

Chapter 1

Introduction

The population is aging – in developed as well as in developing countries. In all, there is an upward shift in the age structure, where the proportion of the younger group declines and the number of older people increases; the median age of Australians rose from 32.1 years at 1990 to 36.9 years at 2010 [Australian Bureau of Statistics, 3201.0 - Population by Age and Sex, Australian States and Territories, Jun 2010] (**Figure 1-1**). Better quality of life and improved health care have mostly contributed to increasing life expectancy. However, this has been accompanied by declining fertility rates and improved birth control. The aging population is a major target in government policy making, as it is related to planning of income support, review of retirement age, health and aged care services, as well as its implication in economic growth.

Aging is a physiological change that is expected in every individual, and the process is inevitable. Cardiovascular aging is closely related to blood pressure; increasing age, together with family history, have been known as major risk factors for cardiovascular-related diseases [United States National Institute of Aging, 2010] for over 100 years.

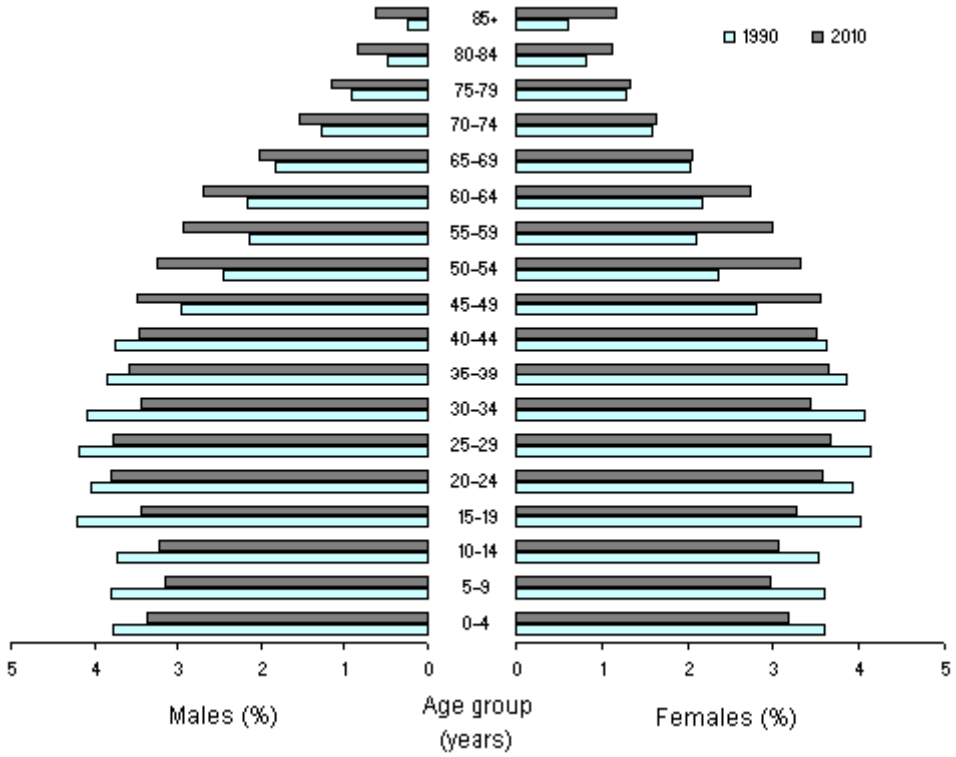


Figure 1-1. Australia's population structure based on age and gender, from 1990 to 2010. The proportion of working age (aged 15 to 64 years) has remained relatively steady, increasing from 66.9% to 67.5% of the total population. The proportion of people aged 65 years and over has increased from 11.1% to 13.6%, while those aged 85 years and older has risen markedly from 0.9% to 1.8% of the total population. In contrast, the proportion aged 15 years and younger decreased from 22.0% to 18.9%. Source: Australian Bureau of Statistics, 3201.0, June 2010.

Aging, with arterial stiffening, and its health implications is an important research area. In Australia, it was estimated in 2011-2012 that approximately 4 million people had at least one long-term cardiovascular condition, and this number is escalating every year. Cardiovascular disease remains the leading cause of death [Australian Institute of Health and Welfare.

Australia's Health 2010; website www.health.gov.au]. Based on data from the Australian Bureau of Statistics, 32% of all deaths in 2010 were associated with cardiovascular disease; 33,000 are related to coronary heart disease and stroke, while a further 6,700 were associated with heart failure, hypertension and cardiac arrhythmia [Australian Bureau of Statistics website. www.abs.gov.au]. Similarly in the United States, approximately one-third of all adults have high blood pressure, defined as brachial systolic blood pressure ≥ 140 mmHg and/ or diastolic pressure ≥ 90 mmHg, shown in the 2010 American Heart Association Statistical Update on Heart Disease and Stroke from 2006 National Health and Nutrition Examination Survey (NHANES) (Lloyd-Jones 2010). Cardiovascular disease is also associated with a high level of disability. The key results from the Global Burden Disease Study in 2010 have been published in a series of papers in the Lancet from late 2012 to 2013, where data of global disease burden were compared between those in 1990 to as recent as 2010 (Lim et al. 2012). This showed that contribution of risk factors to disease burden has shifted to non-communicable diseases in adults (Lim et al. 2012). In 2010, high blood pressure was one of the three leading risk factors, accounted for 7% of global DALYs (disability-adjusted life years) (Lim et al. 2012). Similarly in the United Kingdom, although overall health status has improved substantially, increased blood pressure is still the second leading risk factor after tobacco use, representing 9% of DALYs (Murray et al. 2013). In developing countries such as China, stroke and ischemic heart disease emerged as the two leading causes of death (Redon et al. 2011, Yang et al. 2013) (**Figure 1-2**), with the principal sources of DALYs being cardiovascular disease due to high blood pressure as a risk factor (Yang et al. 2013). All of these recent findings were consistent with those reported previously (Kearney et al. 2005, Perkovic et al. 2007, Lawes et al. 2008, Huffman et al. 2012). The classification of ischemic heart disease as the cause of death, however, does not differentiate the origin of heart disease, whether it is attributable to atherosclerosis (often found in the developed countries), or to high systolic blood pressure, due to aging process and leading to weakening

of heart contraction associated with increased cardiac work (often occurred in the developing countries) (Staessen et al. 2003).

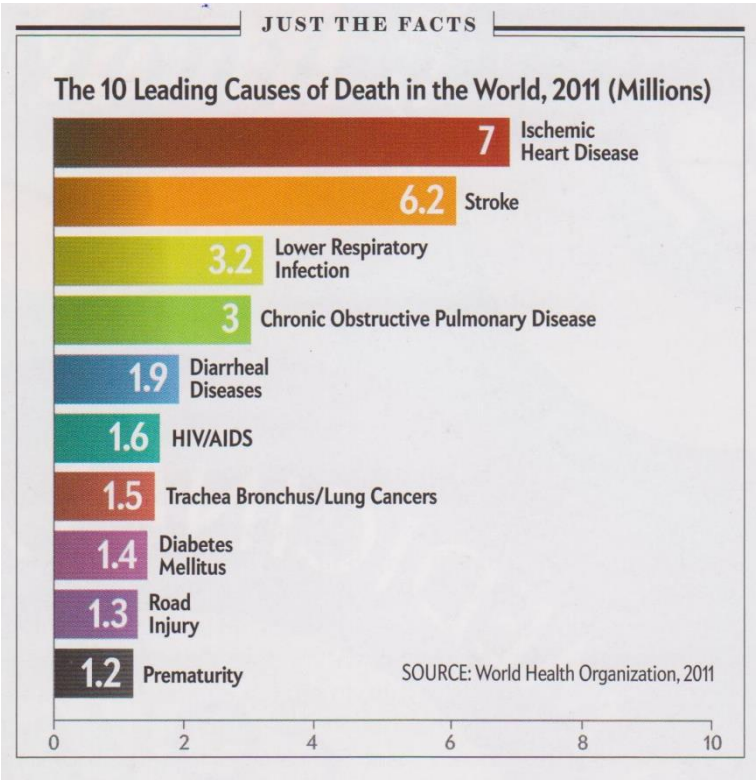


Figure 1-2. The top 10 leading causes of death in the world from the World Health Organization, 2011. Source: Scientific American, 2014. Promoting Cardiovascular Health Worldwide. Recommendation 12: the WHO Monitoring Model. By: S Medis and O Chestnov, page 74.

In contrast to these facts, Australian cardiovascular disease related deaths (adjusted by age) rates fell by an estimated 76% between 1968 and 2007 [Australian Institute of Welfare. Australia's Health 2010; website www.health.gov.au], and this was attributed to improved detection, management and prevention. Management of cardiovascular disease involves monitoring of blood pressure; it is now widely accepted that increasing blood pressure with age can be attributed to the stiffening of the central arteries (Vasan 2008). The elucidation of the mechanism whereby arterial stiffness alters the propagation of pressure (and flow) wave

generated by each action of the pumping heart is still evolving and often is a source of vigorous debate (Avolio et al. 2009).

The arterial pulse felt at the wrist has been used by physicians from ancient times to the modern epoch for diagnosing illnesses. Throughout centuries, the arterial pulse was considered the most basic sign of life, and was considered to contain an abundance of information on the health or disease of a patient. Graphic recordings of the pulse waveform at the wrist were first made in the late nineteenth century and were quickly embraced by physicians as a useful clinical tool, along with the stethoscope and thermometer. The pulse waveform was recognised as providing information on elevated arterial pressure and on effects of arterial stiffening with age. Interest in the pulse lapsed with introduction of the cuff sphygmomanometer to solely measure peak and trough of the arterial pressure wave, and present numbers which provide a veneer of science.

Interest in the arterial pulse returned with introduction of the electronic tonometers, which were far more accurate and easier to use than the 19th century sphygmographs, with possibility of representing the pulse waves with numerical quantities in the time and frequency domain, with emergence of theory to explain the wave contours, and with the digital age that permitted manipulation of such numerical quantities in microseconds. It is increasingly recognised that the pulse waveforms contain important information on arterial as well as cardiac function and the effects of age.

Application of new information requires understanding of the accuracy and limitations of the new techniques. Research work described in this thesis has largely been directed at this subject – to find methods that will help medical science to advance. Initially this was directed at interaction between heart and arteries – on timing of the action of the heart to the arterial system, and the detuning that comes with advancing years in humans. This has progressed,

but leading to unexpected directions – principally to explain damage to small arterial vessels in the brain that acutely can lead to further damage after head injury or stroke, or may have diffuse effects on the microvasculature and lead to disruption of neural circuits, and development of cognitive decline and dementia.

In the process of this research, old established methods have come into question and new applications have emerged which potentially are able to redefine function and dysfunction of the arterial and cardiovascular system. This thesis addresses the above concepts and represents application of classic physiological techniques as espoused by great scientists such as:

- *William James* "Science like life feeds on its own decay. New facts burn old rules; then newly developed concepts bind old and new together into a reconciling law." (James 1956)
- *Carl Ludwig* "Die Methode ist Alles" (Neil 1961)
- *Stephen Hales* "As an animal Body consists not only of a wonderful texture of solid Parts, but also of large proportion of Fluids, which are continually circulating and flowing, thro' an inimitable Embroidery of Blood-Vessels, and other inconceivably minute Canals: and as the healthy State of an Animal principally consists, in the maintaining of a due Equilibrium between those Solids and Fluids; it has ever since the important Discovery of the Circulation of the Blood, been looked upon as a Matter well worth enquiring into, to find the Force and Velocity with which these Fluids are impelled; as a likely means to give a considerable Insight into Animal Oeconomy." (Hales 1733)
- *William Harvey* "I finally saw that the blood, forced by the action of the left ventricle into the arteries, was distributed to the body at large, and its several parts, in the same manner as it is sent through the lungs, impelled by the right ventricle into the

pulmonary artery, and that it then passed through the veins and along the vena cava, and so round to the left ventricle in the manner already indicated. Which motion we may be allowed to call circular…" (Harvey 1628)

The investigation reported in this thesis began with history of the pulse wave until the time of important breakthrough in haemodynamic knowledge, evaluation of a method for generating central aortic pressure from the peripheral pressure waveform, and continue with attention to all responsible criticism that could be raised against the technique, and to undue enthusiasm from other quarters. Next it sought features of the pulse waveform in humans which are sufficiently constant as to provide landmarks against which other information on normal or abnormal function could be obtained. Amongst these is the rate of rise of pressure and flow in the ascending aorta, the timing of peak flow, and its relationship to the peak or shoulder of the pressure wave, the secondary surge of pressure in the ascending aorta after peak flow in older adults, the absence of this in adults with impaired left ventricular contractility, absence of flow in the ascending aorta during diastole, and the way this assists to analyse the aortic pressure wave. New methods emerged to generate flow from aortic pressure waves by utilising the known changes in vascular impedance with age, and compare this with the current routine method of measuring aortic flow waves. This information is also applied to understand the mechanism of how changes in pressure pulse propagation with age may affect the brain resulting in dementia or stroke.

While engaged in research described in this thesis, results steered my research work to realisation that the aging mechanism that affects pressure and flow propagation from the heart will in time affect the brain due to its low resistance and high flow nature. The effect of aortic stiffening to cushion pulsations of flow (and pressure) from the heart is investigated as they extend into the brain. This is an important field of research as microvascular disease of the brain and kidneys and the associated hypertension is known to be the most common cause of

intellectual deterioration and of kidney failure in older individuals, and the major cause of secondary brain damage following traumatic brain injury and acute subarachnoid haemorrhage. The preliminary analysis has been completed, and this project is expected to continue after submission of my thesis. It is expected that from this work, a new perspective begins in understanding the physiology of aging and its related mechanism. Work in this field is continuing.

1.1 Thesis organisation

This thesis is submitted as thesis-by-publication. Since working in the field of cardiovascular hemodynamics over the last 15 years, in studying the quantification of the pulsatile function of the cardiovascular system, I have published over 30 journal articles and produced over 60 accepted abstracts for presentation at scientific conferences. A total of 26 papers in which I am the primary author or co-author during my PhD candidature (part-time enrolment) from 2007 to 2015 are listed in Chapters 3 to 7. These 26 manuscripts, including currently one in the process of review and two ready for submission, have been selected to be incorporated in this thesis as they are related to the core topic of non-invasive characterisation of changes in aortic pressure and flow with aging. Each paper has been listed in the associated chapters and details are provided on my specific contribution to each paper.

The literature review is described in detail in Chapter 2, from ancient times up to the 1960s. The investigation reported in this thesis is continued in Chapter 3 with review of the increase in systolic blood pressure with age as a manifestation of arterial stiffening as generally occurs with age. The most common method to measure stiffening of the large arteries is aortic

stiffness, as assessed non-invasive using carotid-to-femoral pulse wave velocity, and a validation paper has been published and included in section 3.2, in which I was a co-author.

After some 20 years following the initial proposal of the transfer function technique, and 10 years after approval by the United States Food and Drug Administration, large clinical trials which reported central aortic pressure have increased significantly in numbers, in which most of them will be cited in this thesis. Since that time, evaluation of a method for generating central aortic pressure from the peripheral pressure waveform is ongoing, and continues with attention to all responsible criticism that could be raised against the technique, and to undue enthusiasm from other quarters. Currently, the most common method to estimate central aortic pressure non-invasively is by using the SphygmoCor® device (AtCor Medical, Sydney, Australia), which employs a generalised transfer function technique to derive the aortic pressure wave from radial artery tonometry. The radial artery tonometry and generation of aortic pressure non-invasively using a generalised transfer function method has now been accepted in cardiovascular research practice (Herbert et al. 2014, McEniery et al. 2014).

Prior to commencing this PhD thesis, I recorded arterial pulse wave recording from subjects and patients attending an outpatient cardiovascular clinic. From data collected, under supervision of Professor O'Rourke, we were able to refute criticism and opposition of this method by presenting original research and reviews. This issue was further pursued by collecting new data on drug action and physiological principles, and applied findings for use in aging and diseased conditions. All this prior research work strengthened my appreciation of the importance of measuring technique, calibration, and application of physiological principles to achieve realistic and reasonable results. The five papers published prior to my PhD candidature, which relate to the topic of this thesis and have informed work performed during the PhD candidature, have been included in Chapter 4 (sections 4.2, 4.3 and 4.5). Sections 4.7 to 4.9 list four papers that studied the central aortic pressure parameters and

aging, myocardial oxygen demand, the application of aortic flow triangulation on central aortic pressure change.

My work on central aortic pressure has gained recognition from the inclusion of our database in an extensive study on the Reference Values on Central Pressure by the European Network for Arterial Stiffness Collaboration, listed in section 4.6. Many apparent inaccuracies in central aortic pressure measurements are considered as usual occurrence, though these results might be systematically diverse from physiological principles. These include records of imprecise pressure data, and a suspected error in pressure measurement was confirmed. A total of five manuscripts (one original research paper in section 4.4, four reviews in section 7.1, four editorials and commentaries in section 7.2) have been published since the commencement of this PhD, where an explanation of clinical application of aortic pressure is reported and its clinical value strengthened.

The journey of this PhD continues with further exploration of the relationship between central aortic pressure, flow and vascular impedance, and how this is affected by aging. Chapter 5 starts with the technical difficulties in estimating ascending aortic impedance non-invasively, since there was substantial variation in impedance values from various published papers by numerous investigators. Furthermore, no uniformity in central aortic flow measurement existed, blood flow measurement is found to be extremely sensitive to noise, and the arterial impedance is reported in different units. Subsequently, technical issues in pressure and flow measurements are described and examined, and while arterial pressure is relatively easy to measure by both invasive and non-invasive techniques, not all methods are suitable to use. The selection of measurement technique and its appropriate calibration is essential. Arterial flow measurement is shown to be more challenging, as the invasive measurement of flow requires careful placement of sensor for accurate recording according to the flow pattern and minimising noise. The current routine non-invasive measurement of aortic flow performed in

the clinical practice using ultrasound, regarded as the "gold standard" at present, is not entirely suitable to estimate impedance.

The major findings from this work are detailed in Chapter 5. This work has been advanced by utilising non-invasive aortic flow velocity measurement with cardiac magnetic resonance, and a manuscript on this is currently under review for publication (section 5.2). By exploiting the near-linear relationship between accurate measurement of pressure and flow, ascending aortic impedance as a measure of left ventricular hydraulic load can be estimated more accurately. It is expected that the work on impedance calculation and derivation of aortic flow velocity from non-invasive pressure will continue following submission of my thesis. Future work will involve development of a simple, realistic model to characterise aging change in cardiac ejection pattern and its progress with cardiovascular disease. New methods emerged to generate aortic flow from aortic pressure waves by utilising the known changes in vascular impedance with age, and compare this with the current routine method of measuring aortic flow waves. My ultimate goal is to study left ventricular ejection patterns and how these are affected by the aging process, which has not been fully investigated before, since interaction between the heart and blood vessels has previously been largely overlooked due to technical and analytical difficulties, especially when measuring ascending aortic flow velocity to assist in non-invasive assessment of cardiac function. Work in this area is continuing.

The aging mechanism that affects pressure and flow propagation from the heart will in time affect the brain. It is crucial to further explore this field as microvascular disease of the brain is known to be the most common cause of intellectual deterioration in older individuals(O'Rourke et al. 2005). The preliminary analysis on our brain pressure and flow data has been completed and reported in Chapter 6; three abstracts in conference proceedings are published in sections 6.2, 6.5 and 6.6, one original research paper has been published in section 6.4, and another is currently in journal reviewing process (section 6.3). This project is

expected to continue after submission of my thesis. It is expected that from this work, a new perspective begins in understanding the physiology of aging and its related mechanism. Work in this field is continuing.

In Chapter 7, there are other papers that relate to the topic of this thesis. These papers are in the form of reviews and editorials. Chapter 8 is the overall conclusion of all research studies described in this thesis.

Chapter 2

Literature Review

Summary

The arterial pulse has been the most basic sign of life for centuries. The radial pulse palpation has been pictured in the crest of the Royal Academy College of Physicians since 1628. The history of the arterial pulse entails the discovery of pulse, blood pressure and/or flow, and their measurements. This chapter will review the description of the pulse and the related discoveries of pulse and blood pressure and/or flow since the ancient period until the late 1970s where the concept of hemodynamics and importance of pressure and flow pulsatility as well as methods to analyse the pulse in both time and frequency domains gained wider acceptance. The literature review following from that time will be discussed in the corresponding chapters.

2.1 History of the Pulse: Ancient Era

2.1.1 Ancient Era

Since ancient era about 2500 years ago, the pulse has been recognised as an important part of medicine in Chinese, Indian, Egyptian and Greek culture. However, the measurement and interpretation of the pulse were entirely dependent on physicians, the standards of this time, and what had been passed down.

In the Chinese sphygmology, the Yellow Emperor Huang Ti wrote numerous books on the pulse, with graphical representation around 2500 BC (Bedford 1951, Ghasemzadeh et al. 2011). The theory of the pulse was based on the interaction between Yin (disease) and Yang (health) (Ghasemzadeh et al. 2011). Interestingly, in the manuscript it was also stated that "if too much salt is used in foods, the pulse hardens ...", illustrating that Chinese physicians had recognised the effects of sodium on the pulse waveform (Wakerlin 1962). The best known book in Chinese on the analysis of the pulse was written by Wang Shu-he in the late Han dynasty, circa 220 AD (Parker 2009).

In the Indian sphygmology, Sage Kanad had described various pulses and likened them to animals' motion (Bedford 1951, Ghasemzadeh et al. 2011). Egyptians' papyri had described Sekhmet priests measuring pulse, including Imhotep (3000 BC) (Ghasemzadeh et al. 2011). They had also been known to use direct auscultations as part of examination (Wakerlin 1962).

Prior to Galen's era, Greek physicians had been known to examine the pulse in their subjects. Hippocrates (circa 400 BC) described characteristics of the pulse in his book, although it was not known if he truly had studied the arterial pulse himself (Ghasemzadeh et al. 2011). Aristotle (384 BC) believed the heart is the centre of the physiological mechanism (Aird

2011). His student, Herophilus (335-280 BC), is regarded as the creator of ancient sphygmology, with his interpretation of the pulse related to rhythm (Bedford 1951). Herophilus created a water clock, *clepsydra*, which he used when assessing his patients to compare the pulsation of blood vessels to musical rhythm (Bedford 1951, Ghasemzadeh et al. 2011). He also described the pulse by its size, frequency, force and rhythm (Bedford 1951). Around the same time, Praxagoras of Kos (340 BC) was the first physician credited for examining arterial pulse (Ghasemzadeh et al. 2011), and differentiated between arteries and veins (Aird 2011). A contemporary of Herophilus, Erisistratus (304 – 250 BC), stated that the heart and arteries do not move at the same time, and arteries dilate while the heart contracts, where arterial dilation is the passive expansion of the blood vessels (Ghasemzadeh et al. 2011). He also considered the heart to be the source of both veins and arteries, but that arteries only contained air (Aird 2011). Archigenes (97-117 CE), repeatedly cited by Galen on his writings, described various pulses based on four characteristics:- length, depth, breadth and speed (Bedford 1951, Ghasemzadeh et al. 2011). Rufus (200 AD) recognised the heart as the cause of the pulse, where the arterial pulse corresponded with emptying of the heart and filing of the arteries, as well as identifying the pulse by its size, quickness, fullness and rhythm (Bedford 1951).

2.1.2 Claudius Galenus (129-200 AD)

Galen was considered to stand above all of Greek sphygmologists because he wrote more books on the pulse – more than anyone since (he was known to write 18 manuscripts) and his teaching dominated clinical practice for about 16 centuries, even long after William Harvey's time. Galen's circulation model included a permeable heart septum, that circulation had two supplies of "motors" with dual centrifugal currents, there was intervention of vital and natural spirits, while the lungs and brain served as "cooling plants" (Garrison 1931).

Galen was a master of language, hence his teaching could not easily be understood by the common people (Bedford 1951). He defined the pulse as a double movement of the artery – expansion during diastole and contraction during systole (Bedford 1951), and argued that dilation and contraction of heart and arteries are simultaneous (Ghasemzadeh et al. 2011), yet the arterial pulse is an inherent property of blood vessels, it starts from the heart and is transmitted through the coats of the arteries (Aird 2011). He stated that veins contain blood, and the liver is the source of all veins, thus blood moves from liver to periphery and passes from veins to arteries via anastomoses (or "unseen pores") in the lung and periphery. Galen made this statement based on arteriotomy – although Galen only found blood and nothing else, deciding that arteries contain air and blood; and blood from the left ventricle is derived directly from the right ventricle through "invisible pores" in the interventricular septum (Parker 2009, Aird 2011). Galen's understanding was that arterial blood obtains "vital spirit" from the right ventricle, while venous blood acquires "natural spirit" from the liver, and both subsequently converted into animal spirits in the brain (Garrison 1931). Galen was able to describe 27 varieties of pulses and their meaning (Parker 2009).

Galen's teaching on erroneous dual blood distribution system would carry on for centuries. Nonetheless, Galen made advancement on arterial pulse examination, and he made recommendation of feeling the pulse at the wrist as the most convenient (Bedford 1951). Galen described pulse variations due to age, gender, season, country, sleep, pregnancy, exercise, bathing, food and wine (Bedford 1951). Galen's sphygmology demonstrates his complicated and detailed mind, shown in his mastery of words, and led him to drift away from clinical observation (Bedford 1951). During his time, few could appreciate his writings, and he had little personal influence on students or colleagues. After his death, physicians were afraid to question his views.

2.1.3 Middle Ages

Following Galen's era, there was Canon of Avicenna (981-1037) who associated the quality of the pulse to three main factors:- vital power, resistance and elasticity, whereas Moses Maimonides (1135-1204) related arterial pulse rhythm to the severity of disease (Ghasemzadeh et al. 2011). Leonardo da Vinci (1452-1519) was the first to make accurate drawings of the heart, while Andreas Vesalius (1514-1564) detailed realistic illustrations of human body; Vesalius' work then became the first modern textbook of anatomy (Aird 2011).

An important contribution was made by Joseph Struthius who wrote 5 books "*Ars Sphygmica*" in 1540, where he simplified and clarified Galen's work. He was even known to examine the arterial pulse by placing a leaf on the artery and watching its vibrations (Bedford 1951).

2.2 History of the Pulse: Harvey and Hales

2.2.1 William Harvey (1578-1657)

William Harvey published his work as "*Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus*" (or An Anatomical Disquisition On the Motion of the Heart and Blood in Animals) in 1628, followed by two rebuttals to his criticisms in 1649. Harvey was first to discover circulation, fully describing circulation of blood in the body flowing from the heart to the extremities through arteries and from extremities back to the heart via the venous system (Ghasemzadeh et al. 2011). Harvey correctly stated that the heart action was to expel its charge of blood (Harvey 1628). Harvey also stated that "...the intrinsic motion of the heart

is not the diastole but the systole; neither is it in the diastole that the heart grows firm and tense, but in the systole...” (Harvey 1628).

During that time Harvey unquestionably never saw the capillaries (due to limitation during his era with the unavailability of microscopes). However, he concluded that there were small vessels connecting the arteries and the veins through his careful observation (Parker 2009). He was the first to attribute generation of the arterial pulse to left ventricular contraction – therefore recognising the pulse as a wave – and found the source of the heart beat in the right atrium (Ghasemzadeh et al. 2011). Harvey wrote “The motion of the heart, ..., and the one action of the heart is the transmission of the blood and its distribution, by means of the arteries, to the very extremities of the body; so that the pulse which we feel in the arteries is nothing more than the impulse of the blood derived from the heart.” (Harvey 1628)

Harvey showed that ventricular contraction occurs at the same time as the arteries are distended, and arteries and veins both contain the same blood (Aird 2011). The fundamental action of the heart is systole; its purpose to transmit and distribute blood into the periphery, then blood must return to the heart, therefore the circulation is a closed-circuit system (Aird 2011). Harvey concluded “...that the diastole of the arteries corresponds with the time of the heart's systole; and that the arteries are filled and distended by the blood forced into them by the contraction of the ventricles; the arteries, therefore, are distended, because they are filled like sacs or bladders...” (Harvey 1628). Blood enters a limb by arteries and returns from it by veins (Harvey 1628, Aird 2011). Harvey also confirmed that blood flows through the pulmonary system from the vena cava to the aorta, while the right ventricle serves to propel blood through the lungs into left atrium and ventricle (Harvey 1628, Aird 2011). Harvey described the arterial system as an elastic expansion system whose function is to smooth out the pulse generated by the heart action, as well as deliver blood to the tissues (Taylor 1966).

Harvey's work is significant in improving the physiological understanding of arterial pulse mechanisms and its clinical applications. Harvey analysed the mechanisms of events in cardiac cycle; he was able to demonstrate that the heart is a force (active) pump and the effect of pumping action on arteries (Garrison 1931). He showed how contraction played a role in the heart beat, and mechanism of auriculo-ventricular rhythm and heart sounds (Garrison 1931). Harvey performed numerous experiments in comparative anatomy and physiology of blood flow into, through and out of the heart (Garrison 1931), as well as making quantitative hemodynamic measurements and estimation of parameters such as stroke volume, cardiac output and ejection fraction (Ghasemzadeh et al. 2011). His work was a proof of the existence of a major circulation and the necessity for capillary anastomosis. Harvey had described wave reflection under some circumstances, and referred (perhaps incorrectly) to an experiment of Galen (see Harvey's second letter to Jean Riolan, 1649).

2.2.2 Stephen Hales (1677-1761)

Stephen Hales performed the first measurement of blood pressure (Booth 1977). As described in his book "Statical Essays: Containing Haemastatics" in 1733, Hales recorded damped systolic arterial pressure using a tall glass tube attached to the carotid artery of a horse from the height of the blood column within the tube and determined the effects of exsanguinations on arterial pressure (Hales 1733). He reported that the flowing blood exerts a pressure on the blood vessel's wall while the blood circulation obeys hydrostatic laws (Wakerlin 1962). In addition, Hales also measured pulmonary and venous pressure, as well as determining blood volume, calculated flow velocity in arteries and cardiac output, and established the site of peripheral resistance to be arterioles (Wakerlin 1962). Hales also discovered that the diastolic period lasts twice as long as systole, that warmth dilates and cold contracts arterioles and capillaries, while lung capillaries offer less resistance than systemic (Smith 1993).

Hales' discovery of blood pressure made him associate the elastic arterial system to the air-filled chamber of the fire engine, where pulsatile flow at the input is converted into a steady stream at the fire hose nozzle (O'Rourke et al. 1992). He did not take into account the effect of reflection on the pulse wave travel. Hales' view was a reasonable one for the time, especially when one sees Windkessel models referred to often in modern journals.

2.3 History of the Pulse: Modern Medicine

Thomas Young (1773-1829) presented his studies on (blood) hydraulics to the London Royal Society in 1808 in his Croonian Lecture (Young 1809) where he estimated the magnitude of the arterial pressure and the "resistance" in the blood vessels (Fye 1997), thus confirmed the expansion of the arteries was due solely to the heart's action in propelling the blood through the vessels. Young's work on modulus of elasticity went overlooked until rediscovered by German brothers, Ernst-Heinrich and Wilhelm Weber in 1850 and 1866 (Weber 1850, Weber 1866). Young described the celerity (c) of a pressure wave propagating in an incompressible liquid of mass density ρ contained in an elastic tube with elastic modulus or E, which was later, and is still now called Young's modulus.

Young also discussed the travel of pulse waves in arteries, following the concept of the Windkessel from Harvey's era (Taylor 1966). The same Weber brothers published a book on transmission of waves in fluids in 1825 (Weber et al. 1825) and later detailed in the paper of 1850 (Weber 1850), where they gave attention to pulses in arteries and established that the pulse did not occur synchronously in all arteries.

Moens (1846–1891) and Korteweg (1848–1941) (Korteweg 1878, Moens 1878) had at the same time, independently, described the formula of velocity (or the speed of the wave) of travelling fluid oscillations in an elastic pipe (Parker 2009). This was later known as Moens-Korteweg formula (Taylor 1966) which also includes Young's modulus in the formula:-

$$c = \sqrt{\frac{E\,h}{\rho\,D}} \qquad \text{Equation 2-1.}$$

where c = wave velocity, E is the 'static' value of Young's modulus of the arterial wall, h = wall thickness, ρ = blood density, and D = diameter of the vessel. It is an expression for the wave velocity (c) in terms of dimensions and physical properties of the tube (i.e. elasticity) and on the nature of incompressible liquid within it (Taylor 1966). The derivation of the relationship above assumes a thin walled tube, where D (diameter of the vessel) is much greater than h (wall thickness).

Jean Poiseuille (1799-1869) made advancement to Hales' method of measuring blood pressure by replacing the long glass tube with a U-tube mercury manometer (called hemodynamometer), published in his doctoral dissertation (Poiseuille 1828). Poiseulle calibrated his manometer to record arterial pressure level in mmHg, and was able to calculate the force of the heart beat by observing the oscillation of mercury with his manometer (Lawrence 1978). He also found that there is no significant difference in mean pressure between central and peripheral arteries, observed fluctuations in pressure with each heart beat, and demonstrated that arterial pressure was maintained in smaller arteries (O'Rourke et al. 1992). Further modification of the Poiseuille manometer was made by Julius Hérisson of Paris in 1831/1833 by sealing the end of the mercury containing glass tube with a thin membrane which rested on the artery, thus enabled him to obtain crude reading of blood pressure from intact arteries (PHG 1834, Wakerlin 1962). In his book (Herisson 1835),

Hérisson stated that he had no knowledge of Poiseuille's manometer at the time he developed his, and further claimed his manometer was not similar to Poiseuille's. Utilising Hérisson's device, the pulse can be studied by its force, regularity and rhythm.

In 1847, Carl Ludwig (1816-1895) made another modification to Poiseuille's manometer by adding a float, thus invented the *kymograph* (or 'wave writer') to depict arterial pressure (Wakerlin 1962, Booth 1977), hence set out modern methods of graphic representation of the pulse (Lawrence 1978). Ludwig's invention started from his interest on physiological relation between respiration rate and blood pressure (Ludwig 1847).

About the same time as Ludwig, Karl van Vierordt in 1855 suggested that an indirect, non-invasive technique to measure pulse might be generated from the counter pressure required to cause arterial pulsation to cease (van Vierordt 1855, Booth 1977). Vierordt's instrument was large, had two heavily weighted levers which converted the unequal rise and fall of the pulse into a symmetrical curve (Lawrence 1978).

2.4 Sphygmography in the Modern Era

Etienne Jules Marey (1830-1904), frustrated by the bulk of Vierordt's instrument (Marey 1860), developed a simpler and more accurate device to illustrate and measure the arterial pulse (Lawrence 1978), by combining a sphygmograph and a kymograph (Booth 1977). Marey's device was introduced in the Lancet in 1860 with a notice "It may be doubted whether these instruments, though very ingenious, will ever prove actually useful in practice" (Lawrence 1978). While Marey's sphygmograph was accepted widely for recording and studying the pulse, it was still too complicated to use routinely in practice, hence the

sphygmograph went through further modifications in England. John Burden-Sanderson, as described in his "Handbook of the Sphygmograph" (Burdon-Sanderson 1867), together with Francis Anstie (Ainstie 1868) modified Marey's sphygmograph by fixing the pressure to be 300 grams at the centre button and adding a screw to raise and lower the spring's free end by a measured amount at the distal end of the device.

Marey did the first formal study on arterial pulse wave to demonstrate the difference in the pulse of elderly and young adults (Marey 1863). Marey's sphygmograph made apparent the asymmetrical nature of pulse waves and their variation under different physiological and pathological condition (Lawrence 1978). Marey wrote a chapter on arterial blood velocity in his popular textbook of medicine "Le circulation du sang a´ l'e´tat physiologique et dans des maladies (The Circulation of Blood in the Physiological State and in Diseases) (Marey 1881). One of his interesting observation was large reverse flow at the end of systole in more distal arteries such as the femoral artery (Parker 2009).

The first truly accurate estimation of blood pressure in humans was done by Faivre in 1856 (Booth 1977). He connected an artery to a mercury manometer during a surgical operation and was able to obtain direct readings. Faivre found brachial artery pressure to be between 115 to 120 mmHg (Booth 1977). Non-invasive blood pressure measurement was pioneered by von Basch in 1880, where he used an inflatable rubber bag filled with water, then the edges of the bag were tightly drawn up around the neck of a mercury manometer bulb to record pressure indirectly from radial artery (Booth 1977).

In 1875, William Henry Broadbent delivered a series of lectures on the pulse, which was published later in 1890 in his book "The Pulse" (Broadbent 1890). Broadbent advocated careful and systematic evaluation of the pulse, started with frequency and regularity of beats,

then the force or strength, finally the character (i.e. rise, duration and fall) of pulse (Fye 1990).

Frederick Mahomed (1849-1884), one of Broadbent's students, made further modification to Marey's sphygmograph and published his work in 1872 (Mahomed 1872). His modification included placing over the centre of the spring a vertical eccentric turned by a graduated screw, as well as replaced the side wires with ivory bars (Lawrence 1978). Mahomed recorded the pulse graphically, thus permitting the pulse to be studied as a wave (Ghasemzadeh et al. 2011). His first paper quoted:

> "The pulse, ranks the first among our guides; no surgeon can despise its counsel, no physician shut his ears to its appeal. Since, then, the information the pulse affords is of so great importance and so often consulted, surely it must be to our advantage to appreciate fully all it tells us, and to draw from it all that it is capable of imparting. Our sense of touch, however highly educated, is manifestly liable to error and it is to our more reliable sense, that of sight, we appeal, when possible, for confirmation. It is by the aid of this more accurate sense we should study the pulse in its marvellous changes of character and form, as recorded by the sphygmograph." (O'Rourke 1992)

Using the sphygmogram, Mahomed's attention was turned to the characteristic features of the pulse of high tension ("hardness of the pulse" described by Bright), also seen in arterial degeneration:

> "...The tidal wave is prolonged and too much sustained ... indicated in the tracing merely by a slight rounding of the tidal wave, and any such tendency must be looked upon with suspicion; implicit confidence, however, cannot be placed in it, as a similar appearance is produced by degeneration of the arteries, but if due to this cause a very

> slight pressure is sufficient to extinguish the pulse, while a pulse of high tension generally requires a more considerable one." (O'Rourke 1992)

Mahomed made various systematic estimations of pulse tension, similar to recording blood pressure in modern terms, as part of his observation on Bright's disease (Lawrence 1978). Mahomed was the first person to distinguish essential hypertension from hypertension due to glomerulonephritis (Ghasemzadeh et al. 2011), by establishing correlation between the raised tension (i.e. increased pressure) with changes due to essential hypertension (Lawrence 1978) and noting its natural history (O'Rourke 1992).

2.4.1 Mahomed's observation of Bright's disease

In 1827, Richard Bright associated clinical findings of albuminuria, hardness and fullness of the pulse (i.e. high blood pressure), edema and hypertrophy of left ventricle with pathologic findings of sclerosing and contracting kidneys, and emphasised the absence of valvular disease on this (Wakerlin 1962, O'Rourke 1992). Furthermore, in 1836, he proposed increase in flow resistance through capillaries, originating the concept of arterial hypertension with kidney as a cause (Wakerlin 1962). Subsequently, in 1872, William Gull and Henry Sutton recognised Bright's disease to be primary generalised '*arteriocapillary fibrosis*' (Wakerlin 1962). From here, Mahomed then proposed the view that hypertension can cause renal vascular changes (Wakerlin 1962), quoted here:

> "The disease may commence as an acute infection and afterwards become chronic ... what has been the cause in one case may be the result in another; thus, general disorder may cause high arterial pressure and this, in its turn, kidney changes; while on the other hand, kidney changes may be primary and acute and they may in their turn produce impurity of blood and this general pressure. But whether we read the tale backwards or forwards it is the same tale in the end." (O'Rourke 1992)

Robert Ellis Dudgeon (1820-1904) invented a new compact sphygmograph (**Figure 2-1**), which he exhibited in 1881 and published in 1882 (Lawrence 1979). Dudgeon made significant improvements to Marey's and Mahomed's sphygmograph (Lawrence 1979). Dudgeon's sphygmograph was later used by James Mackenzie, founder of Cardiology as a discipline in the English-speaking world.

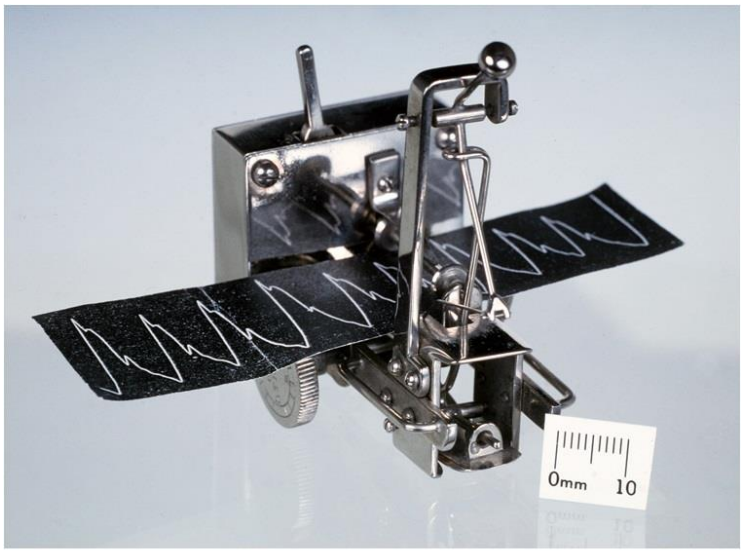


Figure 2-1. The Dudgeon sphygmograph.
Courtesy of M.F.O'Rourke (2014)

Sir James Mackenzie (1853-1925) (Mackenzie 1902) is highly associated with non-invasive investigation of normal and pathological cardiovascular phenomena (Lawrence 1979). He was one of the first observers to be interested in the regularity or otherwise of the pulse, also laid the foundation of modern concept of heart failure, which was being studied by Frank in Germany and by Starling in England at this time (Lawrence 1979).

While the introduction of the sphygmomanometer into clinical medicine in the early 1900s was accepted by some practitioners as a valuable aid for diagnosis, the 'British Medical

Journal' in 1905 stated in relation to use of clinical tools that "we pauperize our senses and weaken clinical acuity" (Booth 1977).

The next development in blood pressure measurement was the introduction of blood pressure measurement by palpation. Scipione Riva-Rocci in 1896 published 2 papers titled "*Un Nuovo Sfigmomanometro*" in Gazetta Medica di Torino (Riva Rocci 1896). His sphygmomanometer was based on established principles of Vierordt and further improvement by Marey and von Basch. Advantages of the Riva-Rocci device was the ease of its application, rapid action, precision and harmlessness (Lewis 1941, Booth 1977). The Riva-Rocci technique involved compression of the arm around its whole circumference by inflating a rubber bag with air. Using the palpation of the radial artery, systolic blood pressure can be determined (Booth 1977). One flaw of this technique was that the cuff was narrow, thus the reading of pressure can be inaccurate (Booth 1977). Later, von Recklinghausen in 1901 fixed this defect by substituting the armband by a wider one (Booth 1977).

Further advancement in pressure measurement was made by Nikolai Korotkoff, where in 1905, he reported that by placing a stethoscope over the brachial artery below the air-pressure cuff, tapping sounds – the sounds of the column of blood– could be heard as the cuff was deflated and blood flowed back into the artery (Lewis 1941). Korotkoff concluded that a perfectly constricted artery under normal conditions does not emit any sounds, and he introduced the *auscultatory method* to measure maximum and minimum level of blood pressure (Booth 1977). This auscultatory method was described in the Imperial Military Medical Academy in St Petersburg (Korotkov 1905).

Popularity of the sphygmomanometric cuff arose from its use in the Life Insurance industry which utilised its value of identifying apparently normal people who had markedly reduced age expectancy. In 1906, Dr. J. W. Fisher, medical director of the Northwestern Mutual Life

Insurance Co., initiated the inclusion of a blood pressure reading in every routine examination by their examiners (Fisher 1914). By 1918, most insurance companies were measuring cuff blood pressures.

2.5 Advancement in Measurement of Arterial Pressure and Flow in the 20th Century

Influence of diastolic filling on contraction level and cardiac output, illustrated in the "Frank-Starling Law", was observed about 30 years prior to Otto Frank's work and 50 years before Ernest Starling's well known law (Zimmer 2002). Early work at Carl Ludwig's Physiological Institute defined control condition in the isolated frog heart preparation (Zimmer 2002). Otto Frank further extended muscle physiology to the heart, before turning his interest to methodological problems of pressure recording (Zimmer 2002). Ernest Starling focussed his research on all possible physiological aspects of the effect of diastolic fibre length on heart function (Zimmer 2002). Based on his experiment with various heart and lung preparations, Starling formulated the 'Law of the Heart', in which 'the total energy liberated at each heart beat is determined by the diastolic volume of the heart and therefore by the muscle fibre length at beginning of contraction' (Patterson et al. 1914, Starling 1918, Zimmer 2002).

Otto Frank was the first to introduce an accurate manometer to measure intra-arterial blood pressure (Frank 1899, Frank 1905). His 1899 work was translated into English by Sagawa et al (Sagawa et al. 1990), where Frank described the mechanical conditions in the arterial system to be similar to the Windkessel of a fire engine. The system consists of a reservoir, the capacity of which depends on the pressure, corresponding to the arterial system and to the

Windkessel of the fire-engine. Connected with this is a tube, in which the fluid flows with a certain friction. The flow velocity is a function of the difference in pressure between the beginning and end of the tube. The latter part represents the capillary system and the hose of the fire-engine (Frank 1899). Frank emphasised that the systolic wave amplification and diastolic wave exaggeration also needed be accounted for, and compared the arterial system to an undamped manometer (Wiggers 1928).

Frank started with his attempts to derive methods of calculating stroke volume from the central arterial pressure pulse based on the classical Windkessel model (Taylor 1966). Frank's attempts were unsuccessful, as the model represented a gross oversimplification (Taylor 1966), however, he was able to explain the pulsatility in more detail than his predecessors.

Ernest Henry Starling with his "Law of the Heart" was introduced in 1914 (and republished in 1918) as the "The Linacre Lecture on the Law of the Heart" book (O'Rourke 1984). His original publications (Patterson et al. 1914, O'Rourke 1984) on the mechanisms of cardiac contraction described that cardiac output is dependent on venous return and independent of arteriolar resistance; that increase in cardiac afterload is associated with increase in venous filing pressure, which in turn maintains cardiac output; presented a graph of cardiac output against venous filing pressure; and lastly, the well-known Law of the Heart which explained these findings on the basis of fundamental properties of heart muscle on the basis on the similarity of heart muscle with skeletal muscle. This law is a manifestation of length-tension relationship seen initially in skeletal muscle by Schwann in 1832 (Katz 2002).

Illustration of Starling's law showed that increase in pressure was developed with increase in muscle length up to a point, and then subsequently the pressure decreased if the muscle lengthened further (O'Rourke 1984). It was not until Suga, Sagawa and colleagues, about 60

years later, at Johns Hopkins University showed that in the ejecting ventricle, there is no constant relationship between peak ventricular pressure and end-diastolic volume, but there is such constant relationship at end of ejection (Suga et al. 1973). The ventricle continues to eject until a particular volume is reached, that is the point on the Starling curve, which described peak pressure achieved at that volume for a non-ejecting beat. This relationship is affected by impaired myocardial contractility (O'Rourke 1984). Thus Starling's law, in other words, is to describe the role of end-diastolic volume in terms of muscle biochemistry and biophysics and the circulatory physiology in health and disease state (Katz 2002). Starling described that the heart has the power of adjusting the force and extent of its contractions to the task set by factors determining its work i.e. inflow to the heart from the veins and the resistance offered to the outflow by the arterial pressure (Fye 2006).

Starling extended earlier research by European physiologists such as Carl Ludwig, Otto Frank and others. Carl Ludwig first described the dependence of cardiac work on diastolic volume in 1856 (Katz 2002). In 1879, Charles S Roy described the dependence of the frog heart work on diastolic volume by showing that "at constant aortic pressure and heart rate, the work of the heart is capable of being varied within wide limits by variations in the venous pressure" (Katz 2002). Etienne Marey included a 'Starling' curve in his 1881 text, while Otto Frank, who studied with Ludwig, illustrated the dependence of peak isovolumic pressure on ventricular volume (Katz 2002).

Besides known for his "Law of the Heart", Starling made important observations relating to electromechanical aspects of cardiac function with William Bayliss. They also developed a technique for measuring intra-aortic and intraventricular pressures more accurately in 1894 (Fye 2006).

Otto Frank's interest in arterial pressure recording was later adopted and extended by Carl Wiggers. Wiggers's basic hemodynamic principles include (Wiggers 1942):

- Pressure variation in the aorta by early discharge of left ventricle has a magnitude, measured by systolic and diastolic pressure readings. However, it is also represented in graphical records of the central arterial pulse and holds significant importance.
- Measurements of systolic and diastolic pressures only carry full information when their relative deviations, i.e. changes in pulse pressure, are also considered. Systolic increases more than diastolic (higher pulse pressure amplitude) when systolic discharge of the heart increases and aortic distensibility decreases. Diastolic pressure increases more than systolic (lower pulse pressure amplitude) due to cardiac acceleration and increase in total peripheral resistance.
- "Hypertension is not defined dynamically as an increase in blood pressure alone; the pulse pressure is always increased to varying degrees. This greater pulse pressure is generally due to decreased distensibility of the aorta and not to the increased peripheral resistance. There is reason to suspect that hypertension with little or no elevation of diastolic pressure is associated with a significant decrease in aortic elasticity".
- Mean pressure represents the average of consecutive pressure changes in the aorta, and can be recorded by a highly damped mercury manometer. "Writers should avoid erroneous statements or inferences that changes in pulse pressure can be gauged by such recordings".
- "... experimental results are no better than the apparatus employed, that the analysis of dubious results cannot be improved by statistical methods, and that the breadth of conclusions drawn should not exceed the limitations permitted by the most accurate results". Wiggers emphasised Carl Ludwig's exhortation "Die Methode ist Alles" (Neil 1961).

His work on hypertension was published in 1938 (Wiggers 1938, Freis 1960), and a few of Wiggers' important views include:

- In hypertension, the magnitude of peripheral resistance increase is varied, thus suggesting that other mechanisms are also involved.
- Diminished elasticity of the aorta and its immediate branches accentuated elevation of systolic pressure and reduce diastolic pressure, hence accounted for higher amplitude of pulse pressure.
- Action of the left ventricle is not impaired by severe hypertension, where cardiac output tends to increase, mechanical efficiency is increased and economy with mechanical energy to propel blood is increased.

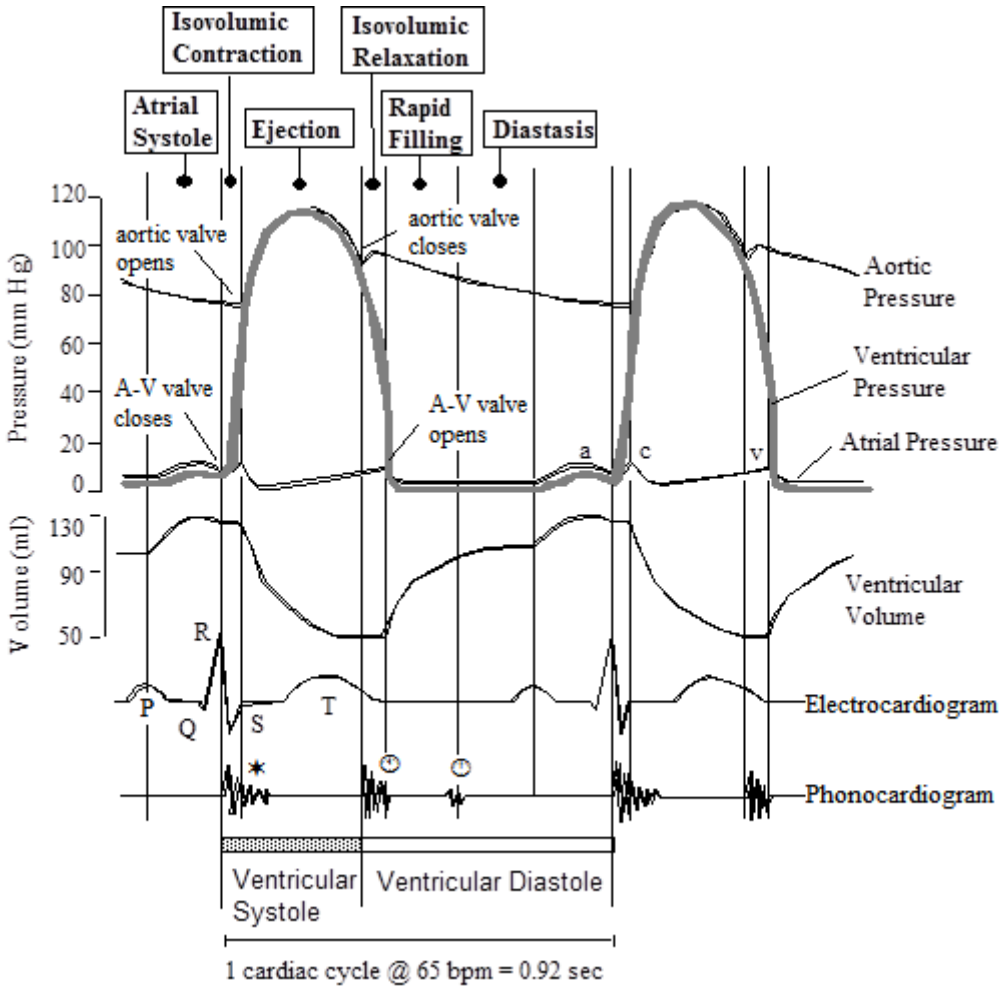


Figure 2-2. Wiggers diagram, as initially known ~ 1920s and has been published in all textbooks of physiology and cardiology over the next 80 years. Adapted from (Mitchell et al. 2014).

Wiggers' diagram (**Figure 2-2**) showed his work in describing the events of the cardiac cycle superimposed on cardiac pressure tracings and electrocardiogram tracings (Landis 1976), and this became standard teaching material in physiology as illustration of the relationship and timing of events during the cardiac cycle.

Following Roy's experiment on the extensibility of the vessel, Crighton Bramwell and Nobel Laureate A.V. Hill showed that the velocity of the pulse could be determined from this, and that arterial pressure has a significant effect on the velocity (Bramwell et al. 1922). Bramwell and Hill were the first to introduce the concept of *pulse wave velocity* in clinical settings, by describing the velocity variation in proportion to the arterial wall tension and blood pressure (Ghasemzadeh et al. 2011). They found that the pulse wave in man travelled in arteries at about 4 to 10 m/s, and was dependant on the elasticity of the arteries (Bramwell et al. 1922). They also showed that there is a general agreement between age and pulse velocity in normal subjects (Bramwell et al. 1922). Bramwell, in his 1924 publication, discussed the influence of pressure on the elasticity of arteries, where at low pressure, healthy arteries are extremely elastic, but as the pressure rises above normal diastolic value, their elasticity diminishes and greater energy is required by the heart in ejecting blood (Bramwell 1924). He also mentioned that disease of the cerebral or coronary arteries is of primary importance (Bramwell 1924).

Similarly to the Moens-Korteweg equation, Bramwell and Hill (Bramwell et al. 1922), and also Otto Frank (Frank 1930), described the pressure-volume relation of the tube regardless of the wall characteristic:-

$$c = \sqrt{\frac{1}{\rho} \times \frac{\delta P}{\delta V} \times V}$$ Equation 2-2.

where c = wave velocity, ρ = blood density, δP/ δV = change in pressure due to change of volume, and V = volume (Taylor 1966).

Intra-arterial blood pressure measurement using accurate manometry, as introduced by Otto Frank, and refined by Carl Wiggers, was later improved by W F Hamilton and his group (Hamilton et al. 1934). Otto Frank emphasised the amplification of the systolic wave and exaggeration of diastolic wave, thus likened the arterial system to an underdamped manometer (Wiggers 1928). Dow and Hamilton (Dow et al. 1938) found that in the abdominal aorta and lower limb arteries, the foot of the wave is progressively delayed, and no evidence of diastolic wave in the middle of descending aorta. The peak pressure wave is almost synchronous in time, while the diastolic pressure fluctuations are reciprocal with those in the proximal aorta (Dow et al. 1938, Hamilton et al. 1938). They introduced the concept of a "standing wave" in the lower aorta with the reflection waves occuring between lower limb arteries and the closed aortic valve (Hamilton et al. 1938, Hamilton 1944), thus creating a node of pressure in the descending thoracic aorta. However, their finding was later challenged by McDonald and Taylor (McDonald et al. 1959, McDonald 1960). The current agreement is a compromise between the two disparate views (O'Rourke 1967).

Hamilton and Dow described a technique for simultaneous recording, directly and adequately, of pressure pulses from different sites (Dow et al. 1938, Hamilton et al. 1938). Their experiments found that pulse pressure increases gradually from aortic arch to femoral artery, while mean pressure remains constant (Hamilton et al. 1938). They also found that the augmented systolic peak is stationary, i.e. the "standing wave", and time from wave foot to peak is a characteristic function of length and elastic properties of central arteries (Hamilton

et al. 1938). In the same year, they were able to show changes in pulse wave velocity from aorta to femoral arteries, and that wave velocity corresponds to different functions of diastolic pressure in the thoracic and abdominal aorta (Dow et al. 1938).

Following their initial goal with the introduction of manometers to calculate flow from the pressure wave contour (Frank 1930, Remington et al. 1948), Hamilton, Dow and Remington published their papers on different indices measured from pressure pulses; these include propagation velocity of the arterial pulse wave (Hamilton et al. 1945), stroke volume from pressure pulse (Remington et al. 1946, Hamilton et al. 1947), cardiac ejection time from pressure pulse (Remington et al. 1946), and evaluation of the work of the heart (Remington et al. 1947). Nevertheless, this technique proved to be unreliable and was superceded for flow measurement with the introduction of electromagnetic and ultrasonic flowmeters (Nichols et al. 2011).

D E Gregg and R E Shipley also published their work on accurate representation of ventricular pressure pulse from pressure contour and value of systolic portion of the arterial curve (Shipley et al. 1943). They show distinctive flow patterns specific to an artery, observed back flow components in femoral and axillary arteries, and some back flow in the carotid artery, while determining the renal artery has only forward flow (Shipley et al. 1943).

In 1956, Werner Forssmann and Dickinson Richards received the Nobel Prize in Medicine for their work on cardiac catheterisation. Around the same time, Earl Wood and Edwin Kroeker published their valuable work in central aortic pressure recording. They measured central (aortic or subclavian), brachial, radial and femoral pulse pressure waves simultaneously by intra-arterial needles and catheters (Kroeker et al. 1955). From these waves, as the pressure pulse wave transmitted peripherally, they observed apparent changes in contour, specifically progressive decrease in diastolic and mean pressure and larger progressive increase in systolic

pressure (Kroeker et al. 1955). The pulse wave velocity increases towards the periphery, while primary systolic wave increases in amplitude, secondary systolic wave decreases, and dicrotic dip exaggerated down the upper limb (Kroeker et al. 1955). Peripheral pulse pressure magnitude can be more than double that of aortic pulse pressure, peripheral dicrotic pressures decreases lower than end-diastolic pressure, and the general contour of the pulse resembled a damped sine wave (Kroeker et al. 1956). Together with John Remington (Remington et al. 1956), Earl Wood concluded that changes in pressure pulse contour through subclavian – brachial – radial arteries and aorta – upper femoral system involves:

- Aorta and upper subclavian artery: anacrotic slope was transmitted with little damping and delayed summation with reflected wave, causing small increase in pulse pressure
- Transition region: anacrotic slope steepened and pulse pressure augmented
- Brachial – radial and upper femoral system: apparent propagated peaks down the arm and leg; first peak showed simultaneous timing and size, second peak showed high pressure value in late systole, and third peak follows the incisura

The concept of a "standing wave" of Hamilton was challenged by Donald McDonald and Michael Taylor, on the basis that wave reflection needs to be total and attenuation absent for resonance to occur (Nichols et al. 2011), although now it is agreed that wave reflection is stronger and attenuation weaker. There is no anatomic location of a pressure 'node' since the nodes of different harmonics of the wave contour occur at different positions along the aorta (Nichols et al. 2011). Further, it is shown that the "standing wave" could only occur if there is no attenuation of the travelling pressure wave, if the wave is completely reflected, and there is no interaction of reflected wave from the scattered arterial termination (O'Rourke 1967).

2.6 A New Era in Hemodynamics

The functions of the arterial system are: to provide a pathway of low resistance from the heart to the higher resistance of the periphery so the total driving pressure is minimised, to present low input impedance for the pulsatile flow from the heart to minimise its work, and to maintain the first two functions over a range of cardiac output and/or heart rate (Taylor 1967).

The arterial pulse wave studied in the time domain provides information such as heart rate, ejection time and pulse wave velocity. The arterial pulse has been analysed in the time domain for centuries, and in the modern era was further studied by Hamilton (Dow et al. 1938, Hamilton 1944), Remington (Remington 1963) and others (O'Rourke et al. 1966) to explain the relationship between pressure and flow fluctuations and their wave contour. However, it was not possible to satisfactorily separate different components of the wave.

It is worth to mention Leonhard Euler's (1707 – 1783) work here, as he was the first to describe that a periodically varying signal over time can be represented in a combination of sine and cosine function, hence it can be expressed as the real part of exponential functions and imaginary exponents using Euler's formula:-

$$e^{ix} = \cos x + i \sin x \qquad \text{Equation 2-3.}$$

This formula would later be applied by Jean-Bapiste Joseph Fourier (1768 – 1830), who made the important contribution to trigonometric series based on the works by Leonhard Euler, Jean le Rond d'Alembert and Daniel Bernoulli. Fourier's series, originally quoted in "Mémoire sur la propagation de la chaleur dans les corps solides" (1807), is known as:-

$$(x) = a_0 + \sum_{n=1}^{\infty} \left(a_n \cos \frac{n\pi x}{L} + b_n \sin \frac{n\pi x}{L} \right)$$ Equation 2-4.

Donald McDonald started his work on pulsatile flow velocity in arteries, however, found this to be challenging due to the inadequate quantitative method of analysis. McDonald was aware that the relation of pressure to flow is "the central problem in haemodynamics" (Burton 1952, McDonald 1955), where the oscillatory nature of arterial flow made the Poiseuille's law (for steady flow) application unacceptable. It was not until he worked together with John Womersley, a mathematician, that they were able to calculate the flow velocity curves from pressure gradients. In 1955, Donald McDonald, a physiologist, published his paper where he recorded the phasic changes in arterial flow during each cardiac cycle and investigated the pressure oscillations which generate this flow (McDonald 1955). The pressure gradient was measured by simultaneous recording of arterial pressure at 2 points in an artery, and then compared to those measured by electrical differentiation of capacitance manometer output. McDonald showed an agreement between the observed and calculated flow curves, hence established the validity of theoretical derivation of pulsatility based on hydrodynamic principles. McDonald discovered that the flow in the femoral artery oscillates in the same way as the pressure gradient but with a phase-lag, thus the differential coefficient of the pulse pressure curve may be used to calculate flow (McDonald 1955).

McDonald's work was a fruitful collaboration with Womersley, which in his paper on the same year reported the formula to calculate the rate of flow from pressure gradient, and illustrated a phase-lag between flow and pressure gradient (Womersley 1955). Womersley produced a table which gave the modulus factor and phase angle needed to derive an oscillating flow from an oscillating pressure gradient (Womersley 1955, Taylor 1966), and later was utilised by McDonald and Taylor (McDonald et al. 1959). Womersley was able to represent the pressure gradient as a Fourier series, and calculate a non-dimensional constant α

for each harmonic using Bessel functions (Womersley 1955). Assuming the artery as a rigid tube and its expansion neglected, the pressure gradient is assumed to be a periodic function of time, obtained by measuring time derivative of pressure at that point over a short length of artery. The complex functions of impedance and wave velocity are functions of α, and α varies as the radius of the artery and as the square root of the pulse frequency (McDonald 1955). McDonald and Womersley each published their work on the relationship between pulsatile pressure gradient and flow in a segment of a vessel (O'Rourke 1982), based on the concept of steady-state oscillation of the arterial system in the frequency domain.

As McDonald wrote in the first edition of "Blood Flow in Arteries" (McDonald 1960), that "the most obvious feature of the 'blood flow in arteries' is that it is pulsatile." Consequently, it is imperative that the character of pulsatile flow is understood, that the pressure (and flow) of the blood was in the form of pulse wave and transmitted along the arterial system. Based on this fact, McDonald emphasised the measurement of pulsatile nature of blood flow on the circulatory system to convey blood to and from tissues (McDonald 1960). McDonald was able to show that changes in arterial pressure are associated with changes in contour of the arterial flow wave (McDonald 1960).

McDonald and colleagues (Attinger et al. 1966) investigated the application of Fourier analysis to the respiratory and circulatory system. They confirmed that Fourier analysis is a valid method to examine the oscillatory components of the circulatory and respiratory system, since it satisfies the basic assumptions of pulsatility, periodicity and linearity (Attinger et al. 1966). Yet they stressed that dynamic calibration of the measuring system is crucial, and "… sophisticated computer programming cannot compensate for sloppy experimental techniques." (Attinger et al. 1966). As stated previously, McDonald, Womersley and Taylor's collaborative work have found that non-linearities in relation between pressure gradient and flow in an artery are quite small and can be neglected to the first approximation

(Womersley 1955, O'Rourke 1982, O'Rourke et al. 1992, Nichols et al. 2011), and surprisingly remains linear across different heart rate (McDonald 1960). In regards to the application of Fourier transformation, according to Milnor (Milnor 1989), ‘‘the Fourier analysis of pressure and flow waves ... had been suggested much earlier by Frank (Frank 1926), championed by Ape´ria (Apéria 1940), and finally introduced into cardiovascular physiology by Porje (Porje 1946)” (Parker 2009).

Michael Taylor joined McDonald in 1955, and their great work on hemodynamics continued. In Taylor’s early work, he wrote a series of papers on “A(n) (new) approach to an analysis of the arterial pulse wave” (Taylor 1957, Taylor 1957). Taylor was interested in theoretical analysis of wave propagation to analyse oscillatory fluid flow in this circulatory system. Each ejection of blood from the heart generates an oscillating pressure about a mean value which travels through an elastic tube network. The difference in pulse contour at different recording sites is due to the non-uniformity character of the circulation system. The application of the Fourier series is valid, since the action of the heart is regular and the response is oscillations with heart rate as the fundamental frequency (Taylor 1957). Taylor found that in an attenuating line, such as the arterial system, the energy supplied at the origin – i.e. the heart – is lost in passage along the line, the (reflected) wave from termination is always of smaller modulus and can never cancel the (initial) wave (Taylor 1957), therefore this conclusion challenged the concept of a “standing wave” (Hamilton et al. 1938). His experiment further justified the use of an electric transmission line as an analogue of a fluid-filled elastic pipe (Taylor 1957), thus supporting Womersley’s important work (Womersley 1955). His next papers dealt with the influence of shear-dependent viscosity upon oscillatory flow, which for larger arteries, was virtually negligible for the flow calculation (Taylor 1959). Consequently, by neglecting the fluid viscosity, the Waterhammer solution can be applied where the elastic properties of the wall are related to the volume elasticity of the tube (Taylor 1959). Womersley’s approach can be utilised in prediction of phase (or wave) velocity and wave

transmission – both are frequency dependent – in studies of the arterial circulation (Taylor 1959).

McDonald and Taylor published a review entitled "The Hydrodynamics of the Arterial Circulation" in 1959 (McDonald et al. 1959), just prior to McDonald's monograph in 1960 (McDonald 1960), to describe the pulsatile nature of pressure and flow in the arterial vasculature. In a steady state system, the relation between mean pressure and mean flow is expressed as resistance, whereas in a dynamic system, it is expressed as impedance (Taylor 1967) depending on the frequency of oscillation (Taylor 1966). Impedance is a complex quantity and consists of amplitude (or modulus) and phase (Taylor 1967), fluctuating around a mean value and calculated using Fourier series (Taylor 1966, Taylor 1973). Because the generated flow is intermittent and periodic (frequency ω), then the pressure at the origin will be pulsatile and depend on input impedance (Zo) (Taylor 1967):-

$$\text{Pressure}(t) = (\text{mean flow} \times \text{resistance}) + \sum \text{Flow}(\omega) \times \text{Zo}(\omega) \qquad \text{Equation 2-5.}$$

The first term, mean flow x resistance, represents the steady components of the equation, while the latter term, $\sum$ Flow(ω) x Zo(ω), denotes the oscillatory components. The oscillatory or pulsatile components represent the extra work to be performed by the heart due to the intermittent nature of ejecting blood.

Vascular impedance, as a description of the opposition of pulsatile blood flow in an artery, includes the effect of elasticity, inertia, viscosity, as well as reflection (O'Rourke et al. 1966). It is frequency-dependent, passing through maximum and minimum values as the system passes through its resonances (Taylor 1967). The input impedance will be at minimum whenever the system is oscillating at a frequency such that there is a node of pressure at the origin (located at a distance of odd multiple of ¼ length of the wave) and maximum whenever

there is an antinode of pressure (Taylor 1967). This is different to the concept of a "standing wave" (Hamilton et al. 1938), where the analysis is done in the time domain, while Taylor's work is based on the frequency domain. The concept of vascular impedance will be described in more details in Chapter 5.

Taylor in his paper of 1965 published his computation of wave travel in a non-uniform system. He used the linearised model where the fluid mass is represented by inductance and the vessel elasticity by capacitance, analogous to an electrical circuit (Taylor 1965). Furthermore, he was able to shown that this simplification does not result in loss of accuracy of computation, since it only involved the aorta and larger central arteries (Taylor 1965). The input impedance of a non-uniform system fluctuates and oscillates around a certain value, thus different from impedance at the terminal tube (Taylor 1965). In the cardiovascular system, the heart is separated ("uncoupled") from the high impedance of peripheral vessels and is presented with a much lower impedance of ascending and thoracic aorta. Therefore, the pulsatile ejection of blood causes smaller pressure pulse than if the input impedance were higher, and results in a reduced pulsatile work of the heart (Taylor 1965), generally only about 5-15 % of total external work (Taylor 1966). This design ensures optimal functioning of the circulatory system irrespective of variation in heart rate within certain limits (Taylor 1965). The overall amplification of the wave corresponds to the increasing wave velocity towards the periphery, and this translates to higher amplitudes of harmonic components (Taylor 1965).

The transformation of the pressure pulse wave in arteries is explicable on the basis of two features of the arterial system, wave reflections and elastic non-uniformity (Taylor 1966). The non-uniform system of the arterial tree provides low reflection coefficient at terminations for the input impedance to remain relatively low over this frequency range (Taylor 1965). This non-uniform elastic property of the arterial tree was the most important function to link

dissimilar impedances; i.e. low input impedance for cardiac ejection and high terminal impedance of peripheral resistance vessels (Taylor 1965). The arterial system has many terminations located at variable distance from the heart, and this arrangement allows the system to behave as though no reflections were present.

The input impedance has frequency dependency which can be divided into 2 ranges; the low frequency range where the system behaves like a single elastic tube with a terminal impedance at one point, and the high frequency range where it behaves like a single elastic tube with apparently matched termination with little or no reflection (Taylor 1966). The low range consists of a steep fall of impedance modulus from zero frequency down to a minimum value, then it rises again to a low maximum. The phase angle becomes large and negative approaching 90^{o}, crosses over zero when the modulus is at its minimum. The high range begins after the first maximum following the first minimum of modulus, showing a number of fluctuations; and the phase angle follows the same pattern (Taylor 1966). This is necessary to stabilise relatively low impedance by gradual transition of stiffness towards the periphery, as well as wave attenuation that increases with frequency, to reduce the amount of energy with reflected wave (Taylor 1966). This is additional to the progressive increase of total cross-sectional area as the arterial branching to minimise the steady pressure drop along the system (Taylor 1967). Viscous properties of the system have apparent effects on travelling waves, with waves transmitted along larger vessels mainly influenced by wall viscosity, whereas in smaller 'peripheral' vessels affected more by fluid viscosity (Taylor 1966).

The tubular design of the arterial system with its branching network and termination in arterioles results in generation of pulse waves which propagate then reflect back at the junction. If there were no reflection, the ascending aortic pressure wave contour would be the same contour as the ascending aortic flow wave (Wetterer 1954, McDonald et al. 1959, O'Rourke 1982, Nichols et al. 2011). However, the ascending aortic pressure wave appears

different to the ascending aortic flow wave; this is the evidence of wave reflection (McDonald et al. 1959, Westerhof et al. 1972, Murgo et al. 1980, O'Rourke 1982, Merillon et al. 1983, Milnor 1989, O'Rourke et al. 1992, Westerhof et al. 1995, O'Rourke et al. 2007).

The unique nature of the human arterial system is that the peripheral reflecting sites located at the extremities of the body, thus the reflected wave seems to arise from one functionally discrete site at each end of the body, as shown by Taylor and O'Rourke (O'Rourke 1967, O'Rourke 1967). The most recent debate on the subject of forward (initial) or backward (reflected) pressure wave has been published as a pros- and cons- by Westerhof and Tyberg et al (Westerhof et al. 2013). This debate is considered disappointing by some (O'Rourke et al. 2013), and less credible than the monograph also commissioned by the (British) Physiological Society in 1960 as the First Edition of the McDonald's book "Blood Flow in Arteries" (McDonald 1960). Westerhof et al have just recently published a review on this issue (Westerhof et al. 2015), which supported by recent papers in the Journal of Hypertension (Mynard et al. 2015, Segers et al. 2015, Westerhof et al. 2015).

The concept of wave reflection from discrete site has its open opponent – those whose disagree with the pulse wave propagation in a vessel with certain constant physical properties. The proposed notion of wave separation (into the forward and backward waves), wave intensity analysis, reservoir pressure and instantaneous wave-free ratio based on the lumped parameter modelling to unravel the arterial function has shown increasing prominence (Wang et al. 2003, Hope et al. 2005, Baksi et al. 2009, Sharman et al. 2009, Davies et al. 2010, Davies et al. 2012, Schultz et al. 2013, Fok et al. 2014, Schultz et al. 2014). These papers have elected to disregard earlier work by McDonald, Womersley and Taylor on pressure wave propagation along the arterial tree, as well as observation of the pulse by Marey, Mahomed, Osler, and the findings from early Framingham Heart Study on the pulse waveform characteristics (Kannel et al. 1971, Dawber et al. 1973). The latest review by Westerhof et al

(Westerhof et al. 2015) has attracted an exchange of comments by supporters of reservoir-theory (see online comments in Hypertension 2015 dated June 24, July 6 and July 22, 2015 by Tyberg et al, Sharman and Schultz, and its rebuttal by Segers and Westerhof). The controversy continues and it is not expected to conclude in the short future, despite the conclusion by Westerhof et al "… the concepts, based on flawed interpretations of arterial dynamics, …" and "… have led to misconceptions that violate physical principles [Ohm's law], and … should be abandoned." (Westerhof et al. 2015)

The low input impedance leads to lower pressure generated during systole in the ascending aorta (Taylor 1966, Taylor 1973). Elastic properties will vary with the degree of wall 'stretching'; the greater the wall extension, the greater the stiffness, hence describing the relation between mean distending pressure and the elastic properties of the vessels indicated as the velocity of the pulse wave (Taylor 1966). The pressure dependency of arterial stiffness is considered a fundamental property of arterial design (Shadwick 1999). The pressure dependency character of the vessel is essential to prevent the vessel from rupture at high pressure. Relation between elastic properties of a tube (calculated as wave velocity) and input impedance is described in physical phenomena as Waterhammer formula (Taylor 1967). Measurement of wave velocity by the 'foot-to-foot' method was previously described by McDonald and Taylor in 1959 (McDonald et al. 1959).

Termination of the arterial tree is in vessels with high resistance, thus wave reflection is present and the system behaves like a close-end tube (Taylor 1966, Taylor 1967, Taylor 1973). Since terminal impedance values vary, the reflection coefficient (determined as

$$\frac{Zt-Zo}{Zt+Zo}$$ Equation 2-6.

where Zt = terminal impedance and Zo = characteristic impedance) is between -1 to +1. O'Rourke and Taylor found this to be about 0.7 to 0.8 (O'Rourke et al. 1966).

The work of McDonald and Taylor (McDonald et al. 1959) was able to demonstrate the oscillation of blood pressure and flow in the steady state using Fourier analysis. Essentially, pulsatile phenomena can be described as a (1) mean value about which oscillation occur; (2) Fourier harmonics in modulus and phase, and (3) the relationship between the two phenomena (i.e. pressure and flow) is linear and periodic (Taylor 1966, Taylor 1973). Further, it has been confirmed that the impedance spectra were consistent and reproducible under control condition with both regular and irregular heart rate, and predicted changes occurred during vasoconstriction and vasodilatation (O'Rourke et al. 1966).

The input impedance characteristics of the human systemic circulation take advantage of the design of human anatomy where the heart is presented with two functionally discrete reflecting sites, one shorter arm in upper (head, neck and upper limbs) and another longer arm in lower body (trunk and lower limbs) (O'Rourke et al. 1967). This asymmetrical T-model was superior in describing the wave pattern (O'Rourke 1967). Previously, the most popular arterial model was a tube with one closed end representing the resultant of all reflecting sites from the periphery, and another end to the closed aortic valve (O'Rourke 1967). This asymmetric T-model was able to explain the patterns of pressure and flow waves attributable to the reflection of the pulse wave from the periphery and heart, with the attenuated wave travelling back and forth along the tube (O'Rourke 1967, O'Rourke et al. 1968).

New work presented here on the cerebral circulation in humans (chapter 6) directs attention to the major functionally discrete reflection site as being in the lower part of the body, since there is very low wave reflection from the brain and upper body arteries. This draws attention away from the asymmetric T-model approach proposed by O'Rourke (O'Rourke 1967) and to

the original view of a simple lower body reflecting site and for upper body reflection as being at least partly due to other closed aortic valve or stiff contracting ventricle.

The pressure wave is compound, and the main factors of pressure wave contour changes and the decrease in pressure amplification are wave reflection and progressive increase in stiffness between proximal aorta and peripheral arteries (O'Rourke 1967, O'Rourke et al. 1968). In younger subjects, pulse pressure increase about 55% between aortic arch and iliac artery (O'Rourke et al. 1968). However, in older people with degenerative arterial disease, there are little changes in pressure amplification (O'Rourke et al. 1968). The fall in pressure is also associated with a decrease in transmission time from aortic arch to iliac artery causing an increase in pulse wave velocity (O'Rourke et al. 1968, O'Rourke 1970). The magnitude of reflected wave depends on the reflection coefficient at each individual reflecting site and the degree of spatial dispersion of many discrete reflecting sites (O'Rourke et al. 1968). Fall in reflection coefficient in older humans corresponds to increase in arterial stiffness and characteristic impedance (O'Rourke et al. 1968). While the pressure amplification indicates the vascular properties, the harmonic component of the aortic wave and its wave contour is determined by ventricular ejection pattern (O'Rourke 1970).

Impedance modulus pattern shows a steep fall from zero frequency to approximately 1/20 (or lower) of the peripheral resistance for the first harmonics, and then varies about that value for higher frequencies (O'Rourke et al. 1967). The actual opposition to pulsatile flow is even less, since the pulsatile pressure is not in-phase with pulsatile flow (O'Rourke et al. 1967). The in-phase impedance, calculated as $|Z|$ cosine φ (or modulus times cosine of phase angle), would be a better representation since it determines the relationship between oscillatory flow and the in-phase component of oscillatory pressure (O'Rourke et al. 1967).

This subject is more complicated that set out here. Even reflection coefficient (estimated at 0.8) is highest at lowest frequencies and lowest at high frequencies, where impedance = characteristic impedance and Zi = Zc. Such frequency dependence of vascular impedance is a consequence of the spatial dispersion of individual peripheral reflecting sites (Taylor 1965, Taylor 1966, Taylor 1966).

2.7 Advancement of Arterial Pressure and Flow Measurement into the 20th Century

Following application of Fourier analysis in the study of hemodynamics, there are numerous publications on different aspects of pulsatile pressure and flow. There are also many important publications on impedance and its clinical application on the study of the circulation. These papers will be discussed further as background in the following chapters as considered appropriate.

Chapter 3

Accuracy of Distance Measurement in the Measurement of "Aortic" Pulse Wave Velocity

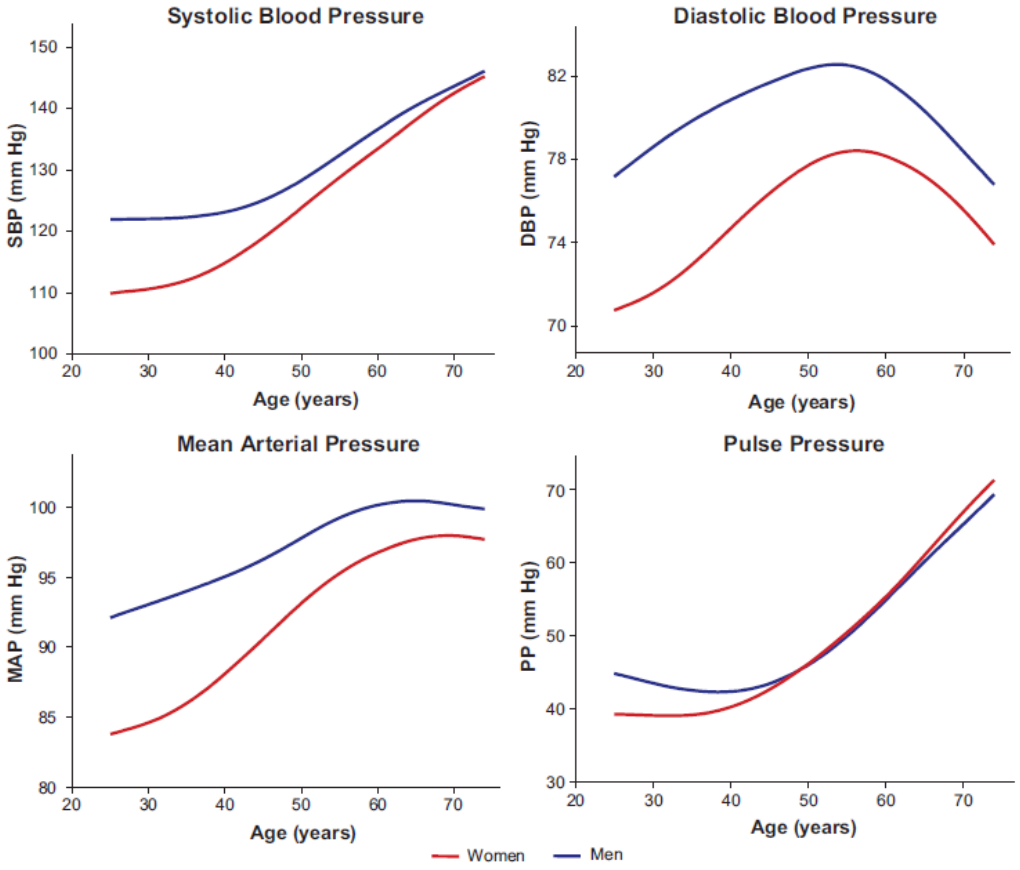
Summary

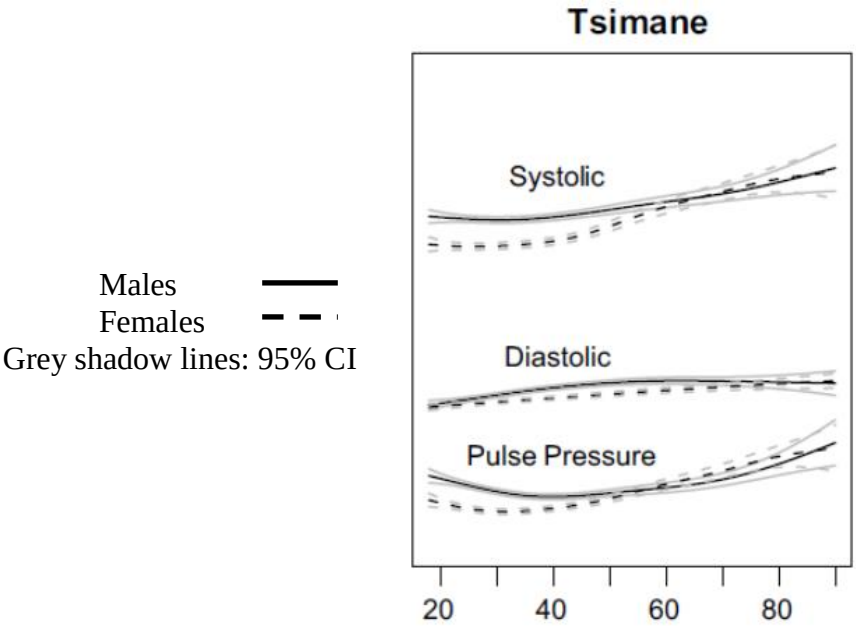
Human aging is associated with an increase in blood pressure, particularly systolic and pulse pressures, and this is attributable to the loss of distensibility of the human aorta of which its function is to cushion pulsation from the ejecting heart. This chapter will briefly describe the principal effect of arterial stiffening and what is the most appropriate method to measure "aortic" (or carotid femoral) pulse wave velocity. In particular, the chapter will assess the effect of distance measurement from the body surface markers in the measurement of the carotid-femoral pulse wave velocity. The accuracy in estimating the pulse wave velocity is crucial, as this is currently the "gold standard" of non-invasive measurement of arterial stiffness due to aging.

3.1 Introduction

Blood pressure will increase with age, even in apparently healthy individuals; it is acknowledged as a feature of human aging (Vasan 2008, Cheng et al. 2012, Gurven et al. 2012). The study of a population relatively isolated from Westernisation (Tsimane forager-holticulturalists) (Gurven et al. 2012) still demonstrated increasing brachial systolic and pulse pressure with age, although this increase was less extreme compared to those from the Framingham Heart Study (Cheng et al. 2012) **(Figure 3-1)**. High blood pressure is a priority target for intervention, and this is supported by the recent study of Cardiovascular Lifetime Risk Pooling Project (Allen et al. 2012) which found individuals with higher blood pressure in middle-age are associated with higher lifetime risk for cardiovascular disease. Therefore efforts should be directed to lowering blood pressure, hence avoiding or delaying hypertension.

In the past, risk evaluation was based on brachial diastolic pressure, led by a misguided therapeutic proposition of James Orr, the literary executor of James McKenzie following his death (O'Rourke 2002). During 1910s, the use of sphygmomanometers gained popularity, especially within life insurance companies, who were able to relate blood pressure level to mortality outcomes (Postel-Vinay 1996). It was not until the 1960s when the investigators from the Framingham Heart Study began to recognise high systolic blood pressure as an important cardiovascular risk factor (Kannel et al. 1961). This recognition was then followed by two major reports from the Veteran Affairs Cooperative Study on Antihypertensive Agents that lowering blood pressure resulted in significant reduction in major adverse events, including stroke and heart failure (Veterans Administration Cooperative Study Group on Antihypertensive Agents 1967, Veterans Administration Cooperative Study Group on Antihypertensive Agents 1970).





Males
Females
Grey shadow lines: 95% CI

Figure 3-1. Increase of brachial blood pressure with aging, as measured in two different populations (Cheng et al. 2012, Gurven et al. 2012).

The Framingham Heart Study (Kannel et al. 1971) went on to conclude the importance of systolic hypertension in the middle-aged and elderly subjects, as opposed to diastolic pressure.

The significance of systolic pressure was finally confirmed with the publication of the Systolic Hypertension in the Elderly Project (SHEP) (SHEP Cooperative Research Group 1991). Subsequently, the (brachial) systolic and pulse pressure emerged as the (modifiable) key risk factor in cardiovascular disease following longitudinal studies of Framingham Heart Study (Franklin et al. 1997, Franklin et al. 1999). They found that coronary heart disease risk is more related to pulsatile stress due to large artery stiffness during systole, thus emphasised the consequence of isolated systolic hypertension and the importance of systolic and/ or pulse pressures level. Franklin et al went further and concluded that the two measures of pressures is superior to any single pressure component in predicting cardiovascular risk because these pressures assessed both arterial stiffness and resistance (Franklin et al. 2009). The latest publication from the Framingham Heart Study cohort again emphasised the importance of pulse pressure as the pulsatile load in increasing brachial blood pressure with age, at least for those over the age of 60 (Cheng et al. 2012).

3.1.1 Arterial Stiffening and "Aortic" Pulse Wave Velocity

The associated changes in systolic and diastolic blood pressure can be characterised as the ill-effects of arterial stiffening (O'Rourke et al. 2005, Najjar et al. 2008, McEniery et al. 2010, Coutinho et al. 2014). It is soundly hypothesised that arterial stiffening is a product of fracture and fatigue process of elastin fibres attributable to the repetitive nature of the pulsating heart (Virmani et al. 1991, O'Rourke et al. 2005). The additional loading of persistent higher pressure in the aorta will accelerate this, causing the aorta to dilate and

stiffen as the wall stresses are transferred to the less distensible collagenous fibres in aortic wall (O'Rourke 1976, O'Rourke et al. 2005).

The principle effect of arterial stiffening and increase in pulse wave velocity on pressure pulse is an earlier return of reflected wave from peripheral sites (Safar 2010, Nilsson et al. 2013, Nilsson et al. 2014), thus the reflected wave will merge with the initial wave generated by ejection of the blood from left ventricle (O'Rourke 1970, Murgo et al. 1980, O'Rourke et al. 1980, Avolio et al. 1983, Kelly et al. 1989, O'Rourke et al. 1993, O'Rourke et al. 2007, O'Rourke et al. 2010). When the pulse wave travels faster, the timing of reflected the pulse wave shifts from diastole to systole (due to the earlier return of the reflected wave), hence explaining the aging changes in pulse waveform, as described in late 1800s and early 1900s by Marey, Mackenzie and Mahomed.

In the 1800s, Moens and Korteweg (Korteweg 1878, Moens 1878) described the arterial properties in terms of the velocity of travelling pulse wave. Later in 1922, Bramwell and Hill formulated an equation to describe cardiac function in relation to the hydraulic load (of blood), which included the speed of the pulse wave as a measure of arterial stiffness (Bramwell et al. 1922). In the modern era, the work by Taylor in vascular impedance (Taylor 1964, Taylor 1965, Taylor 1966) also discussed the relationship between characteristic impedance and pulse wave velocity in terms of Waterhammer formula (Bargainer 1967, Murgo et al. 1980). The association of arterial stiffening and pulse wave velocity have been supported by others in more recent human studies (Avolio et al. 1983, Avolio et al. 1985, Mitchell et al. 2004, McEniery et al. 2005, Shiburi et al. 2006, Wojciechowska et al. 2006, Vermeersch et al. 2008, McEniery et al. 2010, Mitchell et al. 2010, Redheuil et al. 2010, Sugawara et al. 2010, Taviani et al. 2010, The Reference Values for Arterial Stiffness' Collaboration 2010, Redheuil et al. 2011, Kaess et al. 2012).

The latest European Society of Hypertension/ European Society of Cardiology Guidelines for the Management of Arterial Hypertension (Mancia et al. 2013) has included the "aortic" pulse wave velocity measurement as an indicator of target organ damage, and supported by other studies (Agabiti-Rosei et al. 2007, Barodka et al. 2011, Palatini et al. 2011, Mancia et al. 2013, Liao et al. 2014, Singer et al. 2014). "Aortic" (or carotid-femoral) pulse wave velocity is currently the "gold standard" for non-invasive assessment of aortic distensibility assessment due to its reproducibility (Laurent et al. 2006, Nichols et al. 2011). The two latest meta-analyses from different groups (Vlachopoulos et al. 2010, Ben-Shlomo et al. 2014) has shown "aortic" pulse wave velocity to be a strong predictor of future cardiovascular events and all-cause mortality.

Aortic pulse wave velocity has also emerged as an independent marker of cognitive impairment and cerebral abnormalities (Henskens et al. 2008, Mitchell et al. 2011, Watson et al. 2011, Poels et al. 2012, Webb et al. 2012, Hughes et al. 2013, Rosano et al. 2013, Scuteri et al. 2013, Tsao et al. 2013, Zeki Al Hazzouri et al. 2013, Hughes et al. 2014, Wohlfahrt et al. 2014, Zhong et al. 2014). It is attributed to all cause and/ or cardiovascular mortality or poorer outcomes in general populations (Protogerou et al. 2011, van Sloten et al. 2014) and patients with kidney disease (Mitchell et al. 2010, Verbeke et al. 2011, Verbeke et al. 2011, Karras et al. 2012, Avramovski et al. 2014, Baumann et al. 2014), diabetics (Mehrabian et al. 2012, Laugesen et al. 2013, Mansour et al. 2013), as well as stroke (Gąsecki et al. 2012, Gąsecki et al. 2012) and heart failure (Bonapace et al. 2013, Regnault et al. 2014).

Pulse wave velocity is determined by measuring the pulse transit time from two sites of measurements (i.e. the time delay between the wavefoot divided by distance) (Stea et al. 2014) (**Figure 3-2)**, or measuring blood flow velocity using ultrasound or magnetic resonance imaging (Suever et al. 2012, Redheuil 2014, Devos et al. 2015) (**Figure 3-3**). To date, only "aortic" (or carotid to femoral) pulse wave velocity has been established as a strong predictor

of cardiovascular mortality. Other measurements of pulse wave velocity (i.e. carotid to radial, radial to femoral) have so far not been found to be predictor of outcome, possibly because of disparate effect of stiffening in central elastic arteries and peripheral muscular arteries (Pannier et al. 2005, Aquaro et al. 2013), which remains with aging (Zhang et al. 2013).

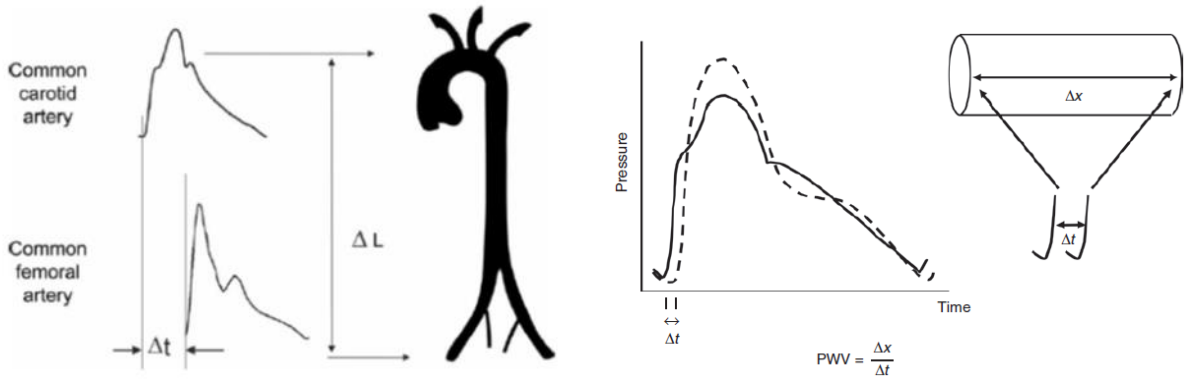


Figure 3-2. "Aortic" (or carotid-femoral) pulse wave velocity calculated by the foot-to-foot method (Laurent et al. 2006).

Due to the structure of central arteries which contain more elastin fibres than peripheral arteries (where the arteries are more "muscular"), the increase with age in pulse wave velocity is greater in the aorta than in peripheral or limb arteries (Avolio et al. 1983, Avolio et al. 1985, Pannier et al. 2005, McEniery et al. 2008, Hickson et al. 2010, Zhang et al. 2013, Devos et al. 2015).

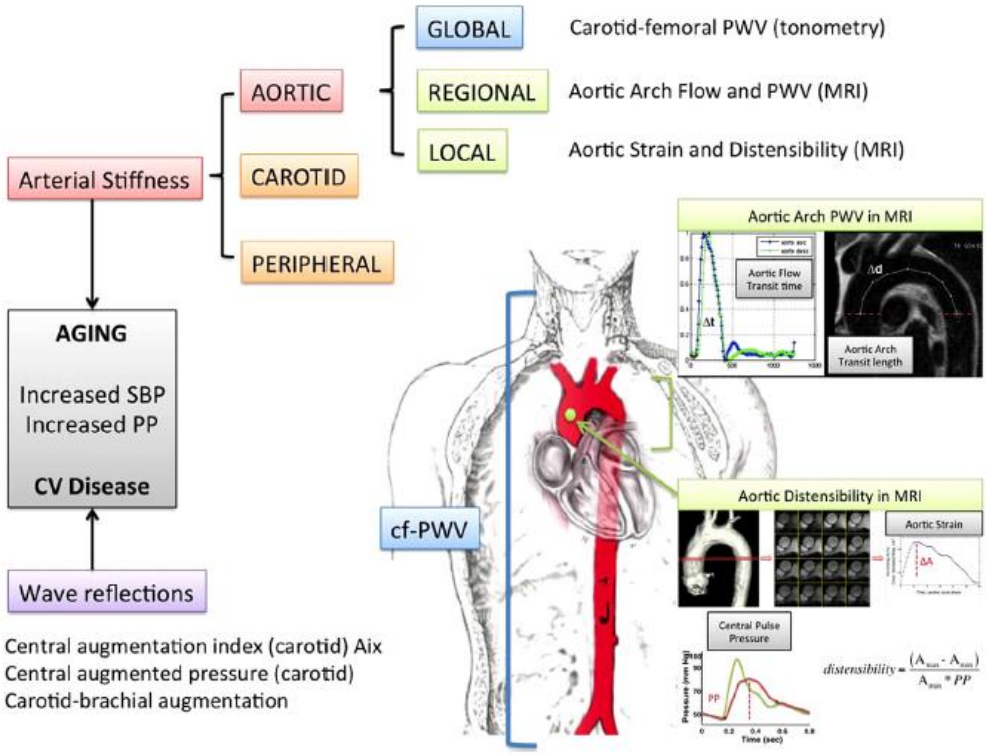


Figure 3-3. Local and regional "aortic" pulse wave velocity measured by cardiac magnetic resonance imaging (Redheuil 2014).

The largest study on carotid-femoral pulse wave velocity on normal population was published by the European initiative group (The Reference Values for Arterial Stiffness' Collaboration 2010) and showed that there was minimal difference between genders, with the aortic pulse wave velocity in males only slightly higher than females. Similar findings were previously reported by McEniery et al (McEniery et al. 2005) and Vermeersch et al (Vermeersch et al. 2008). Pulse wave velocity also was shown to be higher in certain (i.e. African-American) races (Heffernan et al. 2008, Lewis et al. 2010, Morris et al. 2013). A difference in height is not associated with difference in pulse wave velocity (Reeve et al. 2014). In children, reference values of aortic pulse wave velocity has been reported by Reusz et al (Reusz et al. 2010).

Some technical issues continue to confound the aortic pulse wave velocity measurement, especially how the total distance travelled by the pulse wave is measured. A pulse wave velocity of >12 m/s has been recommended as a sign of significant alterations of aortic function in middle-aged hypertensive patients (Agabiti-Rosei et al. 2007, Mancia et al. 2013). The latest recommendation on carotid-femoral pulse wave velocity measurement was published by the European Society of Hypertension Working Group on Vascular Structure and Function together with the European Network for Noninvasive Investigation of Large Arteries in Journal of Hypertension 2012 (Van Bortel et al. 2012). This Working Group has revised the wave velocity value down to 10 m/s, based on the overestimation of distance travelled by the pulse wave (Van Bortel et al. 2012). The utilisation of cardiac magnetic resonance imaging to measure central pulse wave velocity has been increasingly recognised and recently included in an Expert Consensus Document on the measurement of aortic stiffness in daily practice (Van Bortel et al. 2012).

As magnetic resonance imaging is not a practical solution for distance measurement for in-clinic carotid-femoral pulse wave velocity measurement, and the most accurate distance measurement to calculate pulse wave velocity is still debated at the time, a study was designed with the aim to find the most accurate method of measuring the carotid-femoral path length using a measuring tape and body surface markers.

3.2 Study: Non-invasive Determination of Carotid-Femoral Pulse Wave Velocity

A study published as:

Weber T, Ammer M, Rammer M, **Adji A,** O'Rourke, MF, Wassertheurer S, Rosenkranz S, Eber B. **Noninvasive Determination of Carotid-Femoral Pulse Wave Velocity Depends Critically on Assessment of Travel Distance: a Comparison with Invasive Measurement.** *Journal of Hypertension* 2009;27:1624-1630**.**

The effect of different distance estimation was crucial for accurate non-invasive estimation of aortic pulse wave velocity. I participated with the Thomas Weber group from Austria to publish a paper in 2009 where no formal validation for the method used to measure travelling pulse distance non-invasively against direct (or invasive) measurement had been performed. This collaborative work aimed to compare both distances, and concluded that the method of subtracting the distance from the carotid location to the suprasternal notch from the distance between the suprasternal notch and the femoral site of measurement was the best practice for non-invasive measurement of (aortic) pulse wave velocity. I had an active role in the preliminary analysis, where our abstract was presented at the European Society of Hypertension meeting in 2008.

The method of carotid-femoral pulse wave velocity determination by the foot-to-foot method is utilised in the SphygmoCor (AtCor Medical) system (Laurent et al. 2006, Ben-Shlomo et al. 2014). It is one of the widely used techniques to determine pulse wave velocity, together with Doppler and cardiac magnetic resonance. Sufficient evidence has proved the importance of aortic pulse wave velocity to be a predictor of events; it should be included in studies of cardiovascular risk prediction (Vlachopoulos et al. 2014).

Pages 59-65 of this thesis have been removed as they contain published material. Please refer to the following citation for details of the article contained in these pages.

Weber, T., Ammer, M., Rammer, M., Adji, A., O'Rourke, M. F., Wassertheurer, S., Rosenkranz, S., & Eber, B. (2009) Noninvasive determination of carotid-femoral pulse wave velocity depends critically on assessment of travel distance: a comparison with invasive measurement. W2dzNyl·f 2T I èLJŜNűŜyãλ2yΦ 27(8) p. 1624-1630.

DOI: 10.1097/HJH.0b013e32832cb04e

3.3 Chapter Overview

The increase in systolic and diastolic blood pressure with increasing age can be characterised as the ill-effects of arterial stiffening. The latest European Society of Hypertension/ European Society of Cardiology Guidelines for the Management of Arterial Hypertension (Mancia et al. 2013) has incorporated the "aortic" pulse wave velocity measurement as an indicator of target organ damage. However, to calculate the pulse wave velocity accurately, the distance estimation was crucial. There was no formal validation for the method used to measure travelling pulse distance non-invasively against direct (or invasive) measurement performed at the time the paper was written. This work found that the method of subtracting the distance from the carotid location to the suprasternal notch from the distance between the suprasternal notch and the femoral site of measurement was the most accurate for non-invasive measurement of (aortic) pulse wave velocity, and the data I analysed justify this distance-measurement method.

Chapter 4

Non-Invasive Central Aortic Pressure Measurements: Calibration and Clinical Value

Summary

Stiffening of the arteries due to aging will cause the pulse wave velocity to increase, and the reflected wave to occur earlier, therefore will increase central aortic pressure. The pulse wave propagates throughout the body from the aorta, and its contour depends on the cardiac contraction pattern and properties of the arterial system. This chapter will describe the difference between peripheral and central aortic pressure due to the amplification of pressure from the aorta to peripheral arteries, and how the amplification will change with aging. This chapter will also describe the importance of measuring central aortic pressure and the clinical value of central aortic pressure measurement. It will also emphasise the significance of appropriate calibration when measuring pressure, as it will affect the estimation of vascular impedance.

4.1 Introduction

With aging, the central elastic aorta progressively stiffens, thus the speed of the pulse travelling down the aorta, will be faster. The shift in timing of the reflected wave results in higher amplitude of central aortic blood pressure. This is mainly appeared as the increasing peak of the ascending aortic pressure wave due to merging of the earlier return of the reflected wave from the periphery with the initial wave generated by the left ventricle. To understand how arterial hemodynamics is altered by the ageing process is vital and this involves accurate measurement of central (or aortic) pressure (and flow) waves.

The most recent Guidelines in the Management of Hypertension by the European Society of Hypertension/ European Society of Cardiology (Mancia et al. 2013) states that measurement of central aortic blood pressure is specifically important in hypertensive patients, and is especially valuable in predicting adverse cardiovascular events and assessment of antihypertensive drug effects that may not be evident from brachial blood pressure. Central blood pressure is a measure of true load against which the heart has to pump, as well as the effect of pulsation on large arteries, brain and kidneys (Mancia et al. 2013). It has been broadly accepted that due to amplification of the pressure pulse between the heart and periphery, the brachial pressure is not always suitable as a surrogate of central aortic pressure (McEniery et al. 2014). A meta-analysis by Vlachopoulos et al (Vlachopoulos et al. 2010) and many reports since have increasingly shown that central aortic pressure provides more prognostic information beyond the conventional brachial pressure (McEniery et al. 2014, Roman et al. 2014).

4.1.1 Peripheral and Central Blood Pressure

Reliance on blood pressure measured from the brachial artery began over 100 years ago with the introduction of cuff sphygmomanometry. Cuff-based sphygmomanometry is widely used to date because it is easy to perform, despite merely describing the pressure as its peak (systolic) and nadir (diastolic) value. Sphygmographs had been used to gauge information about the state of circulation non-invasively, such as reported by Marey, Mahomed and other pioneers during 1800s.

Mackenzie (Mackenzie 1902) described the degeneration in the arteries without knowledge of arterial pressure that nowadays is measured by cuff sphygmomanometer. His quote:

> "... degeneration in the arteries is practically the physical history of the individual after the zenith of his strength has been reached, accompanied by an imperceptible but progressive limitation of the field of his heart's response to effort. Although ... he may lead a vigorous life within this limitation, with no evident discomfort, yet during the fourth decade of life the ease with which violent efforts are made is gradually lessening, and violent exertions are as a rule carefully avoided. Running after trains is not to be done in comfort, and the ascending of hills is undertaken with more deliberation. All this proceeds pari passu with diminished resiliency of the arterial wall." (Mackenzie 1902)

Similarly, Mahomed also made similar observation on the aging process through the character of the pulse waveform (O'Rourke 2007), quoted here:

> "These persons appear to pass on through life pretty much as other do and generally do not suffer their high blood pressures, ... As age advances the enemy gains ascension of strength ... the individual has now passed forty years, perhaps fifty years of age, his lungs begin to

> degenerate, he has a cough in the winter time, but by his pulse you will know him." (O'Rourke 2007)

Prior to the year 2000, the majority of population studies measured blood pressure with cuff brachial sphygmomanometry. These values of systolic and diastolic pressure have been known to have significant disparities when compared to those measured intra-arterially (Breit et al. 1974). The brachial cuff sphygmomanometry only provides the extremes of pressure, without any detailed information on arterial stiffness and ventricular load. The technique of measuring pressure with brachial cuff has been around for more than 100 years, thus, certainly, needs be advanced to better assessment and management of patients, as well as to utilise different antihypertensive therapies.

The major report from the Framingham Heart Study on brachial blood pressure have shown how systolic, diastolic, mean and pulse pressure change with age (Franklin et al. 1997), and clarify the importance of systolic and pulse pressure **(Figure 4-1)**.

While mean arterial pressure varied little with age, the brachial systolic pressure increased gradually from beyond 30 years of age, and the brachial diastolic increased to 50 then decreased thereafter. Consequently, brachial pulse pressure increased from about 40 to 50 years onwards. Results from the Framingham study (Franklin et al. 1999, Franklin et al. 2001) concluded that brachial diastolic pressure in younger subjects (40 years) was the best predictor of cardiovascular events, both brachial diastolic and brachial systolic pressures were a strong predictor in 40–60 years group, and in people older than 60 years, brachial pulse pressure (i.e. systolic - diastolic) was the best predictor while brachial diastolic pressure was inversely related to outcome.

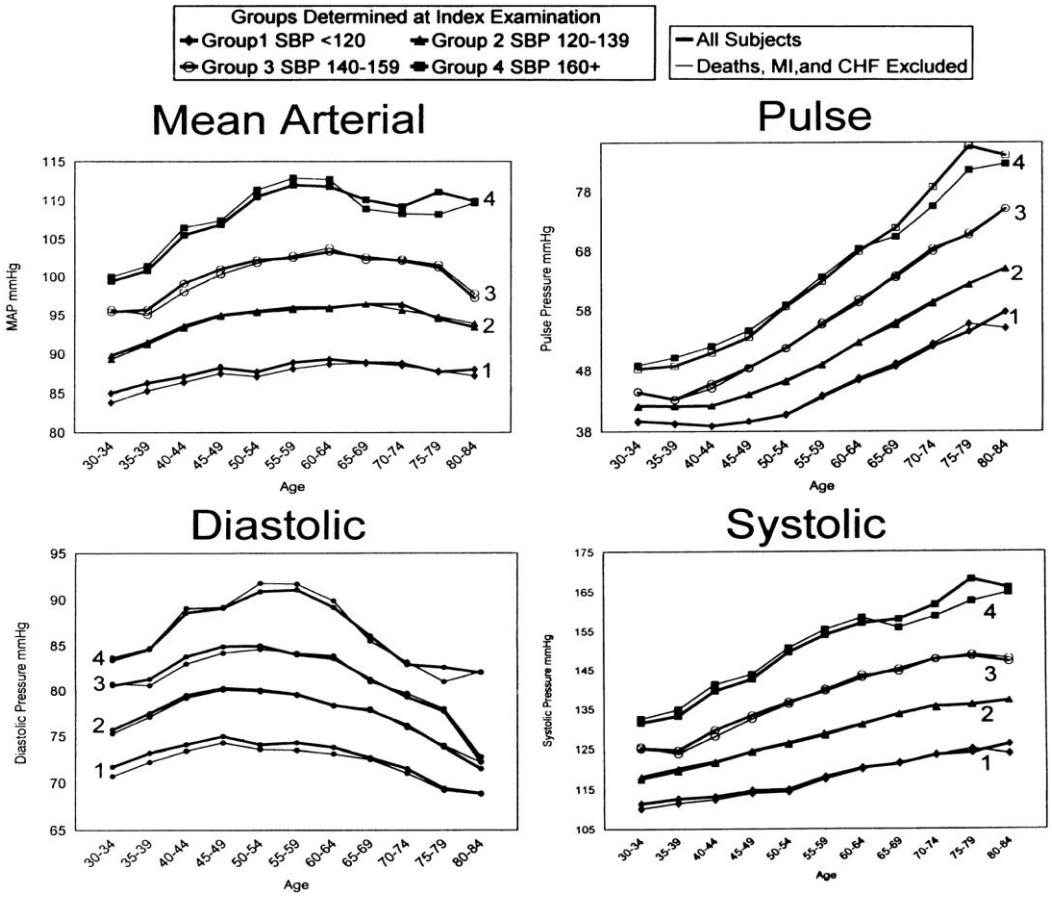


Figure 4-1. Relationship between brachial mean, systolic, diastolic and pulse pressure with age as reported by Framingham Heart Study (Franklin et al. 1997).

It is now widely accepted that the main cardiovascular consequence of aging is arterial stiffening, particularly on large conduit (elastic) arteries (Pauca et al. 2001, Agabiti-Rosei et al. 2007, Williams et al. 2010, Nichols et al. 2011, Gurven et al. 2012, McEniery et al. 2014). The precise mechanism on how stiffening of the major (central) arteries with ageing affects the propagation of pressure pulse along the arterial tree, increases blood pressure, changes the ejection pattern of the heart, and eventually causes cardiac failure, remains in question, and is influenced by many factors. Progressive stiffening of the large elastic arteries is attributable to loss of their distensibility with increasing age, characterised as increase in "aortic" (carotid-femoral pulse wave velocity) and higher aortic systolic pressure (Mitchell et al. 2004, McEniery et al. 2005, McEniery et al. 2008, Avolio et al. 2009, Cecelja et al. 2009, McEniery

et al. 2010, Mitchell et al. 2010, Cheng et al. 2012, Li et al. 2012, Wojciechowska et al. 2012, Nilsson et al. 2013, Nilsson et al. 2014). Stiffening of the central arteries has been recognised as a cause of adverse outcomes, including a higher amplitude of central pulse pressure and an increase in the transmission of pulsatile flow into the microcirculation (Townsend et al. 2015) – published as a Scientific Statement by the American Heart Association. Arterial stiffness is a predictor of cardiovascular risk, and sufficient evidence has shown the incremental clinical value of "aortic" pulse wave velocity as a measure of stiffness (see Chapter 3). Central blood pressure measurement, however, has yet to demonstrate its adding value to what is achieve by arterial stiffness assessment, i.e. "aortic pulse wave velocity". The normal reference values of central blood pressure have been published in over 10,000 subjects (Herbert et al. 2014) (see section 4.6), and in various population studies which examine the relationship between central pressure and adverse outcomes (see section 4.1.4). However, dedicated large population longitudinal studies which investigate the link between central pressure indices and clinical outcomes have yet to commence.

The steady rise of (central) aortic systolic (and pulse) pressure, as an accurate representation of the true load imposed on the heart, is also accompanied by increase in characteristic impedance (McEniery et al. 2005, O'Rourke et al. 2007, Vasan 2008, O'Rourke et al. 2010). The true effect of aging on cardiovascular function has not been fully appreciated. Additionally, it is now recognised that higher amplitude of central aortic pressure will extend the high flow pulsation to vasodilated end organs such as brain and kidneys, and ultimately must contribute to dementia or kidney insufficiency/ failure (O'Rourke et al. 2005, O'Rourke et al. 2010, Nichols et al. 2011) (see section 7.1.3).

The degenerative aging process predominantly affects the elastic large central arteries. When the large conduit arteries are healthy and compliant, the reflected (backward) wave merges with the incident (forward) wave in proximal aorta during diastole, thus enhances diastolic

pressure and aids coronary perfusion (**Figure 4-2**). However, when these arteries become stiff, the reflected wave returns earlier and merges in systole, resulting in higher systolic pressure and decrease in diastolic pressure. When aortic systolic pressure is consistently higher, the left ventricular afterload is increased and the magnitude of reflected wave is greater (**Figure 4-2**). All of these predispose the heart to fail and become hypertrophied. The hypertrophied heart contracts (and relaxes) slower, so that duration of systole is increased and of diastole reduced regardless of the heart rate (O'Rourke et al. 2007). The aortic pressure during diastole is a determinant of coronary perfusion (Agabiti-Rosei et al. 2007).

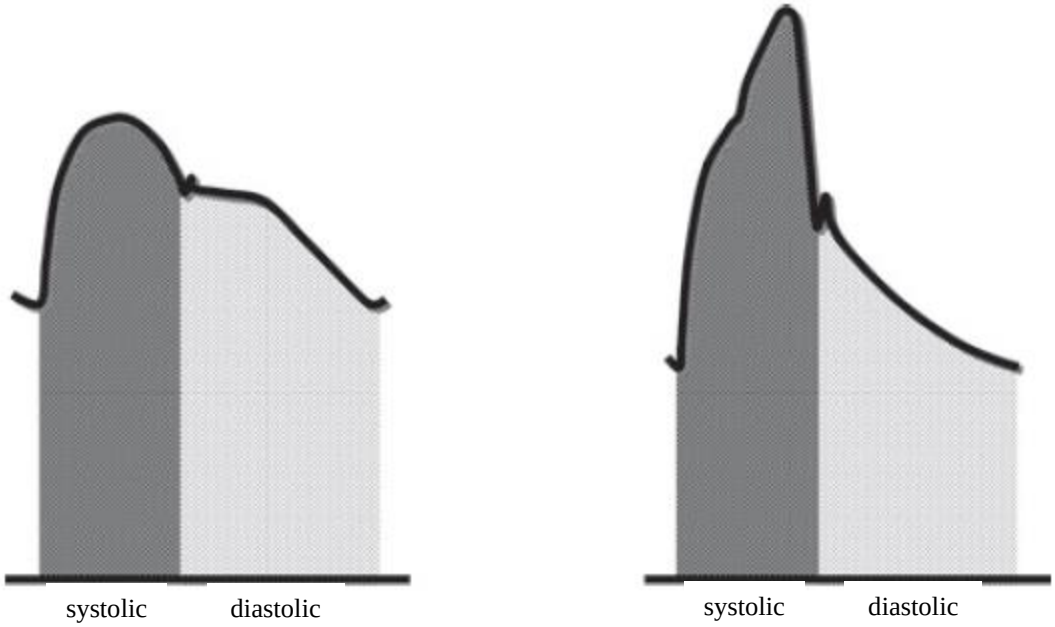


Figure 4-2. Schematic ascending aortic pressure waveform in a young normal subject (left) and in an older patient with left ventricular hypertrophy and diastolic dysfunction (right). Courtesy of M F O'Rourke, 2014.

A pressure wave recorded at any site is the sum of the initial wave caused by ventricular ejection of the heart and the reflected wave attributable to impedance mismatch from the periphery. Depending on factors such as age, gender, heart rate, height, degree of arterial stiffness, the speed of the travelling wave will affect the shape of the pressure wave.

The pressure wave is amplified during its travel from the heart to peripheral arteries. The degree of arterial stiffening will be reflected on the level of pressure amplification. This pressure amplification will markedly affect peak – or systolic – and pulse pressures, with only little effect on diastolic and mean pressures (O'Rourke 2007, Nichols et al. 2011). The properties of the pressure pulse wave are determined by left ventricular contractility, size (diameter and length) and elasticity of the large arteries (Avolio et al. 2009, Nelson et al. 2010, Nichols et al. 2011).

The amplification of pulse pressure between the heart and peripheral arteries has been reported in invasive studies about 60 years ago (Kroeker et al. 1955, Remington et al. 1956, Nichols et al. 2011). This pressure amplification between the central arteries and the upper limb has been comprehensively studied due to universal use of brachial cuff sphygmomanometry, where the pressure is usually measured (**Figure 4-3**). Such proof of amplification has been shown by results from the Anglo-Cardiff Collaboration Trial (McEniery et al. 2005, McEniery et al. 2008, McEniery et al. 2010), Asklepios study (Segers et al. 2009, Mahieu et al. 2010), European Projects On Genes in Hypertension study (Wojciechowska et al. 2012), as well as in different race (Heffernan et al. 2008, Lewis et al. 2010, Chirinos et al. 2011, Li et al. 2012, Pierce et al. 2013), gender (Lieber et al. 2010, Cecelja et al. 2012, Chester et al. 2013) and other recent studies (Benetos et al. 2010, Salvi et al. 2010, Gordin et al. 2011, Huang et al. 2011, Agnoletti et al. 2012, Benetos et al. 2012, Regnault et al. 2012, Wykretowicz et al. 2012, Agnoletti et al. 2013, Cho et al. 2013). All have found that amplification of the aorta-to-brachial pulse pressure is inversely related to large artery stiffness – which can be determined by central (carotid-femoral) pulse wave velocity (described further in Chapter 3) and characteristics of the reflected wave – such as its magnitude (determined by augmentation index) and timing (measured by time to reflection) (**Figure 4-4**).

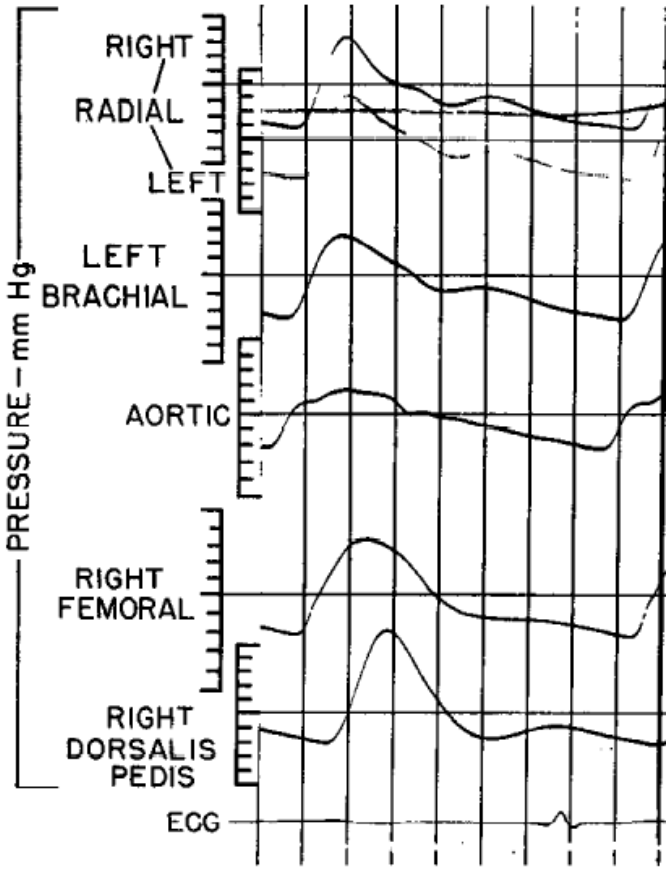


Figure 4-3. Pressure waves recorded simultaneously in ascending aorta, brachial artery, and radial artery. Amplitude of radial and brachial waves are similar, but amplitude of the aortic wave is much smaller. From Kroeker et al. (1956).

The mechanism of how pulse pressure is augmented (i.e. amplified) from aorta to upper limb holds importance in interpretation of blood pressure changes during the human lifetime. The plateau of systolic (and pulse) pressure during 20 to 40 years is predominantly due to exaggerated augmentation of brachial systolic (and pulse) pressure, which in extreme cases presents as spurious systolic hypertension of youth (O'Rourke et al. 2000). The maximal amplification of pressure in the upper limb is achieved when the body is fully grown while the large arteries still retain their elasticity from childhood.

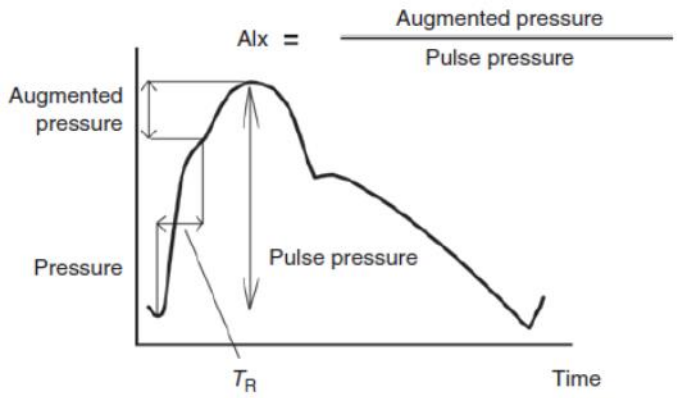


Figure 4-4. Aortic augmentation index (AIx) calculated from the ratio of augmented pressure divided by pulse pressure. AIx, augmentation index; TR, time to beginning of reflected waveform.

4.1.2 Changes in Central Hemodynamics with Aging

The principal changes that occur with age include dilation of the aorta and central major arteries as well as increase in their wall thickness. In contrast, their distensibility decrease (O'Rourke et al. 1992, O'Rourke et al. 2007, Safar 2010, Barodka et al. 2011, Palatini et al. 2011, Safar et al. 2013). Consequently, central arterial pulse wave velocity, central systolic and pulse pressure will be higher, while peripheral resistance increases (**Figure 4-5**). Impaired arterial distensibility will cause alteration of central aortic pressure and flow contour, alteration in pressure amplification between ascending aorta and peripheral arteries, alteration in vascular impedance, mismatch between aortic characteristic impedance and energy expenditure of the left ventricular ejection, and increase in pulsatile energy lost in circulation. Additionally, mean aortic systolic pressure is increased, thus rising ventricular oxygen requirements and adding extra load to ventricular ejection, whereas mean aortic diastolic pressure is decreased, hence coronary blood flow also decreased. All these changes will eventually lead to cardiac hypertrophy and heart failure, as well as reduce cardiac output when cardiac contractility is impaired (Miyashita et al. 1994, Westerhof et al. 1995).

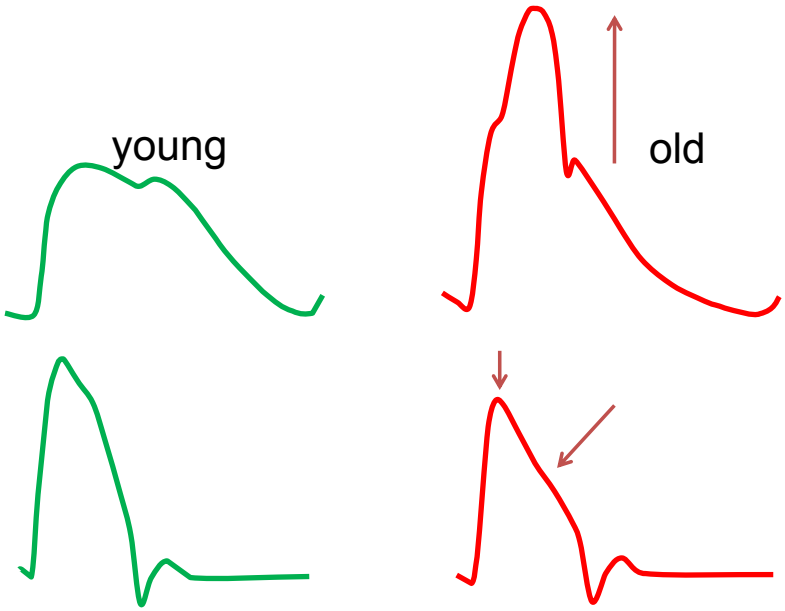


Figure 4-5. Schematic diagram of the aging effect on the pressure (top panel) and flow wave contour (bottom panel). Courtesy of M F O'Rourke, 2014.

The pressure wave shape shows increasingly high late systolic pressure as the reflected wave moves from diastole to systole. The boost in late systolic pressure results in increase in left ventricular afterload and relative decrease in capacity for myocardial blood perfusion (O'Rourke et al. 1992). The terminal ill-effects of these are predisposition to myocardial ischemic diseases, left ventricular hypertrophy leading to cardiac failure, and impaired diastolic function (Nichols et al. 1977, Merillon et al. 1978, Merillon et al. 1982, Nichols et al. 1985, O'Rourke et al. 1992, Westerhof et al. 1995).

The ascending aorta is the initial major artery which receives ejection of blood from the left ventricle. The aortic pressure pulse is generated from the left ventricular ejection flow. In a young normal subject, this aortic flow wave has a characteristic pattern where peak velocity occurs around 80 to 110 msec after the beginning of ejection (i.e. opening of the aortic valve), with peak velocity at approximately 70 to 80 cm/s. Following peak, aortic flow velocity declines gradually during mid- to late systole, until the aortic valve shuts (i.e. incisura)

marked by a small backflow, then fluctuates around zero during diastole (O'Rourke et al. 1992). The aortic pressure wave contour also has a typical pattern, showing a rounded top within the initial wave and a second one following the incisura, where the latter is caused by the reflected wave coming from the periphery (see **Figure 4-5)**. While the aortic flow velocity wave changes subtly in its contour throughout life – a slight decrease in peak velocity (largely attributable to aortic dilation), the pressure wave progressively shows a more prominent late systolic peak with no secondary wave and a steep fall during diastole (Kelly et al. 1989) (see **Figure 4-5)**. This alteration with age is due to increasingly stiffened arteries as well as faster aortic pulse wave velocity. Through registration of pulse wave shape, pressure and flow velocity and the use of harmonic analysis to express relationship between pressure and flow as impedance, more information on mechanism of how the pulse wave is reflected, its intensity and timing can be obtained with relative ease.

Progressive decline in vascular-ventricular interaction with aging has been described by many studies (Merillon et al. 1978, Merillon et al. 1982, Nichols et al. 1985, Westerhof et al. 1995, O'Rourke et al. 2010). The gradual increase in cardiac load with age is related to higher systolic pressure and increase in left ventricular mass with age and hypertension, and is responsible for advancing impairment of left ventricular function (Katz 1990, Miyashita et al. 1994, Westerhof et al. 1995). The best information is provided by quantitative analysis of ascending aortic impedance, although similar information can be obtained from studies of pressure and flow in the time domain. This concept of vascular impedance will be further explored in Chapter 5.

In the ascending aorta, the pressure wave shape is determined by the left ventricular ejection pattern (i.e. aortic flow wave) and properties of the vascular system i.e. ascending aortic impedance (Nichols et al. 2011). The principle effect of arterial stiffening and faster pulse wave velocity on pressure pulse is earlier return of reflected wave from peripheral sites, so it

will merge with the initial wave generated by ejection of blood from left ventricle (O'Rourke 1970, Murgo et al. 1980, O'Rourke et al. 1980, Kelly et al. 1989, O'Rourke et al. 1992, O'Rourke et al. 1993, O'Rourke et al. 2007, O'Rourke et al. 2010). The diastolic wave becomes less prominent, with less pressure amplification between ascending aorta and peripheral arteries. Arterial degeneration affects the aorta and lower-body arteries more than upper-body arteries, therefore pulse wave velocity increases markedly over these central arteries with age compared to relatively constant velocity at upper-body arteries (Choi et al. 2010). As the reflected wave boosts the late systolic peak, it will add extra workload on the ventricle, increases myocardial oxygen demand and decreases ventricular efficiency (Nichols et al. 1977, Hashimoto et al. 2008).

New information on arterial pressure wave change with aging has come from the non-invasive studies initiated by O'Rourke, Kelly, Hayward, Avolio, and others with high-fidelity sphygmographs (O'Rourke et al. 1993) using applanation tonometry to measure pressure wave non-invasively. These supplement invasive studies of aortic and left ventricular pressure wave change with age reported prior to the use of tonometry. Kelly et al (Kelly et al. 1989) showed characteristic aging change in more than 1000 normal subjects from young children to the elderly in carotid, radial and femoral artery pulses. A progressive increase in pressure amplitude with age was apparent, and this was attributable to progressive stiffening of the aorta, illustrated by the increase pressure augmentation of the late systolic wave. This characteristic aging change appears distinctly in the proximal aorta, slightly less marked in the carotid, and the least in peripheral arteries.

4.1.3 Non-invasive Measurement of Central Aortic Pressure

The best method for measuring aortic and left ventricular pressure is by invasive means; i.e. with a catheter threaded from a peripheral artery. However, this method is impractical and unjustified in routine clinical environments, except during a diagnostic cardiac catheterisation procedure.

At present, three procedures can be used to estimate central aortic pressure non-invasively. Yet all three methods are subject to appropriate pressure calibration, as well as accurate registration of the pressure waves. The calibration process depends on the innate error of the cuff pressure measurement, and this is discussed in more detail in the publications in my studies presented as publications in this chapter.

Transfer Function

The first method that is commonly applied employs a generalised mathematical transfer function to correct for distortion of the pressure wave in travel from aorta to the upper limb. The radial pressure waveform is recorded non-invasively using applanation tonometry, then calibrated to brachial (or radial) systolic and diastolic pressure (Kroeker et al. 1955, Kelly et al. 1989).

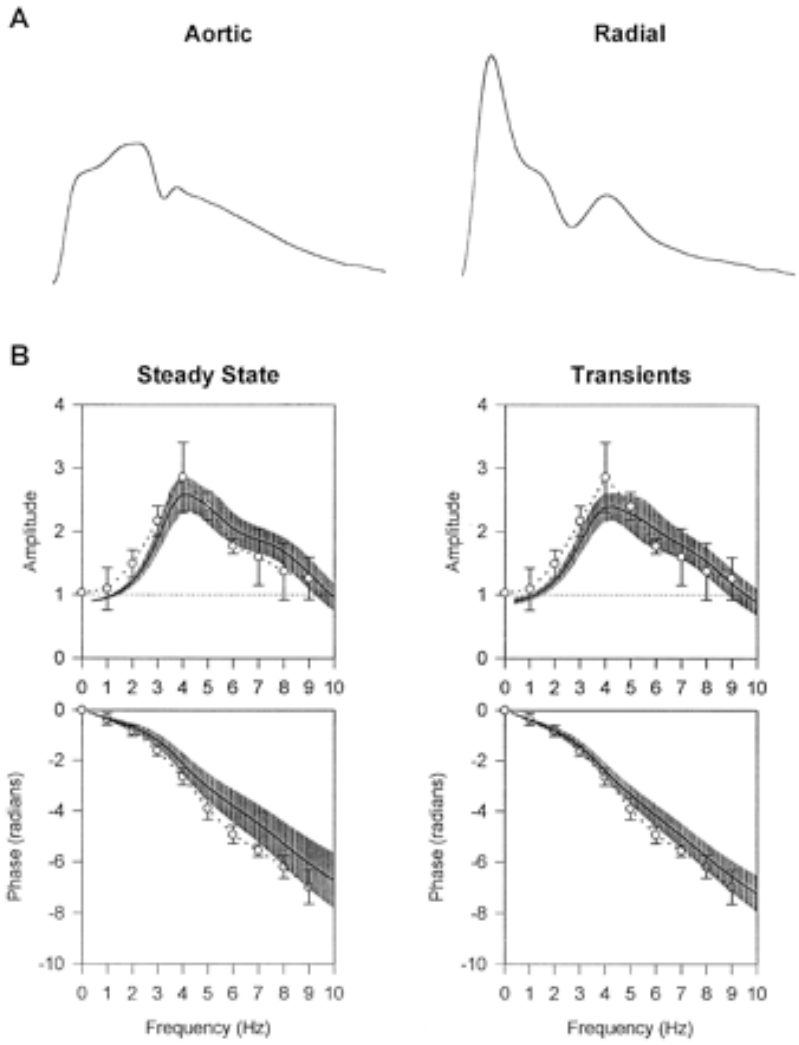


Figure 4-6.

A. A representation of aortic (left) and radial (right) pressure wave.

B. Spectral plots of generalised transfer function (shaded area defines 95% CI) generated from the steady-state (n=20) or hemodynamic transient (n=14) data. The spectra of generalised transfer function previously reported (Karamanoglu et al. 1993) are also shown as the dotted line at integer frequencies, with 95% CI error bars (Chen et al. 1997).

The radial pressure waveform is recorded non-invasively using applanation tonometry, then calibrated to brachial (or radial) systolic and diastolic pressure (Kroeker et al. 1955, Kelly et al. 1989). The radial pressure waveform is then convolved into the central aortic pressure wave, with the same mean pressure applied (Chen et al. 1997) (**Figure 4-6**). The ensemble-averaging process will average a series of pressure waves of about 8 to 10 seconds which include at least 1 respiratory cycle.

Equivalence of Mean and Diastolic Pressures

The second method is based on the equivalence of central and peripheral mean and diastolic pressures throughout the arterial system. Kelly and Fitchett (Kelly et al. 1992) were the first to utilise this method, where the same values of diastolic and mean pressures are applied to the central aortic waveform and the aortic systolic pressure is estimated by extrapolation.

Late Systolic Peak

The third method is based on the identification of the late systolic peak of radial pressure wave, which almost always represents the systolic peak pressure in the ascending aorta. The accuracy of this method has been confirmed by recent studies (Takazawa et al. 2007, Hickson et al. 2009, Lin et al. 2012, Takazawa et al. 2012, Wohlfahrt et al. 2014). Generally, the correspondence between late systolic peak (or second shoulder of the peak) and aortic systolic pressure is good, and it was maintained during vasodilator therapy (Takazawa et al. 2007, Takazawa et al. 2012). Nonetheless, Lin et al and Hickson et al have shown that this method may not be suitable to use in subjects with low blood pressure (Hickson et al. 2009, Lin et al. 2012).

Whilst these methods have been validated to invasive central aortic pressure measurements in various forms, these three methods have not been compared to each other to uncover any significant differences in the results obtained. Section 4.2 describes studies I conducted where such comparison is made. Another study in this section compares the late systolic peak method to the generalised transfer function method in a clinical environment with the acute effects of antihypertensive therapy. These earlier studies provided the basis for later studies performed during my Doctoral candidature.

All methods of central aortic pressure estimation require accurate and reproducible acquisition of the peripheral waveform from which aortic pressure is calculated. Prior to my Doctoral

candidature, I conducted a study to compare the repeatability of two commonly used waveforms in central aortic pressure estimation: the carotid and radial waveforms as acquired by tonometry. This study, which confirmed the superiority of radial artery for pressure measurement in the upper limb, is outlined in section 4.3.

4.1.4 Clinical Value of Measuring Central Aortic Pressure Non-Invasively

Since 2010, most of the non-invasive studies published on central aortic pressure and related indices have shown clear superiority of these in determining clinical end points. These papers employed either radial artery applanation tonometry and a generalised transfer function process to generate ascending aortic pressure waveforms, or tonometry of the carotid artery (without involving brachial artery tonometry), as discussed in this chapter. These studies have established the relationship between central blood pressure (aortic or carotid) and outcomes (Roman et al. 2010, Vlachopoulos et al. 2010, Gordin et al. 2011, Mitchell et al. 2011, Protogerou et al. 2011, Benetos et al. 2012, Chirinos et al. 2012, Gąsecki et al. 2012, Nakano et al. 2012, Regnault et al. 2012, Russo et al. 2012, Janner et al. 2013, Pase et al. 2013, Tanindi et al. 2014).

Central aortic systolic and pulse pressures are increasingly important because these are not affected by amplification of pressure between aorta and upper limb. It is more relevant to left ventricular load than systolic and pulse pressures measured in the upper limb. Systolic pressure varies among arterial segments due to the phenomenon of arterial pulse amplification (Roman et al. 2014). Therefore, the common practice of using conventional brachial cuff sphygmomanometric measurements as pressure load imposed on the heart and on central circulation (including coronary and cerebrovascular arteries) may be erroneous (Roman et al. 2014). Indices derived from the aortic pressure wave, including pressure pulse amplification to the upper limb, its augmentation from peripheral wave reflection, its integral during the

periods of systole and diastole would provide more information on vascular load, cardiac function, and ventricular–vascular interaction.

Central aortic pressures can be measured directly by invasive means, but can also be estimated from the carotid pressure or from use of a pressure transfer function applied to radial pressure waveform (Chen et al. 1997, Pauca et al. 2001, O'Rourke et al. 2006, Westerhof et al. 2008, Avolio et al. 2010, Nelson et al. 2010, Huan et al. 2011, Miyashita 2012, McEniery et al. 2014). A meta-analysis of central blood pressure estimation by different techniques has been published (Narayan et al. 2014), with some important qualifications raised by O'Rourke in subsequent journal correspondence (O'Rourke 2015). The study by Narayan et al (Narayan et al. 2014) found that the estimation of central systolic pressure by non-invasive techniques is subject to significant variability between devices. Furthermore, they found that the expected difference in systolic pressure between the aorta and upper limb, where substantial pressure amplification was anticipated, did not appear (Narayan et al. 2014). These findings are not universally accepted with a certain amount of controversy and at conflict to a review by Roman and Devereux (Roman et al. 2014) in the same year.

Section 4.4 describes an anomaly in pressure amplification from the radial to aorta, and from the brachial to aorta, as there was, up to the present time, no agreement on the most appropriate pressure calibration method to derive aortic pressure waveform from the upper limb. I conducted this study and performed all data analysis.

Section 4.5 extends the understanding of the clinical relevance of central aortic blood pressure measurement with studies into the differing effects of angiotensin-converting enzyme inhibitors and beta blockers on central pressure parameters, and into the effects of sildenafil on central aortic pressure. These earlier studies provided the basis for later reviews published

during my Doctoral candidature, which established the clinical value of central aortic pressure measurement.

If central aortic pressure is to be adopted routinely in clinical practice, population normal values need to be established with the aim of ascertaining risk scores and treatment targets. Section 4.6 outlines a large study to which I contributed data for the establishing of population normal values of central aortic blood pressure.

Sections 4.7 and 4.8 extend the application of central aortic pressure to other derived parameters, in which I contributed to the data analysis. Section 4.9 introduces another feature of central systolic aortic pressure that will increase linearly across the human lifespan, where I performed all data analysis and involved in manuscript preparation.

4.2 Comparison of Techniques to Derive Central Aortic Pressure Non-invasively

4.2.1 Comparison of Derived Parameters of Aortic Pressure

A study published as:

Adji A, O'Rourke MF. **Determination of Central Aortic Systolic and Pulse Pressure from the Radial Artery Pressure Waveform.** *Blood Pressure Monitoring* 2004;9:115-121.

I conducted studies that compare different methods or technique to derive central aortic pressure non-invasively. This earlier study provided the basis for later studies conducted during my Doctoral candidature. Three non-invasive methods of generating central from radial pressure in two clinical data sets were compared; (1) the timing of period from wave foot to systolic peak in the aorta or central arteries, then measuring pressure on the radial artery waveform itself at the same instant after the wave foot, (2) pressure at late systolic shoulder of radial waveform, and (3) an extrapolation of systolic pressure when mean and diastolic pressures are considered equal (Kelly et al. 1992). Data were recorded from a group of normal subjects, and another of comparison between baseline and after drug administration in a group of hypertensive patients. All these records were paper-based, and I performed all the data analysis. All three methods gave a good correspondence to those obtained with the SphygmoCor system for aortic, systolic and pulse pressures using transfer function, thus highlighting the value of simple inspection of the radial waveform to improve the estimation of central systolic and pulse pressure.

Pages 87-93 of this thesis have been removed as they contain published material. Please refer to the following citation for details of the article contained in these pages.

Adji, A., O'Rourke, M. F. (2004) Determination of central aortic systolic and pulse pressure from the radial artery pressure waveform. *. t22Ř tℕŜăădzℕŜ a2yńű2ℕλyƎΦ* 9(3), p. 115-121.

DOI: 10.1097/01.mpb.0000132426.32886.e0

4.2.2 Comparison of Derived Parameters of Aortic Pressure with Antihypertensive Treatment

A study published as:

Adji A, Hirata K, Hoegler S, O'Rourke MF. **Noninvasive Pulse Waveform Analysis in Clinical Trials: Similarity of Two Methods for Calculating Aortic Systolic Pressure.** *American Journal of Hypertension* 2007;20:917-922.

In the substudy of the vasodilator effect on central systolic pressure, we confirmed that central aortic pressure derived from radial pressure waveforms using a generalised transfer function gave similar results for central aortic pressure measured directly from radial waveforms estimated from late systolic shoulder method, in both control and active hypertensive treatment conditions. The hemodynamic benefits of certain (newer) drug class were maintained with both methods of central aortic pressure measurement when compared to another therapy. I organised subjects' enrolment and data recording together with Drs Hirata and Hoegler, as well as performed all analysis of radial and carotid pressure data.

Adji, A., Hirata, K., Hoegler, S., & O'Rourke, M. F. (2007) Noninvasive pulse waveform analysis in clinical trials: similarity of two methods for calculating aortic systolic pressure. *American Journal of Hypertension*. 20(8) p. 917-922.

DOI: 10.1016/j.amjhyper.2007.03.006

4.3 Reproducibility of Carotid and Radial Waveforms in the Estimation of Aortic Pressure

A study published as:

Adji A, Hirata K, O'Rourke MF. **Clinical Use of Indices Determined Non-invasively from the Radial and Carotid Pressure Waveforms**. *Blood Pressure Monitoring* 2006;11:215-221.

I also conducted a reproducibility study to demonstrate the superiority of radial artery pressure measurement compared to carotid. Both radial and carotid pressure waves from over 40 patients were recorded by Dr Hirata and myself independently, then I analysed all the data, and we were able to show that radial tonometry was better than carotid, with less variation between indices.

Adji, A., Hirata, K., & O'Rourke, M. F. (2006) Clinical use of indices determined non-invasively from the radial and carotid pressure waveforms. *Blood Pressure Monitoring*. 11(4) p. 215-221.

DOI: 10.1097/01.mbp.0000218001.50333.b7

4.4 Study: Brachial Artery Tonometry and the "Popeye" Phenomenon

A study published as: Adji A, O'Rourke MF. **Brachial Artery Tonometry and the Popeye Phenomenon: Explanation of Anomalies in Generating Central from Upper Limb Pressure Waveforms**. *Journal of Hypertension* 2012;30:1540-1551.

A group of distinguished researchers published a review on the role of pulse pressure amplification (Avolio et al. 2009) to clarify disparity between peripheral and aortic pressure. Yet no consensus was achieved despite considerable amount of invasive and non-invasive data that supported use of cuff brachial pressure calibration to radial. In our effort to further justify our concern on the brachial tonometry issue, we collected pressure waveforms from a total of 100 subjects from Dr O'Rourke's outpatient cardiovascular clinic to investigate anomalies in generating central from upper limb pressure waveforms. I recorded these subjects radial, brachial and carotid pressures, then calibrated these pressures to brachial cuff values. I performed all data collection, analysis, and contributed to interpretation and scientific writing of this paper. The result of this study was presented at the European Society of Hypertension in 2010 as an oral communication, in which I was the presenter. While our result confirmed some degree of amplification between brachial-to-radial artery, we confirmed that a much larger error had been made in measurement by Asklepios and Framingham Heart Studies' authors of the pulse at the brachial artery site where accurate pressure measurement could not be reliably achieved (Drzewiecki et al. 1983). The technical flaw was inability to gain an accurate tonometry pressure wave when the artery is not supported behind so that anterior surface of the artery is not applanated (flattened) (Drzewiecki et al. 1983). The pressure amplification observed between brachial and radial sites when pressures recorded non-invasively conflicted with the pioneering invasive study by Kroeker and Wood (Kroeker et al. 1955), and with the transfer function similarity between aorta-to-brachial and aorta-to-radial sites (Karamanoglu et al. 1993).

Adji, A., & O'Rourke, M. F. (2012) Brachial artery tonometry and the Popeye phenomenon: explanation of anomalies in generating central from upper limb pressure waveforms. *Journal of Hypertension*. 30(8) p. 1540-1551.

DOI: 10.1097/HJH.0b013e328354e859

4.5 Clinical Value of Central Aortic Pressure Measurement during Intervention

4.5.1 Differing Central Aortic Effects of Angiotensin-Converting Enzyme Inhibitor and Beta Blocker

A study published as:

Hirata K, Vlachopoulos C, **Adji A**, O'Rourke MF. **Benefits from Angiotensin-converting Enzyme Inhibitor 'Beyond Blood Pressure Lowering': Beyond Blood Pressure or Beyond the Brachial Artery?** *Journal of Hypertension* 2005;23:551-556**.**

Despite similar effects on brachial pressure, anti-hypertensive drugs have differential effects on central aortic pressure and this may explain the superiority of certain arterial vasodilating drugs in outcome trials. The aortic pulse wave analysis has shown to be valuable in explaining different effects of drugs on cardiovascular events (Miyashita et al. 2010). There are evidence that some drugs (arterial dilators including nitrates, calcium channel blockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockers) reduce central aortic pressure to a greater degree than brachial pressure, so that benefit cannot be assessed fully by brachial cuff pressure.

The first study which I conducted in collaboration with colleagues compared the effect of angiotensin-converting-enzyme inhibitor to beta-blocker drugs, and found that angiotensin-converting-enzyme inhibitor caused greater decrease in aortic systolic pressure when compared against beta-blocker. I had active collaboration in the subjects' inclusion and in final analysis of data. We enrolled 30 hypertensive patients and compared their pressure indices on three different days. The maximum effect of active treatment was reached after 3 hours following oral administration, and the angiotensin-converting-enzyme inhibitors caused

greater fall in aortic systolic pressure compared to the beta-blocker. Significant differences between the two active treatments were observed in aortic augmentation index. While the absolute value of augmentation index decreased with the angiotensin-converting-enzyme inhibitor, it increased with the beta-blocker. The 'benefit beyond blood pressure' is apparent when pressure is measured 'beyond the brachial artery', or centrally, and this is explicable on the basis of decreased stiffness of peripheral arteries and a reduction in wave reflection.

The importance of this article is highlighted by the accompanying editorial in the same issue of the *Journal of Hypertension* (Williams et al. 2005).

Hirata, K., Vlachopoulos, C., Adji, A., & O'Rourke, M. F. (2005) Benefits from angiotensin-converting enzyme inhibitor 'beyond blood pressure lowering': beyond blood pressure or beyond the brachial artery? *Journal of Hypertension*. 23(3) p.551-556.

DOI: 10.1097/01.hjh.0000160211.56103.48

4.5.2 Effect of Sildenafil on Central Aortic Pressure and Carotid-Femoral Pulse Wave Velocity

A study published as:

Hirata K, **Adji A**, Vlachopoulos C, O'Rourke MF. **Effect of Sildenafil on Cardiac Performance in Patients with Heart Failure**. *American Journal of Cardiology* 2005;96:1436-1440.

In the second study, we also found that a Phospho-Di-Esterase 5 (PDE5) inhibitor improved cardiac performance in heart failure patients. I was actively involved in patients' enrolment; I also performed data collection and analysis. Twenty patients were investigated where we compared their pressure indices and Doppler measurements between placebo and active day. The active response reached a plateau after 60 minutes, and aortic systolic and pulse pressure decreased with active treatment as did wave reflection indices. Our results suggested that PDE5 inhibition is an effective and safe treatment in patients with mild to moderate heart failure, at least acutely.

Hirata, K., Adji, A., Vlachopoulos, C., & O'Rourke, M. F. (2005) Effect of Sildenafil on cardiac performance in patients with heart failure. American Journal of Cardiology. 96(10) p. 1436-1440.

DOI: 10.1016/j.amjcard.2005.06.091

4.6 Reference Values for Central Blood Pressure and Its Amplification

A study published as:

Herbert A, Laurent S, Cruickshank JK, Boutouyrie P, on behalf of the Reference Values of Arterial Measurements Collaboration. **Establishing Reference Values for Central Blood Pressure and its Amplification in a General Healthy Population and According to Cardiovascular Risk-Factors.** *European Heart Journal* 2014;35:3122-3132

The normal reference values of central blood pressure have been recently published by the European Network for Arterial Stiffness Collaboration Group. They published a meta-analysis of over 45,000 adults in whom both brachial and central aortic SP were measured with different methods showed a relatively large number of both males and females under age 25 with amplification from aorta to upper limb of >20 mmHg (see *Appendix A* for full paper). I was invited to contribute data from Dr O'Rourke's clinic database by Dr Herbert, and we are grateful for the opportunity to collaborate with the European Network for Arterial Stiffness Collaboration Group on this project. Part of the paper is attached below, and my contribution is highlighted on page 139.

European Heart Journal (2014) **35**, 3122–3132
doi:10.1093/eurheartj/ehu293

Establishing reference values for central blood pressure and its amplification in a general healthy population and according to cardiovascular risk factors

Annie Herbert[1,2], John Kennedy Cruickshank[3]*, Stéphane Laurent[1], and Pierre Boutouyrie[1]*, on behalf of The Reference Values for Arterial Measurements Collaboration[†]

[1]Department of Pharmacology and INSERM U970, Assistance Publique Hôpitaux de Paris, Université Paris Descartes, 56 rue Leblanc, Paris 75015, France; [2]Research & Development Department, Pennine Acute Hospitals NHS Trust, Crumpsall, Manchester, UK; and [3]Diabetes, Cardiovascular Medicine & Nutrition, King's College University of London & King's Health Partners, London, UK

Received 20 January 2014; revised 19 May 2014; accepted 26 June 2014; online publish-ahead-of-print 11 August 2014

See page 3088 for the editorial comment on this article (doi:10.1093/eurheartj/ehu348)

Aims Estimated central systolic blood pressure (cSBP) and amplification (Brachial SBP-cSBP) are non-invasive measures potentially prognostic of cardiovascular (CV) disease. No worldwide, multiple-device reference values are available. We aimed to establish reference values for a worldwide general population standardizing between the different available methods of measurement. How these values were significantly altered by cardiovascular risk factors (CVRFs) was then investigated.

Methods and results Existing data from population surveys and clinical trials were combined, whether published or not. Reference values of cSBP and amplification were calculated as percentiles for 'Normal' (no CVRFs) and 'Reference' (any CVRFs) populations. We included 45 436 subjects out of 82 930 that were gathered from 77 studies of 53 centres. Included subjects were apparently healthy, not treated for hypertension or dyslipidaemia, and free from overt CV disease and diabetes. Values of cSBP and amplification were stratified by brachial blood pressure categories and age decade in turn, both being stratified by sex. Amplification decreased with age and more so in males than in females. Sex was the most powerful factor associated with amplification with 6.6 mmHg (5.8–7.4) higher amplification in males than in females. Amplification was marginally but significantly influenced by CVRFs, with smoking and dyslipidaemia decreasing amplification, but increased with increasing levels of blood glucose.

Conclusion Typical values of cSBP and amplification in a healthy population and a population free of traditional CVRFs are now available according to age, sex, and brachial BP, providing values included from different devices with a wide geographical representation. Amplification is significantly influenced by CVRFs, but differently in men and women.

Keywords Adult • Aged • Aorta • Arteries • Arteriosclerosis • Blood pressure • Central pressure • Humans • Pulse

Introduction

The measurement of blood pressure (BP) is fundamental in the general health assessment of patients and is usually done at the brachial artery. However, systolic blood pressure (SBP) is highly dependent on the site of measurement, it is thought, due to pressure wave reflections from more distal sites. Specifically, the pressure (and flow) waves travel at finite speed within arteries, and are

* Corresponding author: Tel: +33 1 5609396, Fax: +33 1 56093991, Email: pierre.boutouyrie@egp.aphp.fr (P. B.); Tel: +44 20 7848 4419, Fax: +44 20 7848 4171, Email: kennedy.cruickshank@kcl.ac.uk (J. K. C.)

† A complete list of authors is provided in Supplementary material online, Table S4.

Supplement 4. Participating Centres.

Cardiology Dept., Klinikium Wels-Giesckierchen (Austria)	1)Thomas Weber[a], Martin Rammer[a], Michael F. O'Rourke[b], Eber Bernd[a], Elisabeth Lassnig[a], Michael Porodko[a], Marcus Ammer[a] 2) Thomas Weber[a], Martin Rammer[a], Siegfried Wassertheurer[c], Eber Bernd[a], Michael F. O'Rourke[b], Audrey Adji[d], Stefan Rosenkranz[e], Marcus Ammer[a] 3) Thomas Weber[a], Eber Bernd[a], Michael F. O'Rourke[b], Marcus Ammer[a], Christian Punzengruber[a], Erich Kvas[a]	a) Cardiology Department, Klinikium Wels-Giesckierchen, Wels, Austria b) St Vincent's Clinic and University of New South Wales, Sydney, Australia c) Health and Environment, Austrian Institute of Technology, Vienna, Austria d) Australian School of Advanced Medicine, Macquarie University, Sydney, New South Wales, Australia e) Hermesoft Biostatistics, Graz, Austria	1) 958 2) 565 3) 336	**1,859**
Dijon (France)	The COVADIS Study: Carole Dufouil[a], Christophe Tzourio[a]	a) INSERM U708 and UPMC Paris, Paris, France	1,566	**1,566**
Amsterdam/Maastricht (Netherlands)	1) Hoorn Study: Ciel Nijpels[a] Jacqueline M. Dekker[b] Coen D.A. Stehouwer[c,d] 2) The AGAHLS Study: Isabel Ferreira[c,d,e,f] Jos W. Twisk[h,g] Yvo M. Smulders[b,i] Coen DA. Stehouwer[c,d] 3) The CODAM Study: Isabel Ferreira[c,d,e,f] Roel J. van de Laar[c,d,f] Carla J. van Kallen[c,d] Marleen M. van Greevenbroek[c,d] Casper G. Schalkwijk[c,d] Coen D. Stehouwer[c,d]	a) Department of General Practice, EMGO Institute for Health and Care Research, VU University Medical Center, Amsterdam, The Netherlands b) Department of Epidemiology and Biostatistics, EMGO Institute for Health and Care Research, VU University Medical Center (VUmc), Amsterdam, The Netherlands c) Department of Internal Medicine, Maastricht University Medical Centre (MUMC), Maastricht, The Netherlands d) CARIM School for Cardiovascular Diseases, MUMC, Maastricht, The Netherlands e) Department of Clinical Epidemiology and Medical Technology Assessment, MUMC, Maastricht, The Netherlands f) CAPHRI School for Public Health and Primary Care, MUMC, Maastricht, The Netherlands g) Department of Methodology and Applied Biostatistics, Faculty of Earth and Life Sciences, VU University, Amsterdam, The Netherlands h) Department of Internal Medicine, VUmc, Amsterdam, the Netherlands i) Institute for Cardiovascular Research, VUmc, Amsterdam, the Netherlands	1) 602 2) 373 3) 435	**1,410**
Peripheral vessels and Hypertension unit, 1st Department of Cardiology, Hippokration Hospital, Athens Medical School, (Greece)	HYGEIA (Hippokration-hYpertension AGEing and Arterial function): Charalambos Vlachopoulos[a], Constantinos Aznaouridis[a], Dimitrios Terentes-Printzios[a], Christodoulos Stefanadis[a] Panos Xaplanteris[a]	a) 1st Department of Cardiology, Hippokration Hospital, Athens Medical School, Profiti Elia 24, Athens 14575, Greece.	1,246	**1,246**

Milan (Italy)	InGenious Study: Alberto Zanchetti[a], Gregorz Bilo[b], Chiara Taurino[c], John D McClure[c], Markus P Schneider[c,d], Kalina Kawecka-Jaszcz[e], Katarzyna Stolarz-Skrzypek[e], Łukasz Klima[e], Jan A Staessen[f], Tatiana Kuznetsova[f], Josep Redon[g], Fernando Martinez[g], Enrico Agabiti Rosei[h], Olle Melander[i], Faiez Zannad[j], Patrick Rossignol[j], Stéphane Laurent[k], Cédric Collin[k], Laura Lonati[a], Anna F Dominiczak[c]	a) Istituto Auxologico Italiano, Università di Milano, Milan, Italy b) Department of Cardiovascular, Neural and Metabolic Sciences, S. Luca Hospital, IRCCS Istituto Auxologico Italiano, Milan, Italy c) BHF Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, University of Glasgow, UK d) Department of Nephrology and Hypertension, University of Erlangen-Nuremberg, Erlangen, Germany e) First Department of Cardiology and Hypertension, Jagiellonian University Medical College, Krakow, Poland f) Studies Coordinating Centre, Division of Hypertension and Cardiovascular Rehabilitation, KU Leuven Department of Cardiovascular Sciences, University of Leuven, Leuven, Belgium g) Hypertension Clinic, Internal Medicine, Hospital Clinico, University of Valencia, Valencia, Spain h) Division of Internal and Emergency Medicine, University of Brescia, Brescia, Italy i) Department of Clinical Sciences, Lund University, Malmö, Sweden j) INSERM, Centre d'Investigation Clinique 9501 and Unité 961, Centre Hospitalier Universitaire, and the Department of Cardiology, Nancy University, France k) INSERM U970, Université Paris Descartes, Sorbonne Paris Cité, APHP, Paris, France	712	**712**
St. Vincent's Clinic, Sydney (Australia)	Audrey Adji[a], Michael O'Rourke[a,c]	a) Australian School of Advanced Medicine, Macquarie University b) St Vincent's Clinic c) University of South Wales d) VCCRI	702	**702**
Prague (Czech Republic)	Ondrej Petrak[a], Branislav Štrauch[a], Jan Rosa[a], Jiri Widimský Jr.[a]	a) 3rd Department of Internal Medicine, General Faculty Hospital, First Faculty of Medicine, Charles University, Prague, Czech Republic	570	**570**

4.7 Study: Influence of Aortic Pressure Wave Components Determined Noninvasively on Myocardial Oxygen Demand in Men and Women

A study published as:

Namasivayam M, **Adji A**, O'Rourke MF. **Influence of Aortic Pressure Wave Components Determined Noninvasively on Myocardial Oxygen Demand in Men and Women**. *Hypertension* 2011;57:193-200.

As the reflected wave boosts the late systolic peak with aging, it will add extra workload on the ventricle, hence, increases myocardial oxygen demand. This was especially important to women, as they are more prone to cardiac ischemia due to lack of diastolic perfusion (Nichols et al. 2011). We examined the aortic pressure wave index as an indicator of myocardial oxygen demand, i.e. to evaluate the role of incident and reflected pressure waves on a surrogate of myocardial oxygen demand represented as tension time index. Again, analysing Dr O'Rourke's clinical database as before, we found that women were likely to have higher systolic and pulse pressure and lower diastolic pressures compared to men. The women's tension time index were higher, their mean central systolic pressure (as an indicator of systolic left ventricular load) and ejection time were greater, hence women are predisposed to cardiac ischemia than their men counterparts. I participated in the analysis and contributed to the writing of this paper.

Namasivayam, M., Adji, A., & O'Rourke, M. F. (2011) Influence of aortic pressure wave components determined noninvasively on myocardial oxygen demand in men and women. *Hypertension.* 57(2) p. 193-200.

DOI: 10.1161/HYPERTENSIONAHA.110.160200

4.8 Study: Evaluating the Hemodynamic Basis of Age-Related Central Blood Pressure Change using Aortic Flow Triangulation

A study published as:

Namasivayam M, **Adji A**, O'Rourke MF. **Evaluating the Hemodynamic Basis of Age-Related Central Blood Pressure Change Using Aortic Flow Triangulation.** *American Journal of Hypertension* 2015 (online 4 June, doi: 10.1093/ajh/hpv80)

Together with Dr Namasivayam and Professor O'Rourke, we are currently exploiting the ability to separate forward (initial) and backward (reflected) pressure wave based on the aortic flow triangulation concept (Westerhof et al. 2006). In the aortic flow triangulation method, the aortic flow is substituted by a triangular wave, with the width of the triangular base set to be equal to ejection time, and the peak flow at the inflection point of pressure and/or at 30% of ejection time. The waveform analysis gives the forward and backward pressure waves.

In particular, we explored the contribution of each forward and/ or backward pressure to the rise in aortic systolic and pulse pressure with aging. Our initial analysis, which I have participated, showed that both forward and reflected wave contributions are similar to aortic pressure wave amplitude increase across the lifespan, however, the reflected wave has as more marked role. This paper will support recent studies on the reflection magnitude to predict mortality (Zamani et al. 2014, Zamani et al. 2015) (Wang et al. 2010, Zamani et al. 2014, Zamani et al. 2015).

Namasivayam, M., Adji, A., & O'Rourke, M. F. (2016) Evaluating the hemodynamic basis of age-related central blood pressure change using aortic flow triangulation. *American Journal of Hypertension.* 29(2) p. 178-184.

DOI: 10.1093/ajh/hpv080

4.9 Study: Tracking of Brachial and Central Systolic Pressure over the Entire Life Course

A paper ready for submission:

Adji A, O'Rourke MF. **Tracking of Brachial and Central Systolic Pressure over the Entire Life Course.** Submitted to *Hypertension* **(2015).**

It has been discussed in previous Chapters 3 and 4 that measurement of brachial systolic pressure is inaccurate, and this is attributable to distortion of pressure wave contour as the pulse travels to the upper limb. The brachial systolic (peak) pressure may be 20 mmHg or more higher than arteries that supply the brain, heart and kidneys; i.e. those which are damaged by elevated pressure. Aging, with growth and development, has an unusual effect on amplification of the pulse in the brachial and radial arteries, such that systolic pressure measured by cuff sphygmomanometry often substantially overestimate pressure in young adults (Nichols et al. 2011). Recently, the Chicago Heart Association Detection Project in Industry Study (Yano et al. 2015) has shown that the 20-years incidence rate of cardiovascular mortality is markedly higher in adult (18 to 49 years) males with combined systolic/ diastolic and isolated diastolic hypertension. However, for those with isolated systolic hypertension, their incidence rate is similar with adults with high-normal and optimal-normal blood pressure. In the accompanying editorial, however, those with isolated systolic hypertension are still regarded as "hypertensive" and should be treated (Weber 2015).

Due to continuing disagreement between clinicians on categorisation of "hypertensive" for adult males, especially those aged between 18 to 49 years, we have written a paper on aortic systolic pressure between the "overlooked" ages of 15 to 25 years. In this study, data from the major US studies for adults and children with brachial systolic pressure were analysed and transformed to aortic systolic pressure by subtracting amplification as determined from the

radial pulse wave in published ACCT-II trials. This "second systolic shoulder" method has been shown substantially equivalent to use of the generalised transfer function method, further discussed earlier in Chapter 4, for determining amplification and central systolic pressure in adults. The result confirmed other data in large population studies that brachial cuff systolic pressure in young adults is markedly elevated above central aortic pressure, so that elevation of brachial pressure alone, at this age, is unlikely to be predictive of subsequent events. The high amplification of upper limb pressure accounts for high brachial systolic pressure, and it is not a representation of true aortic systolic pressure. Amplification of the systolic between aorta and upper limb is apparent by age 5 and is maximal between age 13 and 25. Divergence of male from female brachial systolic pressure begins at age 14 and is largely due to faster continuing growth in males. Central aortic systolic pressure increases almost linearly from age 15 to 80, deviating most from brachial pressure during the period of 15 – 30 years. For this study, data collection was limited to measurement of non-invasive radial artery pressure and derived aortic pressure using the "adult" generalised transfer function in 14 recumbent children aged 1 – 16 years, ensemble-averaged over at least one respiratory cycle. The radial pressure waves were calibrated to brachial artery systolic and diastolic pressure in NHBPEP study, 2004 (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004). The central aortic systolic pressure was determined from the transfer function method used in adults (SphygmoCor system), and the second systolic shoulder method, as used in the Omron device. **Figure 4-7** showed the correlation between the two methods in our children subjects as previously found in adults with greater variation.

These results have been presented in abstracts form at local and international scientific meetings, and the manuscript is ready for submission. It challenges present concepts on change in arterial pressure with age. I conducted all data collection, analysis and manuscript preparation; Dr O'Rourke and I contributed equally in this paper.

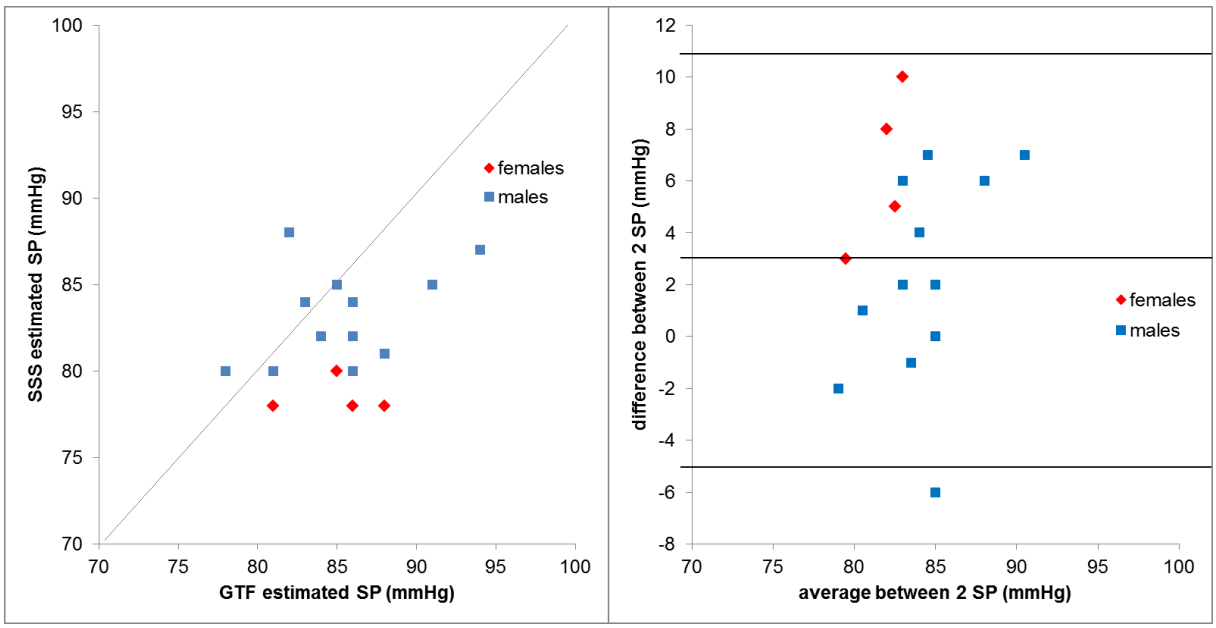


Figure 4-7. Relationship between aortic systolic pressure estimated using the Second Systolic Shoulder (SSS) method and "adult" Generalised Transfer Function (GTF) method (left panel), and when shown in Bland-Altman diagram (mean ± 2 standard deviation) (right panel).

TRACKING OF BRACHIAL AND CENTRAL AORTIC SYSTOLIC PRESSURE OVER THE ENTIRE LIFE COURSE

Michael F O'Rourke MD DSc[1,2,3], **Audrey Adji** MB MBiomedE[1,4]

1. St Vincent's Clinic, Sydney, Australia

2. University of New South Wales, Sydney, Australia

3. Victor Chang Cardiac Research Institute, Sydney, Australia

4. Australian School of Advanced Medicine, Macquarie University, Sydney, Australia

Short title: Tracking of systolic pressure over the life course

Word count: 4762 words (including abstract, text, references, legends)

Figures: 7

Abstract

A blind spot exists in major studies of brachial Blood Pressure (BP) between the ages of 15-30 years, corresponding to the pediatric population covering ages 1-18 years and the adult studies which commence around age 25. We sought to cover this important age group which contains young people making career decisions and often having BP recorded for the first time.

At birth, upper limb SP is approximately 50 mmHg, and rises to 94 at age 5; there is no amplification of the pulse nor significant gender difference. Brachial SP rises less steeply with age up to 14 years, when values of males and females begin to diverge, and with males rising to mean SP 120 and females 110 at around 21 years of age. SP plateaus to age 40, then rises again steadily to age 70 and beyond. SP in males, higher from age 15, approximates that of females after age 70 years.

In contrast to brachial pressure, non-invasively calculated aortic SP rises more slowly, and almost linearly with age from 5 years to 70 years with greatest difference (amplification) between aorta and upper limb seen between 10 and 25 years in both males and females.

A tentative explanation is offered – that the high amplification of upper limb pressure from age 5-40 years of age is due to distortion of the pulse during propagation in the upper limb, and that aortic pressure is more representative of aging changes and their causation.

Keywords: brachial systolic pressure, central aortic systolic pressure, generalized transfer function method, second systolic shoulder method, pressure amplification.

4.9.1 Introduction

Large scale epidemiological studies on arterial blood pressure in the USA and elsewhere show progressive increase in brachial artery Systolic Pressure (SP), measured by sphygmomanometer cuff from age 40 to age 80 and beyond. They also show gender differences with SP higher in men than women from 20 to at least 70 years.

Studies in children have also shown gender differences, but these are relatively small up until age 14 when SP in males continues to rise while that in girls tends to rise less quickly. Differences are associated with differences in height (figure 1) [1].

There are few studies of brachial SP in older children (i.e. adolescents) and young adults since adult studies usually embrace subjects from age 20 upwards. The lowest age in the Framingham study was 25 years [2]. However, prospective studies linking weight at birth with blood pressure, show progressive rise in brachial SP to a peak at age 20, followed by a plateau to age 30 years for all birth weights in 4649 subjects (figure 2) [3].

There is evidence of a localised peak and plateau of SP in males (and females) at around 20-30 years of age in all large population studies. Its significance is not fully understood. It is mentioned in the European Society of Hypertension/ European Society of Cardiology guidelines [4] as a possible reason for determining central aortic SP in young persons, particularly males, around this age with high brachial SP to exclude "Spurious Systolic Hypertension" [5]. A soon-to-be published meta-analysis of over 45,000 adults in whom both brachial and central aortic SP were measured with different methods showed a relatively large number of both males and females under age 25 with amplification from aorta to upper limb of >20 mmHg (Herbert A, Laurent S, Cruickshank JK, Boutouyrie P. Unpublished data. 2014). This largely accounts for the localized peak.

4.9.2 Methods

The purpose of this paper was to analyse data from the major US studies for adults [2] and children [6] with brachial SP transformed to central aortic SP by subtracting amplification as determined from the radial pulse wave in published trials [7]. This "second systolic shoulder" method has been shown substantially equivalent to use of the Generalized Transfer Function (GTF) method by SphygmoCor^{TM} (AtCor Medical, Sydney, Australia) for determining amplification and central SP in adults (figure 3) [7,8]. This method is used in preference to a GTF in the Omron radial tonometric device, where it provides near identical values for pressure amplification and central SP [9]. The GTF method was generated from an adult population. The "second systolic shoulder" method should be applicable at all ages since it is based on very low amplification of the lowest frequency of the pulse [10-12].

In children, the GTF method has not been shown equivalent to the second systolic shoulder method, so the latter "second shoulder' was used for all studies.

Data on brachial SP were taken from the Framingham study over the range of 25-70 years [2]. Using the Anglo-Cardiff Collaboration Trial (ACCT-II) data on pressure wave analysis in over 5,000 subjects [13], we determined amplification of the pressure wave between aorta and upper limb (separately for males and females), and subtracted this from brachial SP at corresponding ages in the Framingham data to obtain central aortic SP separately in adult males and females.

For children's studies, we took brachial cuff blood pressure from the published NHANES data set [6] and subtracted amplification of the waves as determined in our databank of children studied in longitudinal fashion over the range of 2-13 years. We supplemented these data with information on pressure wave amplification in 207 boys and 198 girls aged 8 years

in a cross-sectional study at a neighbouring institution [14]. We reset SP to the NHANES values for boys and girls at 8 years. Information for neonates was taken from data of Gevers et al [15] who measured radial artery pressure invasively in an intensive care ward.

A Student's t-test was performed to detect any significant difference between males and females, and between children and adults brachial and aortic SP. A p-value of less than 0.05 was taken to be significant.

4.9.3 Results

The composite figure 4 provides data published for the 2 major US population studies of male and female adults in the Framingham study [2] and of children in the NHANES study [6], with measurement of central aortic SP published from the largest population study of central aortic and upper limb pressure in adults in the cross-sectional ACCT study [13]. Our own databank on longitudinal change in amplification with age in children was supplemented (and confirmed) by the study of Ayer et al [14], which was originally conducted for another purpose; this however remains the largest study of radial artery waveform analysis in children.

Figure 4 shows that central aortic SP approximates brachial SP at the extremes of life – at birth and at the 8^{th} decade. At both extremes of life the secondary peak of pressure dominates over the first systolic peak (figure 5) and there is no amplification of pressure to the upper limb, and there is no apparent difference between males and females. Between the two extremes of age, brachial SP first rises quickly from around 50 mmHg at birth to around 85 mmHg at age 5, then appears to rise more slowly to a peak of around 120 mmHg at age 20 years in males and around 110 mmHg in females, thereafter falling in males or remaining at a plateau before rising again from age 40 to well beyond 80 years [2].

There was a significant difference between children's and adults central aortic SP, both in males ($p<0.01$) and females ($p<0.01$). Similarly, there was a significance difference between children's and adults brachial SP ($p<0.01$). There was a linear relationship between aortic SP and age between 5 years and 70 years ($p<0.01$), as shown in figure 4.

Figure 5 compares radial artery pressures in infancy and at age 93 years. Amplitude is far greater in the latter (124 mmHg) than in the former (46 mmHg when calibrated to NHANES study). Time to return of wave reflection appears to be much the same (around 100 msec) in both cases; early return of wave reflection appears similar. Similarity of early reflection in infant compared to elderly adult is attributable to shorter distance to reflecting site in the infant matched by lower pulse wave velocity in the infant c.f. elderly adult.

Amplification of the pressure wave from aorta to upper limb was surprisingly high in children. This was first noted by Ayer et al [14], and is confirmed by data in this paper. Amplification remained high down to 5 years of age. We have just one subject in our databank in whom it was possible to measure pulses longitudinally at 2, 4 and 10 years (figure 6). It was only at 4 years and below that the second systolic peak exceeded the first, indicating lack of pressure wave amplification. By age 7 years, amplification was 9 mmHg and by 9 years, amplification was 16 mmHg.

Our own databank contained one pair of twins (male and female). These were studied longitudinally. Values of amplification were virtually identical and high in both; at 8 years (girl 19 mmHg and boy 13 mmHg respectively), and at 13 years (girl 27 mmHg and boy 19 mmHg), similar to the high values of described by Ayer et al [14] at around 20 mmHg (figure 7).

4.9.4 Discussion

This paper must discuss the benefits of and the deficiencies in measurement of blood pressure in population studies and in clinical practice. Up to the present, and well into the future, the cuff sphygmomanometer and measurements of brachial SP and Diastolic Pressure (DP) are and will remain the standard by which patients are assessed and by which hypertension is and will be treated.

Importance and value of cuff sphygmomanometric brachial SP and DP cannot be underestimated. Prior to 1900, hypertension was recognised by "hardness of the pulse" as palpated at the radial artery, and the shape of the pulse waveform measured by mechanical sphygmographs. Sphygmographs were difficult to use and impracticable for routine clinical use. The brachial cuff method for measuring SP by the Riva-Rocci (palpation) technique was improved by the Korotkov auscultatory technique, but neither was used by most physicians in clinical practice, and Osler's textbook (6^{th} edition, 1906) [16], did not refer to either. Most early information on arterial pressure came from the Life Insurance Industry, with Fisher's JAMA article in 1914 [17] (exactly 100 years ago), and his presentation to the Life Insurance Medical Directors of America in 1917 [18] showed clear predictive value of elevated SP in predicting all-cause mortality. In 1915, the Prudential Life Insurance Company reported experience in measurement of brachial blood pressure in 18,637 applicants [18]. Over the past 100 years, the cuff sphygmomanometer has become ubiquitous in medical and hospital as well as life insurance practice, and well over 100,000 automatic devices have found the way into homes (Omron Company data, Kyoto, Japan). The value of measuring arterial pressure using brachial cuff methods has been of undisputed value in identifying hypertension and high risk asymptomatic persons. Guidelines have been developed by august bodies [19], with the help of well conducted trials, and population studies such as those which form the basis of this paper.

One hundred years after Fisher's paper in JAMA [17], a number of issues have arisen on interpretation of arterial pressure values provided by sphygmomanometer. The first of these was relative importance of systolic and diastolic pressure in diagnosing hypertension. The short answer to this question was provided by the Framingham study [20] which showed that both systolic and diastolic pressure are important, but that elevation of DP is more predictive of events in young adults (< 40 years), and SP more important over 40-60 years of age. Other issues under debate are the circumstances under which blood pressure is measured, and whether office measurements should be supplemented by home or ambulatory measurement of SP and DP. The American Heart Association (AHA) has provided advice in its journals on a regular basis, last addressing these issues in 2005 [21]. The most recent controversy concerns "refractory hypertension" and consideration of renal nerve ablation therapy where office blood pressure measurements created a groundswell of enthusiasm [22], but was tempered by apparent lack of efficacy where blood pressure was recorded by ambulatory techniques [23].

This paper addresses another issue on measurement of arterial pressure at the brachial artery where the cuff device is convenient, but where the pulse waveform providing top (systolic) and lowest (diastolic) pressure is distorted and where systolic (peak) pressure may be 20 mmHg or more [13] higher than arteries to the brain, heart and kidneys which are damaged by elevated pressure. Related issues are the findings that some drugs (arterial dilators including nitrates, calcium channel blockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockers) reduce central aortic pressure to a greater degree than brachial pressure [24], so that benefit cannot be assessed completely by brachial cuff pressure [25,26]. Another issue, focussed on in this paper, is that aging, with growth and development, has an unusual effect on amplification of the pulse in the brachial and radial arteries such that blood pressure measured by cuff sphygmomanometry may overestimate arterial pressure in young adults

[5,26], and under some conditions such as exercise [27] and with administration of arterial dilating drugs [27]. These issues are not widely known or appreciated by clinicians.

The issue of Isolated Systolic Hypertension in Youth (ISHY) has been addressed [1,5], and considered by the ESH and ESC [4]. Measurement of central aortic pressure is deemed desirable by the ESH and ESC in young people (indeed in persons < 60 years) where no mortality benefit has been established, before any diagnosis of "hypertension" is made. USA authorities are silent on this issue and measures available from the pressure pulse waveform are not recognised or authorised for reimbursement except in persons with peripheral arterial disease [28].

In this paper, we confirm from data in large population studies that brachial SP in young adults is markedly elevated above central aortic pressure, so that elevation of brachial pressure alone, at this age, is unlikely to be predictive of subsequent events, whereas it is predictive over age 60. No decisive data are available on this issue. No studies have confirmed benefits of treating Isolated Systolic Hypertension (ISH) at age 15-30 years whereas such benefits are well established for treating ISH in persons over 60 years [1,4,29-31].

Through our study of children, we show that the difference between brachial and aortic SP extends from 20 years down to at least 5 years of age, and that amplification is great in the region of 15-25 mmHg, not only in males, but in females as well. The most reliable data on this comes from the study of Ayer et al [14] which showed amplification of 17 mmHg in 8 year old girls and 18 mmHg in 8 year old boys. Authors of this study concentrated on difference in augmentation of carotid pressure, which was marginally higher in girls than boys at age 8. This study is ongoing, and further longitudinal data in the cohort will soon be available at average age 12 years.

The biggest surprise of the present study is the high amplification of the brachial/ radial pulse in children, which continues on through adolescence into early adulthood in both males and females. Implications of this are apparent in figure 4 which shows that central aortic pressure in girls as well as boys increases in a near linear fashion with age from 5 – 70 plus years with only the brachial SP showing fluctuations that can be attributed to growth and development, as well as gender differences which are largely (but not completely) attributable to differences in body height (averaging about 10 cm in most studies).

We are not confident in data for children <5 years of age. Amplification of the pulse decreases dramatically below this age as seen in figures 5 and 6, to that one would expect it to be zero at or shortly after birth. The NHANES data [6] gives values of brachial SP at one year of age which are only marginally less than at 5 years. We have concerns on the accuracy of the cuff method in infants under 5 years. Gevers et al's pressure for neonates [15] averaged just on 50 mmHg, but these children were often born prematurely or had other illnesses which caused admission to intensive care and radial cannulation. Further we acknowledge the difference between brachial cuff and intra-arterial SP and DP in the contra-lateral arm. These are substantial in adults and approach the AAMI limits for mean and standard deviation identity [32]. In neonates, we are confident of the arterial pulse waveforms which consistently show that the second systolic wave represents SP, both in Gevers et al data [15], and in our own report on aortic waveforms at cardiac catheterisation in infants [33].

4.9.5 Perspective

The conventional view of arterial pressure as measurable accurately by the cuff sphygmomanometer and of hypertension as a condition definable by the cuff sphygmomanometer alone, are challenged by the data presented here. While confident of the perspective presented, we must emphasise that the cuff sphygmomanometer remains as the

gold standard; for the foreseeable future, other measures will have to prove their worth as incrementally useful. It will be difficult for any new method to achieve the success that the sphygmomanometer has in the 20 years following its introduction for prediction of risk in life insurance, and over the last 50 years in detection and monitoring of persons at risk, and in the treatment of hypertension with remarkably effective drugs.

What is new?

- Systolic pressure triples over the normal life span in central and peripheral arteries, in males and in females.
- Amplification of systolic pressure between aorta and upper limb is apparent by age 5 and is maximal between age 13 and 25.
- Amplification of systolic pressure is the same in males and females up until the late teens.
- Divergence of male from female systolic pressure begins at age 14 and is largely due to faster continuing growth over the next 4 years in males.
- Central aortic systolic pressure, measured by different techniques, increases almost linearly from age 15 to 80, deviating most from brachial pressure during the period of 15 – 30 years.
- Non-linear increase in brachial pressure throughout life can be attributed to distortion of the pressure wave in the upper limb with growth and development.

What is relevant?

Information provided overturns previous perspectives on blood pressure and its difference in different arteries, different ages and different genders.

References

1. O'Rourke MF, Adji A. Guidelines on Guidelines: Focus on isolated systolic hypertension in youth. J Hypertens 2013;31:649-654.

2. Cheng S, Xanthakis V, Sullivan LM, Vasan RS. Blood pressure tracking over the adult life course: patterns and correlates in the Framingham Heart Study. Hypertension 2012;60:1393-1399.

3. Uiterwaal CS, Anthony S, Launer LJ, Witteman JC, Trouwborst AM, Hofman A, Grobbee DE. Birth weight, growth, and blood pressure: an annual follow-up study of children aged 5 through 21 years. Hypertension 1997; 30:267–271.

4. Mancia G, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F; Task Force Members. 2013 ESH/ ESH Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2013l;31:1281-1357.

5. O'Rourke MF, Vlachopoulos C, Graham R. Spurious systolic hypertension in youth. Vasc Med 2000;5:141-145.

6. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The Fourth Report on the Diagnosis, Evaluation,

and Treatment of High Blood Pressure in Children and Adolescents. Pediatrics 2004;114:555-576.

7. Pauca AL, Kon ND, O'Rourke MF. The second peak of the radial artery pressure wave represents the aortic SP in adult hypertensives and in elderly patients. Br J Anesth 2004;92:651-657.

8. Adji A, O'Rourke MF. Determination of central aortic systolic and pulse pressure from the radial artery pressure waveform. Blood Press Monit 2004;9:115-121.

9. Ding FH, Li Y, Zhang RY, Zhang Q, Wang JG. Comparison of the SphygmoCor and Omron devices in the estimation of pressure amplification against the invasive catheter measurement. J Hypertens 2013;31:86-93.

10. Hickson SS1, Butlin M, Mir FA, Graggaber J, Cheriyan J, Khan F, Grace AA, Yasmin, Cockcroft JR, Wilkinson IB, McEniery CM; Anglo-Cardiff Collaboration Trial Investigators. The accuracy of central SBP determined from the second systolic peak of the peripheral pressure waveform. J Hypertens 2009;27:1784-1788.

11. Chen CH, Nevo E, Fetics B, Pak PH, Yin FC, Maughan WL, Kass DA. Estimation of central aortic pressure waveform by mathematical transformation of radial tonometry pressure. Validation of generalized transfer function. Circulation 1997;95:1827-36.

12. O'Rourke MF, Adji A. Letter to the Editor "Central pressure and pulse wave amplification in the upper limb". Hypertension 2010;55:e1-2.

13. McEniery CM, Yasmin, McDonnell B, Munnery M, Wallace SM, Rowe CV, Cockcroft JR, Wilkinson IB, on behalf of the Anglo-Cardiff Collaboration Trial II. Hypertension 2008;451:1476-1482.

14. Ayer JG, Harmer JA, Marks GB, Avolio A, Celermajer DS. Central arterial pulse wave augmentation is greater in girls than boys, independent of height. J Hypertens 2010;28:306-313.

15. Gevers M, van Genderingen HR, Lafeber HN, Hack WWM. Radial artery blood pressure measurement in neonates: an accurate and convenient technique in clinical practice. J Perinat Med 1995;23:467-475.

16. Osler W. Principles and Practice of Medicine. 6th ed. Appleton; New York 1906.

17. Fisher JW. The diagnostic value of the sphygmomanometer in examinations for life insurance. JAMA 1914;63:1752-1754.

18. Postel-Vinay N. A Century of Arterial Hypertension 1896-1996. Wiley; New York 1996, pages 39-48.

19. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, Lackland DT, LeFevre ML, MacKenzie TD, Ogedegbe O, Smith SC Jr, Svetkey LP, Taler SJ, Townsend RR, Wright JT Jr, Narva AS, Ortiz E. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014;311:507-520.

20. Franklin SS, Gustin W 4th, Wong ND, Larson MG, Weber MA, Kannel WB, Levy D. Hemodynamic patterns of age-related changes in blood pressure: the Framingham heart Study. Circulation 1997;96:308-315.

21. Pickering TG, Hall JE, Appel LJ, Falkner BE, Graves J, Hill MN, Jones DW, Kurtz T, Sheps SG, Roccella EJ; Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. Hypertension 2005;45:142-161.

22. Symplicity HTN-2 Investigators, Esler MD, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, Bohm M. Renal sympathetic denervation in patients with treatment-resistant hypertension (the Symplicity HTN-2 Trial): a randomised controlled trial. Lancet 2010;376:1903-1909.

23. Persu A, Renkin J, Thijs L, Staessen JA. Renal denervation: ultima ratio or standard in treatment-resistant hypertension. Hypertension 2012;60:596-606.

24. O'Rourke MF, Safar ME, Dzau V (eds). Arterial Vasodilation: Mechanism and Therapy. Lea and Febiger, 1993.

25. Kelly RP, Gibbs HH, O'Rourke MF, Daley JE, Mang K, Morgan JJ, Avolio AP. Nitroglycerine has more favourable effects on left ventricular afterload than apparent from measurement of pressure in a peripheral artery. Eur Heart J 1990;11:138-144.

26. Nichols WW, O'Rourke MF, Vlachopoulos C. McDonald's Blood Flow in Arteries. 6th ed. Hodder Arnold, 2011.

27. Sharman JE, Lim R, Qasem AM, Coombes JS, Burgess MI, Franco J, Garrahy P, Wilkinson IB, Marwick TH. Validation of a generalized transfer function to noninvasively derive central blood pressure during exercise. Hypertensio 2006;47:1203-1208.

28. Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, Foster E, Hlatky MA, Hodgson JM, Kushner FG, Lauer MS, Shaw LJ, Smith SC Jr, Taylor AJ, Weintraub WS, Wenger NK, Jacobs AK; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2010;122:e584-636.

29. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). JAMA 1991;265:3255-3264.

30. Trial SE, Staessen JA, Fagard R, Thijs L. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension (Syst-Eur Trial). Lancet 1997;350:757-764.

31. Liu L, Wang JG, Gong L, Liu G, Staessen JA, for the Systolic Hypertension in China (Syst-China) Collaborative Group. Comparison of active treatment and placebo in older Chinese patients with isolated systolic hypertension. J Hypertens 1998;16:1823-1829.

32. White WB, Berson AS, Robbins C, Jamieson MJ, Prisant LM, Roccella E, Sheps SG. National standard for measurement of resting and ambulatory blood pressures with automated sphygmomanometers. Hypertension 1993;21:504-509.

33. Hsieh KY, O'Rourke MF, Avolio A, Doherty JB, Kelly RP, Chen YT. Pressure wave contour in the ascending aorta of children: paradoxical similarity to the elderly. Aust NZ J Med 1989;19:555. [abstract]

Figure Legends

Figure 1. Composite figure showing published values of the 90th brachial SP percentile (above which a diagnosis of hypertension is warranted) in boys and girls from age 7 to 18 years. Inset are the 50th percentiles for height in boys (blue) and girls (red) from age 7 to 18 years. Figure adapted from ref [1]. Values of brachial SP in boys and girls overlap up to 14 years of age, after which divergence is apparent. Differences between males and females apparent over age 14 are associated with body height, and may be largely due to difference in height, which is maintained over the adult life span.

Figure 2. Change in brachial SP between age 10 and 32 years in a cohort of 4649 persons in whom birth weight had been recorded, with data separated into tertiles of those with low (=<3200 g), medium (3200-3600 g), and high (=>3600 g) birth weight. Males and females shown together. All three groups showed a peak at around age 20, with a plateau or decline between 20-30 years. Figure adapted from ref [1,3].

Figure 3. Method for estimation of aortic SP from the second systolic shoulder of the radial artery pressure waveform, as described in refs [8-10], and as used in this study and in the Omron instrument. Amplification is measured from the peak of the radial artery pressure peak to the beginning of the second shoulder in the radial pressure wave, which corresponds to the peak of central aortic pressure.

Figure 4. Difference between brachial SP plotted separately for males (blue broken line) and females (red broken line) over the normal life span in the Framingham adult cohort from 25 to 70 years, and in the NHANES cohort for children from age 5 to 17 years in males (blue broken line) and females (red broken line). The central aortic SP values were calculated in adults from the Framingham data by subtracting amplification of the pressure pulse from the

brachial values in males and females from age 25-70 years of age. The data points for children come from our longitudinal study on ensemble-averaged pressure waveforms in 6 children between age 2 and 13 years (blue circles for boys and red circles for girls), with brachial pressure set at those from the NHANES study at the different ages. These individual data points were supplemented by data on 207 boys and 198 girls aged 8 years in the study of Ayer et al [14], again set to the NHANES value of brachial BP at 8 years (red cross for girls and blue cross for boys). Linear regression lines are shown separately for males and females from age 5-70 years, and did not include the Ayer data [14].

Figure 5. Similarity of radial artery pressure waveforms in a young 2 year old child (left) and a 93 year old woman with isolated systolic hypertension (right). Waveforms are similar in both, with evidence of early wave reflection form peripheral sites boosting pressure in late systole. While wave shapes were similar, radial artery pulse pressure was almost three times as high (124 mmHg) in the old compared to the young subject (46 mmHg).

Figure 6. Radial pressure waves, calibrated to brachial systolic and diastolic pressure from NHANES [6] in a young male at age 2 (left), 4 (centre) and 10 years (right). While we used NHANES data to calibrate all waveforms, we had doubts on accuracy of NHANES cuff values to measure brachial or radial pressure under age 5 years (fine broken lines in figure 5).

Figure 7. Ensemble-averaged radial artery pressure in twins with the girl (left) and boy (right) at 8 (top) and 13 years (bottom). Beginning of the reflected wave is detected automatically with derivatives from the tag on the time axis, to signify central aortic SP. Amplification was high and similar in the girl and boy twins, 19 and 13 mmHg respectively at 8 years and 27 and 19 mmHg respectively at 13 years.

Figure 1.

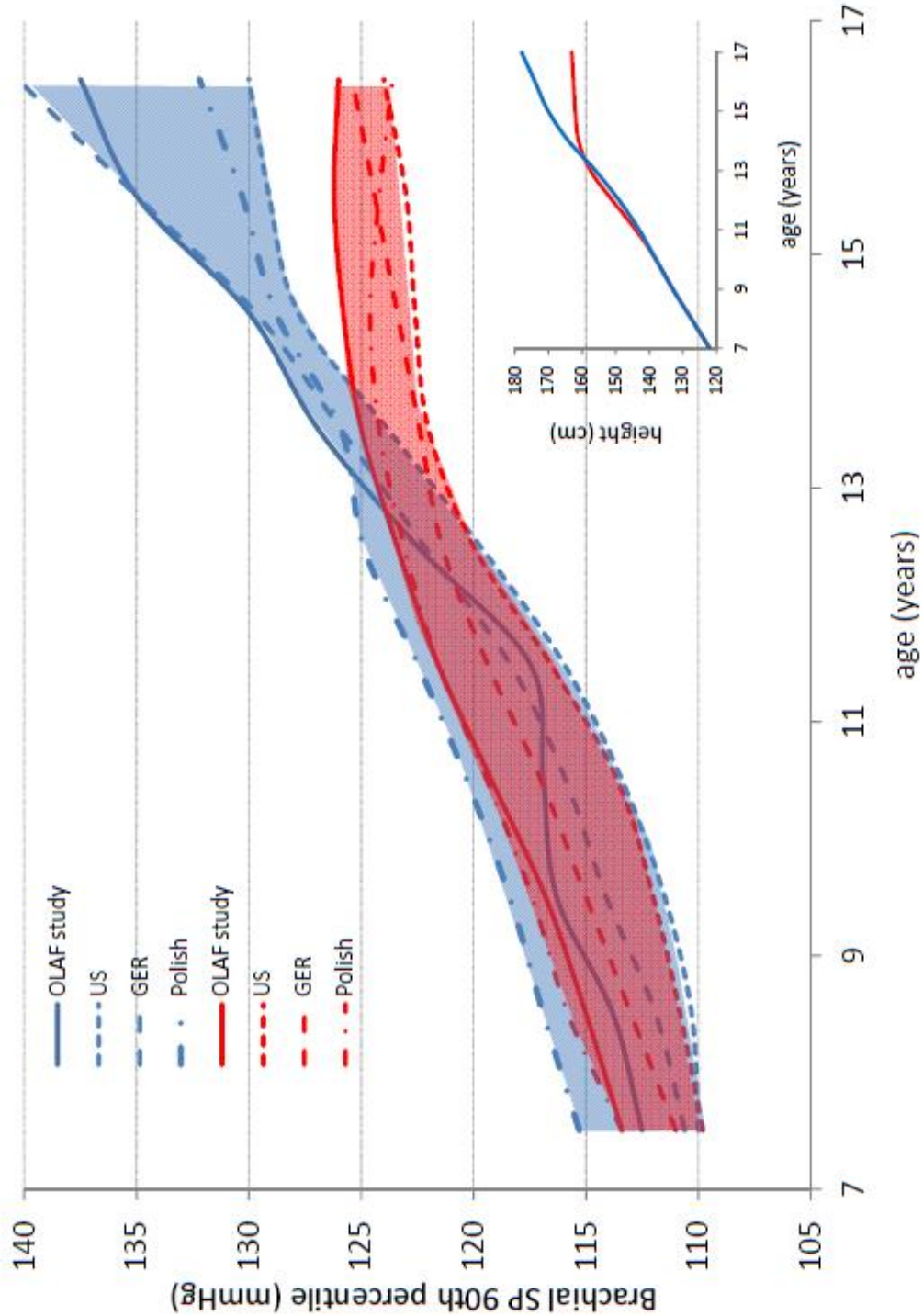

Brachial SP 90th percentile (mmHg)
140
135
130
125
120
115
110
105
7
9
11
13
15
17
age (years)
OLAF study
US
GER
Polish
OLAF study
US
GER
Polish
height (cm)
180
170
160
150
140
130
120
7
9
11
13
15
17
age (years)

Figure 2.

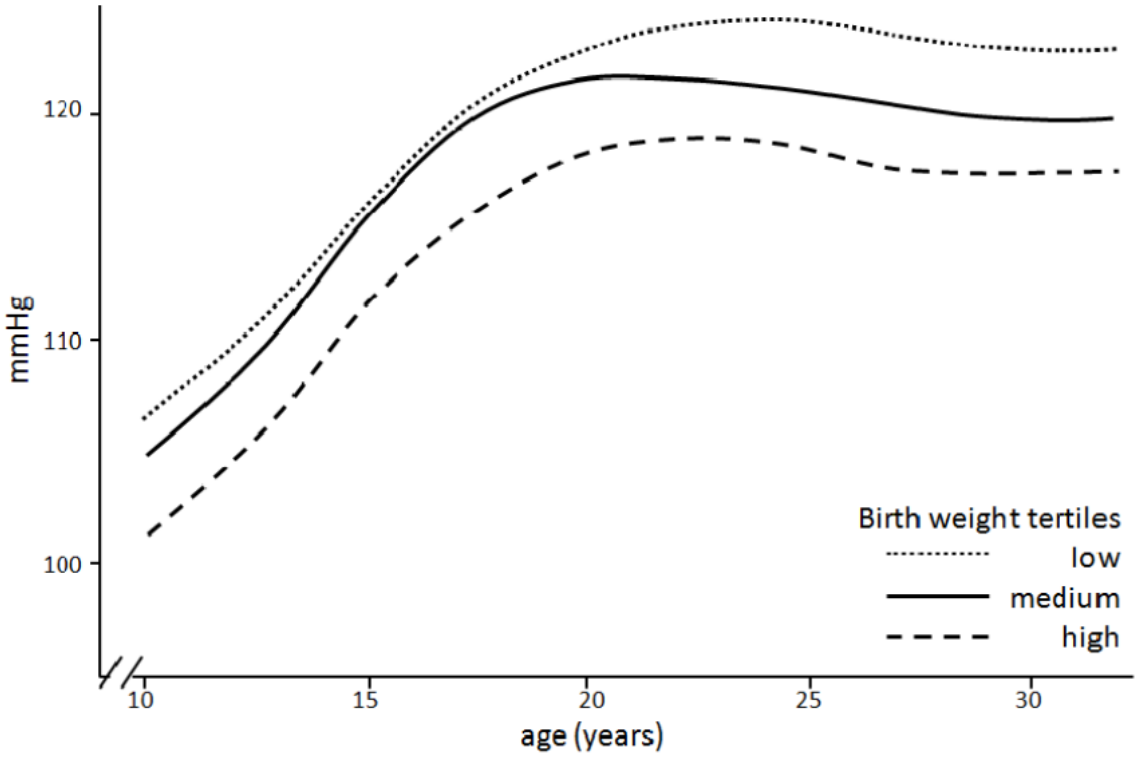

120
110
100
mmHg
10
15
20
25
30
age (years)
Birth weight tertiles
low
medium
high

Figure 3.

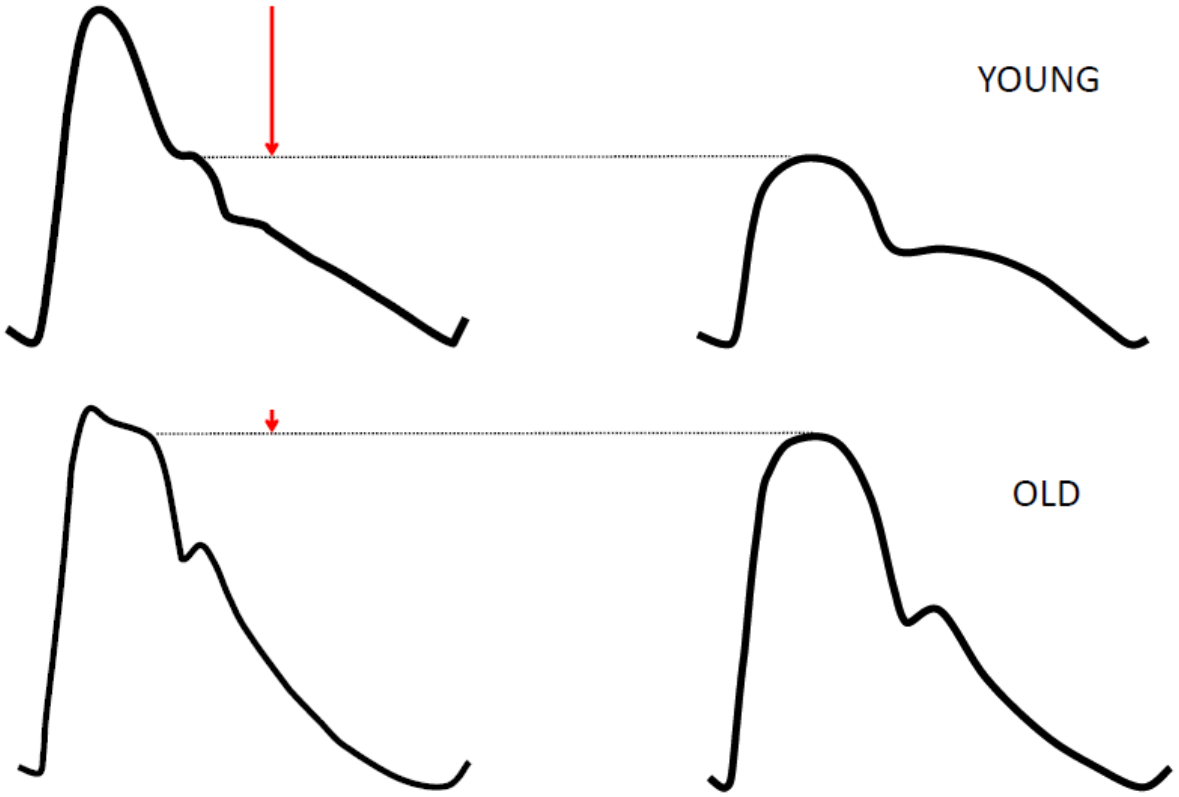


Figure 4.

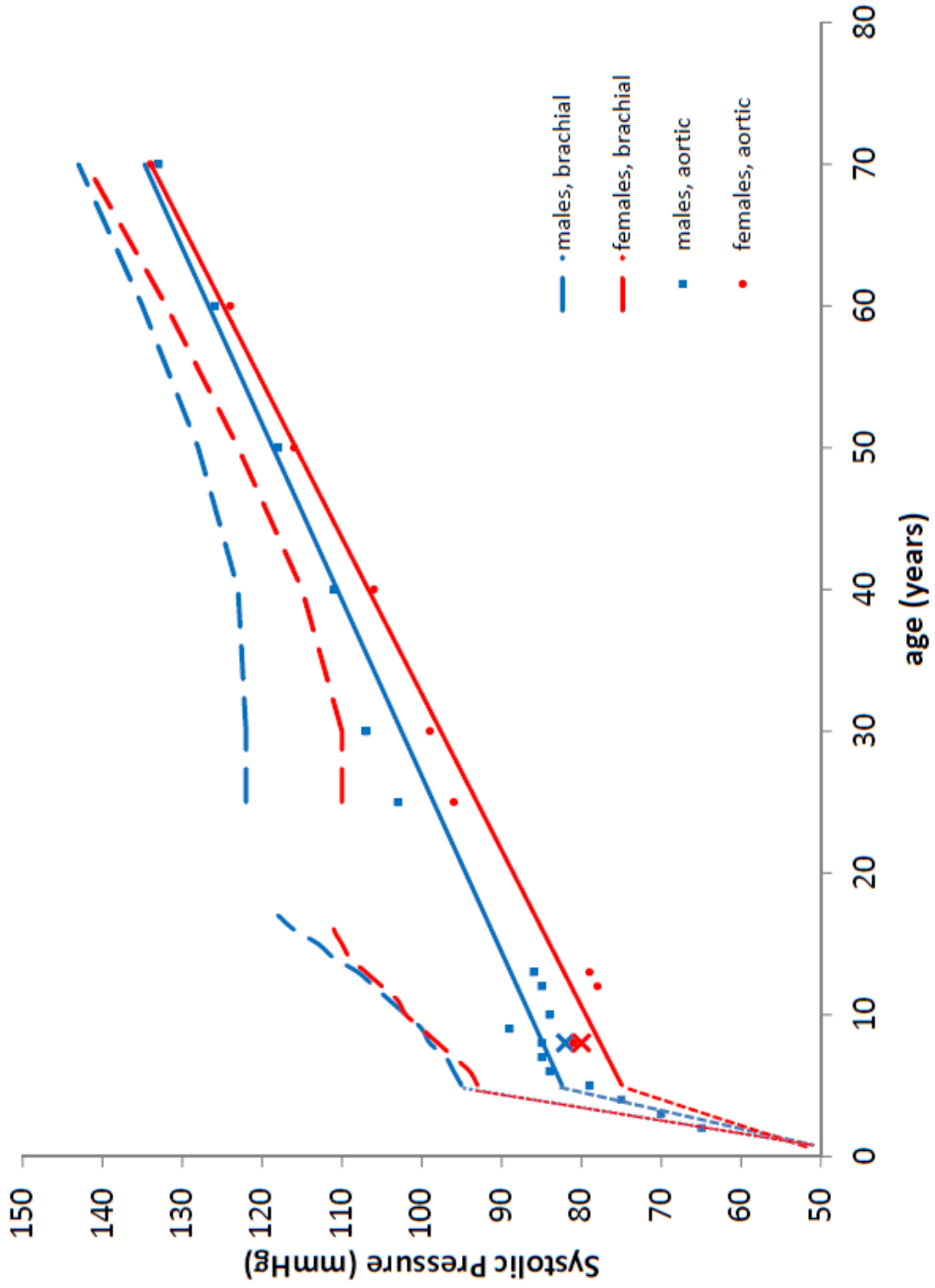

Systolic Pressure (mmHg)
150
140
130
120
110
100
90
80
70
60
50
0
10
20
30
40
50
60
70
80
age (years)
males, brachial
females, brachial
males, aortic
females, aortic

Figure 5.

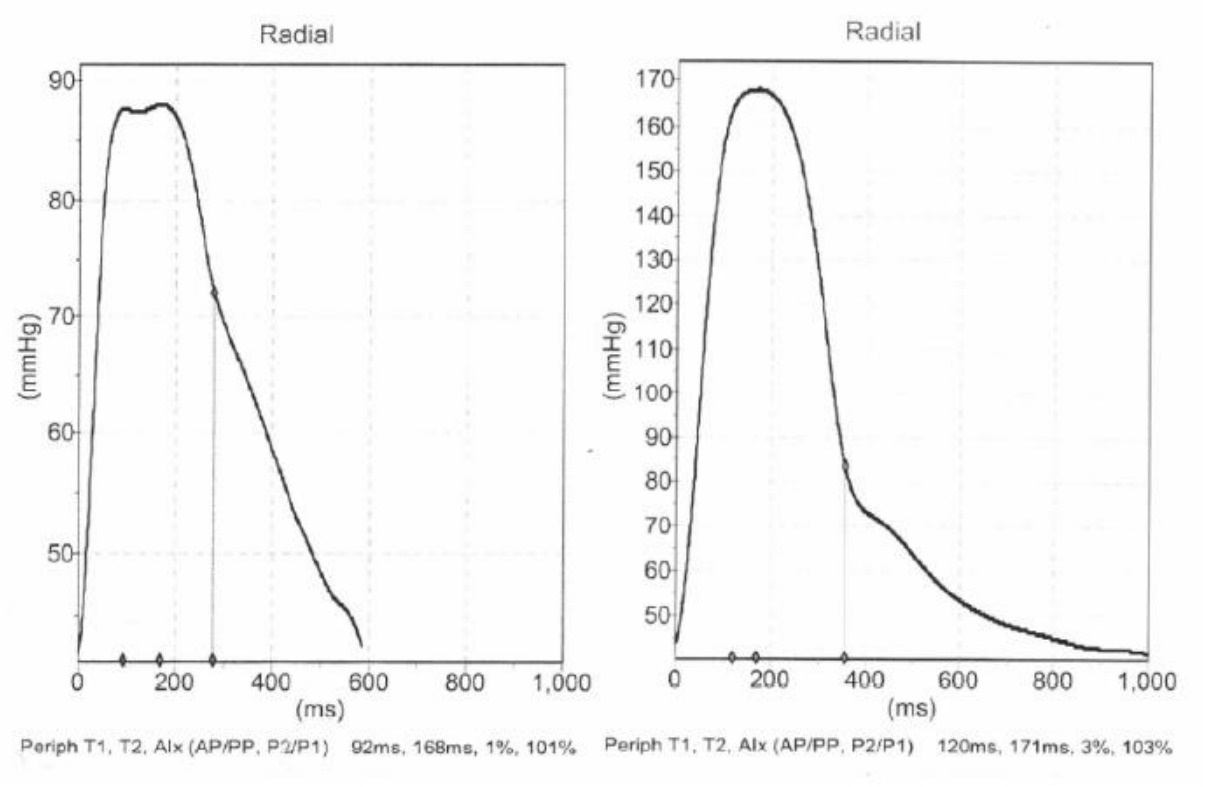

Radial
90
80
70
60
50
(mmHg)
0
200
400
600
800
1,000
(ms)
Periph T1, T2, AIx (AP/PP, P2/P1) 92ms, 168ms, 1%, 101%
Radial
170
160
150
140
130
120
110
100
90
80
70
60
50
(mmHg)
0
200
400
600
800
1,000
(ms)
Periph T1, T2, AIx (AP/PP, P2/P1) 120ms, 171ms, 3%, 103%

Figure 6.

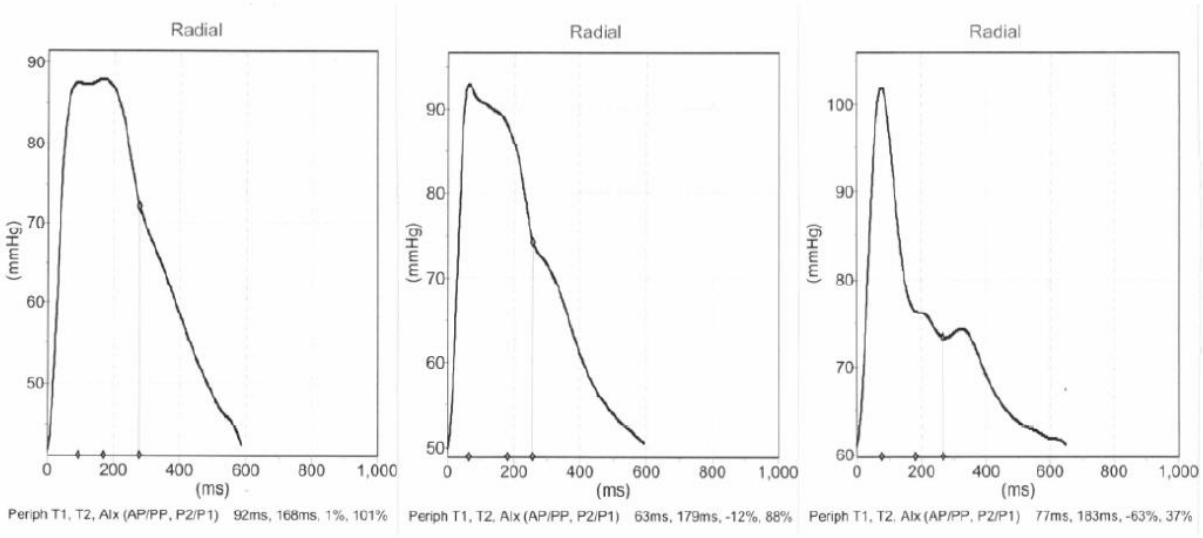
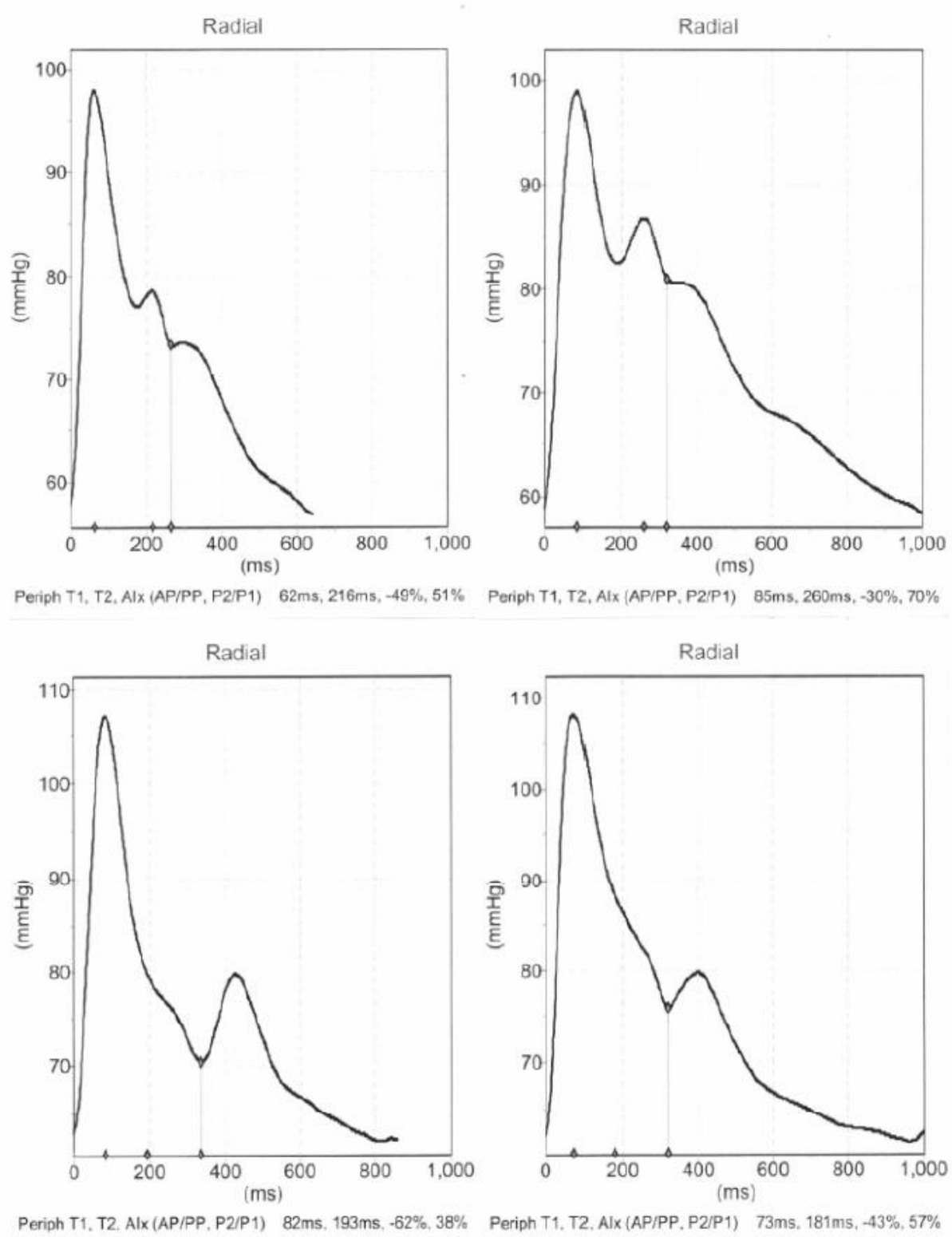

Radial
90
80
70
60
50
(mmHg)
0
200
400
600
800
1,000
(ms)
Periph T1, T2, AIx (AP/PP, P2/P1) 92ms, 168ms, 1%, 101%
Radial
90
80
70
60
50
(mmHg)
0
200
400
600
800
1,000
(ms)
Periph T1, T2, AIx (AP/PP, P2/P1) 63ms, 179ms, -12%, 88%
Radial
100
90
80
70
60
(mmHg)
0
200
400
600
800
1,000
(ms)
Periph T1, T2, AIx (AP/PP, P2/P1) 77ms, 183ms, -63%, 37%

Figure 7.


Radial
100
90
80
70
60
(mmHg)
0
200
400
600
800
1,000
(ms)
Periph T1, T2, AIx (AP/PP, P2/P1) 62ms, 216ms, -49%, 51%
Radial
100
90
80
70
60
(mmHg)
0
200
400
600
800
1,000
(ms)
Periph T1, T2, AIx (AP/PP, P2/P1) 85ms, 260ms, -30%, 70%
Radial
110
100
90
80
70
(mmHg)
0
200
400
600
800
1,000
(ms)
Periph T1, T2, AIx (AP/PP, P2/P1) 82ms, 193ms, -62%, 38%
Radial
110
100
90
80
70
(mmHg)
0
200
400
600
800
1,000
(ms)
Periph T1, T2, AIx (AP/PP, P2/P1) 73ms, 181ms, -43%, 57%

4.9.6 Study: Interpreting Blood Pressure in Younger Adults

A study published as:

O'Rourke MF, **Adji A**, Namasivayam M. **Interpreting Blood Pressure in Younger Adults**. *Journal of the American College of Cardiology* 2015;66:329-30.

This journal correspondence is written to support the findings of Yano et al (Yano et al. 2015), based on the manuscript in Section 4.9.1 to 4.9.5 which I have involved (in all data collection, analysis and manuscript preparation). Drs O'Rourke, Namasivayam and I contributed equally in this correspondence.

O'Rourke, M.F., Adji, A., Namasivayam, M. (2015) Interpreting Blood Pressure in Younger Adults. *Journal of the American College of Cardiology*. 66(3) p. 329-30.

DOI: 10.1016/j.jacc.2015.04.070

4.10 Chapter Overview

The pulse wave propagates throughout the body from the aorta, and its contour depends on the cardiac contraction pattern and properties of the arterial system. The pressure wave contour shows increasingly high late systolic pressure as the reflected wave moves from diastole to systole with the faster travels of the pulse wave due to arterial stiffening caused by aging. This pressure boosts in late systole results in increase in left ventricular afterload and relative decrease in capacity for myocardial blood perfusion. In this chapter, I conducted studies to assess different methods to generate aortic pressure wave and their reproducibility. The studies presented in this chapter confirm the radial artery to be the most appropriate site for measuring upper limb pressure, and my data analysis is able to describe and explain the anomaly of pressure amplification in the upper limb. The normal reference values of central aortic pressure and its amplification between periphery and aorta are published by the European study group in which we have participated. The papers which extend the application of central aortic pressure in other clinical settings are presented, wherein I actively participated in the data analysis. From all these studies, the age-related changes in the central aortic pressure are shown.

Chapter 5

Characterisation of Age-Related Changes in Aortic Pressure and Flow

Summary

The arterial pressure pulse is generated by the flow pulsation of blood with each heart contraction. This chapter will describe the concept of vascular impedance, which represents the "gold standard" for manifestation of cardiac load to pulsatile flow from the heart. Determination of vascular impedance requires pressure and flow pulse wave analysis in the frequency domain. This chapter will explore the technique of measuring the aortic flow wave, and both advantages and limitations of current practice. A new approach is applied to estimate aortic flow wave from derived aortic pressure waveform, and this was analysed with three available methods. Results show that this approach is achievable and realistic, although further work is warranted.

5.1 Introduction

5.1.1 Ascending Aortic Flow Waveform

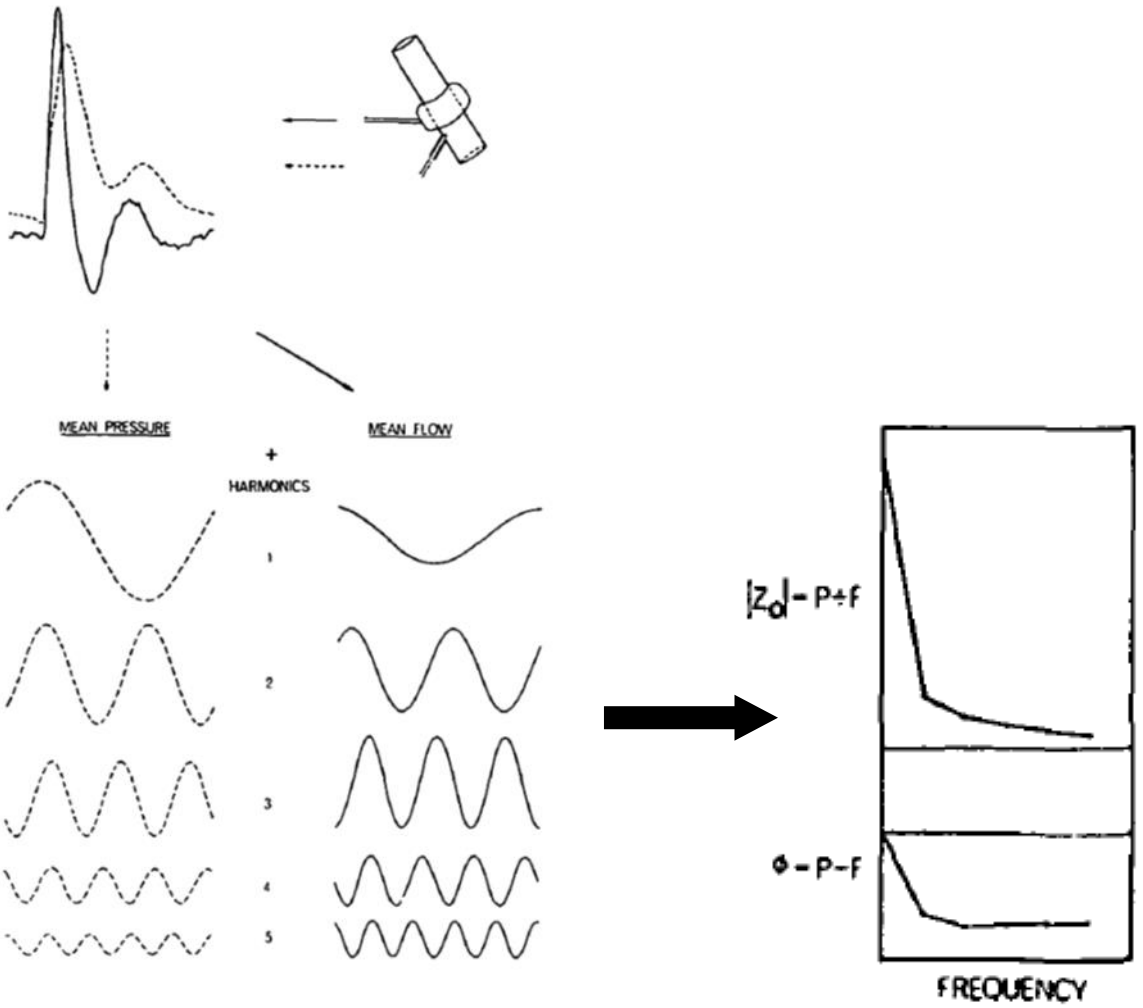


Figure 5-1. Determination of vascular impedance. Pressure and flow measured are each resolved into a mean value and a series of harmonic sine waves. The corresponding terms of pressure and flow are related to give modulus $|Z_o|$ and phase φ of impedance. Only the first five harmonics are shown. Pressure is shown as broken line, flow as unbroken line. From (O'Rourke et al. 1966).

A pressure or flow wave, like any other periodic biological signal which fluctuates around a mean value, can be analysed in the time or the frequency domain. This has been described in more detail in Chapter 2. The pressure and flow waves are decomposed into their mean

values and harmonic component, then impedance is determined by relating mean values of pressure and flow, as well as their corresponding harmonics (Patel et al. 1963, Patel et al. 1965, Patel et al. 1965, Attinger et al. 1966, O'Rourke 1967, O'Rourke 1967, O'Rourke 1982) (**Figure 5-1**).

Carl Wiggers in his work on hemodynamics principles emphasised Carl Ludwig's advice "Die Methode ist Alles" (Neil 1961), that "... experimental results are no better than the apparatus employed, that the analysis of dubious results cannot be improved by statistical methods, and that the breadth of conclusions drawn should not exceed the limitations permitted by the most accurate results".

In the ascending aorta, the left ventricular flow wave is determined by the pattern of ventricular ejection (Nichols et al. 2011). Due to technical difficulties in measuring flow, there have been only few reported studies on the effect of aging on left ventricular ejection flow contour. The effects of reflected wave on flow waves are less apparent, usually occurring during deceleration period by reducing the area under the flow wave curve (convex shape from the right rather than concave) (Nichols et al. 1986, O'Rourke et al. 1993, Miyashita et al. 1994).

Generally, fluid velocity will vary across the vessel's diameter, where flow in the centre is usually faster than that near the wall due to friction. In a smooth, rigid tube with slow continuous flow, the flow appears to be parabolic, and the Doppler spectrum will have the same grey level for all velocities up to the maximum. This flow profile is normally seen in the diastolic phase of some arterial flows and in veins. As the flow in the tube becomes faster, the velocity profile is flatter where all the fluid across the vessel moves within a narrow range of high velocities, known as flat velocity profile. This flow profile is typically observed at the systolic peak of arterial waveform. Poiseuille established the relationship

between flow and pressure gradient, where pressure gradient varies linearly with the rate of flow (Nichols et al. 2011) (**Figure 5-2**).

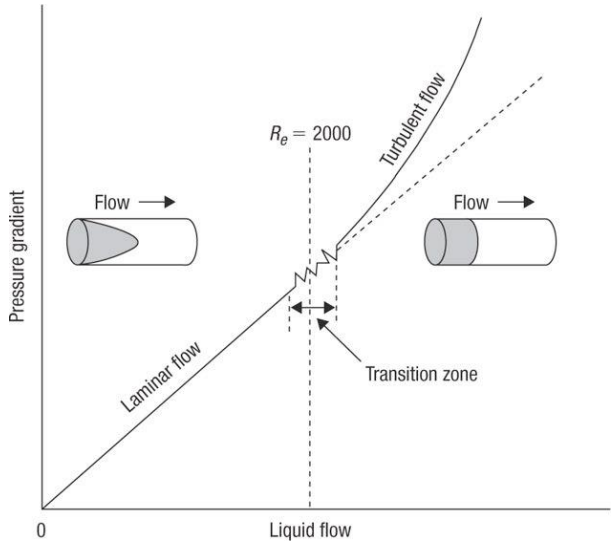


Figure 5-2. Variation of flow rate with the pressure gradient for steady flow in a long, straight circular tube to indicate the changing relationship as flow rate increases. The figure shows that below a Reynolds number (Re) of 2000, flow is linearly related to the pressure gradient (i.e. laminar) and the velocity profile is parabolic; above an Re of 2000, the flow is approximately equal to the square root of the pressure gradient, is turbulent, and exhibits a flat velocity profile. From (Nichols et al. 2011).

Reynolds number represents the critical velocity, or "transition" zone, where laminar flow changes to turbulent flow and there is an increase in the pressure gradient. In the aorta, the critical velocity is 0.26 m/s for aortic diameter of 2.6 cm (Oates 2001), thus turbulence can occur. McDonald has shown in the rabbit aorta, that laminar flow with parabolic profile could be seen in early systole, but flow appeared to be turbulent during peak systolic ejection (McDonald 1952). The turbulence will affect measurement of flow, because there are gradients of pressure and of flow across the cross-sectional area of the aorta as far as the aortic arch. When recording was performed using a catheter, there was evidence of the catheter being flicked about in the aorta, creating artefactual signals which may be exactly the

same from beat to beat, but can be identified as partially artefactual when the pattern changes with twisting of the catheter at the site of insertion (O'Rourke 1968). O'Rourke showed that the differential pressure can be distorted if pressure is measured end-on to the direction of flow, while when measured side-on, may be distorted by Venturi effect at high flow velocity (>80 cm/s). This is further supported by Takazawa (Takazawa 1987), who McDonald, Womersley and Fry were the pioneers who established the relationship between pressure gradient and flow (Milnor 1989). When comparison was made between an observed flow curve (as the 'peak-to-peak' wave velocity) and one calculated from the 'pressure gradient' (or time derivative of pressure) measured at the same time, their correlations were acceptable (Hale et al. 1955). This correlation between measured and calculated flow curves is maintained during peripheral vasodilatation (McDonald 1974). Womersley's equation were applied initially by Helps and McDonald (Helps et al. 1954), Hale et al (Hale et al. 1955), McDonald (McDonald 1955), and McDonald and Taylor (McDonald et al. 1959) on measurements of the pressure gradient in the femoral artery of dogs. Since then, it has been applied to the canine ascending aorta (McDonald et al. 1973) and pulmonary artery (O'Rourke et al. 1971), as well as the human aorta (Gabe et al. 1964) and the pulmonary artery (Milnor et al. 1969).

Due to the complex nature of the Womersley equation, Fry et al attempted a simpler derivation of flow from pressure gradient based on the Navier-Stokes equation (Fry et al. 1956, Fry et al. 1957), and then used this method to measure flow in the human aorta (Greenfield et al. 1968, Greenfield et al. 1971) and in animal studies (Greenfield et al. 1965). The difference between flow measurements was found to be insignificant. Jones et al introduced another method for computing flow velocity from pressure by introducing the "constant" pulse wave velocity and a "resistance" term in Fry's original equation (Jones et al. 1959). The 'resistance' term was found by manipulating the flow velocity to be zero during diastole, and the velocity time integral was matched against previously measured stroke

volume to produce a calibration factor. Stroke volume obtained with this method has also been tested in humans (Jones et al. 1966, Jones et al. 1968). There are 3 disadvantages of this method; that stroke volume was measured prior to calculation by another method for calibration, that pressure gradient must be measured over a very small interval thus require precise calibration matching of manometers, that pulse wave velocity was considered constant.

In further development for flow velocity derivation from pressure gradient, McDonald and Nichols (McDonald et al. 1973) substituted the constant pulse wave velocity above with 'apparent phase velocity'. Comparisons were made during control condition and intervention with flow acquired by electromagnetic flowmeter. Mean flow velocity gave better correlation, whereas peak flow was less accurate.

For the mathematical analysis of Womersley to be considered valid for its application to blood flow, basic assumptions have to be made:

- The flow is laminar, although the laminar pattern probably breaks down in large arteries near the heart attributable to high Reynolds number as suggested by McDonald (McDonald 1974).
- The length of the ascending aorta is sufficiently long.
- The fluid (i.e. blood) is homogeneous, following the investigation by Taylor (Taylor 1959) that the effects of anomalous viscosity of blood at high shear rates is negligible.
- The flow is through a cylindrical tube with constant diameter.
- The flow may be expressed as the sum of harmonic components calculated from individual harmonic terms of pressure gradient. Non-linearity of the arterial system is considered negligible; this has been discussed in Chapter 2.

The work by Fry et al was not pursued beyond the 1970s, partly because of the need to place electromagnetic flowmeter probes around the ascending aorta – which was possible only at open heart surgery. Subsequent application to humans has been slow because of technical difficulties in measurement of flow velocity. A catheter-mounted electromagnetic flowmeter device was introduced by Mills (Mills 1966) together with Shillingford, for use at diagnostic catheterisation (Mills et al. 1970). This instrument was subject to gross movement artefact in the aorta, and was subsequently abandoned on account of such artefact, and on account of expense when single use of the catheter system was necessary. From 1967 to the 1990s, these flow velocity waves were measured using catheter-mounted electromagnetic sensors (Nichols et al. 1977, Merillon et al. 1982, Merillon et al. 1984, Laskey et al. 1985, Nichols et al. 1985, Nichols et al. 1986, Yaginuma et al. 1986, Kelly et al. 1992), in which they showed potential value for new information on aging and drug action in humans.

Murgo et al (Murgo et al. 1980) have explained the change in pressure wave contour with age, and the change in flow wave in the central arteries can be attributed to the same mechanism. Others have also shown gradual change in ascending aortic flow wave contour with age (O'Rourke et al. 1980, O'Rourke et al. 1993, Miyashita et al. 1994). In late systole, the descending part of aortic flow is normally convex to the right in normal subjects. With increasing age, convexity in the flow velocity wave disappears and steadily becomes concave to the right, corresponding to the increasing late systolic augmentation of the aortic pressure wave (Takazawa 1987, Miyashita et al. 1994, Westerhof et al. 1995). These alterations in flow wave contour are due to early return of the reflected wave and faster pulse wave velocity. Westerhof and O'Rourke (Westerhof et al. 1995), supported by Denardo et al (Denardo et al. 2010), indicated that this phenomenon is exaggerated when contractility of the heart is impaired, and where the ventricular ejection is very sensitive to afterload, with shorter ventricular ejection time and decreased stroke volume. The opposing effect of wave reflection on pressure and flow waves has been discussed in Chapters 2, 3 and 4; reflected

pressure waves ***add*** to the incident or forward traveling wave, while reflected flow waves ***subtract*** from the incident wave (McDonald 1974, O'Rourke 1982, Milnor 1989) (**Figure 5-3**).

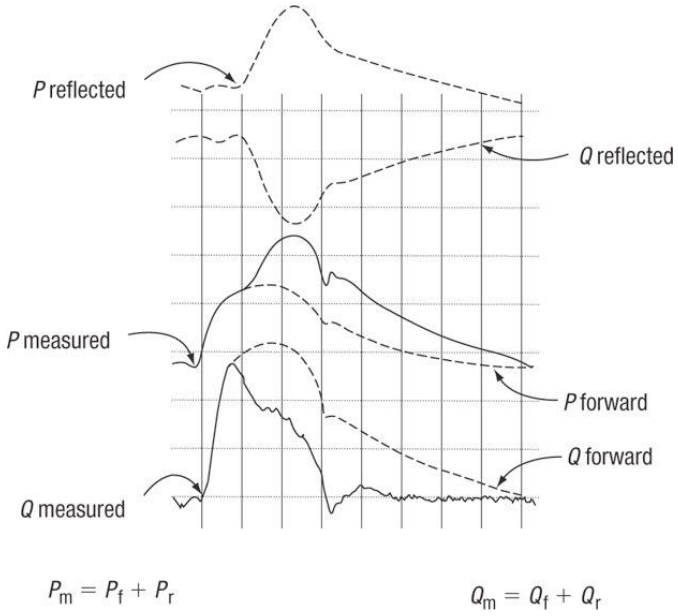


Figure 5-3. The influence of pulse wave reflections on ascending aortic pressure (P) and flow (Q) waveforms. Incident or forward (f) and backward or reflected (r) pressure and flow waves are summed to yield measured (m) pressure (Pm) and flow (Qm) waveforms. From (Nichols et al. 2011).

Such changes in aortic flow wave are more apparent in flow velocity waves recorded using cardiac magnetic resonance imaging than Doppler; with the former taking into account the forward and backward flow across aortic cross-sectional area, while the latter is operator-dependant and affected by turbulent flow in the short inlet length from the left ventricle. This will be discussed in more detail below.

Studies on vascular impedance in humans since year 2000 have measured aortic flow wave mainly from left ventricular outflow tract using Doppler echocardiography (Mitchell et al. 2004, Segers et al. 2007, Chirinos et al. 2009, Mitchell et al. 2010, Coutinho et al. 2013).

Velocity-encoded magnetic resonance imaging with phase contract sequences allows more accurate aortic flow velocity determination (Redheuil et al. 2010, Cavalcante et al. 2011, Dogui et al. 2011), and also allows measurement of certain regions of the aorta more accurately (Hickson et al. 2010). Recent cardiac magnetic resonance imaging studies have shown aging changes in proximal aorta, usually characterised by dilation and elongation of proximal aorta (Nelson et al. 2009, Redheuil et al. 2011, Aquaro et al. 2013, Martin et al. 2013). Latest paper by the Multi-Ethnic Study of Atherosclerosis study has shown ascending aortic distensibility measured by cardiac magnetic resonance technique to be a predictor of all-cause mortality and incident cardiovascular events (Redheuil et al. 2014). It has also been shown that aortic arch stiffness is associated with LV mass and lacunar brain infarcts in hypertensive patients (Brandts et al. 2009). Latest study from Uretsky et al (Kar et al. 2015, Uretsky et al. 2015) found that cardiac magnetic resonance imaging is more accurate than echocardiography in assessing the severity of mitral regurgitation.

The boost to late systolic pressure due to aging has been confirmed by the work of Murgo et al (Murgo et al. 1980) and others (Yaginuma et al. 1986, Kelly et al. 1989). Some studies have shown that the increase in pressure augmentation is related to impaired diastolic relaxation and heart failure (Weber et al. 2006, Abhayaratna et al. 2008). Others (Sakai et al. 1992, Sakai et al. 1993, Miyashita et al. 1994) have extended prior observation that this late systolic pressure is accompanied by deceleration of flow. Miyashita et al (Miyashita et al. 1994) introduced an index of aortic flow wave contour by relating the flow velocity at one third of deceleration time to peak flow velocity (see **Figure 5-23**). This ratio, named DR 1/3, showed an inverse relationship to the pressure wave augmentation. This supports the previous finding of Westerhof et al (Westerhof et al. 1972), where aging affects pressure and flow wave contour in an opposite manner through early wave reflection (Westerhof et al. 1972, Westerhof et al. 1995, O'Rourke et al. 2007).

5.1.2 Vascular Impedance

The concept of vascular impedance has been discussed briefly from an historical perspective in Chapter 2. Vascular impedance represents properties of the whole systemic circulation and characterises the hydraulic load of systemic circulation presented to the left ventricle. Impedance is described in terms of modulus (amplitude of pressure ÷ flow) and phase (delay between pressure and flow) against frequency (see **Figure 5-1)** (O'Rourke et al. 1980, O'Rourke 1982, Chirinos et al. 2010, Chirinos et al. 2010).

A typical ascending aortic impedance pattern in humans shows a relatively high modulus at zero frequency – which is the peripheral resistance, then fall of modulus with increasing frequency to a minimal value, before rising to a low maximal value around twice the minimal frequency, then to its characteristics impedance value at high frequencies (approximately 5% of peripheral resistance) (O'Rourke et al. 1980, Nichols et al. 2011) (**Figure 5-4)**. The phase value is negative at low frequencies – indicating flow leading pressure – then crosses zero at the frequency where modulus is minimum, and becomes positive at higher frequencies (O'Rourke et al. 1980, Nichols et al. 2011). In the lower frequencies, the effects of phase delay between pressure and flow further reduces the component of pulsatile pressure that is in-phase with pulsatile flow (Z cosine φ) to some 2% of peripheral resistance. These impedance patterns are affected by proximal aorta distensibility, arterial pulse wave velocity, distance to peripheral reflecting sites (approximately 25% of wavelength), and magnitude of peripheral reflection (O'Rourke 1982). The frequency of minimal modulus value and phase cross-over depends on the proximity to arterial terminations, while the minimum value of impedance modulus and in-phase impedance depends indirectly to body length.

O'Rourke and Taylor (O'Rourke et al. 1966) published their detailed study of input impedance of the femoral bed. A dog with heart block was paced at different heart rate and

the resulting impedance plot for variety of heart frequency fell on the same curve. This finding justified the assumption that pressure/ flow relations of the arterial system may be regarded as linear (O'Rourke et al. 1966).

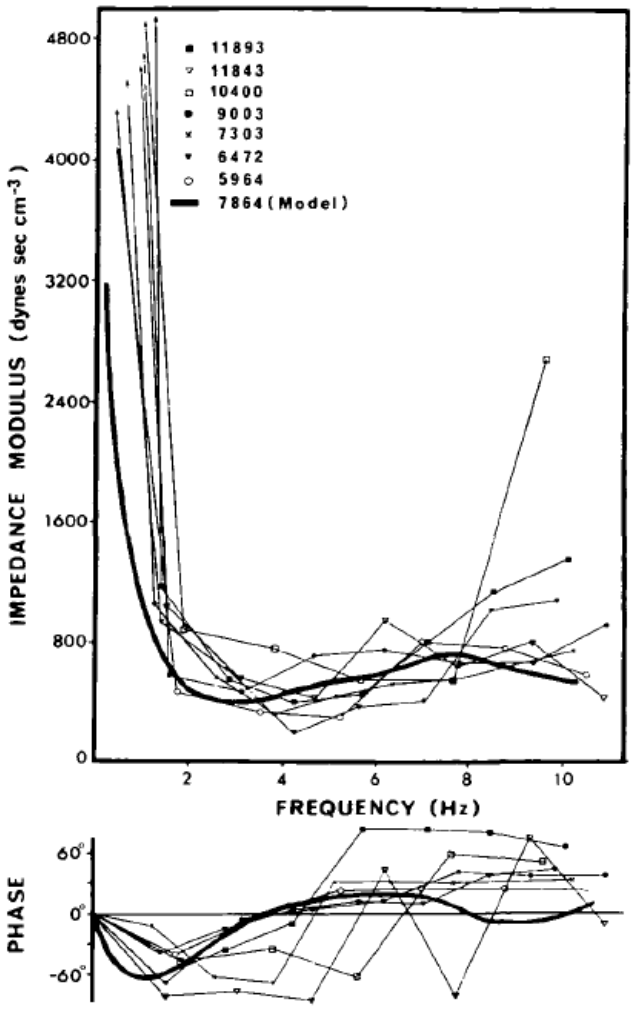


Figure 5-4. A typical pattern of human's ascending aortic impedance, in terms of its modulus (top) and phase (bottom). The thick black line represents an impedance modelling of a 47 year old person (O'Rourke et al. 1980).

O'Rourke and Taylor also reported change with vasodilatation and vasoconstriction change; if the mean pressure did not change and it was solely the effect of vasoconstriction and

vasodilation, only impedance phase would change without any associated frequency shift in minimum frequency or phase crossover (**Figure 5-5**). A different effect was seen if the mean pressure were altered during vasoconstriction or vasodilation (**Figure 5-6**).

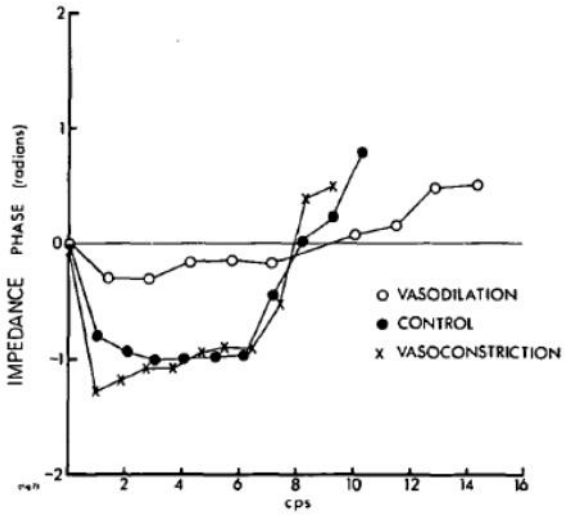


Figure 5-5. Effect of vasodilation and vasoconstriction on the impedance phase. The negative phase means flow leads pressure.

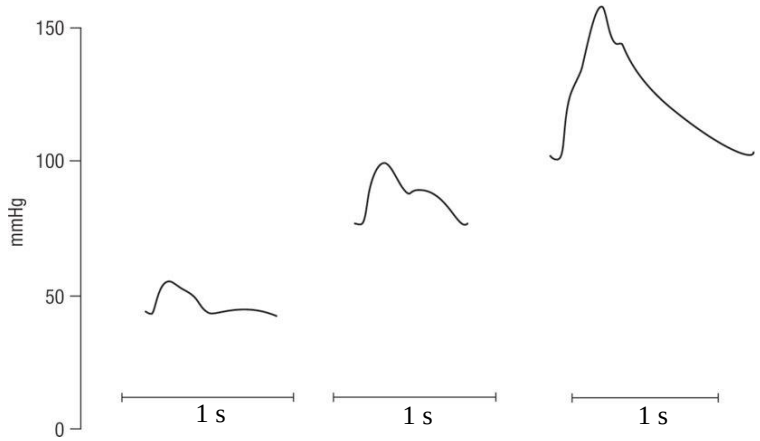


Figure 5-6. Effects of decreasing (left) and increasing (right) mean arterial pressure on the contour of the pressure wave in the ascending aorta of a rabbit. During hypotension, the diastolic wave is displaced later into diastole. During hypertension, this wave moves into systole to create a late systolic peak while pressure during diastole falls almost exponentially. From (Nichols et al. 2011), after (Wetterer 1954).

Along with the alteration of pressure wave contour, there was a shift in frequency to the right while mean pressure increased, and to the left while mean pressure decrease (**Figure 5-7**). This indicates that wave reflection in the arterial system is due to the arterial tone in the peripheral vascular bed (O'Rourke et al. 1966).

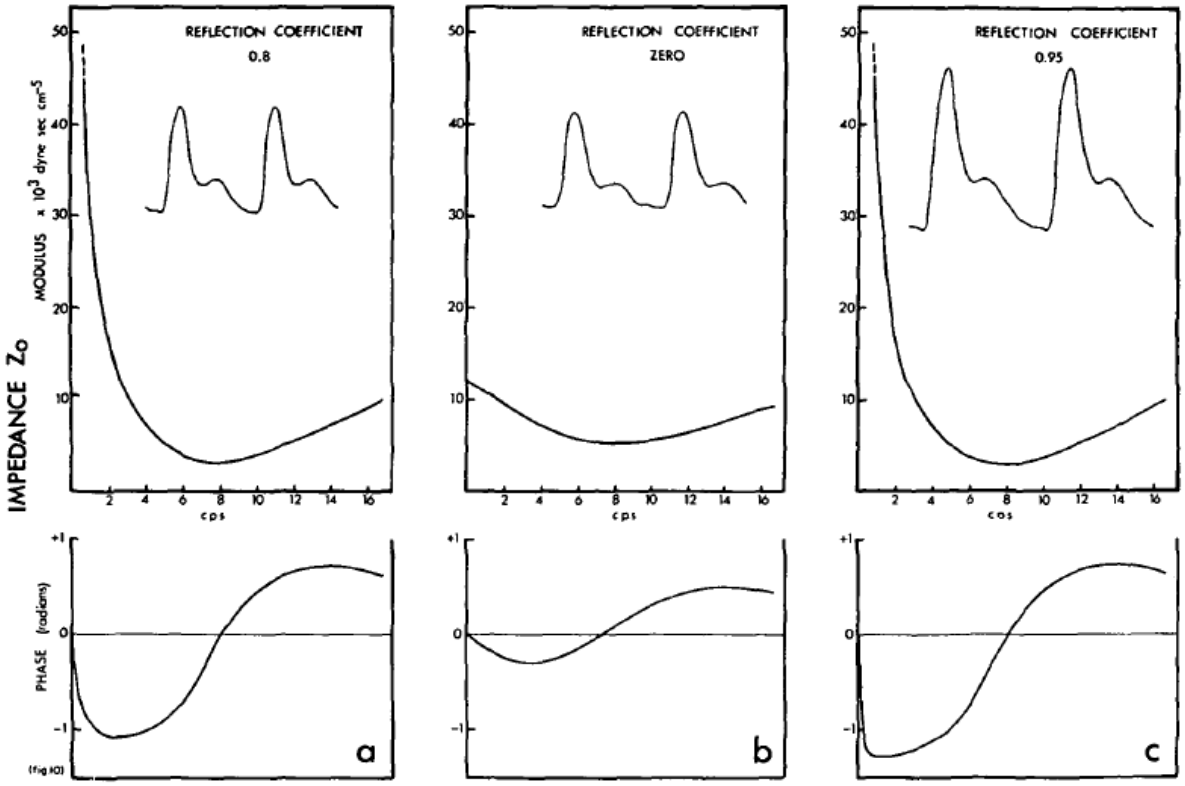


Figure 5-7. Values of vascular impedance determined from the mathematical model with reflection coefficients were 0.8 (control conditions) (left), zero (during vasodilation) (centre), and 0.95 (during vasoconstriction) (right).

The stiffening of the proximal aorta due to aging has led to increase in characteristic impedance and shift of impedance curve to the right. As a consequence, a mismatch occurs between ventricular ejection – where most of the energy contained at low frequencies – and impedance curve. Reported studies have shown this aging effect on ascending aortic impedance, mostly in normal adults and a few on other populations. **Figure 5-8** shows impedance plot from Murgo et al (Murgo et al. 1980) where they showed the effect of aging

on impedance modulus and phase. Type A waveform is a typical of an elderly subject, type B is a middle-aged subject, and type C is a young adult.

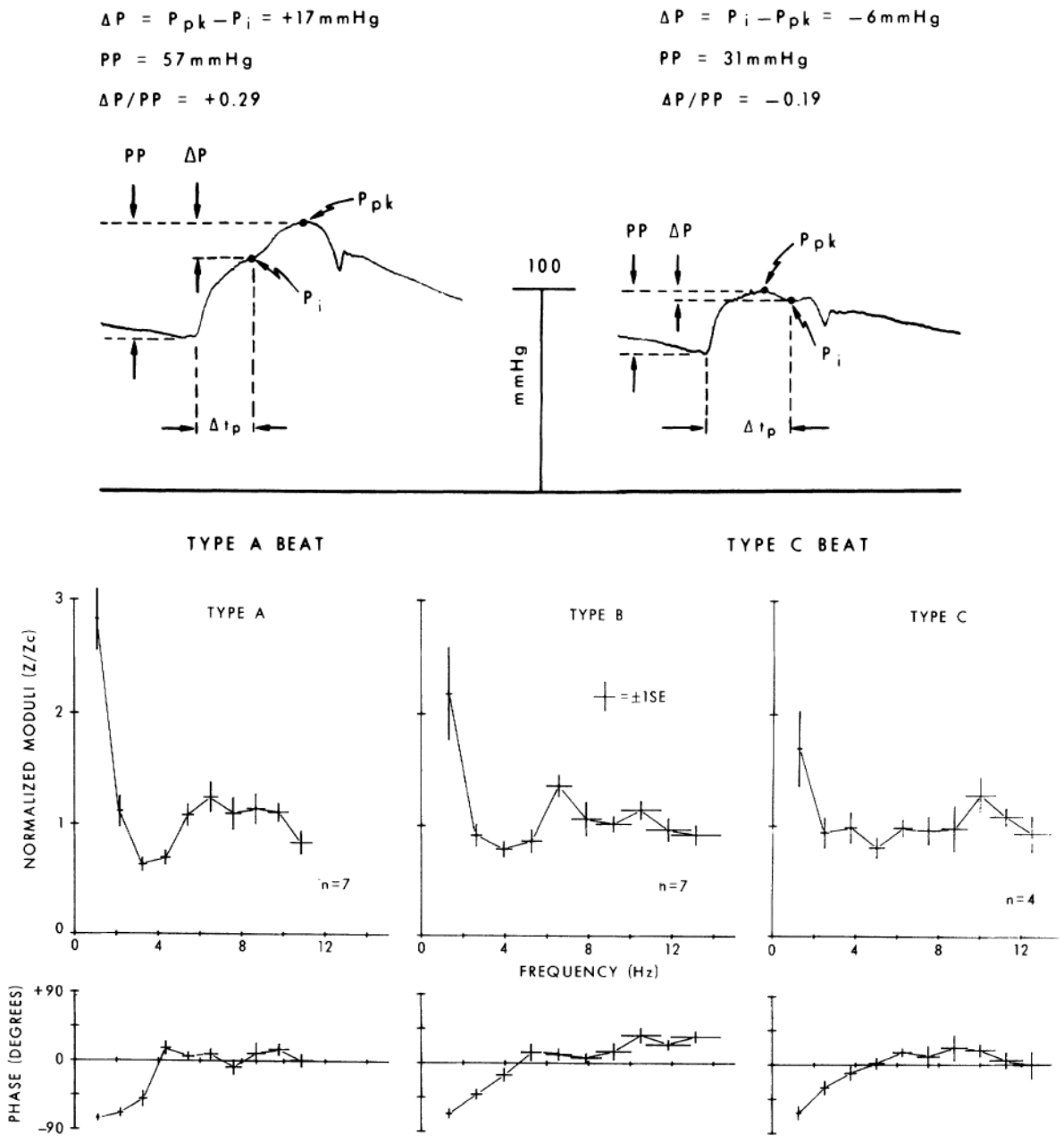


Figure 5-8. Ascending aortic impedance patterns based on the pressure waveform shape; normalised modulus on top panels and phase on bottom panels (Murgo et al. 1980).

Vascular impedance has proved to be useful in examining the intensity and sites of wave reflection within the arterial system (O'Rourke 1982). In the ascending aorta, the peak of pressure occurs in the mid-systole following peak flow. This pressure then falls gradually for the rest of systolic period, interrupted when aortic valve shuts, and secondary (reflected) wave emerged during early diastole (O'Rourke 1967). In peripheral arteries, the arterial pressure wave is increasingly amplified, thus the pulse pressure in the limbs can be 50% higher than in the aorta, while the diastolic wave tends to be exaggerated.

The flow wave shape in the ascending aorta shows an early systolic peak, decreasing during late systole, a little backflow with incisura and fluctuates around zero during diastole (O'Rourke 1970, O'Rourke 1982). In contrast to the pressure wave, the amplitude of flow wave decreases progressively towards the peripheral arteries (O'Rourke 1970, O'Rourke 1982). This flow waves possesses an unusual feature, which is the alteration of contour in the major arteries supplying the upper body (brachiocephalic and left subclavian arteries) and lower body (descending thoracic aorta) (Mills et al. 1970, O'Rourke et al. 1980, Hashimoto et al. 2010, Hashimoto et al. 2013). Both show prominent flow fluctuations during diastole, to indicate that blood sloshes back and forth between the upper and lower body. Moreover, the systolic period of brachiocephalic and left subclavian arteries shows abbreviated forward flow and backflow appears prior to closure of aortic valve, while in the descending aorta, its flow wave shows a widened systolic peak (O'Rourke et al. 1980, O'Rourke 1982, Hashimoto et al. 2010, Hashimoto et al. 2013).

The impedance pattern and asymmetric T model of the human arterial system explains these flow contours; where early return of reflected waves occur from upper body shortens systolic flow, and early backflow from upper body along with continuing ventricular ejection appears as a broader flow peak. The low value of characteristic impedance in the ascending aorta is attributable to the high distensibility of the proximal aorta, therefore the left ventricle only

requires to oppose this low value of impedance. The impedance value at ascending aorta determines aortic systolic pressure (Nichols et al. 2011). Latest study by Chirinos et al (Chirinos et al. 2009) has confirmed that components of ascending aortic impedance, i.e. peripheral resistance, characteristic impedance and measures of early wave reflection, predict left ventricular mass.

The study of vascular impedance in humans has enabled characterisation of vascular bed properties independent of the left ventricular flow wave as the input (O'Rourke et al. 1992). Furthermore, the efficiency of coupling between left ventricle and systemic circulation can be explained from the relationship between ascending aortic impedance and frequency content of left ventricular ejection (or ascending aortic flow) wave. In youth, the minimal value of impedance corresponds to the maximal value of flow wave harmonics, and the maximal pulsatile flow from the heart generates minimal pressure fluctuations. The efficiently timed circulation system leads to minimal energy lost in pulsations; this is apparent in the time domain as a small rise in pressure during systole. The reflected wave occurs during diastole (O'Rourke et al. 1992) and maintains coronary perfusion pressure of heart muscles during diastole, without adding extra load to the heart work.

However, with aging, this ideal relationship increasingly deteriorates, illustrated in the frequency domain by increasing impedance modulus at low frequencies while flow harmonics unchanged or even reduced. The characteristic impedance (average of impedance modulus value above the minimum modulus value, when effects of wave reflection are trivial) is increased due to stiffening of the proximal aorta caused by increasing age. The phase of impedance frequency zero-crossover, as the effect of early wave reflection, will cause the minimal value of phase to occur at higher frequency, and will result in higher peak of systolic pressure due to the boost late systolic peak with aging (O'Rourke et al. 1992) (**Figure 5-9**). Increased aortic stiffness is attributable to change in load-bearing elements of the arterial

media; this becomes disorganised, elastic laminae have fractures and more collagenous material appears (O'Rourke et al. 1992). Arterial stiffening causes progressive dilation of the aorta and major arteries (Redheuil et al. 2011, Milan et al. 2013).

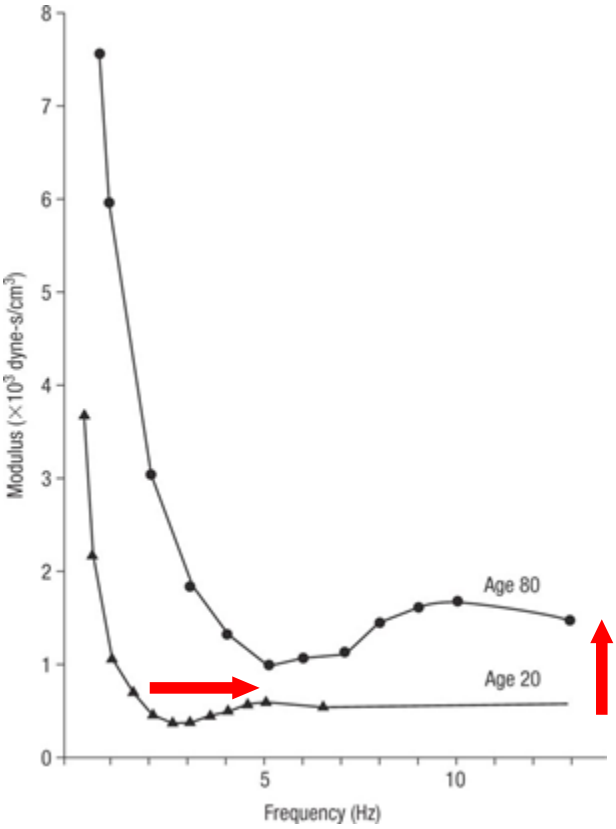


Figure 5-9. A representation of impedance modulus of a young, 20 year old, and the aging changes, shown as the impedance modulus of an old, 80 year old. From (Nichols et al. 2011). The red arrows show different effects of arterial stiffening: increase in characteristic impedance (vertical arrow), and early wave reflection (horizontal arrow, causing shift in impedance minimum to higher frequency).

Studies have shown change in human ascending aortic impedance with age (Murgo et al. 1980, Merillon et al. 1982, Nichols et al. 1985, Mitchell et al. 2004, Segers et al. 2007); these includes increase in characteristic impedance, a shift of the curves to the right with higher frequency of the modulus minimum and phase crossover, and increase in fluctuation of impedance modulus. However, there has been much variation in impedance values from

various papers, and this can be attributed to the difficulty in measuring pressure and flow from the same artery site accurately. It is further complicated by dilatation of the ascending aorta with age (Nichols et al. 1985), when impedance is expressed as volume flow velocity (dyne s cm^{-5}), instead of from linear flow velocity (dyne s cm^{-3} unit). Nichols et al has suggested using the latter than the former (O'Rourke 1982, Nichols et al. 2011); this is to compare impedance values of different arteries and different species without the effect of body size (**Figure 5-10)**.

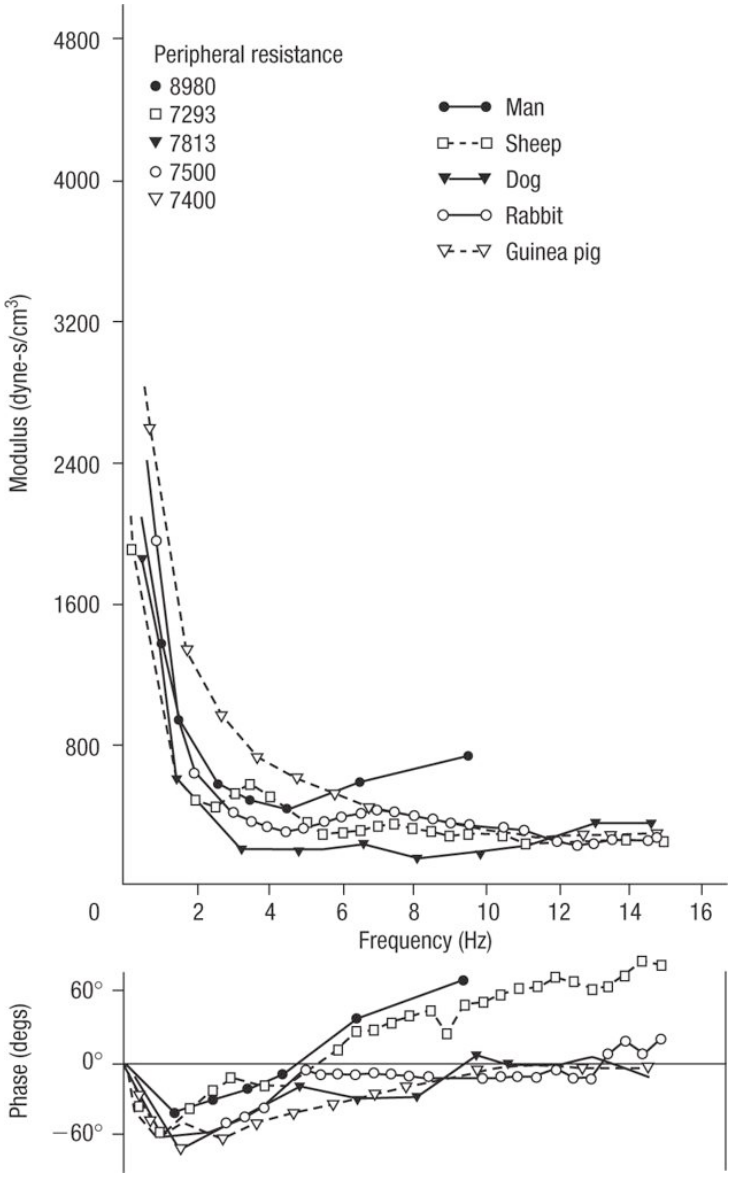


Figure 5-10. Vascular impedance in the ascending aorta of five different mammals. The modulus is expressed as dyne-s/cm3, as determined from linear flow velocity. From (Avolio 1976).

Another useful feature of vascular impedance is to estimate the steady and pulsatile components of external heart work. The external ventricular work is the hydraulic work to eject blood from the heart, and the work lost as the blood flows through the circulation. It separates energy losses in the vascular system into either component. The energy used for steady flow is considered physiologically useful as it is lost as the blood is flowing through circulation system (conduit function), whereas the pulsatile energy corresponds to those wasted in vascular pulsations (cushioning function). The steady and pulsatile components of external heart work were first introduced by Bramwell and Hill (Bramwell et al. 1922), then further studied by others (Porje 1946, O'Rourke 1967). The ratio of pulsatile to total external ventricular work can estimate the arterial efficiency in accepting pulsatile flow from the heart (O'Rourke 1982). In experimental animals, this ratio is around 10% (O'Rourke 1967), depending on heart rate, cardiac output and peripheral resistance (O'Rourke 1982). This ratio tends to increase as the mean pressure increases.

There have been many publications on modelling of the arterial system and vascular impedance (Mills et al. 1970, Nichols et al. 1977, Merillon et al. 1978, Pepine et al. 1978, Pepine et al. 1979, Murgo et al. 1980, O'Rourke et al. 1980, Murgo et al. 1981, Murgo et al. 1981, Merillon et al. 1982, Nichols et al. 1985, Nichols et al. 1986, Yaginuma et al. 1986, Latson et al. 1988, Kelly et al. 1992, Karamanoglu et al. 1994, Karamanoglu et al. 1995). Kelly and Fitchett (Kelly et al. 1992) showed that aortic impedance and ventricular load could be estimated non-invasively from aortic Doppler flow and carotid tonometry. This is the basis of the method used by Mitchell et al in the Framingham study (Mitchell et al. 2004, Mitchell et al. 2010), and a similar method was reported by others (Mazzaro et al. 2005, Segers et al. 2007, Chirinos et al. 2009, Chirinos et al. 2010, Chirinos et al. 2010, Coutinho et al. 2013). Problems noted by Kelly and Fitchett and others, with carotid and particularly brachial

tonometry, and with Doppler flow have been discussed in previous chapters. Neither Kelly nor Fitchett pursued this method subsequently.

Recent studies of vascular impedance have utilised non-invasive pressure and flow measurements, namely flow in the ascending aorta or left ventricular outflow tract, and pressure in the carotid artery or aorta derived from radial. The largest human data set available is published by the Asklepios investigators (Segers et al. 2007, Chirinos et al. 2009) between age 35 to 55 years, as well as the Framingham Heart Study (Mitchell et al. 2004, Mitchell et al. 2010) and Mayo Clinic (Coutinho et al. 2013). Results of these do not show the change with age, previously shown in cross-sectional studies using electromagnetic flow methods. Both Asklepios and Framingham study are longitudinal, so that new information will be available in the years ahead.

Determination of ascending aortic impedance in humans relies on the accurate measurement of ascending aortic pressure and flow. Until recently, the aortic flow is usually recorded using an electromagnetic catheter, which is prone to artefacts due to catheter movement, or to change in position of the catheter where aortic velocity profile is not completely flat (Nichols et al. 2011). Other issues include that the sample population in which data were measured is restricted due to ethical consideration, thus these subjects may not be representative of normal aging, and mostly were undergoing diagnostic cardiac catheterisation for exclusion of cardiovascular disease. Measurement of flow velocity using Doppler ultrasound, in particular at the ascending aorta, has its limitations due to the flow velocity profile, unlike the flow further down around the descending aorta where the profile is likely shown to be laminar (Hashimoto et al. 2010). The increasingly routine practice of recording aortic flow velocity with cardiac magnetic resonance imaging similarly has its own advantages and disadvantages; this will be described later.

5.1.3 Estimation of Aortic Flow Velocity from Derived Aortic Pressure Waveform

As discussed earlier, non-invasive estimation of central aortic pressure has enabled better interpretation of age-related changes in the pressure waveform and the mechanisms involved. However, non-invasive recordings of aortic flow velocity wave have not been fully utilised. While the electromagnetic cuff flowmeters have shown promising results at the beginning, they have now been abandoned due to movement artefact at the aorta and its limitation of single use during cardiac catheterisation. The non-invasive Doppler ultrasound has gained popularity to measure aortic flow velocity waves and currently is performed routinely at most outpatient cardiology clinics. By unravelling the mechanisms of age-related changes of the ejection pattern of blood from the left ventricle, apparent from alteration in aortic flow wave contour and through relating aortic flow with aortic pressure waveform, changes in aortic impedance with age can be characterised as a marker of cardiac load.

Applying a simple harmonic analysis to define a physical relation – in this case between pressure, flow and vascular impedance – requires assumption of the system linearity. This has been discussed in Chapter 2; the general consensus since McDonald, Womersley and Taylor pioneering work is that the periodicity of pulse wave justifies application of Fourier series. In application of harmonic analysis, however, both amplitude and phase hold similar importance when resynthesising curve from each harmonics. Error in determining phase relation can result in error in resynthesis, particularly when computing flow from pressure (McDonald et al. 1973). Error in deriving central from peripheral pressure was likely due to inaccurate phase angle calculation by Hope et al (Hope et al. 2007), as pointed out by Segers et al in their editorial on the paper by Hope et al (Segers et al. 2007).

The vascular input impedance in the ascending aorta holds an important role; it describes the relationship between pressure and flow at the root of the aorta, thus characterise the whole systemic circulation properties. It can also be taken to represent the hydraulic load presented by the systemic circulation to the left ventricle of the heart (O'Rourke et al. 1967, Nichols et al. 1977). When these arterial properties remain constant, the ascending aortic impedance remains constant, so that there is a unique relationship between pressure and flow in the ascending aorta. For any flow ejection pattern, the contour of the resulting pressure waves can be precisely determined (Milnor 1975, Nichols et al. 1980). Values of aortic impedance have been published by various groups using different methods of pressure and flow measurements.

Fry and colleagues were one of the first to plot impedance modulus and phase (Gabe et al. 1964, Patel et al. 1965), then followed by Mills et al (Mills et al. 1970), Nichols and colleagues in subjects undergoing cardiac catheterisation, normal and hypertensive patients, those with heart failure and intervention (Nichols et al. 1977, Pepine et al. 1978, Pepine et al. 1979, Nichols et al. 1986), Merillon and colleagues in normal cohort and heart failure patients (Merillon et al. 1978, Merillon et al. 1982, Merillon et al. 1984), Murgo and colleagues in normal subjects, during Valsalva manoeuvre and exercise (Murgo et al. 1980, Murgo et al. 1981, Murgo et al. 1981), Yin and colleagues in hypertensive patients during drug intervention (Yin et al. 1983, Ting et al. 1986, Ting et al. 1991, Ting et al. 1993, Ting et al. 1995), Laskey and colleagues in heart failure patients (Laskey et al. 1985), Yaginuma, Takazawa and others studying the effect of nitroglycerine on vascular load (Yaginuma et al. 1986, Fitchett et al. 1988, Latson et al. 1988, Fujita et al. 1999), O'Rourke and Avolio on modelling of vascular impedance (O'Rourke et al. 1980), and Kelly and Fitchett on the use of non-invasive carotid tonometry and aortic flow from Doppler ultrasound to determine impedance (Kelly et al. 1992). This method was taken up by Mitchell et al in the Framingham study (Mitchell et al. 2004, Mitchell et al. 2010) and by others (Mazzaro et al.

2005, Segers et al. 2007, Chirinos et al. 2009, Chirinos et al. 2010, Chirinos et al. 2010, Coutinho et al. 2013), even though results have been inconsistent.

Murgo, Merillon and Nichols (Nichols et al. 1977, Murgo et al. 1980, Merillon et al. 1982, Nichols et al. 1985) showed substantial change in human ascending aortic impedance with age from their studies. The combination of increased characteristic impedance and shift to higher frequency resulted in a significant increase in impedance modulus at low frequency. With the increase in ascending aortic characteristic impedance of about 4-fold from 20 to 80 years, the same ascending aortic flow from a 20 year old person would generate 4 times the pressure amplitude in an 80 year old. If there were no change in impedance with increased age, it will remain consistent throughout human lifespan, hence the increase of central pressure seen with aging could not be explained (Nichols et al. 2011). This change in impedance, however, is partially offset by aortic dilation with age (change in diameter).

Figure 5-11 shows typical pressure and flow waves recorded in three normotensive subjects aged 28, 52, and 68 years, and their ascending aortic impedance spectra calculated from the pressure and flow waves. The age-related change of the cardiac ejection pattern is apparent from the alteration in the aortic flow wave contour. While there are many techniques to measure aortic flow wave, each will have its own advantages and disadvantages. Attempts have been previously made (Fry et al. 1956, Fry et al. 1957) to derive flow wave from pressure gradient, yet this has not been pursued further. Non-invasive estimation of aortic flow wave has been the major objective of this project, and three approaches will be undertaken and reported in this thesis, when all assumptions and limitation illustrated previously have been taken into consideration.

I performed two studies to achieve the objective above, as follows. Firstly, I undertook a study to measure aortic flow velocity waves, and to determine aortic impedance from the

aortic flow velocity waves measured by cardiac magnetic resonance imaging, which will be described in section 5.2. This study was performed to show the expected changes with aging in aortic flow velocity waves, and to demonstrate that it is feasible to determine aortic impedance, non-invasively, from the derived aortic pressure, and the aortic flow measured by cardiac magnetic resonance. To date, the published studies that attempted to show the aortic impedance and aortic flow wave changes with age non-invasively have not been able to replicate the studies that measured aortic pressure and flow invasively.

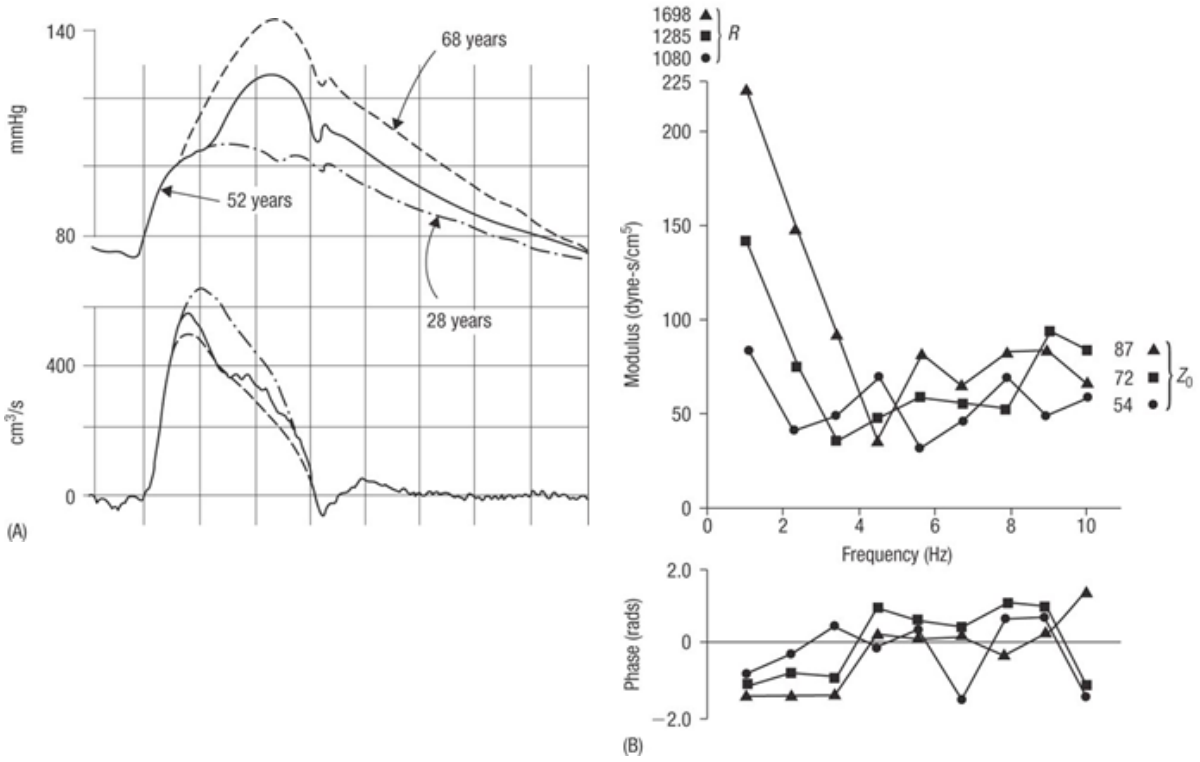


Figure 5-11. (A, left) Typical pressure and flow waves recorded in three normotensive subjects aged 28, 52, and 68 years. (B, right) Ascending aortic impedance spectra calculated from the above pressure and flow waves. R represents the peripheral resistance and Z0 the characteristic impedance. (●) 28 years; (■) 52 years; (▲) 68 years. Impedance modulus is expressed in volume flow terms (mL/s). When expressed in velocity flow (cm/s), assuming differences in aortic cross-sectional area from the same paper, values of characteristic impedance were significantly higher for the youngest to oldest group. From (Nichols et al. 1993).

Secondly, a pilot study was undertaken to determine changes in aortic flow velocity waves in subjects in whom central aortic pressure was available, as described in section 5.3. As determination of aortic impedance requires accurate acquisition of aortic pressure and flow waves, and to date, the aortic flow velocity waveform measured by Doppler ultrasound has not be able to consistently demonstrate the aging changes, this study was performed. In both study, I actively organised and analysed all data, and contributed in manuscript preparation.

5.2 Study: Non-invasive Measurement of Ascending Aortic Flow Waveform and Impedance

A paper under review:

Adji A, Kachenoura N, Bollache E, O'Rourke MF, Avolio AP, Mousseaux E. **Magnetic Resonance and Applanation Tonometry for Non-Invasive Determination of Left Ventricular Load and Ventricular Vascular Coupling in the Time and Frequency Domain.** Submitted to *J Hypertension* **(2015).**

There is technical limitation in the current techniques of measuring aortic flow waveform, as described in the Introduction in this chapter. Due to the difficulties with Doppler measured velocity waves and indices, and underestimation of values generated by the age-specific impedance model and Waterhammer formula, a more accurate method to measure aortic flow velocity waves is crucial. Magnetic resonance flow velocity measurement can overcome the problem by identifying movement of particles in all directions, and so providing an averaged flow velocity wave over the aortic cross-section, and without the artefact caused by changing flow profiles in the aorta throughout the cardiac cycle (Redheuil et al. 2011). The method of measuring wave velocity and distensibility in ascending aorta using magnetic resonance imaging has been reported previously (Hickson et al. 2010, Redheuil et al. 2010, Dogui et al. 2011, Redheuil et al. 2011) (**Figure 5-12**), hence it can be extended to aortic impedance estimation with relative ease together with central aortic pressure measurement non-invasively with applanation tonometry, as reported by Bollache et al (Bollache et al. 2015) and Bargiotas et al (Bargiotas et al. 2015). This technique has proved valuable for providing non-invasive measures of ascending aortic impedance to characterise effects of aortic stiffening with age. The result shows significant reduction of peak aortic flow velocity which physiologically has an inverse relationship with aortic diameter, and an inverse effect on vascular impedance expressed in terms of flow velocity.

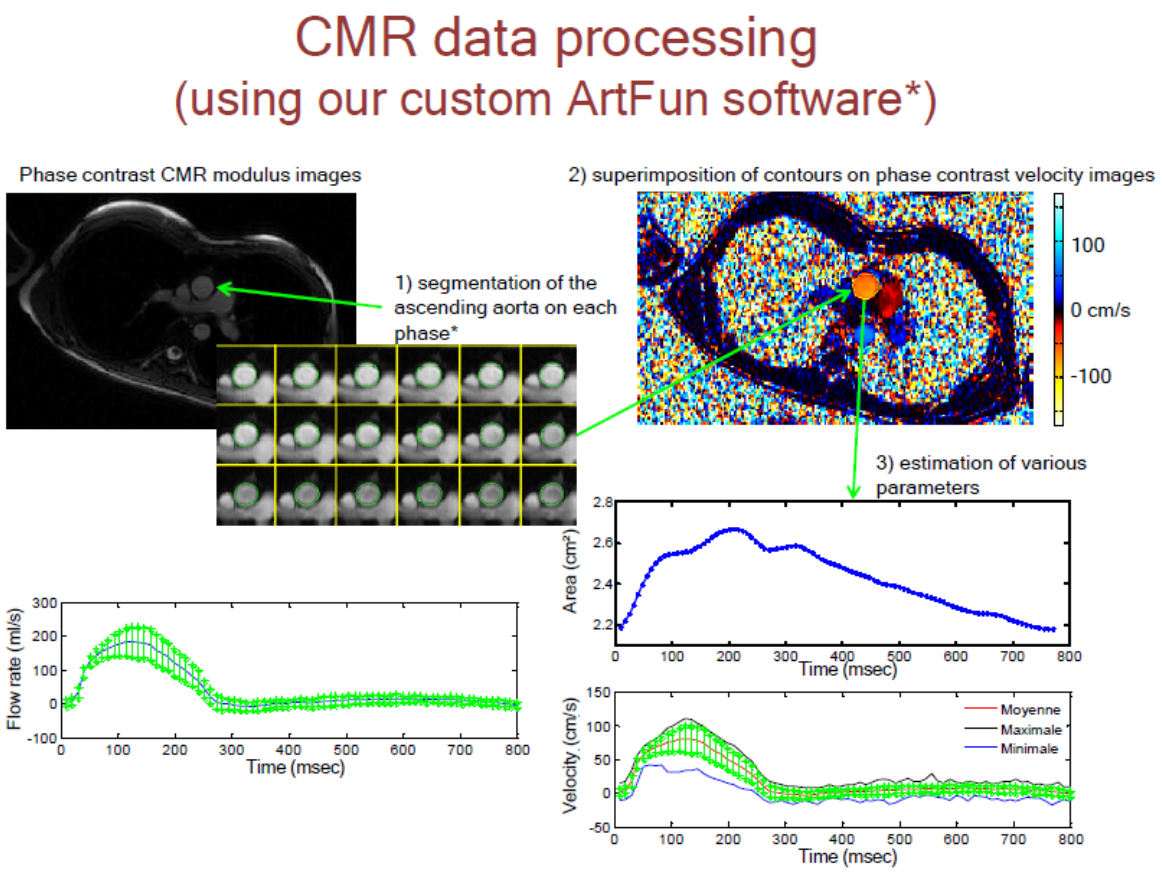


Figure 5-12. Cardiac Magnetic Resonance (CMR) data processing used to measure ascending aortic flow velocity waveform. From (Herment et al. 2010).

There are limitations to this study which need mentioned here, and will be discussed further in Section 5.3. For Doppler flow waves, the envelope of flow velocities travelling at different speeds is customarily traced out by hand. Problems are minor in smaller arteries where laminar flow is usually established, whereas secondary (turbulent) flow is present commonly in the ascending aorta. In contrast to Doppler techniques, Cardiac Magnetic Resonance (CMR) techniques average flow across the aortic diameter, as with cuff-type electromagnetic flowmeters used in the 1970s to 1980s (O'Rourke 1965). CMR has the capability to average directional flow in the presence of secondary flow or turbulence. My study hypothesis is to investigate if the CMR method could provide realistic waveforms with realistic changes with

age and patterns similar to those obtained previously in humans with invasive techniques, as with the cuff-type, and catheter-tipped, electromagnetic flowmeter.

This study was made possible under collaboration with Professor Elie Mousseaux and his colleagues from Cardiovascular Imaging Department, Hôpital Européen Georges Pompidou, Paris, France. Part of the results of this study has been presented at various domestic and international scientific meetings, and subsequently published in abstract form. The manuscript is currently ready for submission. I performed all data organisation and analysis for this manuscript, as well as contributed scientifically to the manuscript preparation.

MAGNETIC RESONANCE AND APPLANATION TONOMETRY FOR NON-INVASIVE DETERMINATION OF LEFT VENTRICULAR LOAD AND VENTRICULAR VASCULAR COUPLING IN THE TIME AND FREQUENCY DOMAIN

Audrey Adji *†, Nadjia Kachenoura ‡, Emilie Bollache ‡§, Alberto P. Avolio †, Michael F O'Rourke †¶, Elie Mousseaux §#††

* Department of Biomedical Sciences, Faculty of Medicine and Health Sciences, Macquarie University, Sydney, Australia

† St Vincent's Clinic, Sydney, Australia

‡ Sorbonne Universités, UPMC Univ Paris 06, INSERM UMRS 1146, CNRS UMR 7371, Laboratoire d'Imagerie Biomédicale, F-75013, Paris, France

§ Institut Jean le Rond d'Alembert, Paris, France

¶ University of New South Wales/ VCCRI, Sydney, Australia

Cardiovascular Imaging Department, Hôpital Européen Georges Pompidou, AP-HP, Paris, France

†† PARCC Inserm 970, Université Paris Descartes, Paris, France

Word count: 6296

Figures: 4; tables: 2

Brief title : Non-invasive determination of LV afterload

Keywords:

Ascending aortic flow velocity, carotid pressure, impedance, wave reflection, hemodynamics

ABSTRACT

Objectives: Cardiac Magnetic Resonance (CMR) is potentially more useful than Doppler ultrasound for quantifying Ascending Aortic (AA) flow velocity in the presence of complex flow patterns. Our aim was to characterize flow velocity wave patterns in the AA with age and their use with central (carotid) pressure waves to estimate AA impedance as Left Ventricular (LV) load, and to interpret vascular/ ventricular interaction.

Methods: AA flow velocity was measured non-invasively, using velocity-encoded CMR, in 50 healthy subjects (21- 70 years) by averaging flow velocities across the aortic cross-section. Pressure waves were measured non-invasively by carotid tonometry as a surrogate of aortic pressure. Impedance was determined in modulus and phase from corresponding harmonics of pressure and flow velocity waves.

Results: With increasing age, AA peak flow velocity decreased from 67±18 cm/s in younger subjects (≤ 50 years) to 48±13 cm/s in older subjects (> 50 years) ($p<0.0001$), largely attributable to increase in aortic diameter 2.5±0.3 cm for 3rd decade to 3.3±0.2 cm for 7th decade ($p<0.001$). With aging, carotid pressure Augmentation Index (AIx) increased ($r2=0.52$, $p<0.001$), as expected from increased aortic stiffness, while AA flow AIx decreased during the mid to late systolic period ($r2=0.26$, $p<0.001$), attributable to progressive impairment in LV contractility. AA impedance spectra showed aging changes seen in previous invasive studies and as predicted from modelling.

Conclusion: CMR provides non-invasive measures of LV pulsatile load in time and frequency domain, with expected differences between young and older subjects. This conforms with and extends the new AHA recommendations for LV afterload and vascular/ ventricular interaction.

5.2.1 Introduction

Cardiac Magnetic Resonance (CMR) is increasingly used in clinical settings to measure arterial pulse wave velocity and arterial flow velocity [1], as well as to provide anatomical imaging [2]. CMR has shown advantages over Doppler ultrasound acquisition of flow velocity, since CMR is relatively independent of the operator, and has higher reproducibility than Doppler [3], as noted in patients with mitral regurgitation [4,5]. Doppler studies have not shown the reduction in Ascending Aorta (AA) peak and mean flow velocity seen with invasive studies [6], and predicted from progressive increase in aortic diameter with age [7]. Increasing AA cross-sectional area with age must result in decreased flow velocity if cardiac output remains constant (or falls) [7].

The most recent studies of AA impedance have utilised non-invasive pressure (from carotid or AA derived from radial) and flow velocity (from Left Ventricular (LV) outflow tract by Doppler ultrasound) [8-11]. These have not shown the change with age, previously documented with invasive studies. CMR flow velocity measurement within the AA may be superior to Doppler since CMR averages axi-symmetrical flow velocity wave over the aortic cross-section [12], as did the cuff type Electro-Magnetic Flowmeter (EMF) used in most animal and the early clinical studies [7,13,14].

A recently published article from French authors [15,16] showed that the aortic characteristic impedance can be estimated in the time domain using phase-contrast CMR and carotid applanation tonometry data. In the present (related) study, we sought to show change in AA flow velocity patterns with age in adults, and through linking these with measurements of carotid arterial pressure as a surrogate of aortic pressure, to determine AA impedance [17] and LV/ vascular interaction. AA impedance is the most complete and comprehensive expression of LV afterload, since it makes minimal assumptions of biological variables [17,18], and has

been accorded the highest grade (I-A) for measurement of vascular load in relation to aortic stiffening in the American Heart Association (AHA) Statement on Scientific Principles [19].

5.2.2 Methods

We studied 50 healthy volunteers (28 males) free from overt cardiovascular disease, aged from 21 to 70 years. All subjects were asymptomatic and had no history of cardiovascular disease, or hypertension or diabetes, or of drug therapy, and had normal ECG. They also had normal LV function according to screening echocardiography (ejection fraction >55%), and normal valvular function (table 1). We were comfortable that this screening procedure indentified a normal population. It was not necessary to exclude any of the volunteers who underwent CMR on the basis of an abnormality detected during the CMR study. The study protocol was approved by the institutional review board and informed consent was obtained from all participants.

CMR flow velocity acquisitions and image analysis

All subjects underwent CMR imaging of the thoracic aorta using a 1.5T system (Signa HDx, GE Healthcare, Waukesha, USA) with a cardiac phased array coil (8 channels).

Steady state free precession (SSFP) cine sequences were acquired in the axial and sagittal oblique planes, during breath-holding, covering the thoracic aorta (three levels per breath-hold). An additional axial cine SSFP plane, using a fast retrospectively gated gradient echo sequence, was acquired with higher temporal resolution at the level of pulmonary bifurcation perpendicular to the aorta, using the following parameters: repetition time (TR) = 3.3ms, echo time (TE) = 1.4ms, flip angle=50°, slice thickness = 8mm, matrix: 224x190, views per segment=6 leading to 8 to 12 ms-temporal resolution after applying a view sharing technique.

The latter slice location was used to acquire velocity images, using a 2D through-plane velocity-encoded sequence with retrospective gating during breath-holding, providing blood flow velocities in both ascending and descending aorta. Velocity-encoded acquisition parameters were: TR = 4.8ms, TE = 2.3ms, flip angle = 50°, number of excitations = 1, slice thickness = 8mm, acquisition matrix: 256x128, views per segment = 2, 50% - rectangular field of view. View sharing was used, resulting in a temporal resolution of 10ms and an acquisition duration of 32 RR intervals. Encoding velocity was Venc = 200cm/s and the acquisition was repeated with Venc = 250cm/s in case of velocity aliasing.

CMR data were transferred for off-line analysis using the custom ArtFun software (Inserm/UPMC) [20]. For both SSFP and velocity encoded modulus CMR images, contours of the AA waves were automatically detected for all phases of the cardiac cycle, for AA areas and diameters as well as for flow velocities estimation, respectively. Indeed, AA contours of the modulus images were superimposed on velocity images and forward and backward flow velocities were averaged for each phase of the cardiac cycle resulting in mean flow velocity waveforms for each subject.

Pressure measurement and calibration

Simultaneous to CMR aortic acquisitions, brachial blood pressure was measured using oscillometric sensor cuff (Vital Signs Monitor, Welch Allyn Inc, USA). Applanation tonometry of right carotid artery was performed using the Pulse Pen device (Diatecne, Milano, Italy), immediately after CMR exam. At least 8 consecutive ECG-gated pressure waveforms were acquired with a temporal resolution of 2 ms. Carotid pressures were calculated after calibrating tonometric measurements by brachial diastolic and mean (calculated as diastolic + 1/3 pulse pressure) pressures, following recommendation made by the PulsePen device manufacturer. Pressure calibration using values measured during CMR

is based on the assumption that mean and diastolic blood pressures remain unchanged throughout the arterial tree, and accounts for any differences in blood pressures inside and outside the magnet. Six to ten pressure waves were included for ensemble-averaging to obtain a representative carotid pressure waveform for each subject.

Flow and pressure waveforms analysis and impedance estimation

Previous studies [6,21,22] and our own observation from over 1,500 individuals [23] have found that the timing of AA pressure wave inflection or shoulder (T1) caused by the peak of the AA flow wave occurred around 106 ms. Hence, both carotid pressure T1 and CMR AA flow velocity waves at peak flow were shifted in the time domain and set to be around 106 ms from the apparent wave foot. This must be a compromise, necessary on account of the known limited time resolution of CMR. It appeared reasonable, knowing that a similar timing error is accepted in measurement of carotid, rather than aortic pressure. Any combined error would be apparent principally in phase (time delay), not in amplitude [14,17,18].

Wave reflection affects pressure and flow waves in opposite manner; the reflected *pressure* wave *adds* to the initial wave, while the reflected *flow* wave *subtracts* from the incident wave [7,24]. The effect of wave reflection on carotid pressure was measured by Pressure Augmentation Index (AIx), as previously described by Kelly et al [25], as:

$$\frac{\text{augmented carotid pressure}}{\text{systolic minus diastolic carotid pressure}}.$$

The effect of wave reflection on AA flow velocity was quantified using a similar metric – DR1/3, which is:

$$\frac{\text{flow at 33\% of time peroid from peak to end systolic flow}}{\text{peak flow}}$$

previously described for this purpose by Miyashita et al [24], to characterize flow velocity deceleration caused by wave reflection during the mid systolic period.

For impedance spectrum estimation, flow velocity and pressure waves were decomposed into their component harmonics using a Fast Fourier Transform (FFT); FFT pressure amplitudes were divided by FFT flow velocity amplitudes for frequencies up to 10 Hz. Any harmonics were excluded if modulus was less than 0.6 mmHg for pressure, or less than 1 cm/s for flow velocity, as in Nichols et al [27]. To take into account the difference in Heart Rate (HR) between Flow (HR-F) and Pressure (HR-P) measurements, pressure and flow harmonics were normalized and interpolated linearly into the nearest integer frequencies, i.e. 1, 2, 3, ... 10 Hz. Even though HR was different (average HR-F 69.22 and HR-P 65.5 beats per minute), it was not significantly so ($p=0.08$). Total peripheral arterial resistance was considered as the input impedance modulus at 0 Hz and characteristic impedance was estimated as the mean magnitude of impedance modulus between 2 and 10 Hz, as in previous studies [21,27].

Statistical analysis

Continuous variables were expressed as mean ($\pm$ standard deviation). Linear regression and the Pearson correlation coefficient were used to assess associations between variables. Differences between groups were assessed using the nonparametric Mann-Whitney test and $p<0.05$ indicated a significant difference.

5.2.3 Results

Subjects' characteristics are summarized in table 1.

Individual CMR AA flow velocity waves are graphed (figure 1) based on gender (males and females) and age (≤ 50 and > 50 years). Waves showed the typical pattern, as previously shown with a EMF cuff-encircling flow probe [6,13,14,17], with a steep rise from foot to a single systolic peak, and with flow velocity falling from this first peak to the zero level between 150-300 ms (depending on HR), then remaining around zero throughout the diastolic period. With increasing age, average peak flow velocity was 67±18 cm/s in younger subjects (≤ 50 years) and 48±13 cm/s in older subjects (> 50 years) ($p<0.001$). There was no apparent difference for each age group between males and females for flow velocity waves (figure 1).

In figure 2, CMR flow velocity waveforms are shown on the left panels, with tonometric carotid pressure waveforms on the right panels, males and females combined, ensemble-averaged for age groups 21-30, 31-40, 41-50, 51-60, and 61-70 years. Amplitude of pressure wave increased with age (table 2), and this was principally due to increase in height of the late systolic peak from earlier return of reflected wave [6,14,26], as widely shown in previous aging studies [14,21]. With aging, there was a significant and progressive decrease in amplitude and peak of the AA flow velocities, along with a significant increase in aortic diameter and cross-sectional area ($p<0.001$ for both) (table 2). Indeed, a multivariate analysis indicated that AA diastolic diameter ($p<0.001$) and gender ($p=0.01$) are significant correlates of the peak of AA flow velocities, independent of Age, Carotid Systolic Pressure (CSP) and Body Mass Index (BMI) (overall $r^2=0.66$, $p<0.001$). Finally, AA flow velocity wave contour appeared virtually similar (figure 2), except for an apparent inflection during the deceleration period, particularly marked in the elderly group (> 61 years).

Miyashita's ratio DR1/3 [26] calculated from AA CMR flow velocity waves significantly decreased with age (r^2=0.26, p<0.001) (figure 3A), but carotid AIx increased with age (r^2=0.52, p<0.001) (figure 3B). The summation of these two indices with the same polarity was strongly and positively associated with age (r^2=0.58, p<0.001) (figure 3C). This confirms the important effect of wave reflection on both AA flow velocity (reduced) and carotid pressure waves (increased). These findings are consistent with physiological knowledge regarding reflection wave [26] and supports theory that indeed, while reflected pressure adds to forward pressure, reflection subtracts from forward flow out of the contracting LV [24]. Multivariate analysis including age, CSP, gender, BMI and HR was performed to define the correlates of DR1/3, AIx and their summation. While age (p<0.001) and CSP (p=0.01) were the only independent correlates of DR1/3 (overall r^2=0.31, p<0.001), age (p<0.001) and gender (p<0.001) were the principal independent correlates of AIx (overall r^2=0.66, p<0.001) and its summation with DR1/3 (overall r^2=0.68, p<0.001).

Amplitude and phase of AA impedance are shown in figure 4. Figure 4A showed low values of amplitude in the ≤ 60 years groups up to the sixth harmonic, since the first 6 harmonics contained more than 99% of power [25] and the effect of noise was higher in the frequencies above 6 Hz, causing fluctuations of the impedance spectra. AA characteristic impedance (Zc) averaged for all subjects, determined between 2 to 10 Hz, was 686$\pm$369 dyne.s.cm^{-3}. A significant difference was not found between Zc values across age decades (p=0.05). However, there was a significant difference (p=0.02) between the eldest (> 60 years, average 1103 dyne.s.cm^{-3}) and the rest of the group (≤ 60 years, average 675 dyne.s.cm^{-3}). Impedance phase (figure 4B) showed similar values for the first harmonic (from -0.5 to -0.9 radians) at all ages, then increased for all age groups, crossing zero to positive values between 3 – 4 Hz. These values are close to those found in our previous study of AA impedance using the encircling cuff electromagnetic instrument and direct aortic pressure measurement [14], and in the earlier study by Patel et al [13].

There was an age-related increase in impedance modulus at zero frequency (Z_T). For the younger (≤ 50 years) group, Z_T was 8581 ± 2180 dyne.s.cm^{-3}, and an increase of around 78% was found when compared to the older (> 50 years) group (15257 ± 6017 dyne.s.cm^{-3}) ($p<0.001$). When this difference was explored further, this significant rise was associated with increase in mean carotid pressure by 11% between the younger and older cohort and decrease in mean CMR flow velocity by 33%. No gender difference was seen. Z_T was significantly associated to age ($r^2=0.40$, $p<0.001$), and multivariate analysis revealed that such association was independent of gender, BMI and CSP.

5.2.4 Discussion

A major advance in cardiovascular research was the introduction of steady state analysis of arterial pulses in the frequency domain some 60 years ago by McDonald, Womersley and Taylor in London [28-30]. At that time, they were able to calculate the flow velocity curves from pressure gradients, and showed that non-linearities in these relationships were sufficiently small to be neglected to a first approximation [30]. About the same time, McDonald published his first edition of "Blood Flow in Arteries" [28] and together with Taylor [29], described the pulsatile nature of pressure and flow in the arterial vasculature where it is expressed as input impedance. This pioneering advance in data interpretation was quickly taken up by Fry and colleagues at the National Institutes of Health (NIH) in Bethesda, and followed by papers from NIH on AA impedance in experimental animals and in humans [13]. This early work at NIH was not pursued beyond the 1970s, partly because of the need to place EMF probes around the ascending aorta – which was possible only at cardiac surgery. Subsequent application to humans has been slow because of technical difficulties in measurement of AA flow. A catheter-mounted EMF device was introduced by Mills and Shillingford in London [31] for use at diagnostic catheterization, and evaluated at the NIH [32]. This instrument was subject to gross movement artefact in the aorta, and was

subsequently abandoned on account of such artefact, and on account of expense when single use of the complex-miniaturized catheter system was mandated, through not before key papers were presented from the USA, France, Japan and Australia [6,21,32-36], which provided new information on aging and drug action in humans.

Doppler ultrasound was then introduced as a means of measuring flow waves in the LV outflow tract. With introduction of applanation tonometry [22,25,37,38] it was possible to measure ascending aortic impedance non-invasively in humans [39]. However, the same problems from turbulent AA flow created flow artefacts, and unreliable impedance values, as with the EMF catheters [7].

On this background [8], together with progression of Asklepios [40] and other trials [10,11,41], the present study was undertaken. It was hoped that accurate CMR flow velocity waves could be generated in the AA without the artefact caused by changing flow profiles in the AA throughout the cardiac cycle [42-46], and which had proved far less a problem in the descending aorta and other arteries [47]. We sought to show that aging changes in AA flow velocity waves and vascular impedance could be determined non-invasively with similar accuracy [13,14].

Flow waveforms

Flow waveforms (figure 1) were similar to those reported previously in humans, using cuff type EMF probes at thoracotomy [14,32]. Due to the difference between the average (CMR estimate) and the maximal velocity (Doppler estimate) within cross-sectional area, peak flow velocity (59 cm/s) by CMR was substantially lower than peak flow velocity as measured by Doppler (70 – 110 cm/s) [48] for normal subjects, but similar to that (~50 cm/s) with the invasive cuff EMF used by Patel et al [13] and O'Rourke and Avolio [14] and similar to that

measured by Hashimoto and Ito with Doppler (~41 cm/s) [47] for the descending aorta (where flow is more nearly laminar than in the AA).

The low peak flow velocity in our older subjects is attributable to aortic dilation. Stroke volume (average 76 ml, table 2) was similar in young and old subjects.

We expected that the downslope of the flow velocity wave would be convex to the right in the younger subjects, and convex to the left in older subjects, as found by Miyashita et al [26], and by others [27,34,49], but could not be convinced on the basis of flow wave shape alone (figures 1 and 2). However, the DR1/3 of the flow velocity waves did show significant decrease with age, whereas AIx of the pressure wave showed significant increase (figure 3), as in similar study [26,27,49]. These findings are consistent with the concept that wave reflection in older subjects augments pressure in late systole while having an opposite effect on LV ejection. We see the two reflection phenomena as being related, and dependent not only on peripheral wave reflection, but also on the capacity of the LV to eject against rising pressure in late systole [49].

Data on flow waveforms presented here also provide some comfort for those who rely on AIx or synthesized forward/ backward wave ratios as measures of wave reflection [22,24,49]. Clearly, aortic pressure waves change more than flow waves with aging, and in normal subjects at least, the AA flow wave is nearly triangular through adult life. However, the effects of wave reflection in reducing forward flow during mid-systole just after peak flow are apparent in older subjects (figure 3) and are expected to be even more marked in the presence of impaired contraction and systolic heart failure [49-51]. Lower AIx than expected is attributable to weakened LV contractility [49].

Pressure waveforms

The carotid pressure waves were used by us and others as a surrogate of aortic pressure. There is contention on how these carotid waves should be calibrated from the brachial pulse. We took the usual approach of assuming mean pressure to be brachial cuff diastolic pressure plus one-third pulse pressure (assuming Form Factor (FF) to be 33% in the brachial artery), while using measured carotid FF and assuming diastolic and mean pressure to be identical in the brachial and carotid arteries [39]. Such calibration may have caused underestimation of carotid pulse pressure by 10% in older persons if FF was 40% rather than 33%, and so a like underestimation of AA impedance. When we recalculated the pressure values using a FF of 40% in persons over age 50, there was an increase of about 6 mmHg in CSP; suggesting that we could indeed have underestimated increase in aortic impedance modulus with age. This does not change our interpretations of impedance to any material degree.

AA impedance

Values of AA impedance in this study at different ages are similar to those previously reported in predominantly young subjects by Patel et al [13] and older subjects by ourselves [14] in previous invasive studies using cuff type EMF probes. These have been validated under conditions where flow is presumed to be axisymmetrical [51]. The patterns of impedance are similar to those previously shown [6,32-36] with a minimal value of modulus around 3 – 4 Hz and with impedance phase, initially negative, crossing zero at 3 – 4 Hz. Data in figure 4 generally conform to the human data and modelling study of O'Rourke and Avolio [14].

Limitations

Limitations of the study include the non-simultaneous measurements of central pressure (which require calibration of carotid pressure) and AA flow velocity waves. As measurement of AA flow velocity was performed in the magnet room, and we did not have CMR-compatible tonometric recording apparatus, the pressure and flow recordings were acquired separately. Therefore adjustments had to account for the minor differences in heart rate, and mean pressure between measurements. The fixed FF of 33% (or mean pressure calculated as diastolic pressure + 1/3 of pulse pressure) was suggested by the PulsePen manufacturer for calibrating carotid pressure, as used in Europe and in the US, but does assume the same contour of the brachial pulse wave at different ages [32]. We assumed carotid pressure waves to be surrogates of aortic, knowing that these underestimate changes of aortic pressure waveforms with age [7,38].

Despite limitation above, the data presented here were consistent with those obtained invasively from earlier studies. The advantage with our study is the fully non-invasive feature of such processes, which can be included in a routine imaging procedure. CMR is more costly than an echocardiographic examination but generally less than angiography. Measurement of flow velocity waves by CMR adds arterial function to the CMR procedure, and at modest incremental cost, since only a single breath-hold is required for aortic flow measurement. The known age-related changes in flow behaviours and impedance were found in this study and would be expected to be more compelling had the pressure been determined for the AA rather than for the carotid artery, and simultaneously with the CMR flow acquisition. In the future, we plan to use magnet-compatible tonometry to measure pressure waves simultaneously with flow velocity in the magnet room, and generate AA pressure using

a generalized transfer function from the radial wave. Measurement of central aortic pressure from radial applanation tonometry waveforms using a generalized transfer function [7,53] can be performed during CMR flow acquisition with greater reproducibility and accuracy than the carotid tonometry used in this study.

This is the first paper to show that measurement of aortic flow non-invasively by CMR and central pressure by applanation tonometry can be used to show as well as to characterize LV load as input impedance of the systemic circulation, the adverse effects of aortic stiffening in humans with age on both flow and pressure patterns. This has not been possible with Doppler ultrasound since flow tracings in the aorta or left ventricular outflow tract do not show consistent flow contour change with age. Findings are relevant to and supportive of recent studies on wave reflection and left ventricular load in humans [19,41], while extending the application of recent work in humans and initial studies of arterial impedance with invasive measurements over 50 years ago [13,17,24,25]. Ability to measure AA flow and impedance opens up new areas of research into vascular/ ventricular interaction, and provide a logical explanation on differences and similarities between patients with systolic and diastolic LV dysfunction as cause of cardiac failure [7,49]. The approach is fully consistent with the new American Heart Association statement on arterial stiffness [19], which gives the highest recommendation (class I, level of evidence A) to methods which measure arterial pressure and flow in assessment of arterial stiffness, and its ill-effects on the heart and vascular system, and as cause of cardiovascular events. While we have great confidence in the capabilities of CMR for non-invasive characterization of LV load, and vascular/ ventricular interaction, we confirm that at this stage the method remains in the domain of a research study. Practically, aortic flow and functional assessment could be added to clinical routine CMR as a “one-stop

shop" imaging modality for the non-invasive evaluation of LV load, and vascular/ventricular coupling.

References

1. Redheuil A, Yu WC, Mousseaux E, Harouni AA, Kachenoura N, Wu CO, Bluemke D, Lima JA. Age-related changes in aortic arch geometry: relationship with proximal aortic function and left ventricular mass and remodeling. J Am Coll Cardiol 2011;58:1262-1270.

2. Pennell DJ. Cardiovascular magnetic resonance. Circulation 2010;121:692-705.

3. Grothues F, Smith GC, Moon JC, Bellenger NG, Collins P, Klein HU, Pennell DJ. Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. Am J Cardiol 2002;90:29-34.

4. Uretsky S, Gillam L, Lang R, Chaudhry FA, Argulian E, Supariwala A, Gurram S4, Jain K, Subero M, Jang JJ, Cohen R, Wolff SD. Discordance between echocardiography and MRI in the assessment of mitral regurgitation severity: a prospective multicenter trial. J Am Coll Cardiol 2015;65:1078-1088.

5. Kar S, Sharma R. Current assessment of mitral regurgitation: not making the grade. J Am Coll Cardiol 2015;65:1089-1090.

6. Nichols WW, O'Rourke MF, Avolio AP, Yaginuma T, Murgo JP, Pepine CJ, Conti CR. Effects of age on ventricular vascular coupling. Am J Cardiol 1985;55;1179-1184.

7. Nichols WW, O'Rourke MF, Vlachopoulos C. McDonald Blood Flow in Arteries. 5th ed. London; Arnold Hodder, pp 210-212.

8. Segers P, Rietzschel ER, De Buyzere ML, Vermeersch SJ, De Bacquer D, Van Bortel LM, De Backer G, Gillebert TC, Verdonck PR; Asklepios investigators. Noninvasive (input) impedance, pulse wave velocity, and wave reflection in healthy middle-aged men and women. Hypertension 2007;49:1248-1255.

9. Mitchell GF, Parise H, Benjamin EJ, Larson MG, Keyes MJ, Vita JA, Vasan RS, Levy D. Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: the Framingham Heart Study. Hypertension 2004;43:1239-1245.

10. Coutinho T, Borlaug BA, Pellikka PA, Turner ST, Kullo IJ. Sex differences in arterial stiffness and ventricular-arterial interactions. J Am Coll Cardiol 2013;61:96-103.

11. Chirinos JA, Kips JG, Jacobs DR, Brumbach L, Duprez DA, Kronmal R, Bluemke DA, Townsend RR, Vermeersch S, Segers P. Arterial wave reflections and incident cardiovascular events and heart failure: MESA (Multiethnic Study of Atherosclerosis). J Am Coll Cardiol 2012;60:2170-2177.

12. Pennell DJ. Ventricular volume and mass by CMR. J Cardiovasc Magn Reson 2002;4:507-513.

13. Patel DJ, Greenfield JC Jr, Austen WG, Morrow AG, Fry DL. Pressure-flow relationships in the ascending aorta and femoral artery of man. J Appl Physiol 1965;20:459-463.

14. O'Rourke MF, Avolio AP. Pulsatile flow and pressure in human systemic arteries. Studies in man and in a multibranched model of the human systemic arterial tree. Circ Res 1980;46:363-372.

15. Bollache E, Kachenoura N, Bargiotas I, Giron A, De Cesare A, Bensalah M, Lucor D, Redheuil A, Mousseaux E. How to estimate aortic characteristic impedance from magnetic resonance and applanation tonometry data? J Hypertens 2015;33:575-582.

16. Bargiotas I, Bollache E, Mousseaux E, Giron A, deCesare A, Redheuil A, Kachenoura N. MR and applanation tonometry derived aortic impedance: association with aging and LV remodellins. J Magn Reson Imaging 2015;41:781-787.

17. O'Rourke MF. Vascular impedance in studies of arterial and cardiac function. Physiol Rev 1982;62:570-623.

18. Milnor WR. Arterial impedance as ventricular afterload. Circ Res 1975;36:565-570.

19. Townsend RR, Wilkinson IB, Schiffrin EL, Avolio AP, Chirinos JA, Cockcroft JR, Heffernan KS, Lakatta EG, McEniery CM, Mitchell GF, Najjar SS, Nichols WW, Urbina EM, Weber, T, on behalf of the American Heart Association Council on Hypertension. Recommendations for Improving and Standardizing Vascular Research on Arterial Stiffness: A Scientific Statement From the American Heart Association. Hypertension 2015; online 9th July.

20. Herment A, Kachenoura N, Lefort M, Bensalah M, Dogui A, Frouin F, Mousseaux E, De Cesare A. Automated segmentation of the aorta from phase contrast MR images: validation against expert tracing in healthy volunteers and in patients with a dilated aorta. J Magn Reson Imaging 2010;31:881–888.

21. Murgo JP, Westerhof N, Giolma JP, Altobelli SA. Aortic input impedance in normal man: relationship to pressure wave forms. Circulation 1980;62:105-116.

22. Kelly R, Hayward C, Avolio A, O'Rourke M. Noninvasive determination of age-related changes in the human arterial pulse. Circulation 1989;80:1652-1659.

23. Adji A, O'Rourke MF. Can aortic wave reflecting site be estimated from the early systolic shoulder? Circulation 2012;126 (suppl): A17711.

24. Westerhof N, Sipkema P, van den Bos GC, Elzinga G. Forward and backward waves in the arterial system. Cardiovasc Res 1972;6:648-656.

25. Kelly R, Hayward C, Ganis J, Daley JE, Avolio AP, O'Rourke MF. Noninvasive registration of the arterial pressure pulse waveform using high-fidelity applanation tonometry. J Vasc Med Biol 1989;1:142-149.

26. Miyashita H, Ikeda U, Tsuruya Y, Sekiguchi H, Shimada K, Yaginuma T. Noninvasive evaluation of the influence of aortic wave reflection on left ventricular ejection during auxotonic contraction. Heart Vessels 1994;9:30-39.

27. Nichols WW, Conti CR, Walker WE, Milnor WR. Input impedance of the systemic circulation in man. Circ Res 1977;40:451-458.

28. McDonald DA. Blood Flow in Arteries. 1st ed. London 1960; Edward Arnold.

29. McDonald DA, Taylor MG. The hydrodynamics of the arterial circulation. Progress in Biophysics and Chemistry 1959;9:107–173.

30. Womersley JR. Methods for the calculation of velocity, rate of flow and viscous drag in arteries when the pressure gradient is known. J Physiol 1955;127:553-563.

31. Mills CJ, Shillingford JP. A catheter tip electromagnetic velocity probe and its evaluation. Cardiovasc Res 1967;1:263-273.

32. Mills CJ, Gabe IT, Gault JH, Mason DT, Ross J Jr, Braunwald E, Shillingford JP. Pressure-flow relationships and vascular impedance in man. Cardiovasc Res 1970;4:405-417.

33. Merillon JP, Fontenier GJ, Lerallut JF, Jaffrin MY, Motte GA, Genain CP, Gourgon RR. Aortic input impedance in normal man and arterial hypertension: its modification during changes in aortic pressure. Cardiovasc Res 1982;16:646-656.

34. Laskey WK, Kussmaul WG, Martin JL, Kleaveland JP, Hirshfeld JW Jr, Shroff S. Characteristics of vascular hydraulic load in patients with heart failure. Circulation 1985;72:61-71.

35. Ting CT, Chou CY, Chang MS, Wang SP, Chiang BN, Yin FC. Arterial hemodynamics in human hypertension. Effects of adrenergic blockade. Circulation 1991;84:1049-1057.

36. Yaginuma T, Avolio A, O'Rourke M, Nichols WW, Morgan JJ, Roy PR, Baron DW, Branson J, Feneley MP. Effect of glyceryl trinitrate on peripheral arteries alters left ventricular hydraulic load in man. Cardiovasc Res 1986;20:153-163.

37. Drzewiecki GM, Melbin J, Noordergraaf A. Arterial tonometry: review and analysis. J Biomech 1983;6:141–153.

38. Kelly R, Karamanoglu M, Gibbs H, Avolio AP, O'Rourke MF. Non-invasive carotid pressure wave registration as an indicator of ascending aortic pressure. J Vasc Med Biol 1989;1:241–247.

39. Kelly R, Fitchett D. Noninvasive determination of aortic input impedance and external left ventricular power output: a validation and repeatability study of a new technique. J Am Coll Cardiol 1992;20:952-963.

40. Chirinos JA, Rietzschel ER, De Buyzere ML, De Bacquer D, Gillebert TC, Gupta AK, Segers P; Asklepios Investigators. Arterial load and ventricular-arterial coupling: physiologic relations with body size and effect of obesity. Hypertension 2009;54:558-566.

41. Zamani P, Jacobs DR Jr, Segers P, Duprez DA, Brumback L, Kronmal RA, Lilly SM, Townsend RR, Budoff M, Lima JA, Hannan P, Chirinos JA. Reflection magnitude as a predictor of mortality: the multi-ethnic study of atherosclerosis. Hypertension 2014;64:958-964.

42. Firmin DN, Nayler GL, Kilner PJ, Longmore DB. The application of phase shifts in NMR for flow measurement. Magn Reson Med 1990;14:230-241.

43. Gatehouse PD, Keegan J, Crowe LA, Masood S, Mohiaddin RH, Kreitner KF, Firmin DH. Applications of phase-contrast flow and velocity imaging in cardiovascular MRI. Eur Radiol 2005;15:2172-2184.

44. Bogren HG, Buonocore MH. 4D magnetic resonance velocity mapping of blood flow patterns in the aorta in young vs. elderly normal subjects. J Magn Reson Imaging 1999;10:861-869.

45. Bogren HG, Buonocore MH. Measurement of coronary artery flow reserve by magnetic resonance velocity mapping in the aorta. Lancet 1993;342:899-900.

46. Bissell M, Ermellina E, Choudhury R. Flow vortices in the aortic root: in vivo 4D MRI confirms predictions of Leonardo da Vinci. Eur Heart J 2014;35:1344.

47. Bulwer BE, Rivero JM. Echocardiography Pocket Guide: The Transthoracic Examination. Chapter 4: Blood Flow Hemodynamics, Cardiac Mechanics, and Doppler Echocardiography. Jones & Bartlett Publishers, 2010.

48. Hashimoto J, Ito S. Aortic stiffness determines diastolic blood flow reversal in the descending thoracic aorta: potential implication for retrograde embolic stroke in hypertension. Hypertension 2013;62:542-549.

49. Westerhof N, O'Rourke MF. Haemodynamic basis for the development of left ventricular failure in systolic hypertension and for its logical therapy. J Hypertens 1995;13:943-952.

50. Sonnenblick EH. Force-velocity relations in mammalian heart muscle. Am J Physiol 1962;202:931-939.

51. Uebaba K, O'Rourke MF, Sindone A, Keogh A, Siswanto, McDonald P, Ishiyama H, Amano K, Xu F. Arterial pulse wave analysis for the assessment of cardiac failure: value of non-invasive applanation tonometry of radial artery. Japanese J. Applied Physiology 2002;32:147-157.

52. O'Rourke MF. Dynamic accuracy of the electromagnetic flowmeter. J Appl Physiol 1966;20:142-147.

53. O'Rourke MF, Adji A. Clinical use of applanation tonometry: Hope remains in Pandora's box. J Hypertens 2010;28:229-233.

Figure Legends

Figure 1. Ensemble-averaged MR AA flow velocity waveform shown separately for males (left) and females (right) and for ≤ 50 years (top) and >50 years of age (bottom). Black lines are individual subjects. Coloured lines are average for group (males = blue, females = red).

Figure 2. Ensemble-averaged MR AA flow velocity (purple line, left panels) and tonometric carotid pressure waves (green line, right panels) for each age decade. Each age-decade includes males and females combined.

Figure 3.

A. (Top) Relationship between DR 1/3 estimated from flow wave velocity and age. Males = blue, females = red, black line represents linear regression line.

B. (Middle) Relationship between carotid pressure AIx and age. Males = blue, females = red, black line represents linear regression line.

C. (Bottom) Effect of wave reflection on flow (= 100 – DR 1/3) was added to pressure AIx and plotted against age. This showed the combined effect of age-related wave reflection on pressure and flow, where reflected pressure adds to initial pressure, while reflected flow subtracts from initial flow. For all, regression lines are for males and females combined. Males = blue, females = red, black line represents linear regression line.

Figure 4A. (Top) Amplitude of the impedance harmonics averaged for each decade, 21-30 years (average 23 years, blue), 31-40 years (average 35 years, red), 41-50 years (average 44 years, green), 51-60 years (average 55 years, purple), 61-70 years (average 66 years, orange). Vertical lines represent standard errors. Black line represents the value of impedance modulus as published by O'Rourke and Avolio [25].

Figure 4B. (Bottom) Phase of the impedance harmonics averaged for each decade, 21-30 years (average 23 years, blue), 31-40 years (average 35 years, red), 41-50 years (average 44 years, green), 51-60 years (average 55 years, purple), 61-70 years (average 66 years, orange). Vertical lines represent standard error of the mean. Black line represents the value of impedance phase as published by O'Rourke and Avolio [25].

Table 1A. Subjects' characteristics

	mean (combined) ± SD	Males ± SD	Females ± SD	p-value
Number of subjects	50	28	22	
Age (years)	45 ± 15	46.2 ± 16	42.5 ± 14	NS
BSP (mmHg)	114 ± 14	118 ± 13	109 ± 13	0.02
BDP (mmHg)	70 ± 10	73 ± 10	66 ± 10	0.02
CSP (mmHg)	112± 15	117 ± 15	106 ± 14	<0.01
CDP (mmHg)	70 ± 10	72 ± 10	65 ± 11	0.01
Weight (kg)	69 ± 13	76 ± 11	60 ± 11	<0.01
Height (cm)	172 ± 8	176 ± 6	165 ± 7	<0.01
HR – F (bpm)	69 ± 12	69 ± 11	70 ± 11	NS
HR – P (bpm)	66 ± 10	65 ± 12	66 ± 8	NS

BSP = Brachial Systolic Pressure, BDP = Brachial Diastolic Pressure, CSP = Carotid Systolic Pressure, CDP = Carotid Diastolic Pressure, HR = Heart Rate – Flow velocity measurement, HR = Heart Rate – Pressure measurement
A p-value for difference between males and females is provided, NS = not significant

Table 1B. Basal left ventricular data for this normal cohort

	Mean ± SD
CMR LV mass (g)	121 ± 26
CMR LV mass/BSA (g/m²)	66 ± 10
CMR end-diastolic volume (ml)	124 ± 30
CMR end-systolic volume (ml)	43 ± 13
CMR LVEF (%)	65 ± 6
Echocardiographic E' (cm/s)	15 ± 4
Echocardiographic E/A	1.2 ± 0.4
Echocardiographic E/E'	5.3 ± 1.7

CMR = Cardiac Magnetic Resonance, LV = Left Ventricular,
BSA = Body Surface Area, LVEF = LV Ejection Fraction

Table 2. AA diameter, area and flow velocity characteristics as well as carotid systolic and diastolic blood pressures. Values are expressed as mean (SD). A p value for the Anova analysis across age groups is provided.

Age groups (n)	21-30 y (10)	31-40 y (10)	41-50 y (10)	51-60 y (11)	61-70 y (9)	p-value
Mean age (years) (n for Males/ n for Females)	23 (1.8) 4/6	35 (3.1) 8/2	44 (2.9) 4/6	55 (2.8) 5/6	66 (2.6) 7/2	<0.001
Carotid systolic pressure (mmHg) (M/F)	102 (12) 114/94	112 (18) 116/94	109 (12) 112/106	115 (16) 113/116	123 (14) 125/117	NS
Carotid diastolic pressure (mmHg) (M/F)	61 (9) 65/58	69 (9) 72/60	70 (9) 73/67	73 (12) 75/71	75 (9) 76/72	NS
Aortic diameter (cm) (M/F)	2.5 (0.3) 2.5/2.6	2.8 (0.4) 2.7/3.0	2.9 (0.4) 3.0/2.9	3.2 (0.5) 3.4/3.0	3.3 (0.2) 3.3/3.3	<0.001
Aortic area (cm^2) (M/F)	5.2 (1.0) 5.0/5.3	5.8 (1.8) 5.4/7.4	6.8 (1.9) 6.9/6.7	7.9 (2.5) 8.9/7.1	8.3 (1.1) 8.4/8.2	<0.001
Peak flow velocity (cm/s) (M/F)	69 (17) 71/68	69 (23) 74/49	62 (12) 64/60	51 (13) 51/52	44 (11) 48/28	0.002
Average flow velocity (cm/s) (M/F)	14 (2) 14/14	13 (4) 14/11	14 (3) 14/14	10 (3) 9/11	9 (4) 9/6	<0.001
Stroke volume (ml) (M/F)	69 (9) 67/71	73 (12) 73/75	91 (30) 93/90	74 (15) 80/69	70 (40) 76/48	NS

Figure 1. Individual AA flow (black) and ensemble-averaged AA flow for males (blue) and females (red)

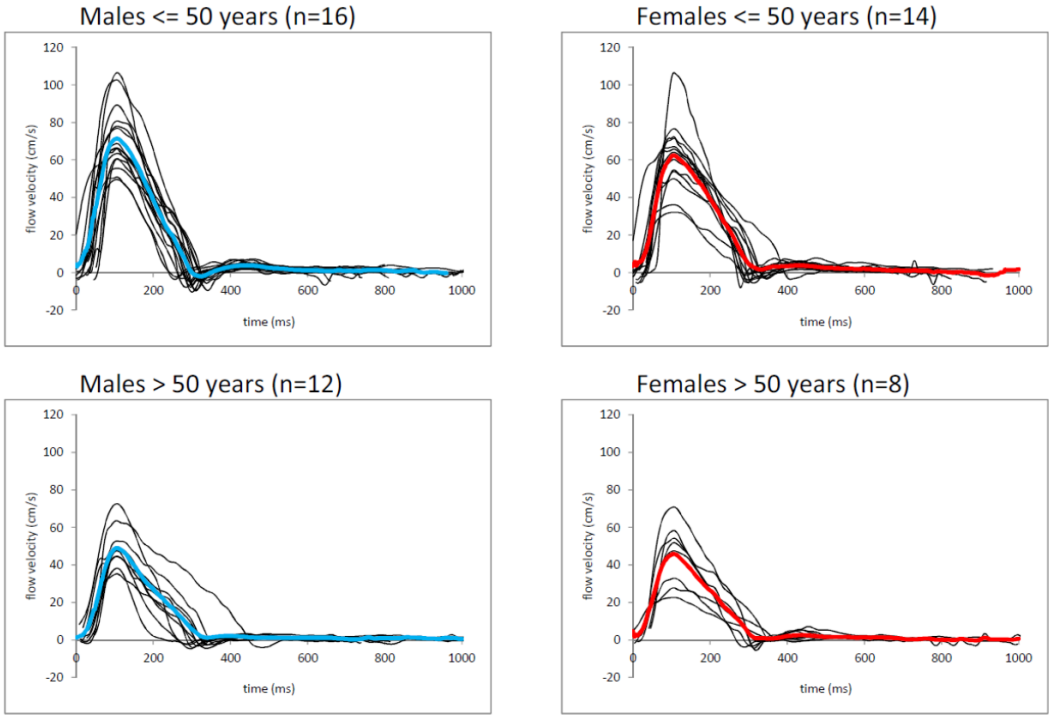


Figure 2. AA flow (left) and carotid pressure (right) for each age decades

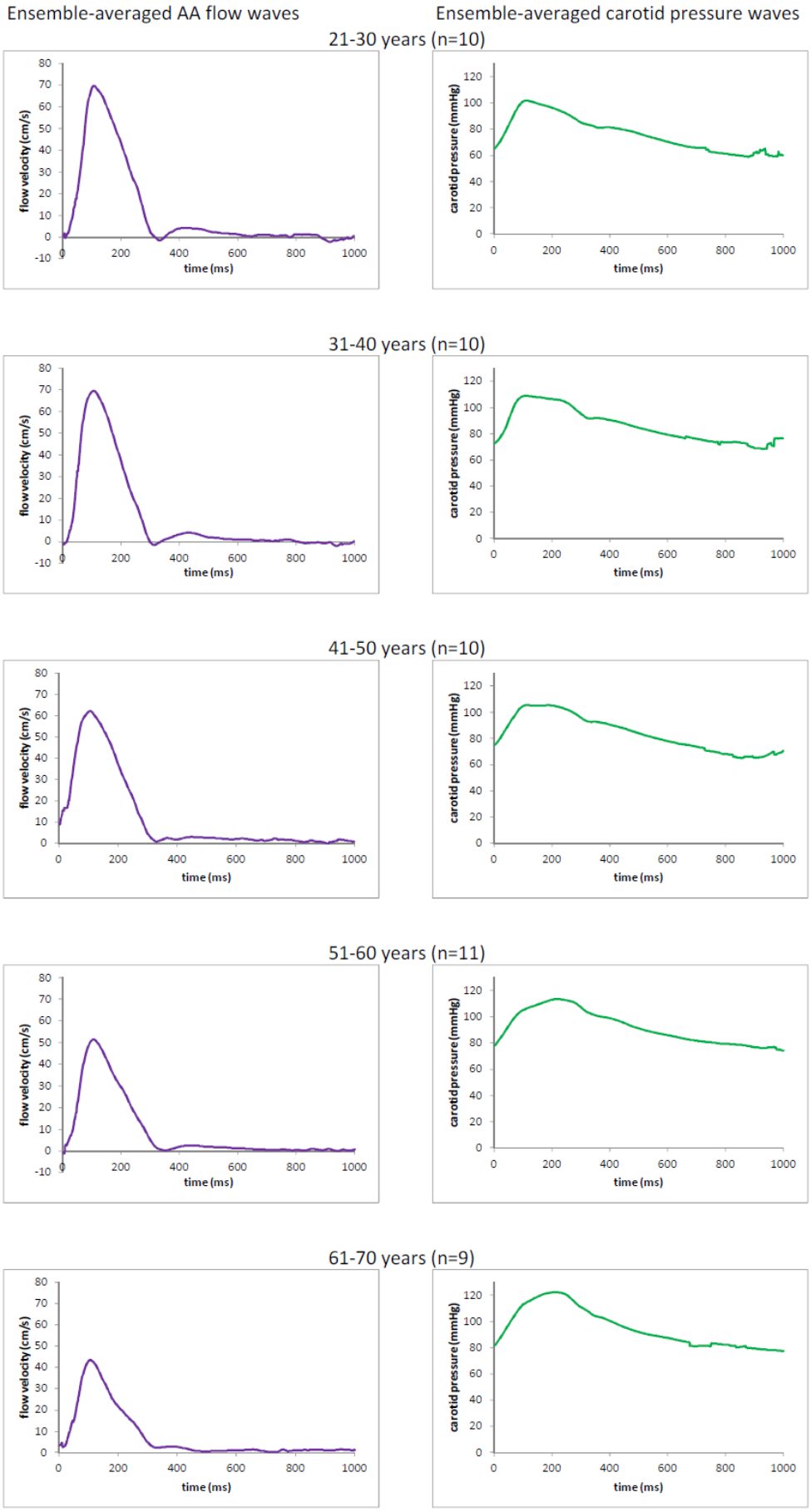
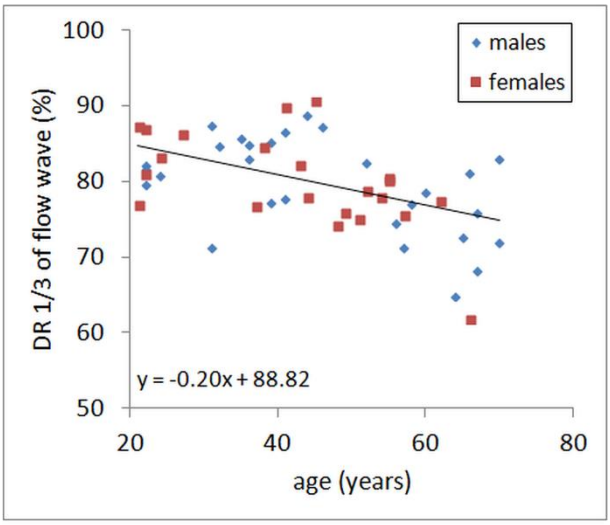
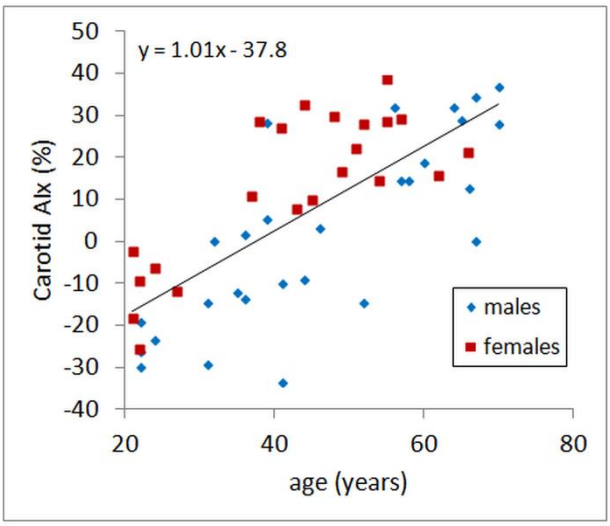


Figure 3. Relationship between DR 1/3 estimated from flow wave velocity and age (top), carotid pressure AIx and age (middle), and effect of wave reflection on flow (= 100 – DR 1/3) was added to pressure AIx and plotted against age (bottom).





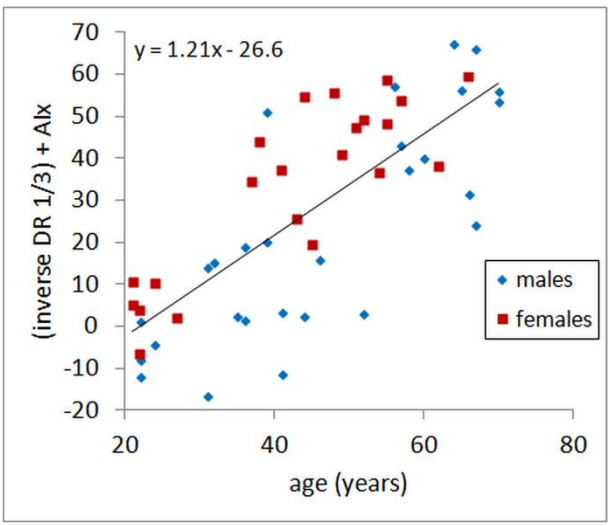
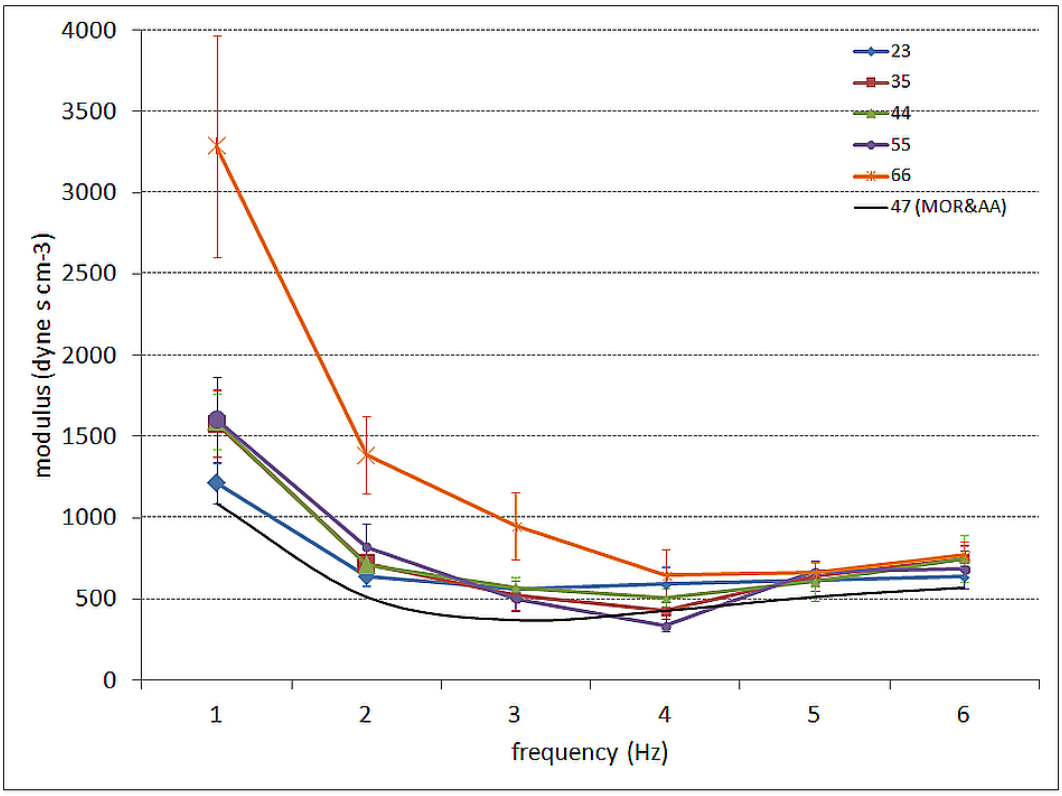
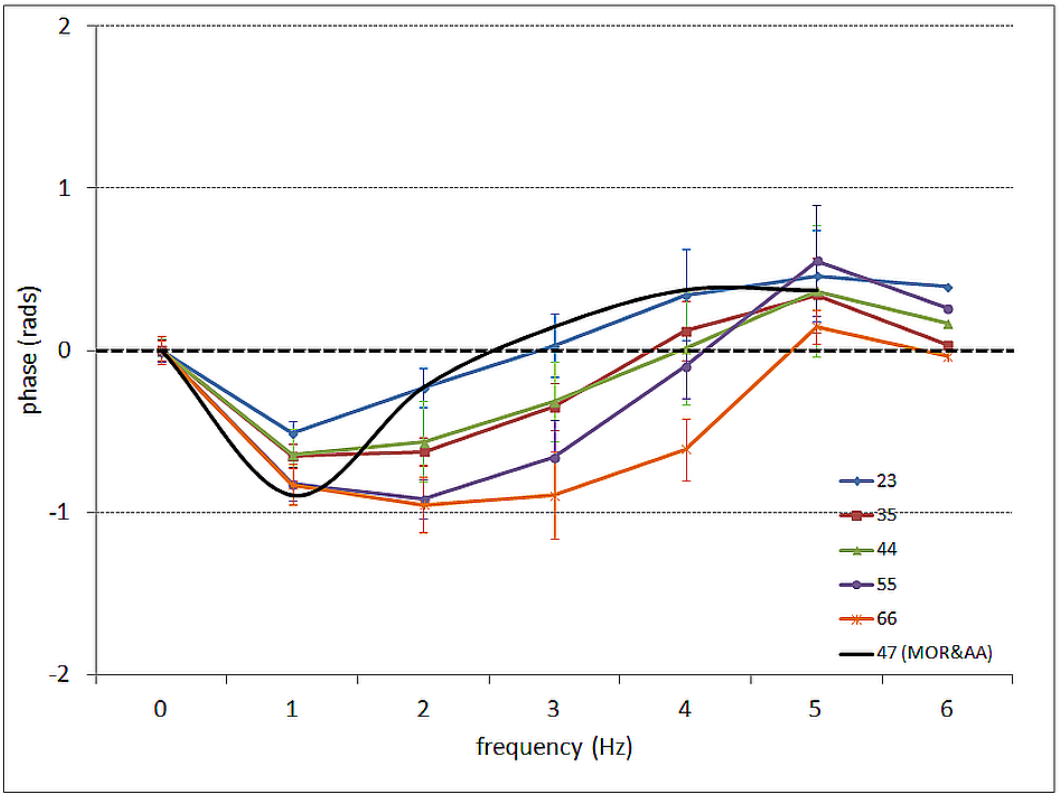


Figure 4. Amplitude (top) and phase (bottom) of the impedance harmonics averaged for each decade.





5.3 Study: Comparison of Aortic Flow Measured using Doppler to that Derived using the Impedance Model and the Waterhammer Formula

A paper under preparation:

Adji A, O'Rourke MF, Avolio AP, Weber T. **Comparison of Aortic Flow Measured using Doppler to that Derived using the Mathematical Models. (2015)**

5.3.1 Introduction

A pilot study was designed to determine changes in aortic flow velocity in subjects in whom central aortic pressure was available, based on known age-related changes in aortic impedance. The aortic flow velocity derived from these models then compared with those measured using Doppler ultrasound. This study was made possible under collaboration with Professor Thomas Weber and his colleagues from Cardiology Department, Klinikum Wels-Grieskirchen, Austria.

Part of the study results has been presented at various domestic and international scientific meetings, and subsequently published in abstract form.

The waterhammer formula can be applied in the situation where the elastic properties of the vessel wall are related to the volume elasticity of the tube (Taylor 1959). The investigation on derivation of the aortic flow velocity from the impedance model leads to application of waterhammer formula as an alternative. This formula illustrates the relationship between pressure, flow and impedance:-

$$Z_c = \frac{P}{Q\rho} \approx PWV \qquad \text{Equation 5-1.}$$

The application of waterhammer formula arises from an attempt to determine cardiac output (calculated from flow velocity) through analysis of the non-invasive pressure waveform measurement. This is based on the description by Taylor (Taylor 1967), which associated elastic properties of a tube (calculated as wave velocity) and input impedance since blood density is close to unity.

Non-invasive determination of cardiac output has been an objective in clinical practice for many years. However, due to the differences in arterial properties with age and alteration of flow ejection pattern from the heart attributed to aging and left ventricular weakening, this has not been successfully achieved. An equation is written to calculate velocity of blood flow ejected from the heart into the ascending aorta for each beat (as mean flow velocity during systole and for one heart cycle). The same formula to calculate flow velocity is applied here. In addition to the attempt to derive the aortic flow velocity wave from the aortic pressure wave using the age-specific impedance model, another attempt is made to apply the waterhammer formula. This, however, only allows determination of velocity, without generation of the flow wave. Hence in this thesis, peak flow velocity derived from the waterhammer formula is compared to peak velocity calculated from Doppler recording as in the previous section, and estimated cardiac output compared to those measured from Doppler recording. Similarly, the derived aortic flow velocity wave from aortic pressure will be compared to those measured from Doppler recording.

5.3.2 Methods

Age-specific Impedance Model

One hundred and sixty males adult patients aged from 33 to 80 years (mean 59 $\pm$ 10) were studied. These patients were part of various ongoing projects performed at the Klinikum

Wels-Grieskirchen, Wels, Austria. Subjects were undergoing cardiac catheterisation for suspected coronary artery disease, including those with left ventricular ejection fraction of >50% and dyspnoea on exertion, as part of an ongoing project at the time on "Hemodynamics in Diastolic Heart Failure". Those with known systolic heart failure/ cardiomyopathy (left ventricular end-diastolic pressure of ≤12 mmHg and NT-proBNP <120 pg/ml) were excluded from this analysis. Details of this study have been published elsewhere (Weber et al. 2013). The study protocol was approved by the Macquarie University Ethics Review Board (approval number 5201100493).

Brachial systolic and diastolic pressures were measured with a validated, automated, oscillometric sphygmomanometer (Omron M5-1, Omron Healthcare, Kyoto, Japan). Radial artery pressure waveforms were recorded using applanation tonometry technique and SphygmoCor® device, and calibrated by brachial systolic and diastolic pressure according to the manufacturer specification and in conformity with US Food and Drug Administration K002742 requirement. Radial pressures were recorded in the supine position for 8 to 10 seconds to include at least one respiratory cycle in a quiet, temperature-controlled room (22 ± 1°C) after a brief period (at least 5 minutes) of rest on the day. Central (aortic) pressure waveforms were derived using a generalised transfer function from radial artery waves.

A two-dimensional Doppler echocardiogram was obtained in all patients immediately before or after radial artery pulse recording according to recommendations of the American Society of Echocardiography, using a Philips iE33 (Philips) or Vivid 7 (GE Healthcare) device. For pulsed wave tissue Doppler imaging, the transducer was located at the medial and at the lateral border of the mitral annulus in the apical 4-chamber view, where peak systolic velocity (S′) was estimated.

Ascending aortic impedance modelling and aortic pressure waveform analysis

The derived aortic pressure waves were ensemble-averaged to a single representative pressure wave for each patient. Pressure waves were then decomposed into their component harmonics using a Fast Fourier Transform (FFT), and any harmonics excluded (considered as noise) if pressure modulus is less than 0.8 mmHg or flow modulus is less than 1 cm/s. This had been applied in the previous practice for impedance measured from electromagnetic flow catheter system (Nichols et al. 1977, Murgo et al. 1980). Pressure harmonics were normalised to take into account the difference in heart rate between pressure and flow velocity measurements, by linear interpolation between two adjacent frequencies to the nearest integer frequencies, i.e. 0.7 and 1.7 to 1 Hz, 1.7 to 2.7 to 2 Hz, and so on. The first five harmonics generally contained about 99% of power (Kelly et al. 1989), therefore for generation of aortic flow, only the first 4 to 6 harmonics were included.

This study was performed to compare the aortic flow velocity waves generated using the age-specific impedance model with those recorded using Doppler ultrasound. Ascending aortic impedance values in humans and their change with age were determined from the O'Rourke and Avolio model (O'Rourke et al. 1980) (**Figures 5-4, 5-9** and **5-13**). The impedance model was applied to generate aortic flow velocity wave from aortic pressure wave using the formula:

$$Q_n = \frac{P_n}{Z_n} e^{i(\theta_n - \varphi_n)} \qquad \text{Equation 5-2.}$$

where Q is flow, P is pressure and Z is impedance.

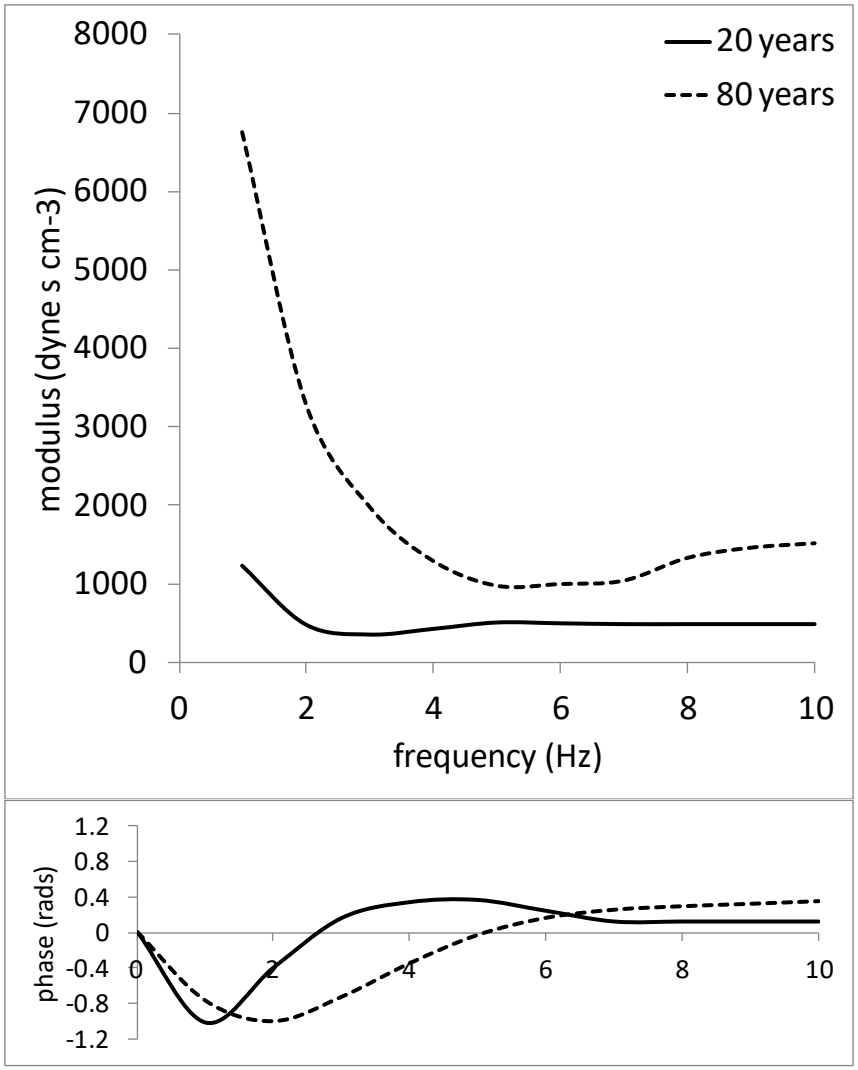


Figure 5-13. Impedance modulus (top) and phase (bottom), similar to **Figure 5-4**, estimated from a person age 20 years (continuous line) and 80 years (dashed line).

From these values, a linear interpolation was applied for each frequency to estimate modulus and phase for a subject age 30, 40, 50, 60 and 70 years, to adapt to the aging change, known from the expected increase in aortic pulse wave velocity (Nichols et al. 1985, O'Rourke et al. 2007) (**Figure 5-14**). Impedance modulus increase and phase shift were estimated by for each integer frequency (i.e. modulus for 2 Hz was estimated by finding the average between 1 and 3 Hz, similarly for phase).

.

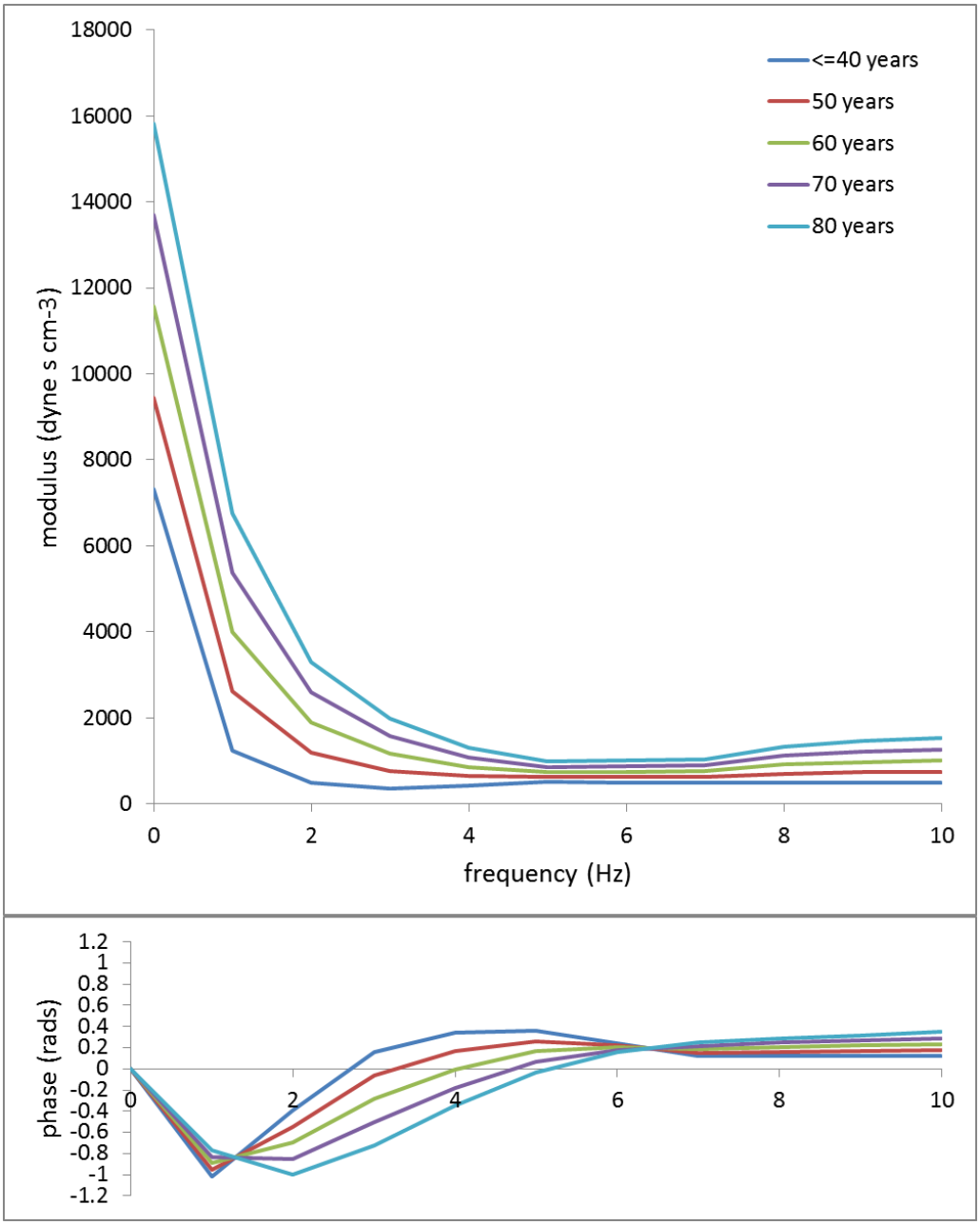


Figure 5-14. Age-specific impedance curve with linear interpolation applied to age between 30 to 80 years.

After a spectrum of impedance modulus and phase was developed, the age-specific impedance model was applied to generate aortic flow velocity wave from aortic pressure wave. **Figure 5-15** shows an example of a patient's worksheet. The steps taken as follows:

1. Determine the mean aortic pressure and the fundamental frequency from the heart rate when aortic pressure was recorded. This was taken as the first harmonic frequency, then the second to tenth harmonic frequencies were calculated. The modulus and phase for each harmonic were calculated by decomposing the aortic pressure waveforms using Fourier equation as described in **Equation 2-4**. All 10 harmonics were included providing the modulus of pressure is ≥ 0.5 mmHg.
2. For this particular subjects' age, determine the resistance (static) term, as well as modulus and phase for each integer frequency (that is 1Hz, 2Hz, 3Hz, … 10Hz). Next a linear interpolation (using the *"slope"* and *"integer"* function of a spreadsheet) was applied to obtain the same frequencies as those from the aortic pressure waveform harmonics.
3. The aortic flow velocity harmonics were calculated for each of those frequencies by dividing the pressure modulus with impedance modulus, and subtracting the impedance phase angle from the pressure phase angle, as in the **Equation 5-2**.
4. Finally, the aortic flow velocity waveform was composed by summation of all 10 harmonics and plotted against time scale. All 10 harmonics were included providing the modulus of flow velocity is ≥ 1 cm/s.
5. The generated aortic flow velocity waveform was then compared to the flow velocity measured using Doppler ultrasound, currently the "gold standard" of stroke volume/ cardiac output.

		pressure			impedance for 62 years old							flow velocity		
	frequency	modulus	phase		frequency	modulus	phase	frequency	modulus	phase		frequency	modulus	phase
H0	0.00	114890.59			0.00	15814.61	0.00	0.00	15814.61			0.00	7.26	0.00
H1	0.93	25343.85	-0.16		1.00	1711.26	-0.88	0.93	1823.68	-0.94		0.93	13.90	0.78
H2	1.87	11399.09	-1.12		2.00	1044.31	-0.73	1.87	1131.94	-0.75		1.87	10.07	-0.37
H3	2.80	4584.46	-2.00		3.00	632.85	-0.33	2.80	713.94	-0.41		2.80	6.42	-1.59
H4	3.74	1100.62	-2.61		4.00	433.48	-0.04	3.74	485.87	-0.12		3.74	2.27	-2.50
H5	4.67	583.84	-0.39		5.00	531.95	0.15	4.67	499.61	0.08		4.67	1.17	-0.47
H6	5.61	1459.86	-1.14		6.00	655.94	0.20	5.61	607.07	0.18		5.61	2.40	-1.31
H7	6.54	1198.50	-1.97		7.00	614.53	0.19	6.54	633.57	0.19		6.54	1.89	-2.17
H8	7.47	364.04	-2.38		8.00	850.53	0.21	7.47	726.50	0.20		7.47	0.50	-2.58

Figure 5-15. An example of worksheet of a 62 years old male subject as described in the calculation steps above. H = harmonics #, frequency in Hz, all phase in radians, pressure modulus in dyne.cm^{-2},impedance modulus in dyne.s.cm^{-3}, flow modulus in cm/s.

The images of left ventricular outflow tract flow velocity recorded were digitised using a purposely-written Matlab program to detect the traced-outside envelope of the flow velocity waves (**Figure 5-16**).

Statistical Analysis

Continuous variables were expressed as mean (standard deviation). Linear regression and the Pearson correlation coefficient were used to assess associations between variables. Differences between groups were assessed using t-tests and $p<0.05$ indicated a significant difference.

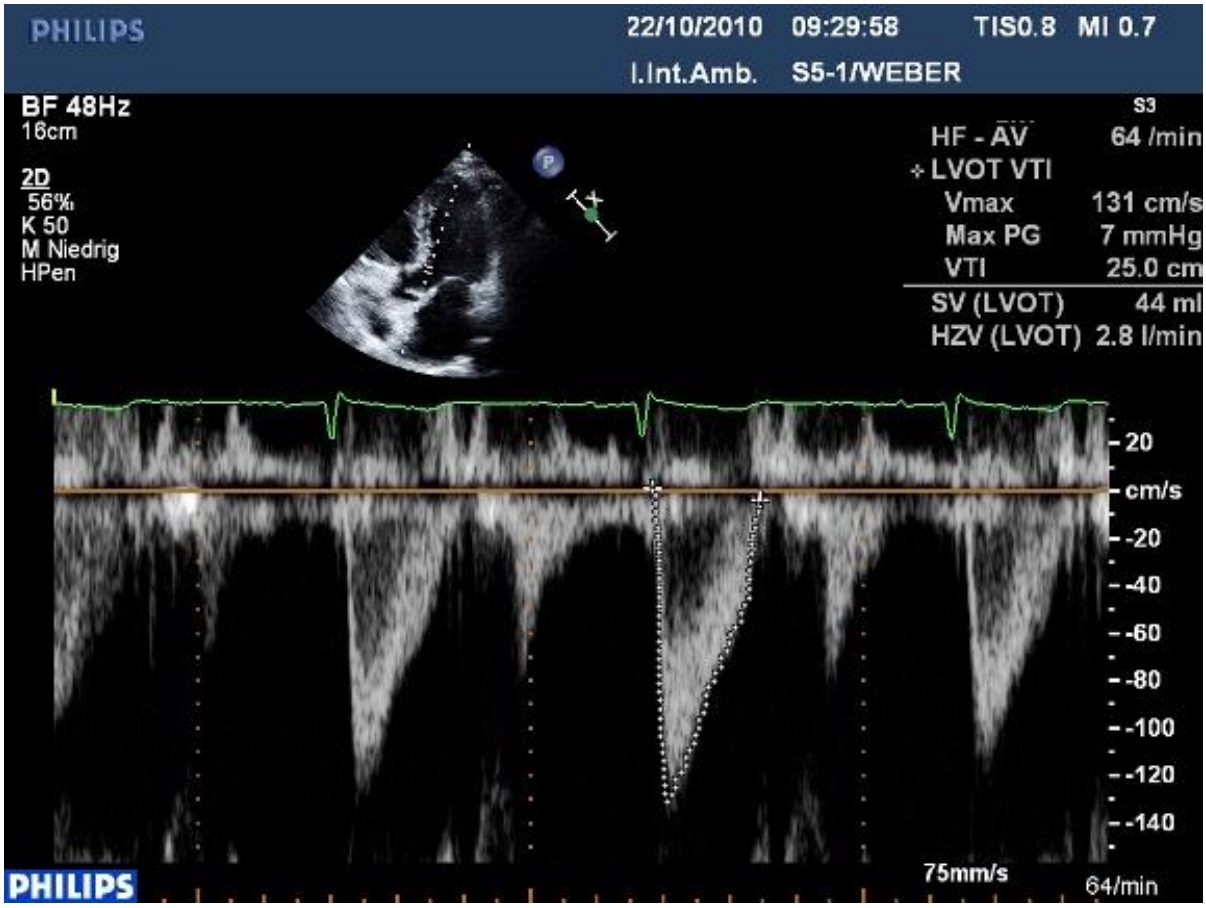


Figure 5-16. Routine clinical recording with Doppler echocardiography; the outer envelope is traced to calculate Velocity Time Index (VTI), peak velocity (Vmax), maximum Pressure Gradient (Max PG), Stroke Volume (SV) and Cardiac Output (HZV in German); the ECG signal was used to calculate heart rate (HF – AV in German) and to determine the beginning of the cardiac contraction.

Waterhammer Formula

SphygmoCor-calculated indices will be utilised in this study. Initially, the pressure pulsation generated by the flow pulsation needs be determined. This corresponds to the rise from zero to peak flow in the aorta, where the boost to pressure during mid to late systole caused by augmentation (or reflection) has not taken effect. In SphygmoCor, this corresponds to P1 in mmHg, the pressure amplitude at the peak of the first shoulder in aortic pressure waveform. In this cohort, average P1 is 29.9 (SD 8.1) mmHg. As the unit for flow velocity is cm/s, and pressure is in mmHg, the P1 is converted to dyne.cm^{-2}. Peak (systolic) flow velocity (PFV) is calculated as:-

$$PFV = \frac{P_1}{\rho \times C} \qquad \text{Equation 5-3}$$

where ρ is the blood density (=1.05 g/ml) and C is the aortic pulse wave velocity (cm/s). Peak flow velocity was calculated = (P1 height * 980 * 1.36) ÷ (1.05 * PWV); P1 height is in mmHg, thus needs be converted to standard pressure unit (N/m^2) by multiplying with gravity of 980 m/s^2 and 1.36 Pascal. Values of pulse wave velocity for specific age were calculated from previously published papers, described below. Non-invasive aortic (carotid-femoral) pulse wave velocity as the surrogate of characteristic impedance was determined using two previously published formulae:-

1. Values of pulse wave velocity for specific age were calculated from previously published papers, described below. Non-invasive aortic (carotid-femoral) pulse wave velocity as the surrogate of characteristic impedance was determined using two previously published formulae: First calculation of aortic pulse wave velocity was by using the formula published by the Baltimore Longitudinal Study of Aging (BSLA) (Vaitkevicius et al. 1993):-

$$PWV = 3.14 + (8.2 \times age)$$ Equation 5-4 (method 1)

2. Second calculation of aortic pulse wave velocity was by using the formula published by the Anglo-Cardiff Collaboration Trial (ACCT) (McEniery et al. 2005):-

$$PWV = 549 - (1.7 \times age) + (0.1 \times age^2)$$ Equation 5-5 (method 2)

Since aortic pulse wave velocity is related to the mean pressure, further adjustment was necessary to correct wave velocity due to level of mean pressure above or below 100 mmHg (Asmar et al. 2001). Aortic pulse wave velocity values determined from both methods were virtually similar. An example of the worksheet is given below (**Figure 5-17**):

Surname	Age	HR (bpm)	P1 height (mmHg)	ED (%)	MP (mmHg)	PWV BLSA (cm/s)	PWV ACCT (cm/s)	Peak flow (1)	Peak flow (2)
H	33	62	30	31	89	506.5	523.7	75.18	63.28
N	40	83	22	38	99	634.9	633.9	43.98	43.57
G	50	69	26	35	107	773.7	763.7	42.66	46.22
M	60	55	26	30	86	706.6	707.6	46.71	40.90
Z	80	53	25	28	98	955.8	1038.8	33.20	30.14

Figure 5-17. Example of the worksheet of peak flow velocity calculation from 5 patients of different ages. Age in years, HR is heart rate, ED is ejection duration, MP is mean pressure, PWV is pulse wave analysis, BLSA is method 1, ACCT is method 2, Peak flow velocities are in cm/s.

The duration of cardiac ejection from the foot of the pressure wave to cardiac incisura is determined by SphygmoCor, typically around 30 – 40% of the cardiac cycle.

5.3.3 Results

Age-specific Impedance Model

The subjects were distributed across age groups (**Figure 5-18**).

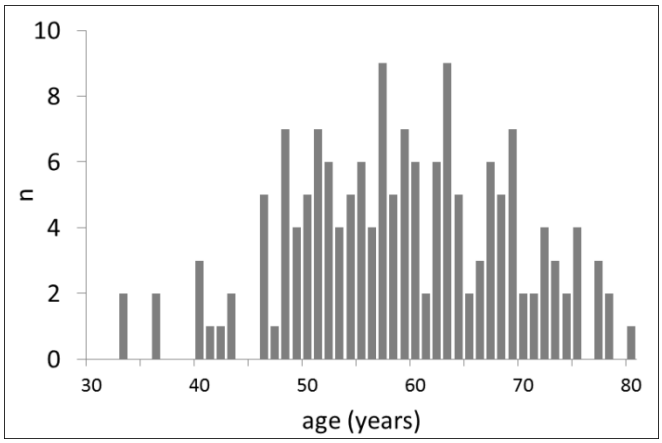


Figure 5-18. Number of subjects for each age group in this cohort.

The contour of generated flow velocity waves were compared with those recorded using Doppler ultrasound. Doppler ultrasound is currently performed routinely at cardiac imaging clinic to measure a subject/ patient's stroke volume and/ or cardiac output. Peak flow velocity estimated using the impedance model was much lower than recorded by Doppler (53.0 c.f. 105.3 cm/s) (**Table 5-1**). Subjects' characteristics are detailed in **Table 5-1**.

	Mean (SD)
SphygmoCor-calculated	
Aortic Systolic Pressure (mmHg)	124.5 (18.4)
Aortic Diastolic Pressure (mmHg)	83.9 (11.0)
Aortic Pulse Pressure (mmHg)	40.6 (13.1)
Mean Pressure (mmHg)	100.5 (13.1)
Heart Rate (bpm)	63.7 (10.9)
Peak/ maximum flow velocity (cm/s)	53.0 (18.6)
Doppler-measured	
Peak/ maximum flow velocity (cm/s)	105.3 (17.6)
LVOT cross-sectional area (cm^2)	3.4 (0.8)
Heart Rate (bpm)	66.7 (12.1)
Cardiac Output (L/m)	4.9 (1.3)

Table 5-1. Baseline characteristics of 160 males subjects included in this study. Top panel shows indices calculated using SphygmoCor, bottom panel shows indices measured by Doppler ultrasound.

Peak flow velocity for each decade was examined (**Table 5-2**). With increasing age, the estimated peak flow velocity became lower, while, those recorded with Doppler remained consistent around 70 to 150 cm/s, and cross-sectional area of the left ventricular outflow tract also remained unchanged (**Table 5-3**).

Peak flow velocity (cm/s) for each decade (mean±SD)	**Impedance-model estimation**	**Doppler-measured**
< 40 years	79.4 (12.8)	113.4 (9.6)
41 - 50 years	60.0 (11.6)	99.4 (20.2)
51 - 60 years	62.3 (15.5)	106.5 (17.5)
60 - 70 years	44.5 (12.6)	106.6 (17.3)
71 – 80 years	27.2 (6.2)	103.9 (16.8)

Table 5-2. Peak flow velocity for each decade of age; estimated by the impedance model (middle column) and by Doppler ultrasound (right column).

Cross-sectional area (cm^2) for each decade(n=108) (mean±SD)	**Doppler-measured**
< 40 years	3.1 (0.8)
41 - 50 years	3.5 (0.7)
51 - 60 years	3.5 (0.8)
60 - 70 years	3.4 (1.0)
71 – 80 years	3.4 (0.8)

Table 5-3. Left ventricular outflow tract cross-sectional area as measured by Doppler. Data were only available from 108 patients.

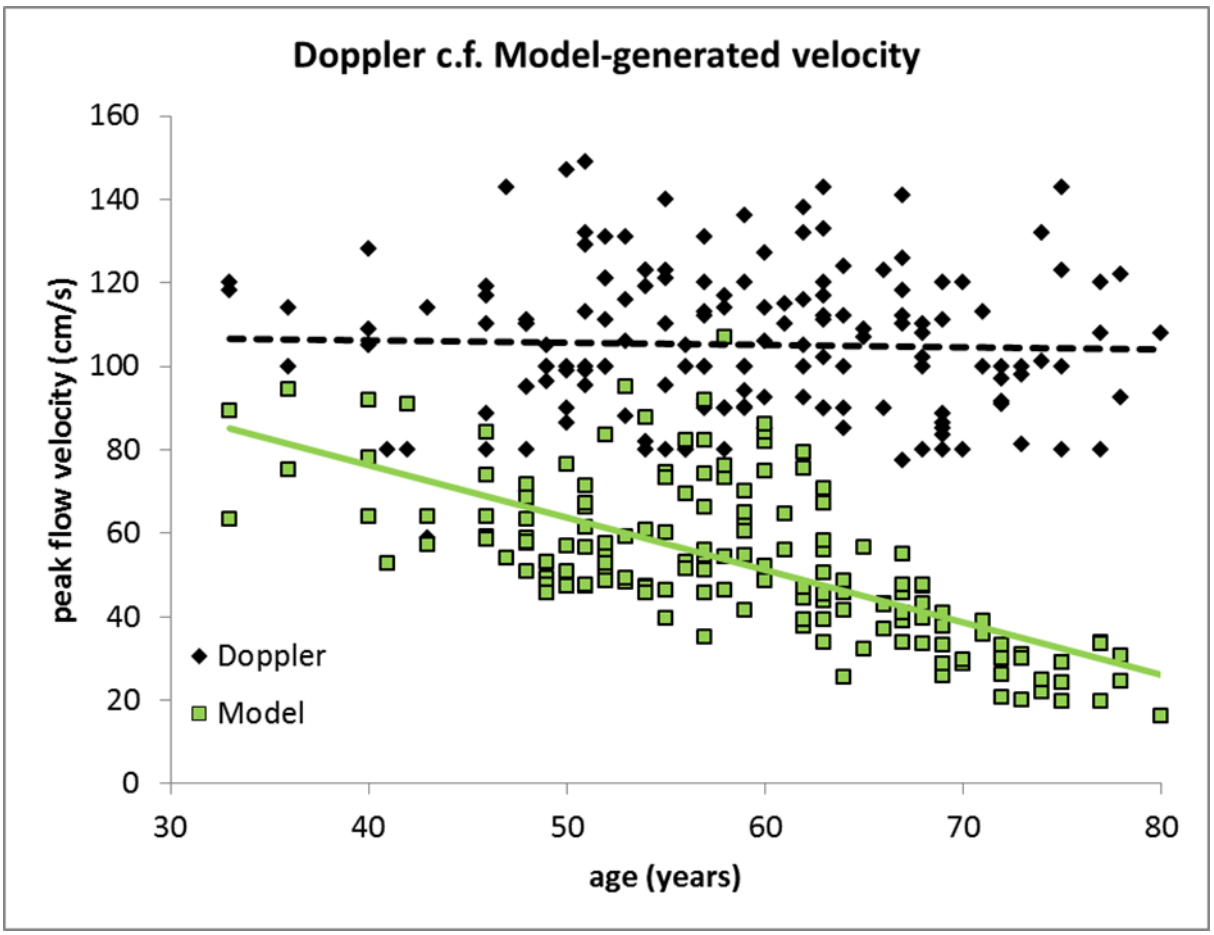


Figure 5-19. Peak flow velocity measured by Doppler (black diamonds) compared to those estimated from the impedance model (green squares). When measured by Doppler, the peak flow velocity does not change with age ($y = -0.05 x + 109$, $r^2 = 0.001$). However, when estimated from the impedance model, the peak flow velocity decreases with age, as expected with the known dilation of aorta as age increases ($y = -1.3 x + 127$, $r^2 = 0.45$). Difference between the peak velocity measured by Doppler and estimated by the impedance model is significant ($p<0.001$).

Changes were evident in aortic flow velocity wave patterns with increasing age, while these were not apparent with Doppler flow velocity waves (**Figure 5-19**). It was evident that the aortic flow velocity measured by ultrasound did not show expected reduction in flow velocity with age (from progressive aortic dilation and increase in aortic cross-sectional area), nor the previously-described changes in flow wave contour (**Figures 5-19** and **5-20**). Doppler peak flow velocities appeared to be consistent regardless of age, when values estimated from the model showed decreasing peak flow velocity expected with aging.

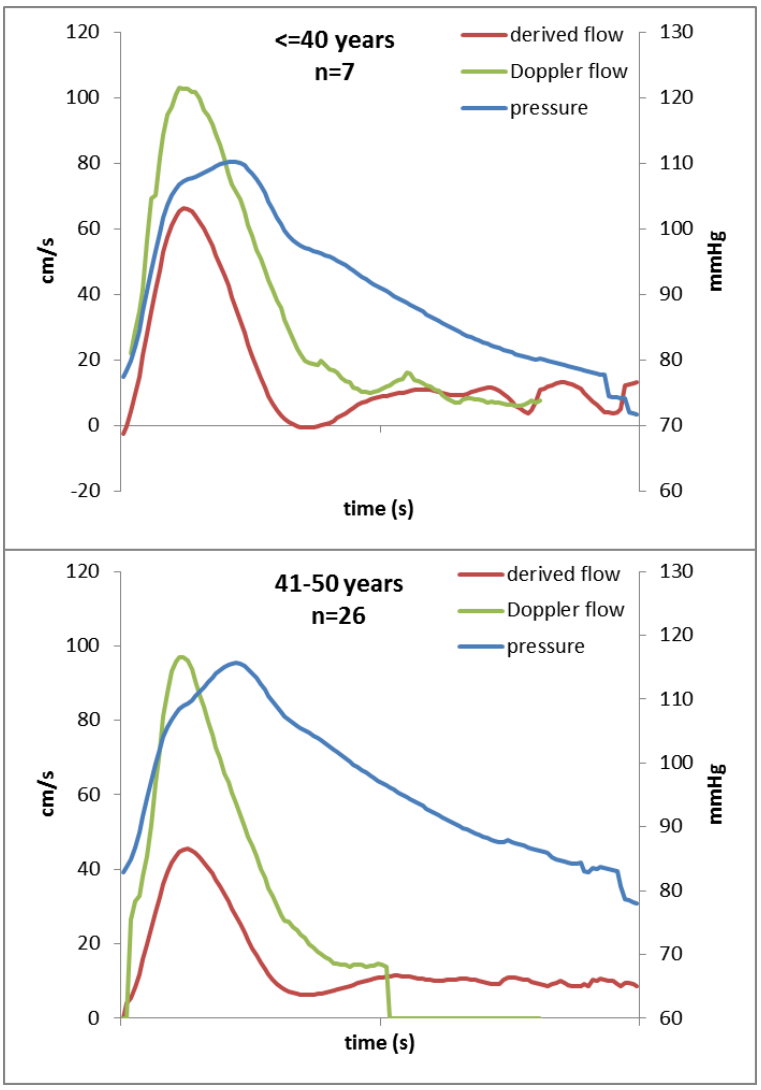


Figure 5-20. Ensemble-averaged aortic pressure (blue), model-derived (red) and Doppler-measured (green) aortic flow velocity waves for each decade. Time period is 1 second for all. (continued next page)

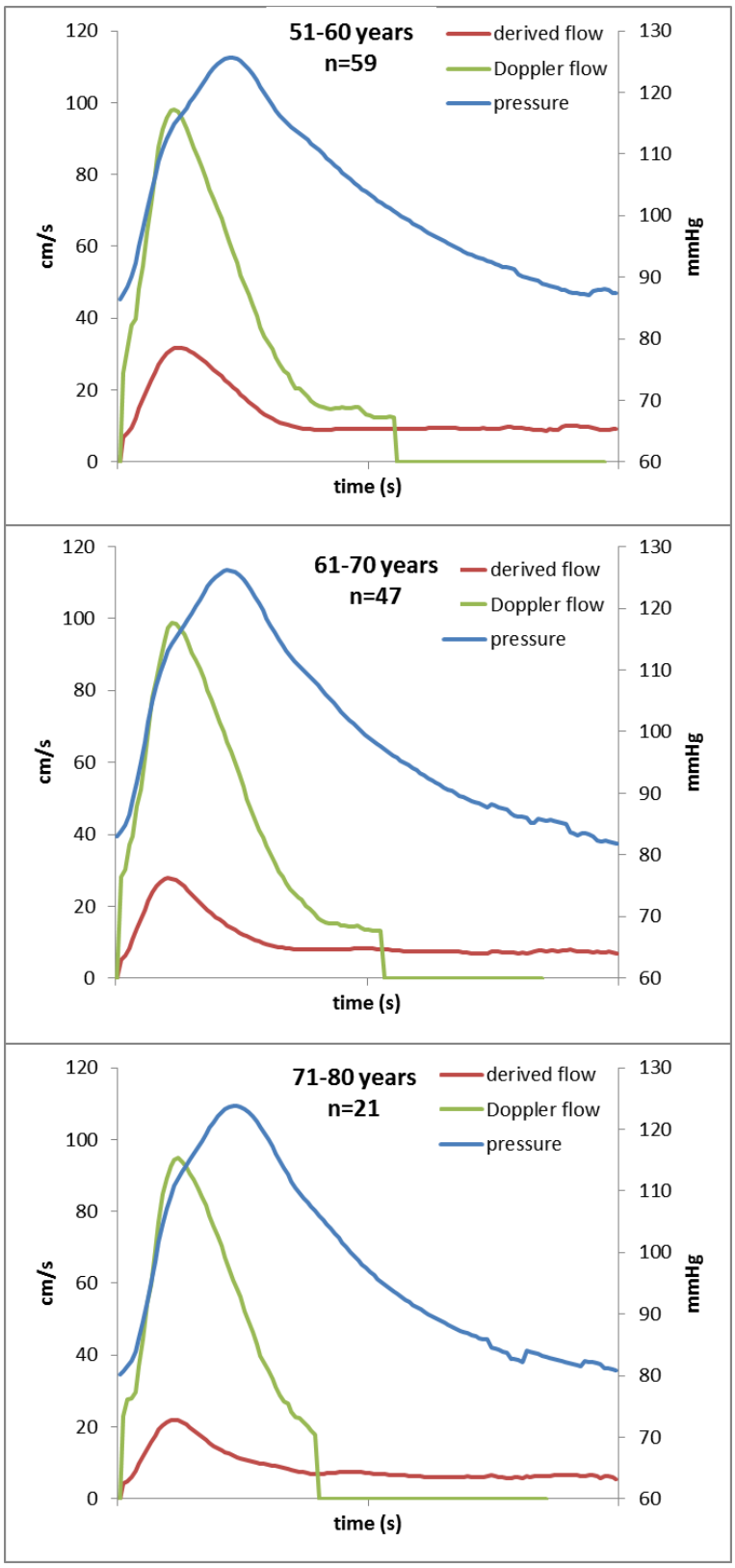


Figure 5-20. Ensemble-averaged aortic pressure (blue), model-derived (red) and Doppler-measured (green) aortic flow velocity waves for each decade. Time period is 1 second for all. (continued from previous page)

Changes were evident in aortic flow velocity wave patterns with increasing age, while these were not apparent with Doppler flow velocity waves (**Figure 5-19**). It was evident that the aortic flow velocity measured by ultrasound did not show expected reduction in flow velocity with age (from progressive aortic dilation and increase in aortic cross-sectional area), nor the previously-described changes in flow wave contour (**Figures 5-19** and **5-20**). Doppler peak flow velocities appeared to be consistent regardless of age, when values estimated from the model showed decreasing peak flow velocity expected with aging.

This alteration corresponds to the increasing late systole augmentation of the aortic pressure wave, due to earlier return of the reflected pulse wave and faster pulse wave velocity. Westerhof and O'Rourke (Westerhof et al. 1995), supported by Denardo et al (Denardo et al. 2010), further indicated that this phenomenon is exaggerated when contractility of the heart is impaired, and where the ventricular ejection is very sensitive to afterload, with shorter ventricular ejection time and decreased stroke volume.

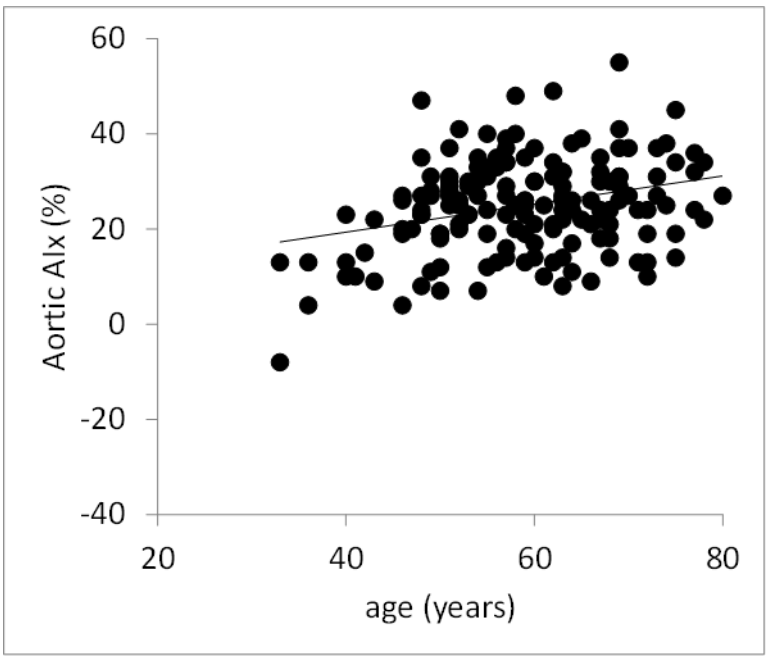


Figure 5-21. Aortic pressure Augmentation Index (AIx) plotted against age, with $y = 0.3x + 7.5$ ($r^2 = 0.09$). The increase in AIx increase with age was significant ($p<0.001$).

The analysis was extended to calculation of wave reflection indices for both aortic pressure and flow velocity waves. Aortic augmentation index (for calculation of aortic pressure augmentation index (AIx), see **Figure 4-4**) was related to age (**Figure 5-21**), which showed the expected increase with age.

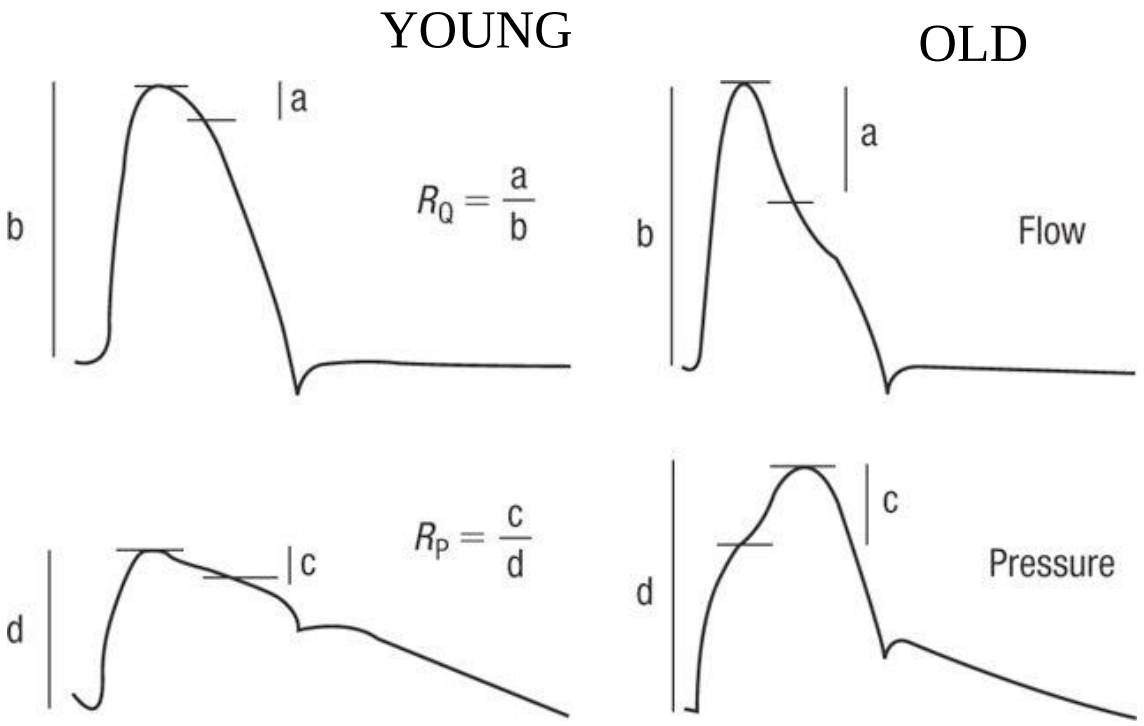


Figure 5-22. Schematic representation of ascending aortic flow (above) and pressure (below) in a young human adult (left) and an older human subject (right). The effects of wave reflection on flow are indicated by the decrease in flow at a point one-third in time from peak flow (a) to the incisura and expressed in relation to peak flow (b) as RQ = a/b. The effects of wave reflection on pressure are indicated by the boost to late systolic pressure peak after the initial shoulder (c) relative to pulse pressure (d) as RP = c/d. This is defined as pressure augmentation. RQ and RP are indices of the effects of wave reflections on flow and pressure waves, respectively. After (Miyashita et al. 1994), from (Nichols et al. 2011).

Figures 5-22 and **5-23** showed the effect of wave reflection on central pressure and flow. Wave reflection is exaggerated when contractility of the heart is impaired, and where the ventricular ejection is very sensitive to afterload, with shorter ventricular ejection time and decreased stroke volume. The opposing effect of wave reflection on pressure and flow waves

has been discussed in Chapters 2, 3 and 4; reflected **pressure** waves ***add*** to the incident or forward travelling wave, while reflected **flow** waves ***subtract*** from the incident wave (**Figures 5-22** and **5-23**).

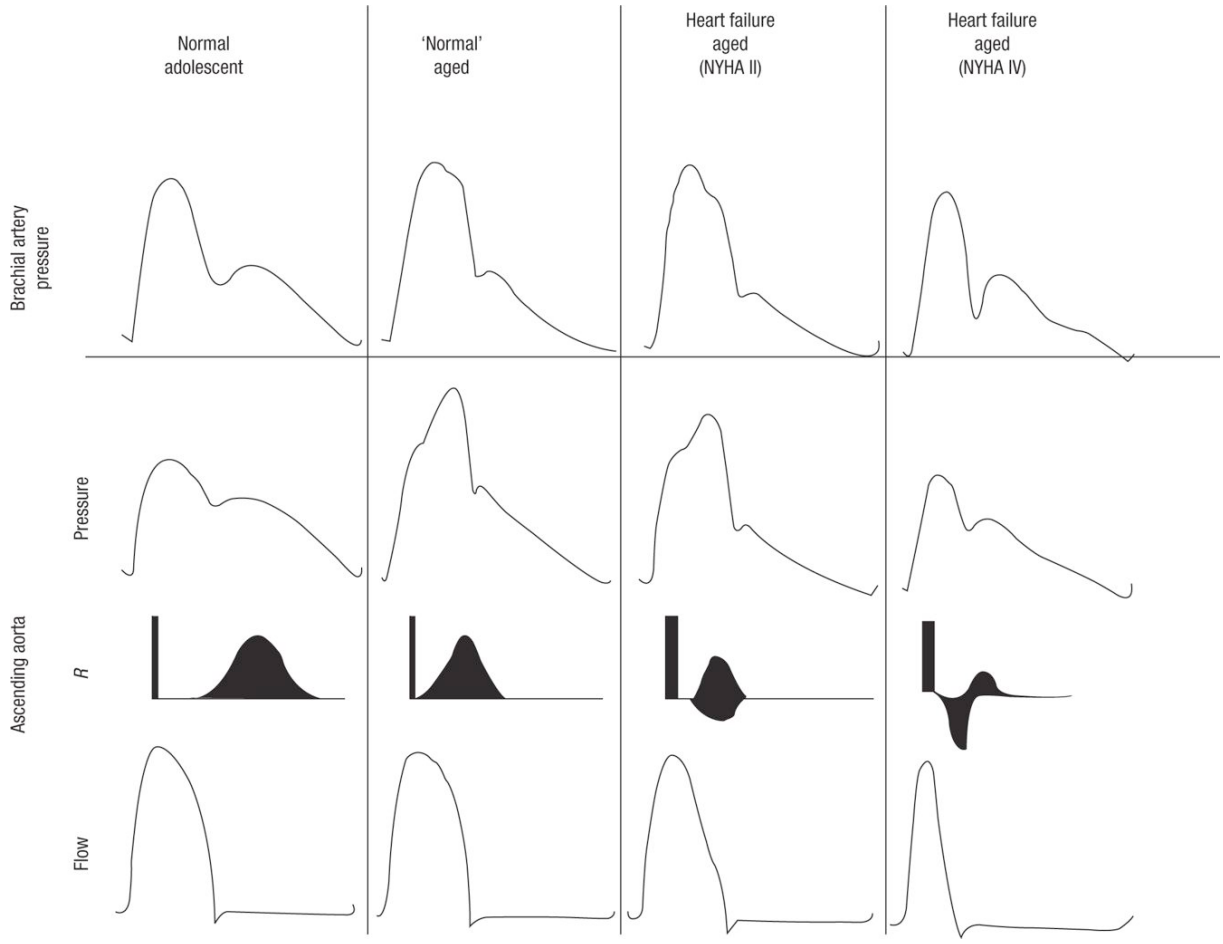


Figure 5-23. Effects of wave reflection on aortic pressure and left ventricular output with the development of heart failure in a patient with isolated systolic hypertension, all shown schematically. From above: brachial artery pressure, aortic pressure, wave reflection (R) (with effect on pressure shown as upward deflection, and effect on flow as downward deflection) and ascending aortic flow (bottom tracing). From (Westerhof et al. 1995).

Wave reflection index of aortic flow velocity contour recorded by Doppler was determined as DR 1/3 (**Figure 5-24**). Miyashita et al (Miyashita et al. 1994), supported by earlier publication by Sakai et al (Sakai et al. 1992, Sakai et al. 1993), reported that DR 1/3

decreased with the rise in aortic augmentation index (**Figure 5-25**); thus similar fall in DR 1/3 of flow velocity is inevitable with increase in age.

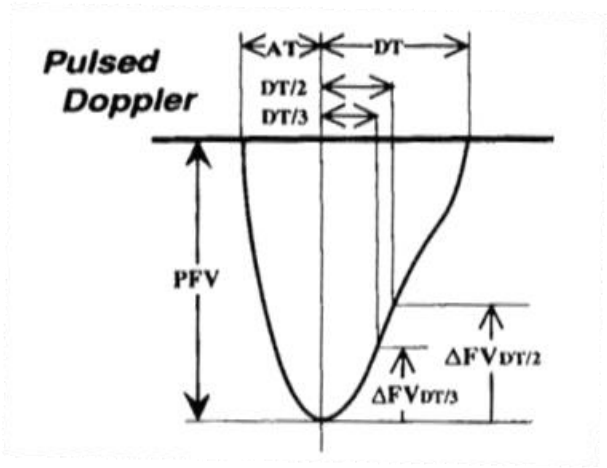


Figure 5-24. Doppler-measured aortic flow velocity reflection index calculated as DR 1/3 = (ΔFV DT/3x100) ÷ PFV, where ΔFV DT/3 is PFV – FV at 1/3 of DT; PFV = peak flow velocity, FV = flow velocity, DT = deceleration time (Sakai et al. 1992, Sakai et al. 1993, Miyashita et al. 1994).

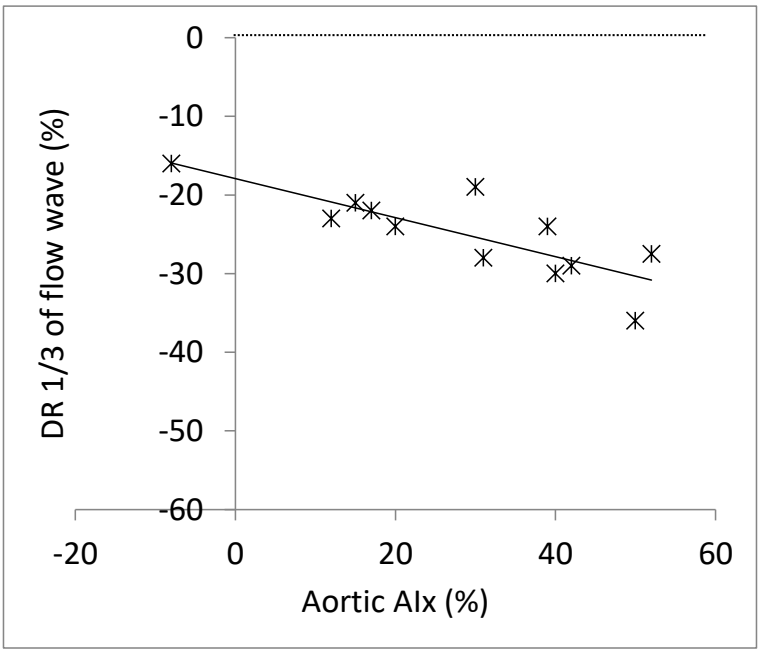


Figure 5-25. DR 1/3 of the flow wave plotted against aortic augmentation index, with y = - 0.2x - 18 (adapted from (Miyashita et al. 1994)).

Figures 5-22 and **5-23** illustrate the expected physiological alteration in aortic flow velocity contour with age. Hence, both flow velocity waves derived from impedance model and measured by Doppler ultrasound were explored, and I expected to see these changes in the waves from both methods. The results, however, were not as expected.

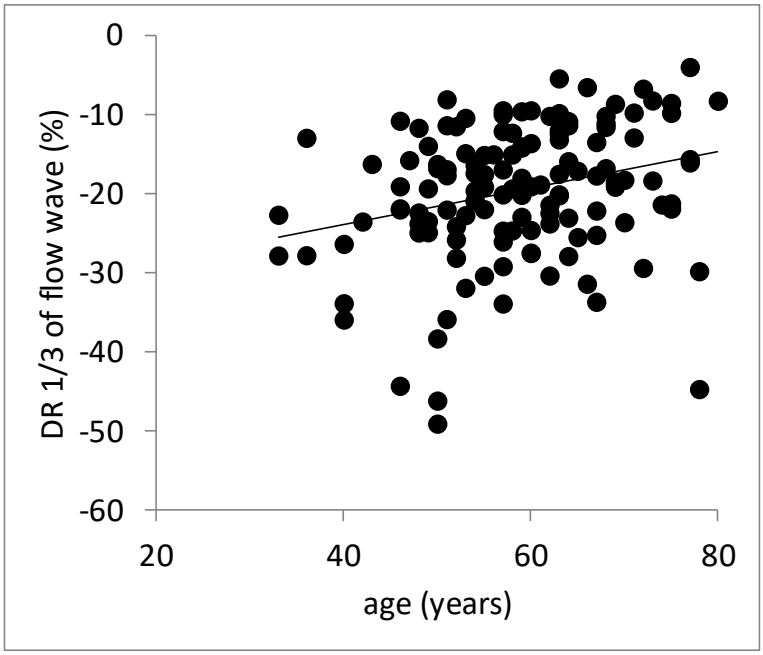


Figure 5-26. Doppler-measured aortic flow velocity reflection index calculated as DR 1/3 plotted against age, with $y = 0.2x - 33.1$ ($r^2 = 0.07$, $p<0.001$).

From **Figure 5-26**, however, it was apparent that the aortic flow velocity recorded by Doppler hardly shows opposite changes with advancing age, in contrast with the physiological changes expected with age, i.e. reduction in flow velocity in late systole.

The regression line of DR 1/3 estimated from the impedance model when plotted against age suggests that the changes in DR 1/3 values (as a decrease in DR 1/3 when the difference in flow velocity is taken as the negative number) characterise the flow velocity curve changes (with reduction in flow velocity during mid to late systole period) as the age increased

(**Figure 5-27**). Generated flow velocity waves show aging changes which were not apparent from Doppler flow velocity patterns (compare **Figures 5-25, 5-26** and **5-27**).

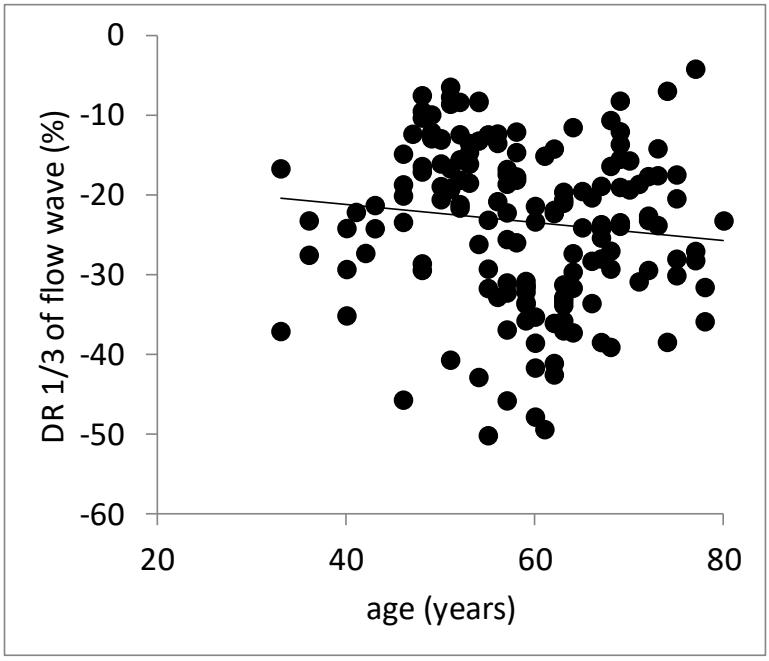


Figure 5-27. Model-generated aortic flow velocity reflection index calculated as DR 1/3 plotted against age, with $y = -0.1x - 16.8$ ($r^2 = 0.01$, $p<0.001$). The regression line is in agreement with those found by Japanese investigators (Miyashita et al. 1994).

The flow velocity waves derived from the impedance model are realistic in their contour, and changes from increasing age are explicable on the basis of left ventricular weakening and earlier return of the reflected pulse wave, affecting flow velocity wave in late systole.

Changes not seen in the flow velocity from left ventricular outflow tract recorded by Doppler can be attributed to the insensitivity of Doppler to show subtle alteration caused by age in the heart ejection pattern. The higher peak flow velocity calculated from Doppler may be due to narrow left ventricular outflow tract, which may cause Venturi effect and subsequent turbulent flow around the ascending aorta. Any underestimation of peak flow velocity from

model may be attributable to inaccurate estimation of impedance spectrum change with age. This will be further explored in the next attempt to improve the model.

Another approach to explore how central pressure and flow are affected by the aging process is by identifying the opposing effect of wave reflection on pressure and flow wave (**Figures 5-3, 5-22** and **5-23**).

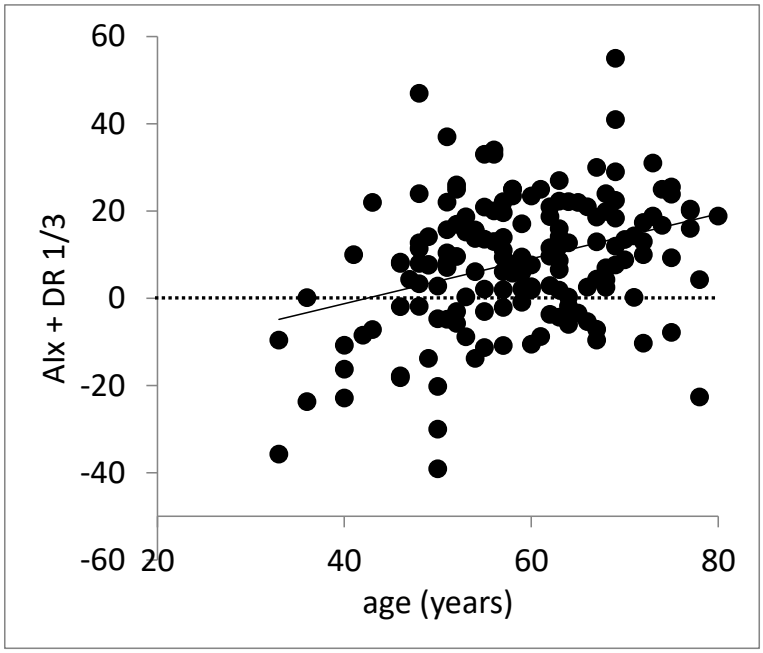


Figure 5-28. Combined effect of wave reflection in aortic flow (DR 1/3 measured in aortic flow recorded by Doppler) and in aortic pressure (AIx) plotted against age ($y = 0.5 x + 22$ ($r^2 = 0.12$), $p<0.001$).

This was done by adding wave reflection index for aortic flow velocity (as negative DR 1/3) and wave reflection index for aortic augmentation (as positive AIx). If the relationship between them were true, the summation will be (close to) a straight line close to zero (**Figures 5-28 and 5-29**). Comparing **Figures 5-28** and **5-29**, the relationship is more realistic with aortic flow velocity derived from impedance model, than those recorded by

Doppler ultrasound. The finding of relationship between DR 1/3 of flow velocity and aortic AIx will be investigated further upon improvement of the impedance model.

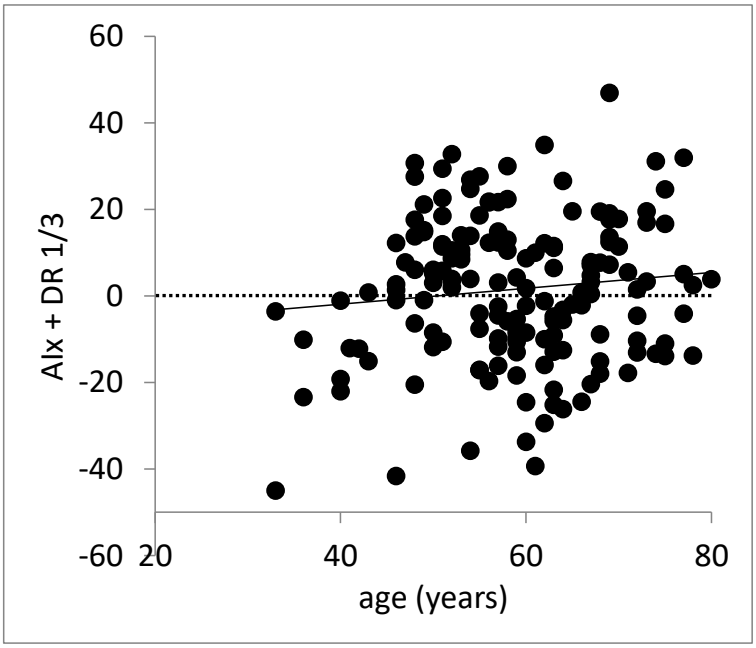


Figure 5-29. Combined effect of wave reflection in aortic flow (DR 1/3 measured in derived aortic flow waves from model) and in aortic pressure (AIx) plotted against age ($y = 0.2 x + 9$ ($r^2 = 0.01$)).

To confirm if these peak flow velocity and DR 1/3 values from Doppler ultrasound and impedance model were realistic, these plots are compared with the same indices obtained from ascending aortic flow velocity recorded by cardiac magnetic resonance imaging (MRI) (**Figures 5-30** and **5-31**). The details of this study has been described in section 5.2, however, some graphs are presented here for comparison with values derived from the impedance model.

As shown below, how central pressure and flow are affected by the aging process is explored by identifying the opposing effect of wave reflection on pressure and flow wave, by adding

wave reflection index for aortic flow velocity (as negative DR 1/3) and wave reflection index for aortic augmentation (as positive AIx) (**Figures 5-32** and **5-33**).

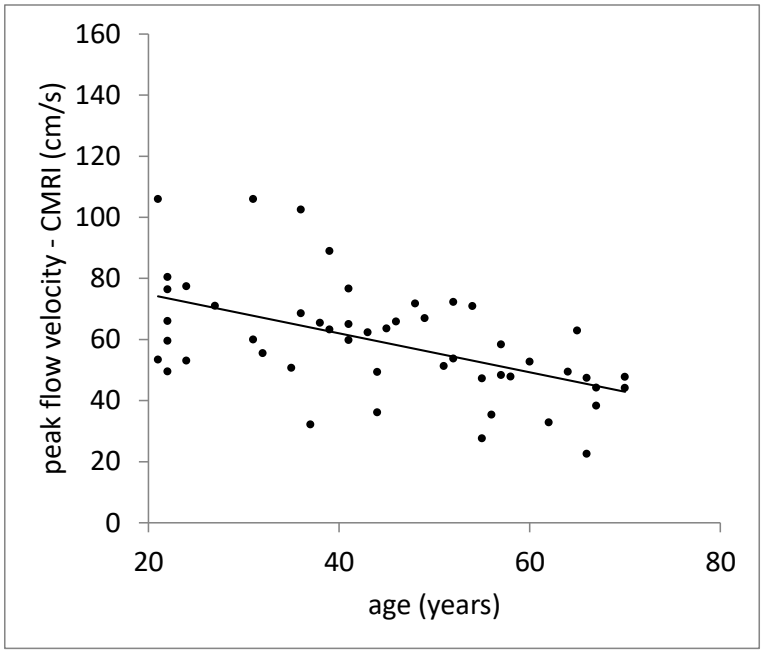


Figure 5-30. Peak flow velocity measured by cardiac MRI plotted against age (y = - 0.6 x + 88, r2 = 0.28, p<0.001).

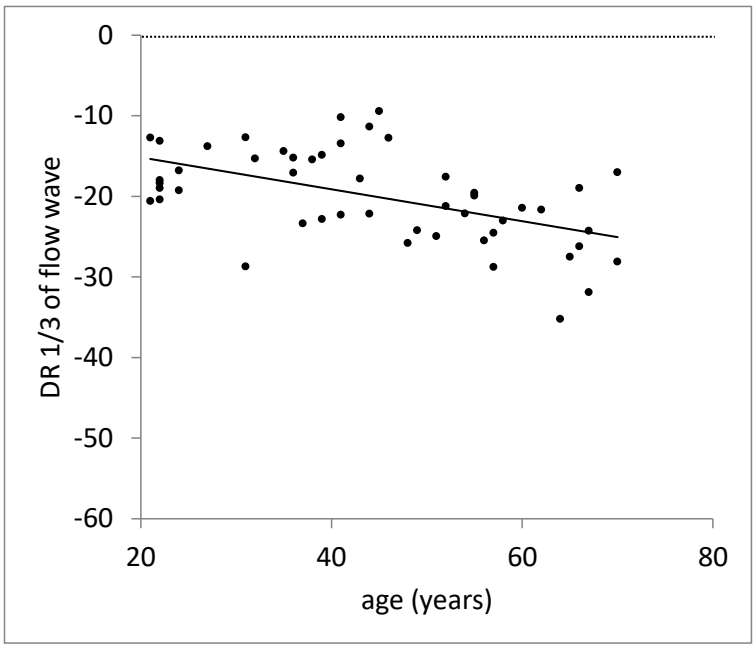


Figure 5-31. Relationship between DR 1/3 measured by cardiac MRI and age. There is a negative relation between DR 1/3 and age (y = -0.2x = 11, r^2 = 0.28, p<0.001).

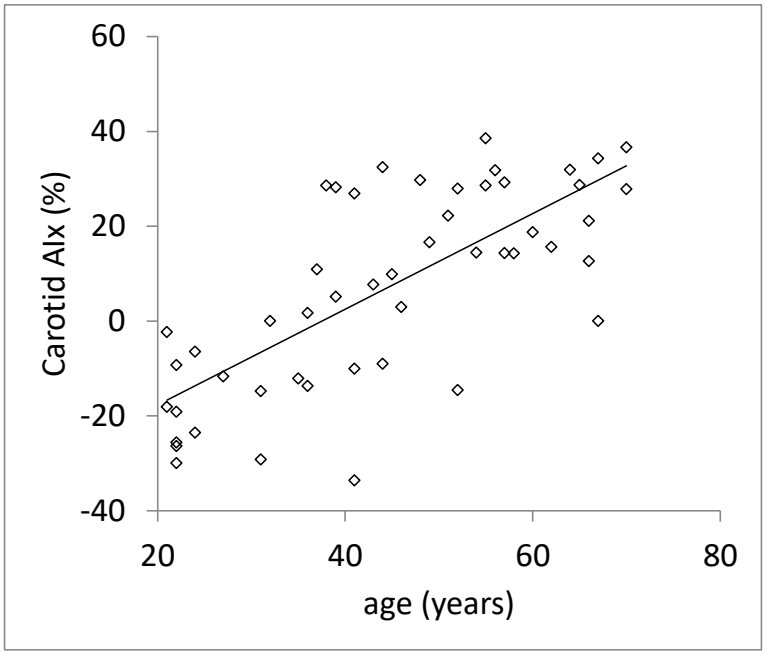


Figure 5-32. Relationship between carotid pressure AIx measured by PulsePen and age. There is a negative relation between DR 1/3 and age (y = 1.0 x -38, r2 = 0.28, p<0.001).

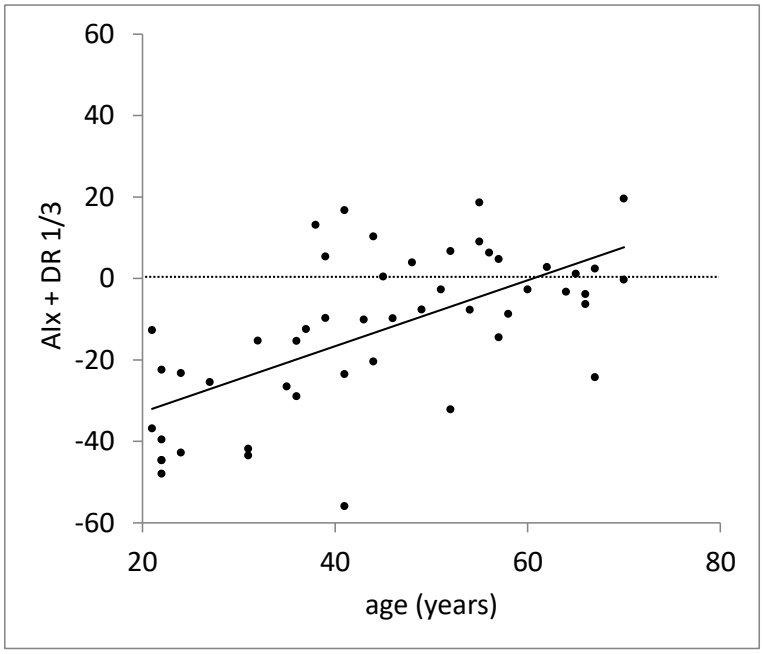


Figure 5-33. Combined effect of wave reflection in aortic flow (DR 1/3 measured by cardiac MRI) and in aortic pressure (AIx) plotted against age (y = 0.8 x - 49 (r2 = 0.41), p<0.001)

The expected zero-level relationship was not found; instead, a positive relationship is apparent (**Figures 5-33**). This may be attributable to a greater contribution of increase in carotid augmentation index with age compare to a lesser contribution of decrease in late systolic aortic flow velocity with age. This anomaly will be further explored.

The reflected wave is known to play a major role in decelerating cardiac ejection (Nichols et al. 1990), and this can be represented as the magnitude of deceleration in flow velocity waveform. Miyashita et al (Miyashita et al. 1994) have shown the value of this DR 1/3 index in evaluating the effect of vasodilator therapy, in particular the effect of wave reflection in heart failure patients (**Figure 5-34**).

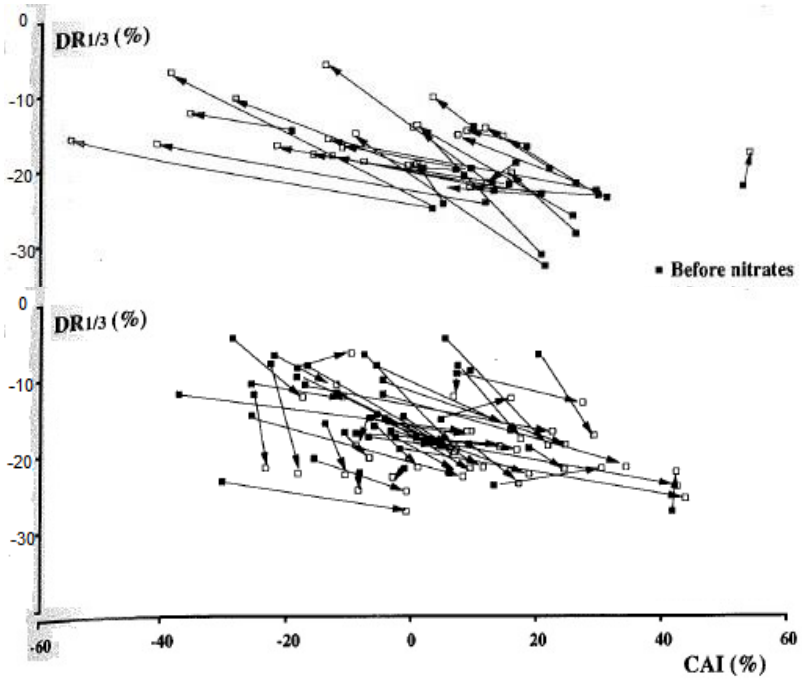


Figure 5-34. Effect of vasodilator agents nitrates (top) and calcium-channel blocker nifedipine (bottom) in reducing carotid pressure augmentation index (CAI) and flow velocity DR 1/3. From (Miyashita et al. 1994).

This is further supported by another study by Uebaba et al (Uebaba et al. 2002). Uebaba et al suggested that in severe cardiac failure patients, especially those with systolic left ventricular dysfunction, vasodilator such as nitrates does not alter the pressure wave contour, yet causes greater flow in late systole, thus increases ejection duration (**Figure 5-35**) (Uebaba et al. 2002).

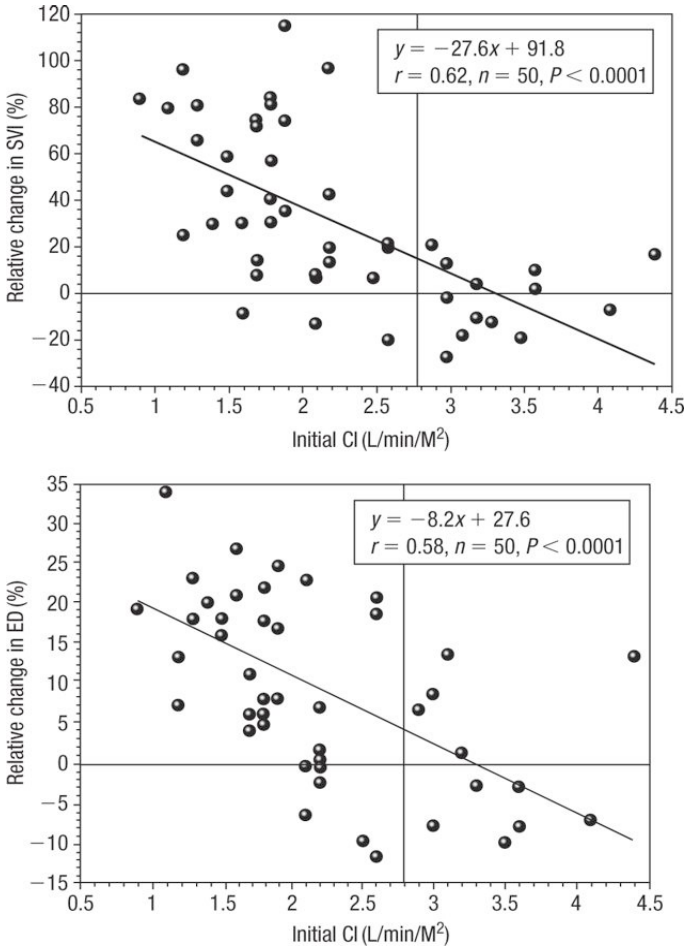


Figure 5-35. Effect of nitroglycerin infusion to increase cardiac output in patients with cardiac failure is inversely related to the severity of failure. Response measured in relation to change in stroke volume index (SVI) (top), and to change in ejection duration (ED) (bottom), when graphed against cardiac index (CI). From (Uebaba et al. 2002).

Results of this pilot study on impedance modelling warrants further investigation on the applicability of age-related impedance modelling to generate aortic flow velocity for different age and conditions.

Waterhammer Formula

The peak flow velocities calculated are given in **Table 5-4** and **Figure 5-36** below:

Peak flow velocity (cm/s)	Mean (SD) – method 1	Mean (SD) – method 2
< 50 years	51.4 (15.4)	52.4 (15.0)
50 to < 60 years	46.5 (11.7)	46.9 (11.8)
60 to < 70 years	47.8 (10.3)	47.1 (10.2)
≥ 70 years	42.5 (8.6)	45.2 (8.9)

Table 5-4. Peak flow velocity estimated from the Waterhammer formula where pulse wave velocity was determined by 2 methods; method 1 (BLSA = Baltimore Longitudinal Study of Aging (Vaitkevicius et al. 1993)), method 2 (ACCT = Anglo-Cardiff Collaboration Trial (McEniery et al. 2005)).

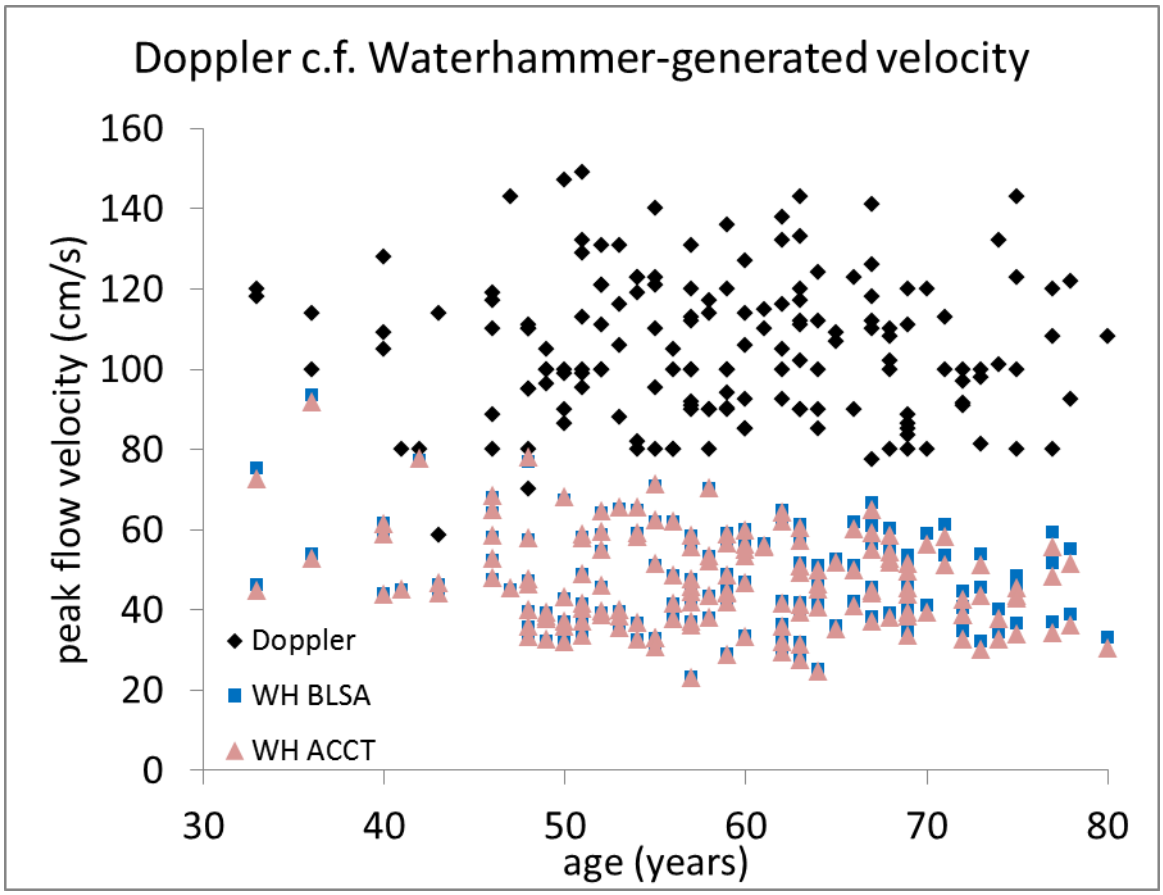


Figure 5-36. Peak flow velocity determined from Doppler measurements compared to those estimated by the Waterhammer formula, there was significant difference between each of estimate using method 1 (blue squares) and method 2 (pink triangles) to Doppler ($p<0.001$).

This approach was initiated by Prof O'Rourke (personal communication, 2006). Mean flow velocity for each heart cycle is determined from the product of systolic flow velocity and ejection duration. Average ejection duration in this cohort is 32.4 (SD 4.2) %. Finally, cardiac output (**Table 5-5**) can be estimated from 109 patients which aortic cross-sectional area was estimated from Doppler (see **Table 5-3**). The initial pressure pulsation is taken to be peak of the first shoulder at aortic pressure wave (P1 height in SphygmoCor). The triangular flow concept, published by Westerhof group (Westerhof et al. 2006), will be applied in further work.

Cardiac output (L/min)	Mean (SD) – BLSA	Mean (SD) - ACCT
< 50 years	2.6 (0.9)	2.6 (0.9)
50 to < 60 years	2.4 (1.0)	2.5 (1.0)
60 to < 70 years	2.6 (1.2)	2.6 (1.2)
≥ 70 years	1.7 (0.5)	1.6 (0.5)

Table 5-5. Estimated cardiac output resulting from peak velocity calculated from the Waterhammer formula.

It was apparent from these results that the estimated flow velocity and cardiac output were lower than those determined from Doppler measurements and the difference was significant ($p<0.001$). Questions arise from these findings whether the Doppler-measured parameters tend to overestimate velocity and cardiac output values due to its technical limitations (measuring the higher particle velocities of the outer envelope), or the model-estimated velocity and cardiac output are underestimated. It is also expected that further refinement to the application of Waterhammer formula to estimate cardiac output will happen in the future.

5.3.4 Discussion

In this study, comparison between different methods to estimate peak flow velocity non-invasively the ascending aorta is made. The results show significant reduction of peak aortic flow velocity when measured by a more accurate technique (cardiac magnetic resonance imaging), whereas this reduction cannot be seen when peak flow is measured using Doppler ultrasound. Doppler technique has been assumed to be accurate in measuring flow velocity, widely accepted as routine procedure and applied in major studies, such as the Asklepios (Segers et al. 2007) and Framingham Heart studies (Mitchell et al. 2010). The Asklepios study showed no significant difference in impedance modulus or phase up to 10 Hz in persons of different age (35 – 56 years) compared cross-sectionally (Segers et al. 2007), and to date, there are no studies that reported any benefit of aortic impedance measured with ultrasound over and above the simpler measures such as aortic augmentation index or reflection magnitude.

Figure 5-37 shows aortic peak flow velocity when measured using Doppler ultrasound and cardiac magnetic resonance, and when estimated by the impedance model or using Waterhammer formula. The graph indicates that peak flow velocity measured by Doppler did not decrease with aging, in contrast to the known aortic dilation with age, while velocity estimated by other four methods shows reduction of varying degree. This finding implies that peak flow velocity estimation is feasible and the model warrants further refinements.

To further test the impedance model, the impedance modulus and phase calculated from carotid pressure and aortic cardiac-magnetic resonance-measured flow velocity was applied to derive aortic flow waveform from 160 male patients of Professor Weber's database in whom aortic pressure were estimated from radial pressure applanation tonometry. This is shown in **Figure 5-38**.

When compared to **Figure 5-20**, the contour of aortic flow velocity wave are improved, with reduction of peak flow velocity as age increases and alteration during late systolic period from convexity in the younger group to concavity in the older group more apparent.

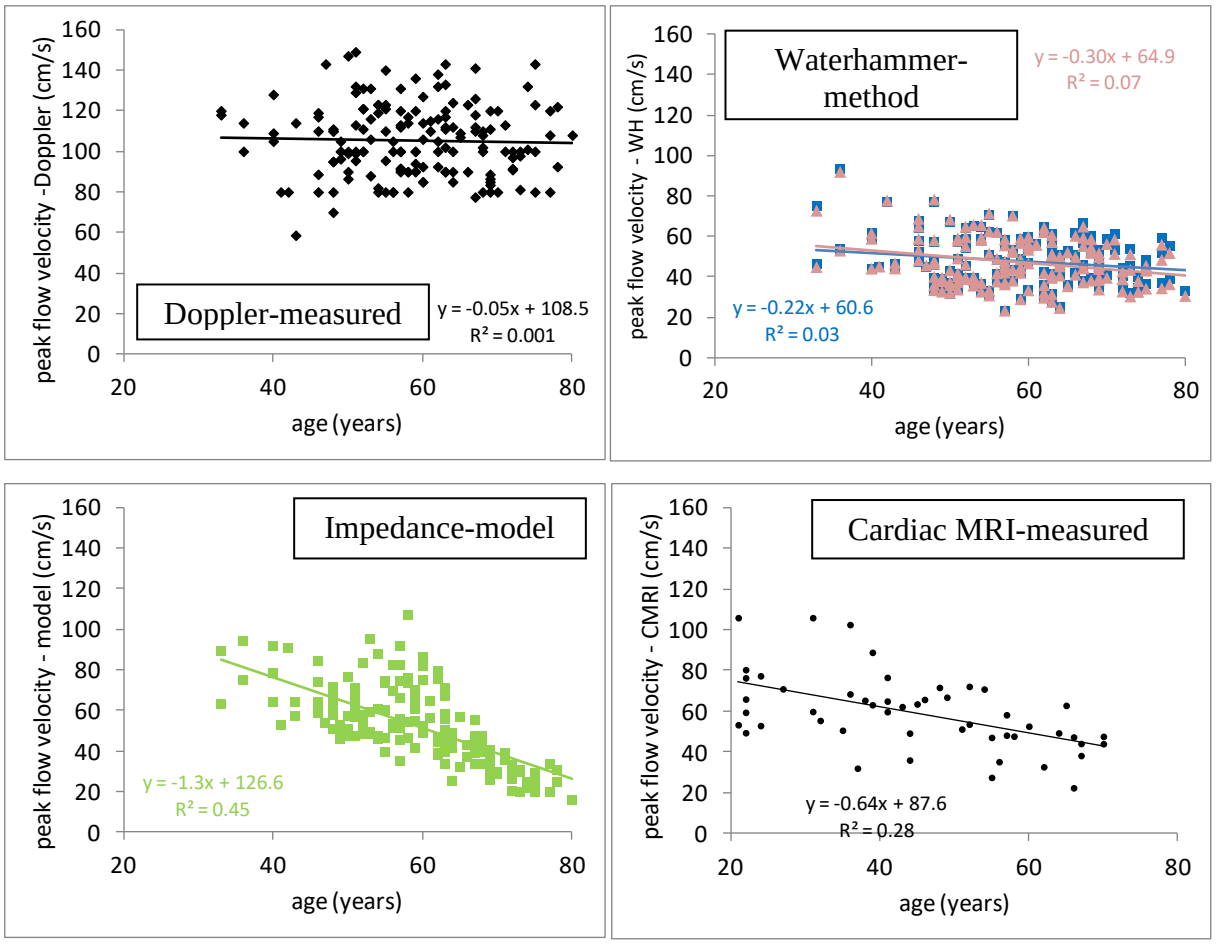


Figure 5-37. Peak flow velocity measured/ estimated by 5 methods: Doppler (top left), Waterhammer formula method 1 and method 2 (top right), impedance model (bottom left), and cardiac magnetic resonance imaging (bottom right).

Figures 5-37 and **5-38** show that aortic pressure, flow and impedance can be modeled with realistic and reasonable outcome, that derivation of aortic flow velocity from aortic pressure and impedance can be achieved, and aortic impedance is a measure of hydraulic load to the heart; increasing as human aged, affecting the ejection pattern of the heart. The work is continuing at the time this thesis is written.

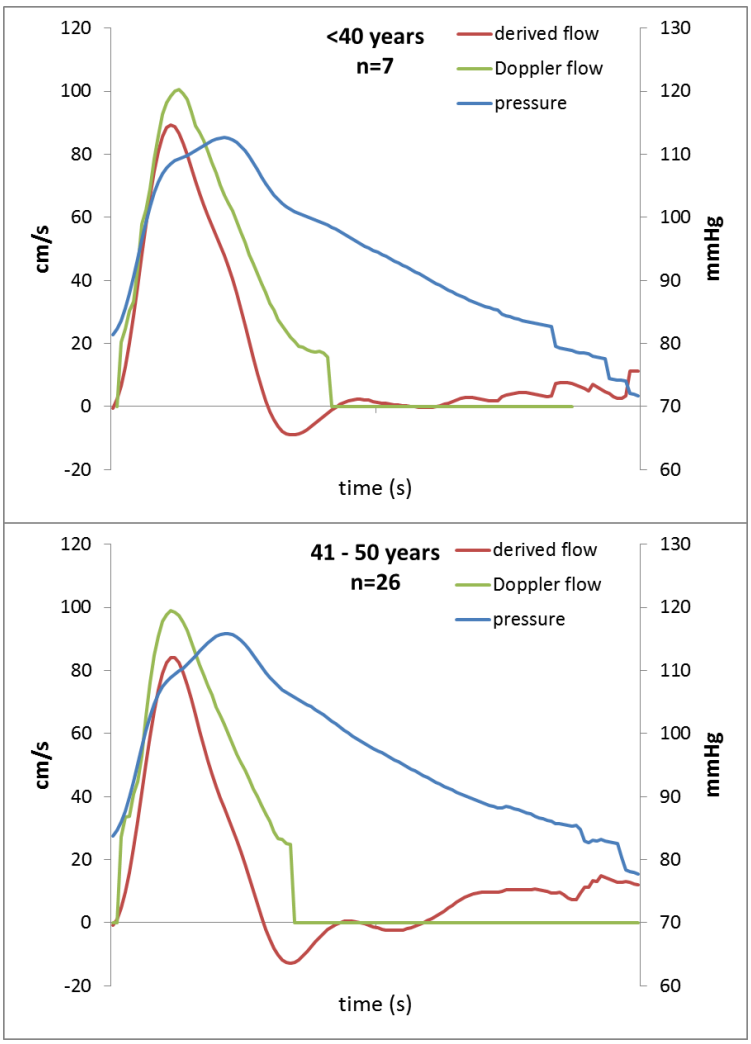


Figure 5-38. Ensemble-averaged aortic pressure (blue), model-derived (red) and Doppler-measured (green) aortic flow velocity waves for each decade. Time period is 1 second for all. (continued next page)

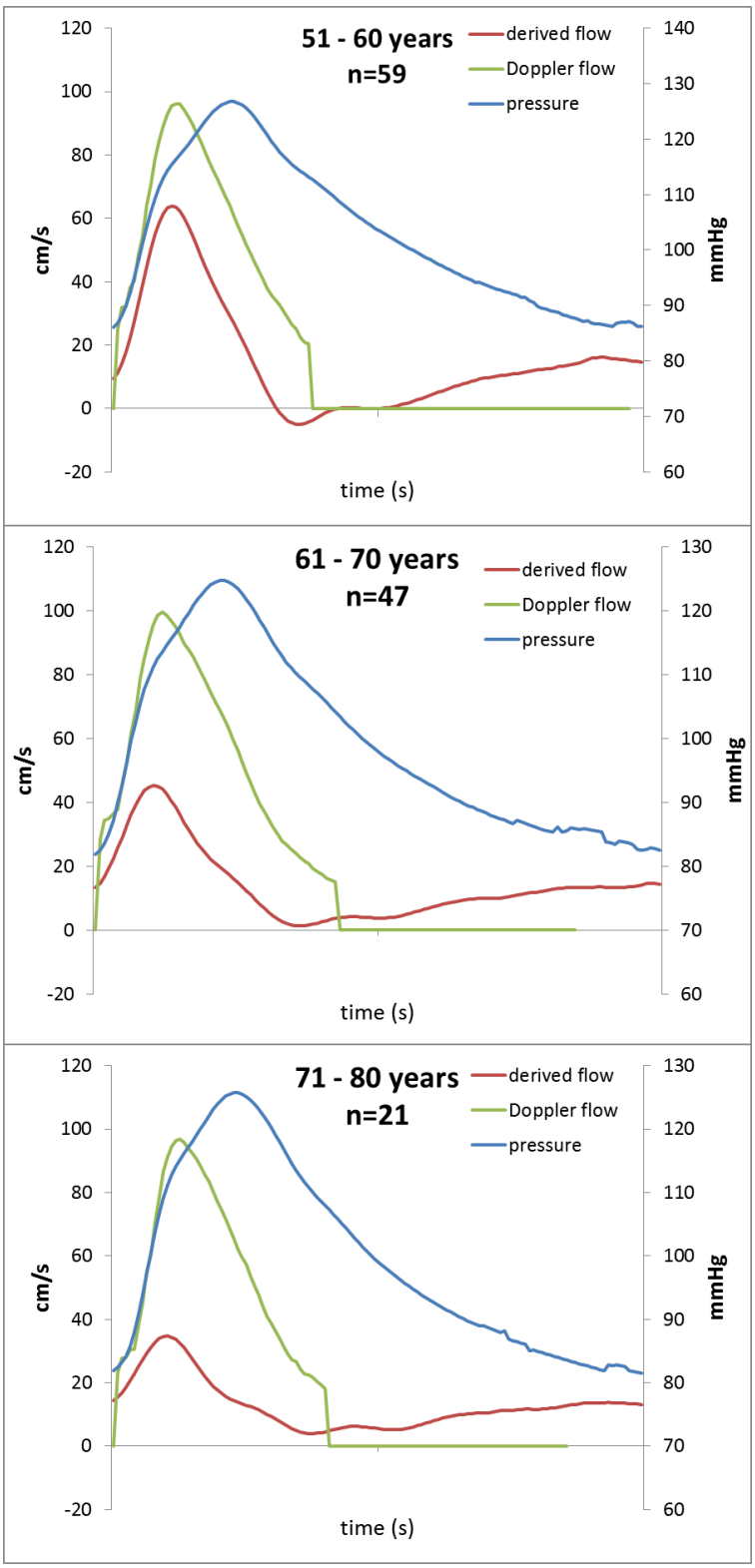


Figure 5-38. Ensemble-average aortic pressure, model-derived and Doppler measured aortic flow velocity waves for each decade. Time period is 1 second for all (continued from previous page).

Further extension of this study is currently under way to develop a simple computer age-specific impedance model that can be applied for any central pressure wave to generate aortic flow velocity wave. This study involves application of two new methods. The first is an iteration method as initiated by Fry and colleagues, as described in details in the earlier part of this chapter. The second is the "aortic flow triangulation" introduced by Westerhof group, also described in the earlier part of this chapter. It is expected that the impedance model will be much improved and the derived aortic flow wave to be more realistic in values.

5.4 Chapter Overview

The arterial pressure pulse is generated by the flow pulsation of blood with each pulsating heart. Determination of vascular impedance non-invasively requires accurate pressure and flow pulse measurements, and current studies have not been able to achieve this satisfactorily. This chapter investigates the technique of measuring the aortic flow wave, and both advantages and limitations of current practice, in particular, between the Doppler ultrasound – currently the most common practice – and cardiac magnetic resonance imaging. A new approach is applied to estimate aortic flow wave from derived aortic pressure waveform, and this was analysed with two available methods. I performed all data analysis to assess different methods to generate aortic pressure wave, their reproducibility and feasibility, as well as to compare the derived aortic waves with those measured by Doppler ultrasound. From these analyses, the age-related changes in the aortic flow velocity contour as a representation of cardiac ejection pattern are evident. The current practice of measuring the left ventricular outflow tract velocity non-invasively with Doppler ultrasound is not sufficiently sensitive to show subtle changes in cardiac ejection pattern with aging. The increasing practice of measuring ascending aortic flow waves with cardiac magnetic

resonance emerges to be more accurate and this method is able to show the changes with age in both aortic flow and impedance. The study also shows that the aortic impedance can be estimated non-invasively from accurate measurement of derived aortic pressure wave and measured aortic flow wave. The aortic impedance pattern illustrated in this chapter demonstrates the aging change in impedance, which is the increasing characteristic impedance in older subjects than the younger cohort. The pilot study of generating aortic flow velocity wave from central aortic pressure is feasible. However, work is continuing in this field.

Chapter 6

Relationship of Cerebral Arterial Pressure and Flow with Aortic Pressure and Flow

Summary

With stiffening of the arteries with age, the elastic aorta cannot cushion the pulsation generated by every beat of the heart, therefore, these pulsations can pass down into smaller vessels with lower resistance in highly perfused organs such as the brain and kidney. The latest hypothesis proposes that the development of dementia and kidney failure in the aging population is linked to large artery disease. This hypothesis has been presented (O'Rourke et al. 2005, O'Rourke et al. 2010), and the latest analysis is presented in this chapter.

6.1 Introduction

Pathological changes in the brain are attributable to excessive energy losses in the microcirculation, caused by increased pulsations of pressure and flow within these. Increased pulsatile pressure pulsations are likely to cause medial damage, while increased pulsatile flow pulsations are likely to cause endothelial dysfunction and damage (Nichols et al. 2011). The 'pulse wave encephalopathy' described by Bateman (Bateman 2004) and Henry-Feugeas (Henry Feugeas et al. 2005) as the cause of cerebral damage and dementia appears to be a chronic representation of the acute cerebral arterial damage, which earlier has been described by Byrom in 1969 (Byrom 1969). It is attributable to the same factors – of physical damage to weakened arterial walls as a consequence of aging, with a combination of thrombosis and lacunar infarction caused by increased pulsatile shear stress, endothelial damage, fluid exudation, and thrombosis, and of increased pulsatile tensile stress with microaneurysm formation and microbleeds, with these turning into amyloid plaques (Cullen et al. 2005, Cullen et al. 2006, Stone et al. 2014). All are explicable on the basis of aortic stiffening with high pulse pressure and flow caused by early return of wave reflection from the lower body (O'Rourke et al. 2005, Nichols et al. 2011). Due to the low vascular resistance of the brain, arterial pressure and flow waves can extend further into the cerebral microvessels.

Hashimoto and Ito (Hashimoto et al. 2015) showed that the flow reversal in the descending thoracic aorta, due to the "sloshing" of flow, caused by stiffening of the aorta and impedance mismatch, affects the upstream (i.e. carotid) flow. While the diastolic flow reversal has been identified in patients with embolic stroke, Hashimoto and Ito (Hashimoto et al. 2013) found a positive association between diastolic flow reversal with aortic augmentation index, and the reverse flow from the lower body augments the flow pulsation through the aortic arch toward carotid arteries, and is likely extend upstream to the brain. They have confirmed previous observations the evidence of strong wave reflection from the lower body (Spencer et al. 1963,

O'Rourke 1967, Gabe et al. 1969). Hashimoto and Ito have performed a series of studies on (carotid) pressure and (aortic arch and descending thoracic aortic) flow waves (Hashimoto et al. 2010, Hashimoto et al. 2011, Hashimoto et al. 2013, Hashimoto et al. 2015) (**Figure 6-1**), and shown that aortic stiffening increases flow pulsation to the kidneys which contributes to renal microvascular damage. It is likely that similar mechanisms are responsible to microvascular damage in the brain, therefore these studies on cerebral hemodynamics are undertaken.

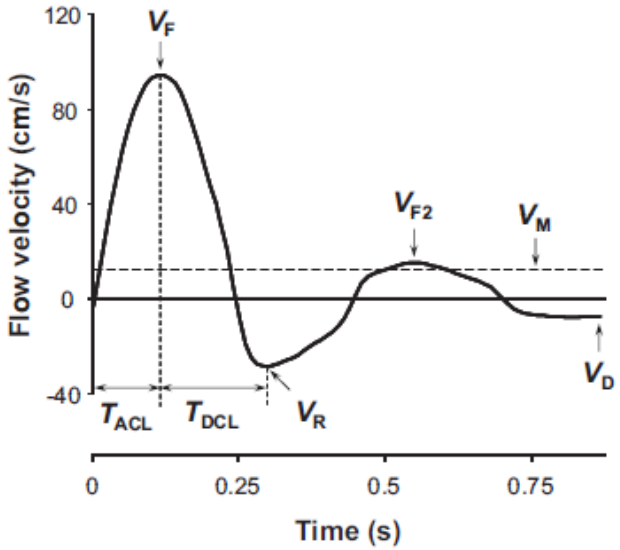


Figure 6-1. Definition of flow and time parameters derived from the ensemble-averaged femoral velocity waveform. VF = systolic forward peak velocity; VR = reverse peak velocity; VF2 = diastolic forward peak velocity; VM = time-averaged mean velocity; VD = end-diastolic velocity; TACL = acceleration time; TDCL = deceleration time. From (Hashimoto et al. 2010).

The work presented in this chapter arises from collaboration with a fellow PhD student, Mi Ok Kim. This involved collaboration with the Neurosurgical Unit in Addenbrooke's Hospital, Cambridge, UK, led by Professors Marek Czosnyka and John Pickard; Department of Neurosurgery, Oslo University Hospital – Rikshospitalet, Oslo, Norway, led by Professor Per Kristian Eide; and Center for Epidemiological Studies, Ruijin Hospital, Shanghai, China, led by Dr Yan Li and Professor Jiguang Wang.

6.2 Study: Association between Cerebral Artery Flow Augmentation and Central Aortic Pressure Augmentation

A study published as:

Kim MO, O'Rourke MF, **Adji A,** Avolio AP. **Central Pulsatile Pressure and Flow Relationship in Time and Frequency Domain to Characterise Hydraulic Input to the Brain and Cerebral Vascular Impedance** (*Acta Neurochirurgica Supplement*) **(2016)**

The unique relationship which exists between pressure, flow and impedance in the systemic circulation also presents in the cerebral circulation. Measurement of cerebral vascular impedance requires measurement of flow waveforms in one or more cerebral arteries, and pressure waveforms from an artery close to the brain. In this case, cerebral flow velocity waves can be recorded from major arteries accessible to the transcranial Doppler technique, i.e. middle cerebral artery from left or right side of the skull. The cerebral pressure wave can be taken to be similar as the ascending aortic pressure wave, which is able to be derived non-invasively from radial artery pressure recordings. Details on generation of aortic pressure wave from radial artery and impedance calculation in the frequency domain have been discussed in previous chapters.

From 24 normal subjects included in the study, a linear relationship was found between pressure and flow augmentation in the time domain, supporting the study of Hirata et al (Hirata et al. 2006). Cerebral impedance pattern was similar to those seen in low resistance vascular beds. With application of Valsalva manoeuvre, marked change in pressure and flow waves was apparent, however, the relationship of pressure augmentation index to flow augmentation index was unchanged, as were the modulus and phase of impedance.

The findings have been presented at the Intracranial and Brain Monitoring conference in 2013, and the expanded abstract on this study has just been published. I actively participated in study protocols, performed part of the data analysis and contributed in manuscript preparation.

Central Pulsatile Pressure and Flow Relationship in Time and Frequency Domain to Characterise Hydraulic Input to the Brain and Cerebral Vascular Impedance

Mi Ok Kim[1], Michael F O'Rourke[2,3], **Audrey Adji[1,2]**, Alberto P Avolio[1]

[1]Australian School of Advanced Medicine, Macquarie University, Sydney, Australia

[2]St Vincent's Clinic, Sydney, Australia

[3]University of New South Wales/ VCCRI, Sydney, Australia

Abstract

Background: In the time domain, pulsatile flow and pressure can be characterised as the ratio of late systolic boost of flow or pressure to the pulse amplitude so as to estimate the hydraulic input to the brain. While vascular impedance has been used widely to represent the load presented to the heart by the systemic circulation, it has rarely been applied to cerebral circulation.

Methods: We set out to study the relationship between pressure and flow augmentation index in the time domain and determine cerebral vascular impedance using aortic blood pressure and cerebral blood flow waveforms in the frequency domain. Twenty-four young subjects were recruited (age 21-39 years); aortic pressure was derived using SphygmoCor from radial pressure. Flow waveforms were recorded from the middle cerebral artery. In three subjects, we performed the Valsalva manoeuvre to investigate their response to physiological intervention.

Results: There was a linear relationship between flow and pressure augmentation index (AIx), and cerebral impedance values were similar to those estimated for low resistance vascular beds.

Conclusion: Substantial change in pressure and flow wave contour was observed during Valsalva manoeuvre, however, the relationship in both time and frequency domain was unchanged. This suggests that aortic pressure and cerebral flow waveform can be utilised to study cerebral impedance.

Keywords: Cerebral vascular impedance, central aortic pressure, pressure waveform analysis.

6.2.1 Introduction

The ascending aortic flow waveform is a manifestation of left ventricular pumping function, while the pressure wave generated in the ascending aorta depends on interaction between this wave and properties of the whole distal systemic circulation. The load presented to the heart by the systemic circulation can be characterised as its vascular impedance, and is displayed in modulus and phase by relating corresponding frequency components of the aortic pressure and flow waves. Peripheral resistance is just one component of impedance, calculated as mean pressure divided by mean flow (at zero frequency). This impedance approach has been applied to the pulmonary as well as the systemic circulation [1,2] and to components of the systemic circulation such as to a kidney or to an arm or leg [1-4]. It has not however been applied systematically to the cerebral circulation.

Measurement of cerebral vascular impedance to sections of the brain requires measurement of flow waveforms in one or more cerebral arteries and pressure waveforms from an artery close to the brain – i.e. the flow waveform entering the brain and the pressure wave generated by this flow wave as a consequence of the properties of the cerebral vascular bed beyond [1-3]. In subjects with raised intracranial pressure, cerebral perfusion pressure rather than arterial pressure should be used.

As for the other body sites previously studied, cerebral vascular impedance has the potential to simplify concepts of resistance and reactance in the cerebral circulation while conforming with the traditional Monro/Kellie doctrine of constant volume of all components within the skull.

6.2.2 Materials and Methods

Data were obtained from 24 normal volunteers aged 21 to 39 years (14 males). Pressure waves were measured at the radial artery with applanation tonometry, and central aortic pressure waveforms were generated from these through use of a validated transfer function in SphygmoCor, and calibrated to brachial cuff systolic and diastolic pressures [2-4]. Middle cerebral artery flow waveforms were measured with transcranial Doppler technique, simultaneously with aortic pressure, and pressure/flow relationships were determined in the time and frequency domain after ensemble-averaging a series of waves over at least one respiratory cycle [5]. In the time domain, attention was directed at the augmentation of the pressure and flow waves (ratio of secondary systolic to primary systolic component of the wave) [5]; in the frequency domain, attention was directed at impedance patterns of modulus and phase, and their interpretation from previous human, experimental animal, and modelling studies at other sites [1-3].

In three subjects data were obtained also during Valsalva manoeuvre as well as under control conditions to test response to a physiological intervention [6]. Valsalva manoeuvre was achieved by raising intrathoracic pressure to 40 mmHg and maintaining this for about 20 seconds as described in previous studies [7].

6.2.3 Results

Baseline data for all subjects are given in the table 1. Figure 1 shows representative middle cerebral artery (MCA) flow and central pressure waves in a typical younger male subject. Younger subjects showed less and older ones showed more late systolic augmentation of the waves. Pressure and flow augmentation index (AIx) were calculated as augmentation ÷ amplitude of the wave – i.e. as flow AIx (FAIx) and pressure AIx (PAIx). Figure 2 shows the

relationship of FAIx and PAIx in the whole cohort is essentially linear, as previously seen in the carotid artery [8]. Impedance values were similar to those seen in low resistance vascular beds such as the kidney or lung [1,2] or in a limb artery following intra-arterial injection of acetylcholine [3]. Despite marked change in pressure and flow waves during the Valsalva manoeuvre (figure 3), the relationship of pressure AIx to flow AIx was unchanged, as were the modulus and phase of impedance.

Results of pressure/flow relationship in this predominantly young volunteer group show a consistent pattern when expressed either in the time or the frequency domain. The early peak of pressure and flow waves (figure 1) around 100msec after the wave foot is related directly to the peak of flow velocity from the heart [1]. The second peak of aortic pressure and of MCA flow is explained, as in other arteries, on the basis of wave reflection from the trunk and lower limbs returning to the upper body while the heart continues to eject [2]. The patterns of modulus and phase of vascular impedance in the MCA territory are similar to those seen in other low resistance vascular beds, and are consistent with low wave reflection (~ 40%) from the cerebral vascular bed [1-3]. The physiological manoeuvre of Valsalva caused no significant change in the pressure/flow relationships in the time or frequency domain, despite marked change in shape of the original pressure and flow waves.

Relationships of flow AIx and pressure AIx have been described by Hirata et al for the common carotid artery [8], with these being similar in normal volunteers, in patients with coronary atherosclerosis before and after administration of nitroglycerine [9] and in patients with known or suspected lacunar infarcts [10]. A higher number of asymptomatic MRI cerebral abnormalities were noted in persons with high values of flow AIx or pressure AIx [10].

6.2.4 Discussion

Our study extends that of Hirata, showing similar patterns of pressure and flow augmentation, while in addition, showing impedance values as expected in a passive, dilated cerebral vascular bed. These studies have been extended to show aging and gender effects on pressure and flow augmentation [11], and effects of cerebral disease. The ill effects of early wave reflection on cardiac function have been established [1-3] and are well known. It is likely that similar ill effects will be confirmed for the cerebral circulation, and that appropriate use of vasodilator agents such as nitroglycerine will be found applicable for the brain as well as they have been for the left ventricle the heart, and as for the heart, can be monitored from aortic pressure and/or cerebral artery flow wave contour.

References

1. O'Rourke MF (1982) Vascular impedance in studies of arterial and cardiac function. Physiol Rev 62:570-623.

2. O'Rourke MF, Taylor MG (1966) Vascular impedance of the femoral bed. Circ Res 18:126-139.

3. O'Rourke MF, Taylor MG (1967) Input impedance of the systemic circulation. Circ Res 20:365-380.

4. Nichols WW, O'Rourke MF, Vlachopoulos C (2011) McDonald's Blood Flow in Arteries. 6th edition. London; Arnold Hodder.

5. O'Rourke MF, Safar ME, Dzau V (eds) (1993). Arterial Vasodilation: Mechanisms and Therapy. London; Edward Arnold/Philadelphia; Lea & Febiger.

6. Murgo J, Westerhof N, Giolma JP, Altobelli SA (1981) Manipulation of ascending aortic pressure and flow wave reflections with the Valsalva maneuver: relationship to input impedance. Circulation 63:122-132.

7. Dawson SL, Panerai RB, Potter JF (1985) Critical closing pressure explains cerebral hemodynamics during the Valsalva maneuver. J Appl Physiol 86: 675-680.

8. Hirata K, Yaginuma T, O'Rourke MF, Kawakami M (2006) Age-related change in the carotid artery flow and pressure pulses implications to cerebral microvascular disease. Stroke 37:2552-2556.

9. Hirata K, O'Rourke MF, Momomura S (2007) Favourable effect of sublingual nitrate on carotid flow and pressure augmentation index. J Clin Hypertens 9(suppl A):A29.

10. Hirata K, O'Rourke MF, Momomura S (2008) Flow augmentation index as a major risk factor for silent lacunar infarction. J Hypertens 26(Suppl 1):S395.

11. Kim MO, Li Y, Wei F, Wang J, O'Rourke M, Avolio A (2013) Influence of wave reflection and lower body arterial properties on cerebral perfusion in apparently normal humans. J Hypertens 31(e-SupplA):e23.

Table 1. Subjects' characteristics.

n	Mean age	Brachial Pressure		Central Pressure		Mean Pressure	MCA flow velocity		
		Systolic	Diastolic	Systolic	Diastolic		Peak	Trough	Mean
24	28	115.6	72.0	102.4	73.7	87.9	84.4	43.4	59.3

Figures and Legends

Figure 1. Typical MCA flow (top), radial (bottom left) and central aortic pressure (bottom right) waveforms from young subject.

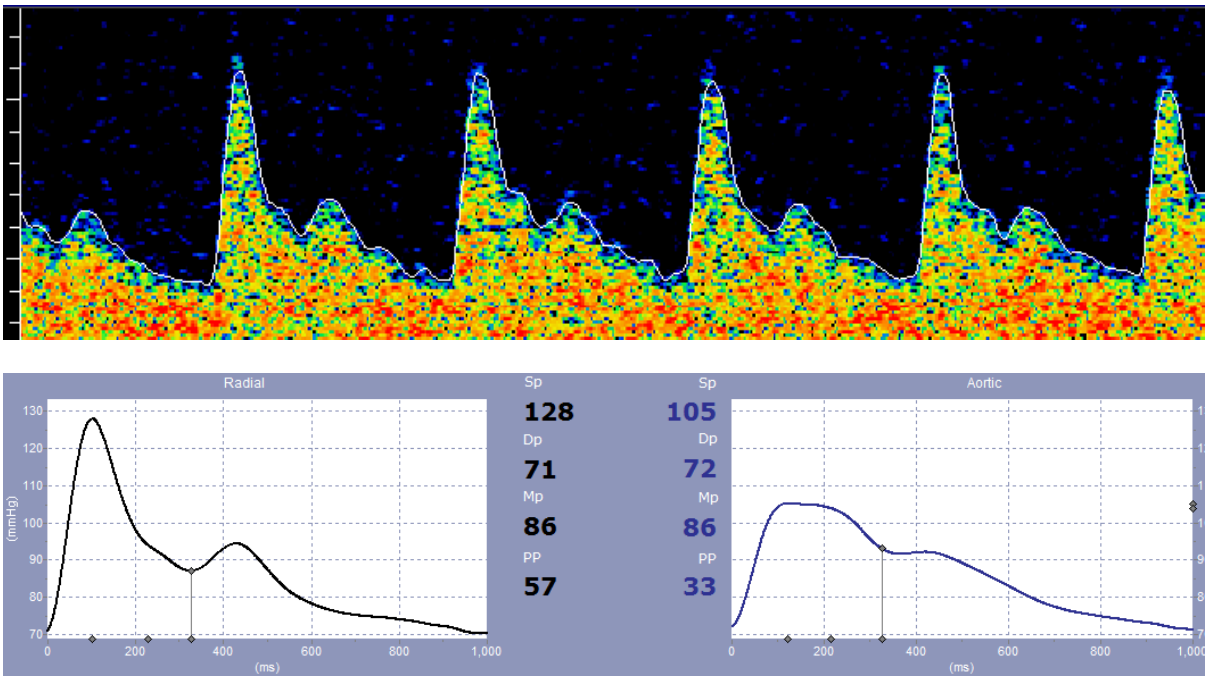


Figure 2. Linear relationship (r=0.77) between pressure and flow augmentation index.

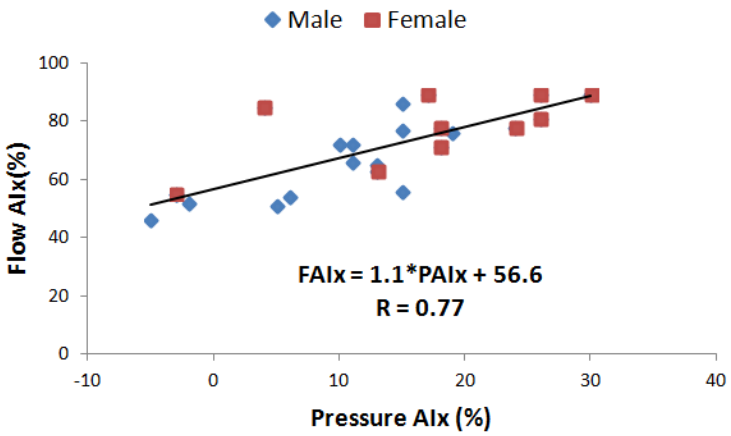
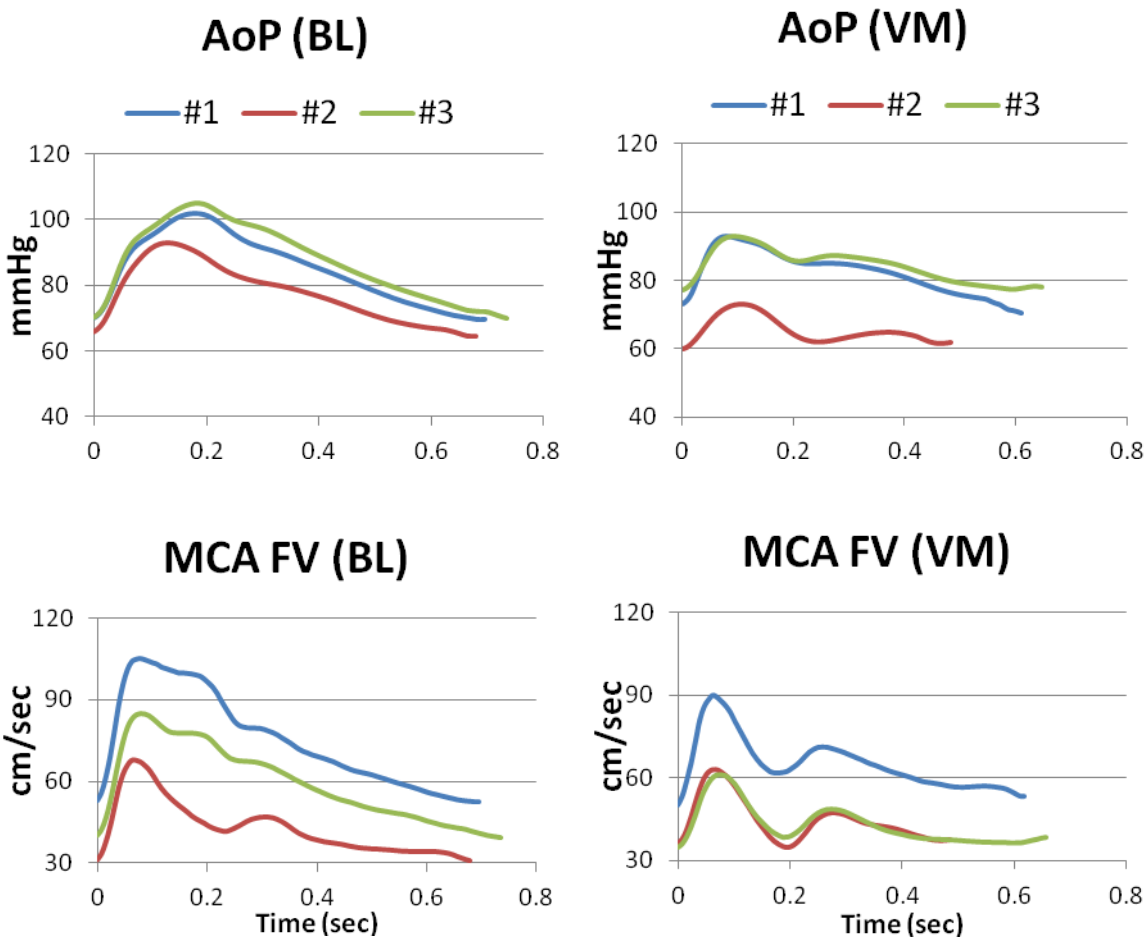
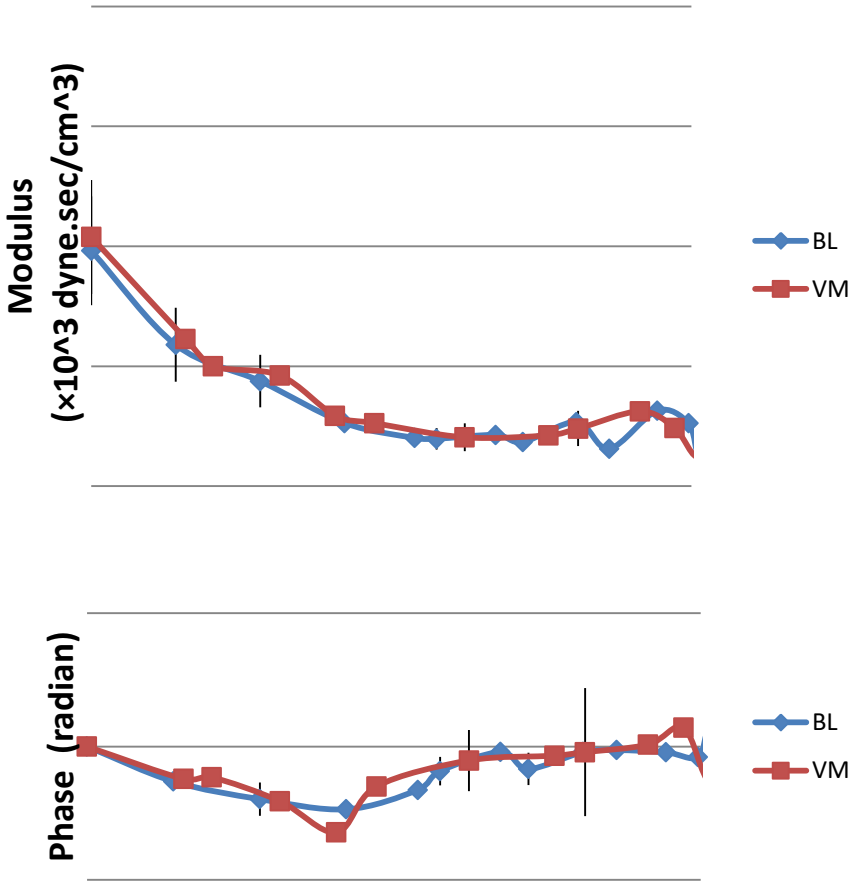


Figure 3. (a) Central aortic pressure (AoP) and flow (MCA FV) waveforms at baseline (BL) condition and during Valsalva Manoeuvre (VM) in 3 subjects (subject numbers (#) 1,2,3),



(b) Cerebral vascular impedance modulus and phase at baseline (blue) and during Valsalva Manoeuvre (red).



6.3 Study: Association between Cerebral Artery Blood Flow Velocity and Central Aortic Pressure Waveforms in Normal Cohort

A paper under review:

Kim MO, Li Y, Wei F, Wang J, O'Rourke MF, **Adji A**, Avolio AP. **Cerebral Vascular Pulsations: Implications for Microvascular Disease.** Submitted to *Journal of the American College of Cardiology* **(2015).**

Following our study of the normal cohort in section 6.2, we, together with colleagues from Shanghai, China, studied a total of 1,020 apparently normal and mildly hypertensive subjects, where their aortic pressure and cerebral flow data were available. The finding shows that the cerebral circulation is dependent on the heart and affected by stiffening of the arteries with aging. I conducted a significant part of the data analysis and interpretation, as well as being actively involved in manuscript preparation, attached below.

CEREBRAL VASCULAR PULSATIONS:

IMPLICATIONS FOR MICROVASCULAR DISEASE

Miok Kim BE PhD *, Yan Li MD PhD †, Fangfei Wei MD †, Jiguang Wang MD PhD †,

Michael F O'Rourke MD DSc ‡§, **Audrey Adji** MB MBiomedE *‡, Alberto P Avolio BE PhD *

*Australian School of Advanced Medicine, Macquarie University, Sydney, Australia

†Center for Epidemiological Studies and Clinical Trials and Center for Vascular Evaluations, Ruijin Hospital, Shanghai, China

‡St. Vincent's Clinic, Sydney, Australia

§University of New South Wales/VCCRI, Australia

Short title: Cerebral vascular pulsations

Total word count: 4933 (abstract 246)

ABSTRACT

Background: Dementia in the elderly, traumatic brain injury in young adults and sickle cell anemia in children are linked by unexplained small cerebral vessel damage. Abnormalities of cerebral blood flow and/ or pressure are involved in pathogenesis. But present data are hard to interpret on account of indistinct boundaries between normal aging and disease.

Methods: Blood flow velocity waves were measured non-invasively in anterior (ACA) and middle cerebral (MCA), basilar (BA) and vertebral (VA) arteries by transcranial Doppler ultrasonography in 1020 apparently normal subjects (497 males, age 21-78 years). Central aortic pressure waveforms were estimated with SphygmoCor from waveforms recorded in radial artery by applanation tonometry. Relationships were described in time and frequency domains.

Results: All waveforms showed an early systolic shoulder or peak at 91 + 12 msec, then a strong secondary surge at 201 + 24 msec, and a subsequent inflection at 307 + 23 msec. Flow augmentation index in cerebral arteries was significantly associated with central aortic pressure augmentation index ($r=0.58$, $P<0.01$), and both progressively increased with age (beta=0.57 and 0.45 respectively, $P<0.01$). Vascular impedance was low in all 4 cerebral vascular beds, at all ages, and in males and females; reflection coefficient was <50% from all cerebral vascular beds.

Conclusion: Cerebral blood flow waveforms are similar to central aortic pressure waveforms; both show late systolic augmentation which increases with age. Low impedance cerebral arteries can be protected by interventions which reduce pulsatility from the heart and wave reflection from the lower body.

Keywords: Cerebral blood flow, Cerebral vascular impedance, Stroke, Small vessel disease, Aging.

6.3.1 Introduction

New approaches to pulsatile arterial hemodynamics were introduced 50 years ago [1-3], but have not until recently been applied to study of cerebral microvascular dysfunction [4], which has been implicated in many human diseases [5], including development of plaques and tangles in brains of persons with cognitive dysfunction and dementia [6], secondary stroke in patients with closed head injury [7], after subarachnoid haemorrhage [8] and thrombotic stroke in children with sickle cell anemia [9]. There is increasing evidence that microvascular disease, consequent on aortic stiffening with age [5], is due to higher pressure (circumferential stress) and flow (longitudinal shear stress) pulsations in small cerebral arteries [6, 10]. After injury or stroke, there is persuasive evidence that management of persons in intensive care units following closed head trauma [11] or subarachnoid haemorrhage [8] can be improved through invasive measurement of IntraCranial Pressure (ICP) and arterial pressure, together with non-invasive measurement of cerebral artery flow velocity pulsations by transcranial Doppler [12]. In sickle cell anemia, high flow velocity pulsations in cerebral arteries identify children with high risk of stroke [13], and stroke can be prevented by reducing such pulsations through timely blood transfusion [13, 14]. While the subject is important in modern medical practice, in public health and in society, basic mechanisms are contentious and poorly understood, and indifferently applied to the host of specialities called on to deal with afflicted persons.

This study applies modern approaches of pulsatile pressure and flow (analysis in both time and frequency domain [15]) to the analysis and interpretation of cerebral arteries in 1020 normal and mildly hypertensive patients over the adult life span. It supplements previous studies of carotid-femoral pulse wave velocity change with age in 2004 subjects with low prevalence of atherosclerosis but different prevalence of hypertension [16, 17], and pulsatile pressure waveforms in the carotid, radial and femoral arteries of 1005 normal persons, using non-invasive applanation tonometry [18]. The study provides a better background that currently available for interpretation of pressure and flow waveforms and their relationships within the cranium, their changes under physiological and pathological conditions, and for introducing and monitoring logical therapies [19,20].

6.3.2 Methods

Study Population and Data Collections

As described previously [19], data were obtained in consecutive persons apparently well, referred for 24 hour Blood Pressure (BP) monitoring to the Hypertension Clinic of Ruijin Hospital in Shanghai, China. Of those referred between December 2008 to December 2012, 2159 were eligible, because they were either never treated or had discontinued their blood pressure lowering drugs for at least 2 weeks pending clinical evaluation over a two-day period. Of these, 1281 (59.5%) gave informed written consent, and 1020 had both transcranial Doppler measurements and pulse wave recordings at radial arteries. Cohort details are provided in table 1.

On the day following 24 hour BP, subjects underwent measurement of carotid/femoral PWV using applanation tonometry [19], then radial artery tonometry with a generalised transfer function was used to determine the central aortic pressure waveform from the radial pulse [20]. This process has been validated against simultaneously-recorded aortic pressure

waveforms [15, 21] according to US FDA requirements as K002742 and K0012487. Following this procedure, flow waveforms of cerebral arteries were recorded with transcranial Doppler by one experienced sonographer as previously described [22]. The number of analysed recordings at anterior (ACA) and middle cerebral (MCA), basilar (BA) and vertebral (VA) arteries was 781, 912, 947 and 973, respectively. Altogether, over 50,000 flow waveforms at 3-6 possible sites were recorded in the 1020 subjects, together with radial and derived aortic pressure waveforms. A preliminary report on the first 334 subjects [19] gives details of data collection of cerebral flow and aortic pressure wave forms, initial analysis and on subject permission and ethics committee approval.

Waveform Data Analysis

An analysis of waveform data was undertaken in Sydney (by MOK, AIA, MFO and APA). Flow waveforms were ensemble-averaged from 3-6 waves in each patient at each cerebral site, and further ensemble-averaged into representative waves for the third, fourth, fifth, sixth, seventh and eighth decades, as had radial, carotid, and femoral pressure waveforms previously [20]. Subjects' flow waveforms were analysed with the SphygmoCor process [15, 21], to identify wave foot, first systolic peak or shoulder, second systolic peak or late systolic shoulder, and incisura (which represented aortic valve closure), after advancement (by eye) of the synthesised aortic wave, to account for delay in transmission to the radial artery. The augmentation of pressure was measured by the difference in amplitude of the second systolic peak or shoulder above the first shoulder or peak. This is usually expressed as Augmentation index (AIx) – and measured as augmented pressure divided by pulse pressure. The same terminology was used to describe the shape of the flow waves in different arteries. Pulsatility index was defined as amplitude of the flow wave divided by mean flow, which was considered in the earlier stage of this study [19], and is used elsewhere rather than resistance. Impedance modulus (Z) and phase (φ) were calculated for the four arteries from individual pairs of all pressure and flow velocity waves [3, 23] using Fast Fourier Transformation (FFT)

by MATLAB® software (Version R2009b). Use of impedance to describe pressure/ flow relationships assumes that cerebral venous pressure is zero and flow velocity negligible as blood exits the skull into the capacious internal jugular vein when the head is supported on a pillow or when the subject sits on a chair [18]. Reflection coefficient was calculated from the formula (ZT – ZC) ÷ (ZT + ZC), where ZT is terminal impedance at zero frequency and ZC is characteristic impedance calculated as average impedance between 2 and 10 Hz [3,15].

Statistical Analysis

For statistical analysis, we used the statistics toolbox of the MATLAB software, version R2009b (MathWorks, Massachusetts, USA). For comparison of means and proportions, we applied the t test and the $\chi 2$ statistic, respectively. We calculated Pearson correlation coefficients and linear regression coefficients to describe the correlations between the indices of interest. To compare between sexes the associations of pressure and flow AIx with age, we introduced appropriate interaction terms with age into the regression model. $P<0.05$ was considered statistically significant.

6.3.3 Results

Similarity between Cerebral Flow and Aortic Pressure Waveforms

Ensemble-averaged flow and pressure waveforms for all subjects at all sites are shown in figure 1 together with the ensemble-averaged radial and aortic pressure wave. Flow waveforms were basically similar at the four sites (MCA, ACA, VA and BA) with the first peak or shoulder of flow at ~89 + 12 msec after the foot of the wave and with a later localised peak or shoulder on average ~106 ± 25 msec later (table 2). This second systolic peak or shoulder, as for aortic pressure [15, 20], corresponded to a second impulse attributable to wave reflection arising in the lower body. Peak systolic flow velocity was similar to that

reported in the ascending aorta (40-110 cm/s) [15], but flow in end-diastole was positive, and so, quite different to the zero flow seen throughout the diastolic period in the ascending aorta (Figure 1). The ascending aortic pressure waveform showed the same general features of the cerebral flow waveforms – with a short, sharp upstroke some 95 + 9 msec to the first peak or shoulder, the second systolic peak or shoulder, and distinct incisura corresponding to aortic valve closure (Figure 1). As for cerebral flow waves, aortic pressure declined slowly during diastole to a nadir which was also positive (the diastolic pressure). When flow waves were recorded on both right and left sides (MCA, ACA, VA, BA) there was no consistent difference (data not shown). Neither was there any consistent difference when aortic pressure was generated from the right or left radial artery.

Flow and Pressure Waveforms according to Age and Sex

Figure 2 shows all synthesised aortic pressure waves together with all ensemble-averaged flow waves for the four cerebral arterial sites in the third to eighth decades of life. As for the radial and carotid pressure waves [18], there were progressive changes with age, which can be attributed to aortic stiffening and early return of wave reflection from the lower body. From the third decade, wave reflection from the lower body boosted the second peak of flow, so that this approached or exceeded amplitude of the initial peak. More pronounced wave reflection effects were seen for flow waves in the BA and VA (Figure 2), and in females compared to males (Supplemental figure 1).

Development of this late systolic peak is readily apparent with age (Figure 2) for all flow waves in intracranial arteries, as well as for the synthesised aortic and radial pressure wave. As shown in figures 1 and 2, pressure AIx is higher in the aorta than in the radial artery. In the radial artery of adolescents, pressure AIx is negative (around -20% for females and -30% for males). Flow AIx is usually negative in cerebral arteries of adolescent males and females (Figures 3 and 4). AIx is consistently higher in females compared to males for both pressure

and flow waves and from an earlier age (Figure 3). AIx change with age was more prominent ($P<0.01$) in males than females; the relationship (Figure 4) between pressure AIx and flow AIx being similar in both sexes ($r=0.46$, $P<0.01$ in male and $r=0.40$, $P<0.01$ in females).

Amplitude of the flow velocity wave (Figure 5) remained relatively constant with age (β=-0.02, -0.05 to 0.11; $P=0.35$), while the pressure wave amplitude increased steadily with age in both males and females and to a similar degree. There was a similar relationship of Flow Pulsatility Index (FPI) between males and females and in the four different intracranial arteries and all increased progressively with age (Figure 6). Pressure Pulsatility Index (PPI) likewise increased slightly with age. In addition, FPI in the cerebral arteries was closely associated with PPI ($r=0.42$; $P<0.01$) (data not shown).

Pressure and Flow Relationship in the Frequency Domain

Figure 7 shows values of impedance modulus and phase calculated for the four different arteries. Values for MCA and ACA were very similar over the range 0 – 10 Hz, whereas there was a similar pattern but considerable variability in values determined from the BA and VA. Impedance modulus reached a minimum at 4-5 Hz after falling from its value at zero Hz – the cerebral resistance. Impedance phase –negative but close to zero at low frequencies, crossed zero at around 5 Hz. These values are similar to those seen in other vasodilated beds such as the kidney and lungs, or in a limb during vasodilatation [3,15]. Averaged reflection coefficient for the vascular beds was similar – 0.40 (for ACA), 0.46 (for MCA), 0.38 (for BA), and 0.40 (for VA). There was no gender or age difference of impedance modulus and phase (Supplemental figures 2 and 3).

6.3.4 Discussion

To the best of our knowledge, this is the largest study yet undertaken of pressure and flow waveforms in human cerebral arteries, or in arteries which connect cerebral arteries with the ascending aorta, aortic arch and left ventricle. Our principal findings are summarised as follows: first, cerebral artery flow waveforms are similar to central aortic pressure waveforms; both show late systolic augmentation. Second, augmentation of flow and pressure are similar in different cerebral arteries, as in the central aorta, and both PAIx and FAIx increase with age, but are consistently higher in females than males, so that in males over 70 years and females at all ages, flow augmentation embraces the peak of the flow pulse, boosting flow shear stress at the arterial intima. Central aortic pressure augmentation increases progressively with age in males and females, so boosting distending pressure and tensile stress in the arterial media [15, 27] (Figure 2).

Pulsatile pressure/ flow relationship can also be expressed in the frequency domain as cerebral vascular impedance [3,15]. This is similar to impedance patterns in the kidney and lungs whose arteries are normally dilated and in peripheral vascular beds when dilated by intra-arterial acetylcholine or with reactive hyperaemia [3,15]. As for other vascular beds, cerebral vascular impedance is independent of flow input or pressure input, and characterises the properties of the vascular bed downstream from the site(s) of pressure and flow measurement [3]. As shown in our current study, cerebral vascular impedance is similar in different cerebral vascular beds (supplied by MCA, ACA, VA, BA) with low impedance at zero frequency (steady component of flow); similar characteristic impedance at high frequencies (> 8 Hz) as in other systemic arteries of comparable size, and low fluctuation of impedance modulus and phase at intermediate frequencies (1-8 Hz) indicative of low wave reflection (<50 %) in the cerebral vascular bed. In contrast to pressure and flow waves entering the cranium (whose contour and amplitude are determined by the heart – pattern of

left ventricular ejection, and by arteries supplying the trunk and lower body – timing and amplitude of wave reflection), cerebral vascular impedance is normally determined by properties of the brain only [1-3]. Cerebral vascular impedance does not change with age or gender (Supplementary figures 2 and 3).

Findings can explain the unfavourable patterns of cerebral pressure and flow waves, which develop with age, and are more marked in females than males, and in shorter than taller individuals. These are attributable, not to cerebral vascular abnormalities, but to earlier and increased wave reflection from the lower body. Such abnormal pulsations predispose to medial and intimal degeneration in older adults, women especially, and may become apparent in younger adults when intracerebral arteries are compressed by rise of ICP after trauma [20].

Our study is based on the detailed studies of pressure, flow and wave reflection in the time domain by Frank, Wiggers, Hamilton and Dow, which were prominently featured in the Handbook of the American Physiological Society in 1963 [24], and by McDonald, Taylor, Womersley and many others since 1950 in both time and frequency domains [3, 15, 24].

Studies already undertaken on systemic arteries in experimental animals, in humans at different ages and in disease since 1890 have provided new information on pulsatile phenomena and have been a useful complement to the ubiquitous cuff sphygmomanometer [15, 21, 26]; which has to date provided virtually all the information used in patient management [8, 27]. The new approach to pulsatile pressure and flow has helped explain the ill effects of aortic stiffening in development of isolated systolic hypertension (ISH) (by far the most common cause of hypertension in men and women over age 50 years of age) [28], and the stronger relationship between aortic stiffening and systolic (not diastolic) pressure with cardiac failure in longitudinal studies including Framingham [28-30]. We undertook the present study in the belief that similar analysis of flow waveforms and their relationship with

pressure waveforms would provide supplementary information to the pressure waveforms alone, and especially at such sites as within the skull where arterial pressure cannot be measured non-invasively, but where flow waveforms can be measured by transcranial Doppler techniques [18].

Our findings carry important implications for studies of aging on cerebral pulsatile blood flow and on how altered cerebral pulsatile flow may damage the walls of small arteries in the brain consequent on aortic stiffening with age and also when intracranial pressure is increased after trauma and stroke [20]. The pressure wave entering the brain from the heart is accompanied by a similarly enhanced late systolic flow wave caused by wave reflection from the lower body [31]. High velocities of flow waves in the brain can dislodge endothelial cells from the wall of small blood vessels especially in the territory of the middle cerebral artery, causing micro thrombosis, when endothelium is denuded, and microhaemorrhage when the wall is breached [5, 26, 32, 33]. Such vascular damage is that described by Byrom [34, 35], Russell [36] and others in small cerebral arteries and arterioles. Donald Fry, of Byrom's and Taylor's vintage, working at the National Institute of Health at Bethesda described such damage to and avulsion of endothelial cells in the aorta in the presence of high and variable shear stress; he compared the endothelial cells to strands of a thatched roof, which are disorganised, then torn off by high and changing winds [37]. Importance is enhanced by knowledge that the component of peak flow, attributable to wave reflection from the lower body, can be decreased by arterial dilating drugs (such as nitroglycerine, angiotensin receptor antagonists and some calcium channel blockers) [38, 39]. Such knowledge provides additional reasons for their use from mid life in persons with arterial hypertension [38], especially when accompanied by high aortic PWV or high aortic pressure wave augmentation (or with high augmentation of flow in carotid Doppler or transcranial Doppler studies of cerebral arteries). Other therapeutic benefits may emerge through use of the same drugs (ARB, CCB, nitrates) in patients with stroke or head injury when intracranial pressure is elevated [40, 41].

Preliminary data have shown high risk in patients with stroke when there is high pressure augmentation [41], and benefits of reducing the pulsatile component of intra-cranial pressure in patients acutely ill with subarachnoid haemorrhage after aneurysm repair [8], and chronically ill with normal pressure hydrocephalus [42].

We hope to obtain more information on dementia and flow pulse abnormalities from follow up of this cohort. This has been arranged. It will be necessary to link associations in a longitudinal fashion so that causation can be established [43]. Ultimately, it will be necessary to separate the effects of aging on the vessels from secondary reactions of the body including inflammation, clearance, and repair [6, 35, 43]. Data of our current study support the optimism of earlier workers [35,36] that the underlying process (small vessel degeneration) is explicable, potentially reversible at an early stage, and not entirely degenerative [15, 34]. Data provide normal values for flow velocity pulsations in small and large intracerebral arteries, and show that consideration of pressure/ flow relationships in the time and frequency domain are useful for describing normal function and have the potential to uncover mechanisms in disease.

References:

1. Taylor MG. The input impedance of an assembly of randomly branching elastic tubes. Biophys J. 1966;6:29-51.

2. Taylor MG. Wave transmission through an assembly of randomly branching elastic tubes. Biophys J. 1966;6:697-716.

3. O'Rourke MF. Vascular impedance in studies of arterial and cardiac function. Physiol Rev. 1982;62:570-623.

4. Greenberg SM. Small vessels, big problems. N Engl J med. 2006;354:1451-1453.

5. O'Rourke MF, Safar ME. Relationship between aortic stiffening and microvascular disease in brain and kidney: cause and logic of therapy. Hypertension. 2005;46:200-204.

6. Stone J, Johnstone DM, Mitrofanis J, O'Rourke MF. The mechanical cause of age-related dementia (Alzheimer's Disease): the brain is destroyed by the pulse. J Alzheimers Dis 2015;44:355-373.

7. Maas AI, Stocchetti N, Bullock R. Moderate and severe traumatic brain injury in adults. Lancet Neurol 2008;7:728-741.

8. Eide PK, Bentsen G, Sorteberg AG, Marthinsen PB, Stubhaug A, Sorteberg W. A randomized and blinded single-center trial comparing the effect of intracranial pressure and intracranial pressure wave amplitude-guided intensive care management on early clinical state and 12-month outcome in patients with aneurysmal subarachnoid hemorrhage. Neurosurgery 2011;69:1105-1115.

9. DeBaun MR, Gordon M, McKinstry RC, Noetzel MJ, White DA, Sarnaik SA, Meier ER, Howard TH, Majumdar S, Inusa BP, Telfer PT, Kirby-Allen M, McCavit TL, Kamdem A, Airewele G, Woods GM, Berman B, Panepinto JA, Fuh BR, Kwiatkowski JL, King AA, Fixler JM, Rhodes MM, Thompson AA, Heiny ME, Redding-Lallinger RC, Kirkham FJ, Dixon N, Gonzalez CE, Kalinyak KA, Quinn CT, Strouse JJ, Miller JP, Lehmann H, Kraut

MA, Ball WS Jr, Hirtz D, Casella JF. Controlled trial of transfusions for silent cerebral infarcts in sickle cell anemia. N Engl J Med 2014;371:699-710.

10. Gorelick PB, Scuteri A, Black SE, Decarli C, Greenberg SM, Iadecola C, Launer LJ, Laurent S, Lopez OL, Nyenhuis D, Petersen RC, Schneider JA, Tzourio C, Arnett DK, Bennett DA, Chui HC, Higashida RT, Lindquist R, Nilsson PM, Roman GC, Sellke FW, Seshadri S. Vascular contribution to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/ American Stroke Association. Stroke 2011;42:2672-2713.

11. Chesnut RM, Temkin N, Carney N, Dikmen S, Rondina C, Videtta W, Petroni G, Lujan S, Pridgeon J, Barber J, Machamer J, Chaddock K, Celix JM, Cherner M, Hendrix T. A trial of intracranial-pressure monitoring in traumatic brain injury. N Engl J Med 2012;367:2471-2481.

12. Carrera E, Kim DJ, Castellani G, Zweifel C, Czosnyka Z, Kasparowicz M, Smielewski P, Pickard JD, Czosnyka M. What shapes pulse amplitude of intracranial pressure? J Neurotr 2010;27:317-324.

13. Steinberg MH. More blood for sickle cell anemia? N Engl J Med 2014;371:775-776.

14. Adams RJ, McKie VC, Hsu L, Files B, Vichinsky E, Pegelow C, Abboud M, Gallagher D, Kutlar A, Nichols FT, Bonds DR, Brambilla D. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. N Engl J Med 1998;339:5-11.

15. Nichols WW, O'Rourke MF, Vlachopoulos C. McDonald's Blood Flow in Arteries. 6th ed. Arnold Hodder, 2011.

16. Avolio AP, Chen SG, Wang RP, Zhang CL, Li MF, O'Rourke MF. Effects of aging on changing arterial compliance and left ventricular load in a northern Chinese urban community. Circulation 1083;68:50-58.

17. Avolio AP, Deng FQ, Li WQ, Luo YF, Huang ZD, Xing LF, O'Rourke MF. Effects of aging on arterial distensibility in populations with high and low prevalence of hypertension: comparison between urban and rural communities in China. Circulation 1985;71:202-210.

18. Kelly R, Hayward C, Avolio A, O'Rourke M. Non-invasive determination of age-related changes in the human arterial pulse. Circulation 1989;80:1652-1659.

19. Xu TY, Staessen JA, Wei FF, Xu J, Li FH, Fan WX, Gao PJ, Wang JG, Li Y. Blood flow pattern in the middle cerebral artery in relation to indices of arterial stiffness in the systemic circulation. Am J Hypertens 2011;25:319-324.

20. Kim MO, Adji A, O'Rourke MF, Avolio AP, Smielewski P, Pickard JD, Czosnyka M. Principles of cerebral hemodynamics when intracranial pressure is raised: lessons from the peripheral circulation. J Hypertens 2015;33:1233-41.

21. Pauca AL, O'Rourke MF, Kon ND. Prospective evaluation of a method for estimating ascending aortic pressure from the radial artery pressure waveform. Hypertension 2001;38:932-937.

22. Wei FF, Li Y, Zhang L, Xu TY, Ding FH, Staessen JA, Wang JG. Association of target organ damage with 24-hour systolic and diastolic blood pressure levels and hypertension subtypes in untreated Chinese. Hypertension 2014;63:222-228.

23. Cecelja M, Jiang B, McNeill K, Kato B, Ritter J, Spector T, Chowienczyk P. Increased wave reflection rather than central arterial stiffness is the main determinant of raised pulse pressure in women and relates to mismatch in arterial dimensions: a twin study. J Am Coll Cardiol 2009;54:695-703.

24. Spencer MP, Denison AB. Pulsatile Blood Flow in the Vascular System. In: APS Handbook of Physiology, 1963;2:839-864.

25. Minor WR, Conti CR, Lewis KB, O'Rourke MF. Pulmonary arterial pulse wave velocity and impedance in man. Circ Res 1969;25:637-649.

26. O'Rourke MF, Safar ME, Dzau V (eds). Arterial Vasodilation: Mechanisms and Therapy. Edward Arnold, London 1993.

27. O'Rourke MF, Hashimoto J. Mechanical factors in arterial aging: a clinical perspective. J Am Coll Cardiol 2007;50:1-13.

28. Franklin SS, Gustin W 4th, Wong ND, Larson MG, Weber MA, Kannel WB, Levy D. Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study. Circulation 1997;96:308-315.

29. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. JAMA 1991;265:3255-3264.

30. Franklin SS, Khan SA, Wong ND, Larson MG, Levy D. Is pulse pressure useful in predicting risk for coronary heart disease? The Framingham Heart Study. Circulation 1999;100:354-360.

31. Hashimoto J, Ito S. Pulse pressure amplification, arterial stiffness, and peripheral wave reflection determine pulsatile flow waveform of the femoral artery. Hypertension 2010;56:926-933.

32. Henry-Feugeas MC, DeMarco G, Peretti II, Godon-Hardy S, Fredy D, Claeys ES. Age-related cerebral white matter changes and pulse-wave encephalopathy: observations with three-dimensional MRI. Magn Reson Imaging 2005;23:929-937.

33. Bateman GA. The role of altered impedance in the pathophysiology of normal pressure hydrocephalus, Alzheimer's disease and syringomyelia. Med Hypo 2004;63:980-985.

34. Byrom FB, Dodson LF. The mechanism of the vicious circle in chronic hypertension. Clin Sci (Lond) 1949;8:1-10.

35. Byrom FB. The Hypertensive Vascular Crisis: An Experimental Study. Elsevier Science, 1969.

36. Russell RW. How does blood-pressure cause stroke? Lancet 1975;2:1283-1285.

37. Fry DL. Responses of the arterial wall to certain physical factors. Amsterdam: Ciba Foundation Symposium, 1973.

38. Dufouil C, Chalmers J, Coskun O, Besancon V, Bousser MG, Guillon P, MacMahon S, Mazoyer B, Neal B, Woodward M, Tzourio-Mazoyer N, Tzourio C. Effects of blood pressure lowering on cerebral white matter hyperintensities in patients with stroke: the PROGRESS (Perindopril Protection Against Recurrent Stroke Study) Magnetic Resonance Imaging Substudy. Circulation 2005;112:1644-1650.

39. Levi-Marpillat N, Macquin-Mavier I, Tropeano AI, Bachoud-Levi AC, Maison P. Antihypertensive classes, cognitive decline and incidence of dementia: a network meta-analysis. J Hypertens 2013;31:1073-1082.

40. Eide PK, Sorteberg A, Bentsen G, Marthinsen PB, Stubhaug A, Sorteberg W. Pressure-derived versus pressure wave amplitude-derived indices of cerebrovascular pressure reactivity in relation to early clinical state and 12-month outcome following aneurismal subarachnoid hemorrhage. J Neurosurg 2012;116:961-971.

41. Soiza RL, Davie MM, Williams DJ. Use of the augmentation index to predict short-term outcome after acute ischemic stroke. Am J Hypertens 2010;23:737-742.

42. Eide PK, Sorteberg W. Diagnostic intracranial pressure monitoring and surgical management in idiopathic normal pressure hydrocephalus: a 6-year review of 214 patients. Neursurg 2010;66:80-91.

43. Gandy S. Lifelong management of amyloid-beta metabolism to prevent Alzheimer's disease. N Engl J Med 2012;367:864-866.

Figure Legends

Figure 1. Ensemble-averaged pressure and flow waves from all 1020 subjects are shown. At top are radial artery (red) and central aortic (orange) pressure, at centre are flow velocity waveforms; from top to bottom, MCA, ACA, BA and VA. Standard Error of the Mean (SEM) of the ensemble averaged values was small (less than 1mmHg and 1 cm/sec). At bottom is an assumed ascending aortic flow waveform (black). Scale for flow velocity at left, pressure at right. Vertical lines identify features common to the recorded waveforms: - T1 corresponds to the peak of flow from the heart, T2 corresponds to peak of wave reflection from the lower body, T3 corresponds to end of ventricular ejection and beginning of ventricular diastole.

Figure 2. Ensemble-averaged flow velocity waves by decade 3 – 8 in ACA, MCA (middle), VA and BA (bottom), together with synthesised aortic and measured radial pressure waves (top) for the whole cohort of 1020 subjects.

Figure 3. Change in flow augmentation index (FAIx) with age in females (red) and males (blue). AIx values at each data point were averaged every 5 years of age and were presented with bar indications of 2 standard error of the mean (SEM). In females, PAIx (see also figure 4) and FAIx were high and remained high at all ages. For males, both PAIx (see also figure 4) and FAIx in all arteries rose progressively with age.

Figure 4. Relationship between cerebral arterial blood flow and ascending aortic pressure augmentation index (FAIx and PAIx respectively) in females (red) and males (blue) is shown. Estimated linear regression line, regression coefficients and correlation coefficients are also presented in each panel.

Figure 5. Change in arterial blood pressure (top) and cerebral arterial blood flow (middle and bottom) pulse wave amplitude with age in females (red) and males (blue). Estimated linear regression line, regression coefficients and correlation coefficients are also presented in each panel.

Figure 6. Change in arterial blood pressure (top) and cerebral blood flow (middle and bottom). Pulsatility Index (PI) in females (red) and males (blue). Estimated linear regression line, regression coefficients and correlation coefficients are also presented in each panel.

Figure 7. Cerebral vascular impedance computed from ascending aortic pressure and cerebral arterial flow at MCA,ACA, BA and VA. Averaged values at every 0.8 Hz were presented with bar indication of 1 Standard Deviation (SD) (left). Multiple polynomial regression models were fit to the mean values for both modulus and phase (right).

Figure 1. Ensemble-averaged waveforms for cerebral blood flow and systemic blood pressure pulses (N=1020)

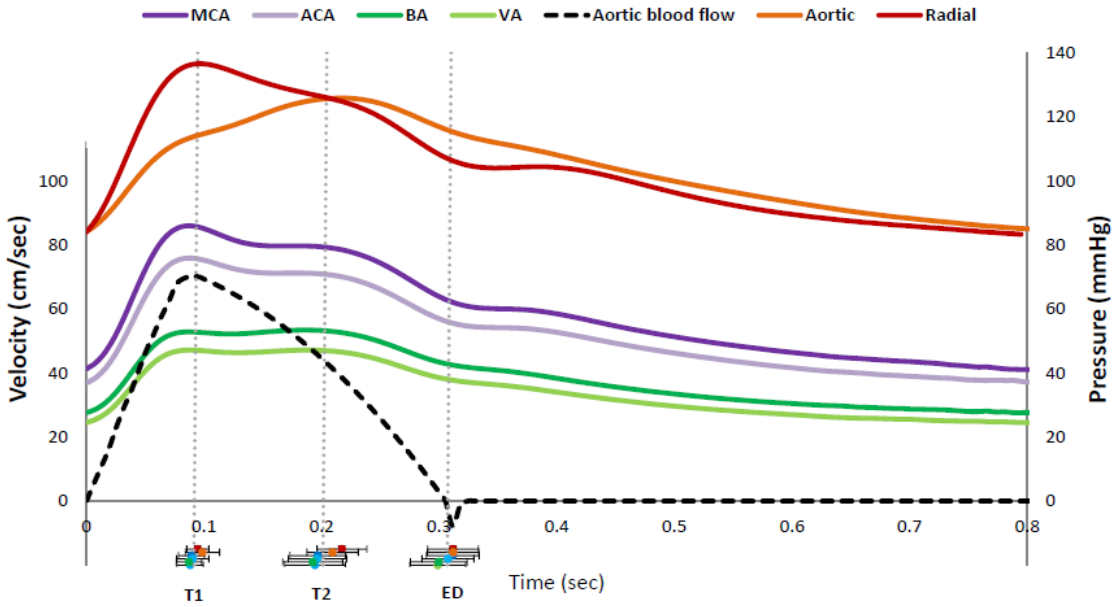


Figure 2.

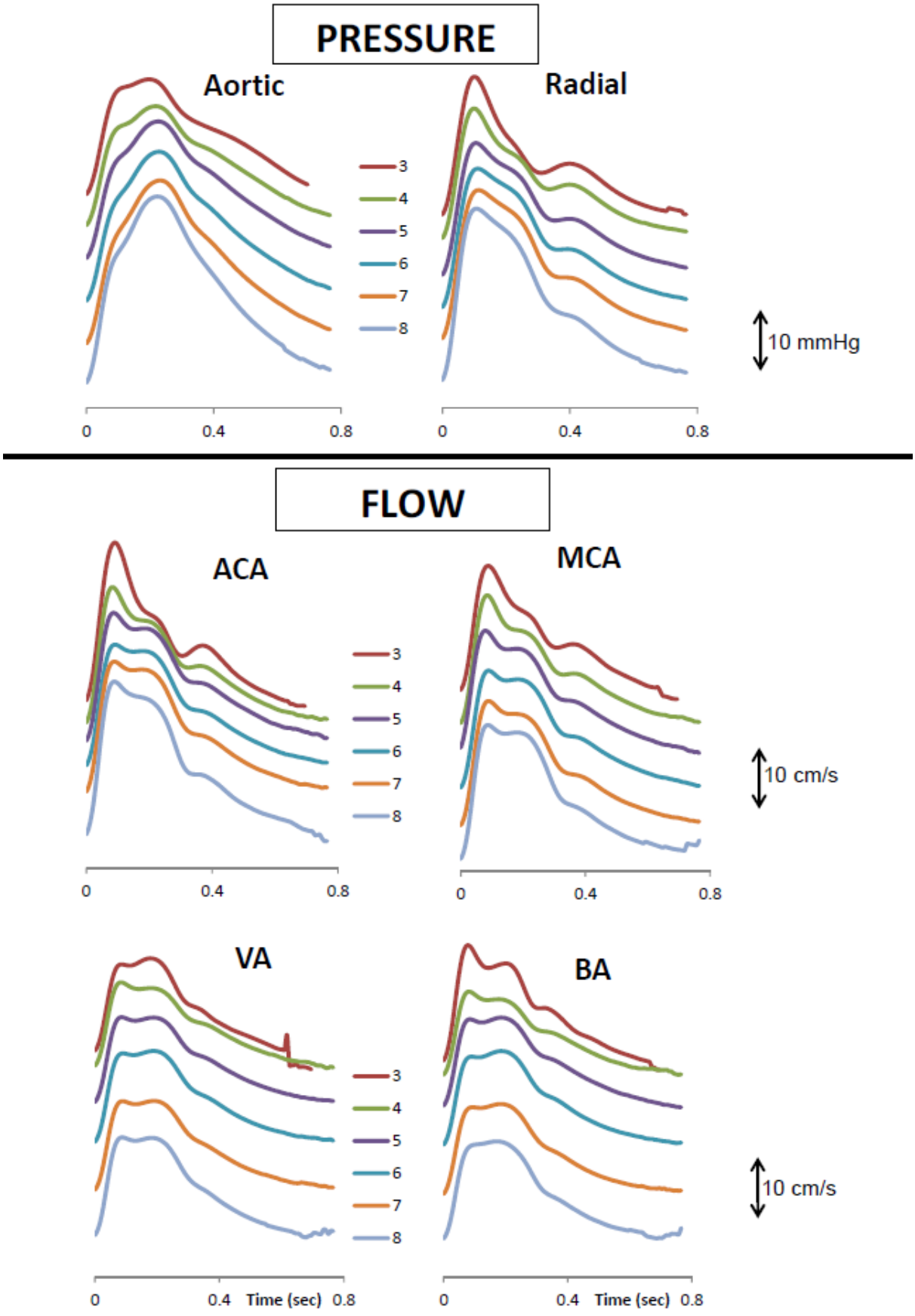

PRESSURE
Aortic
Radial
3
4
5
6
7
8
10 mmHg
0
0.4
0.8
FLOW
ACA
MCA
VA
BA
10 cm/s
Time (sec)

Figure 3. The effect of age and gender on cerebral blood flow augmentation index (FAIx)

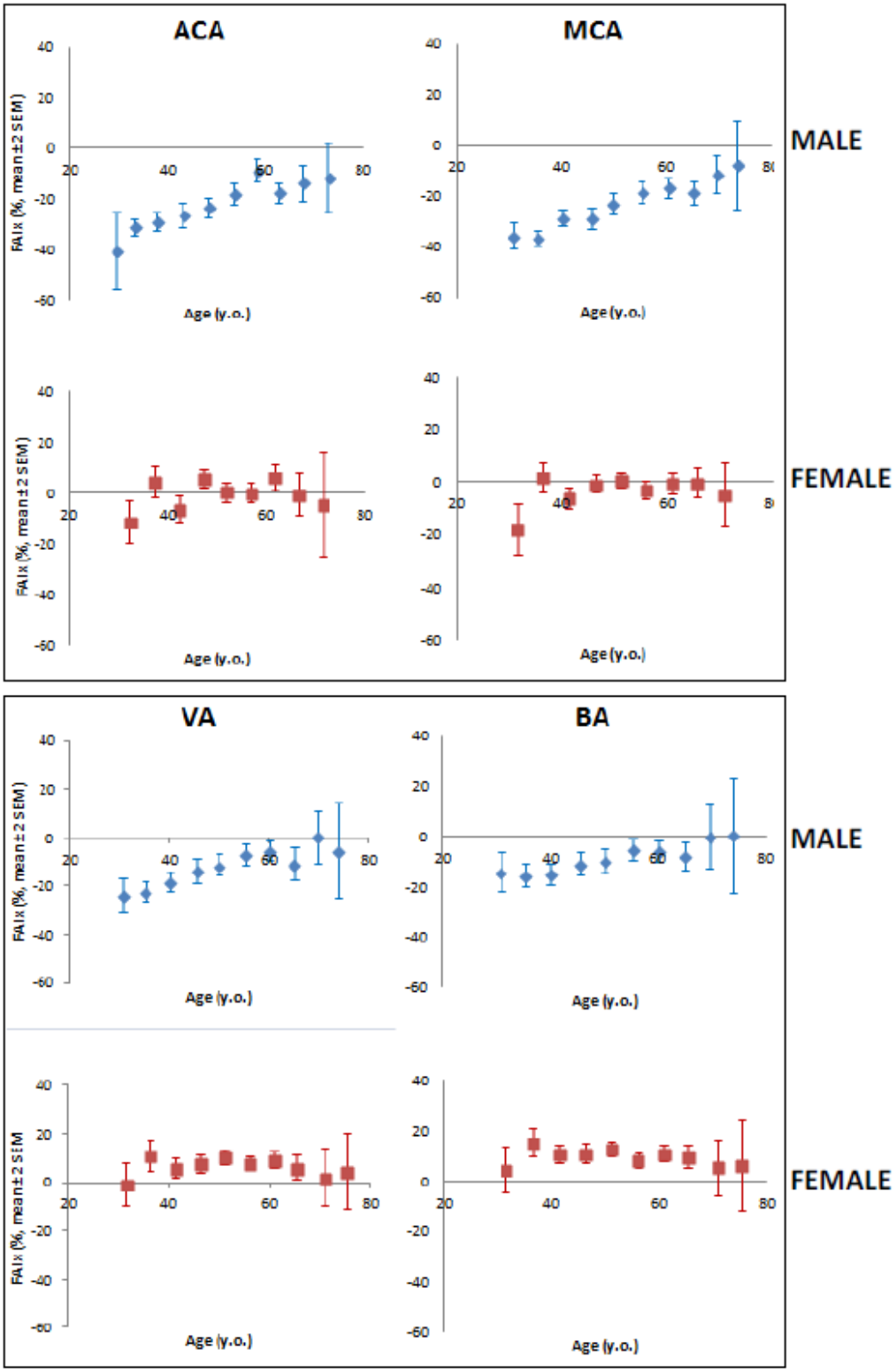


Figure 4. Relationship between cerebral blood flow (FAIx) and aortic pressure (PAIx) augmentation index

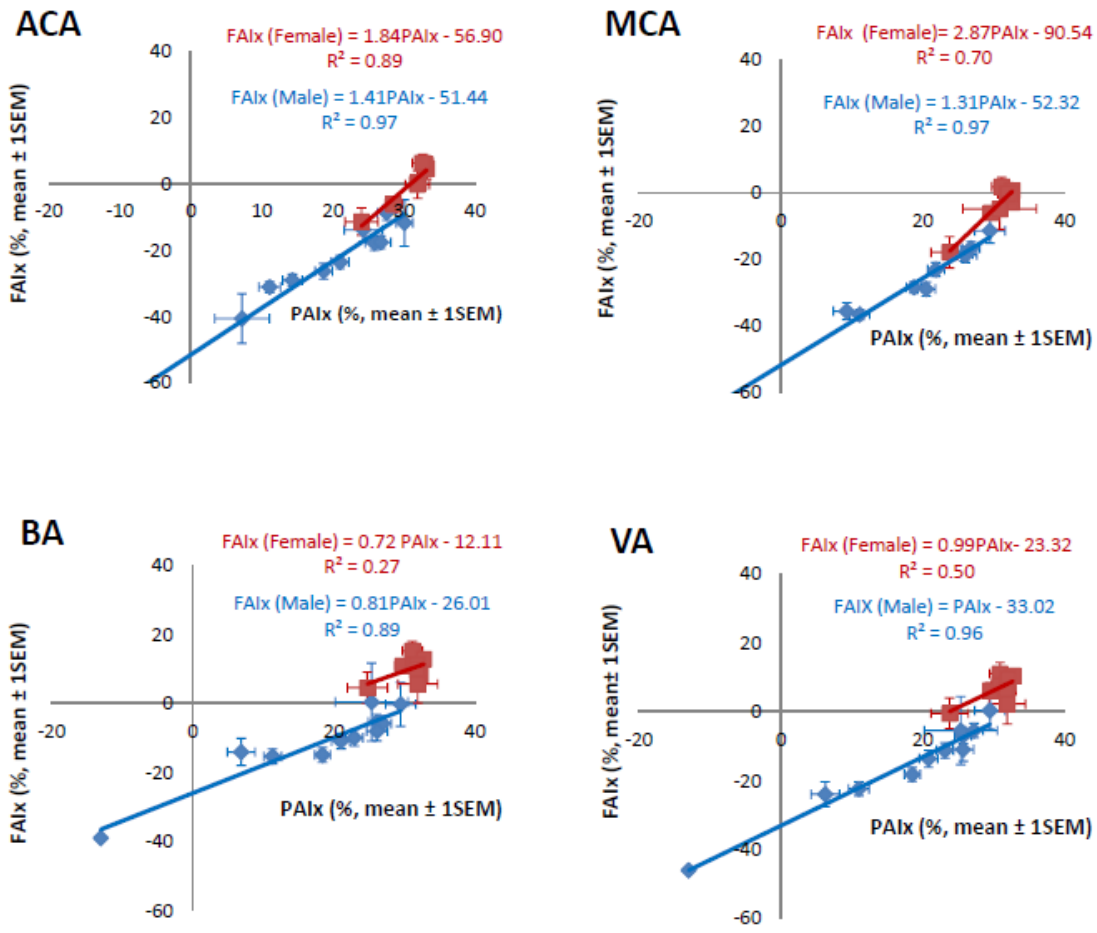


Figure 5. The effect of age on wave amplitude for cerebral blood flow and aortic pressure pulses

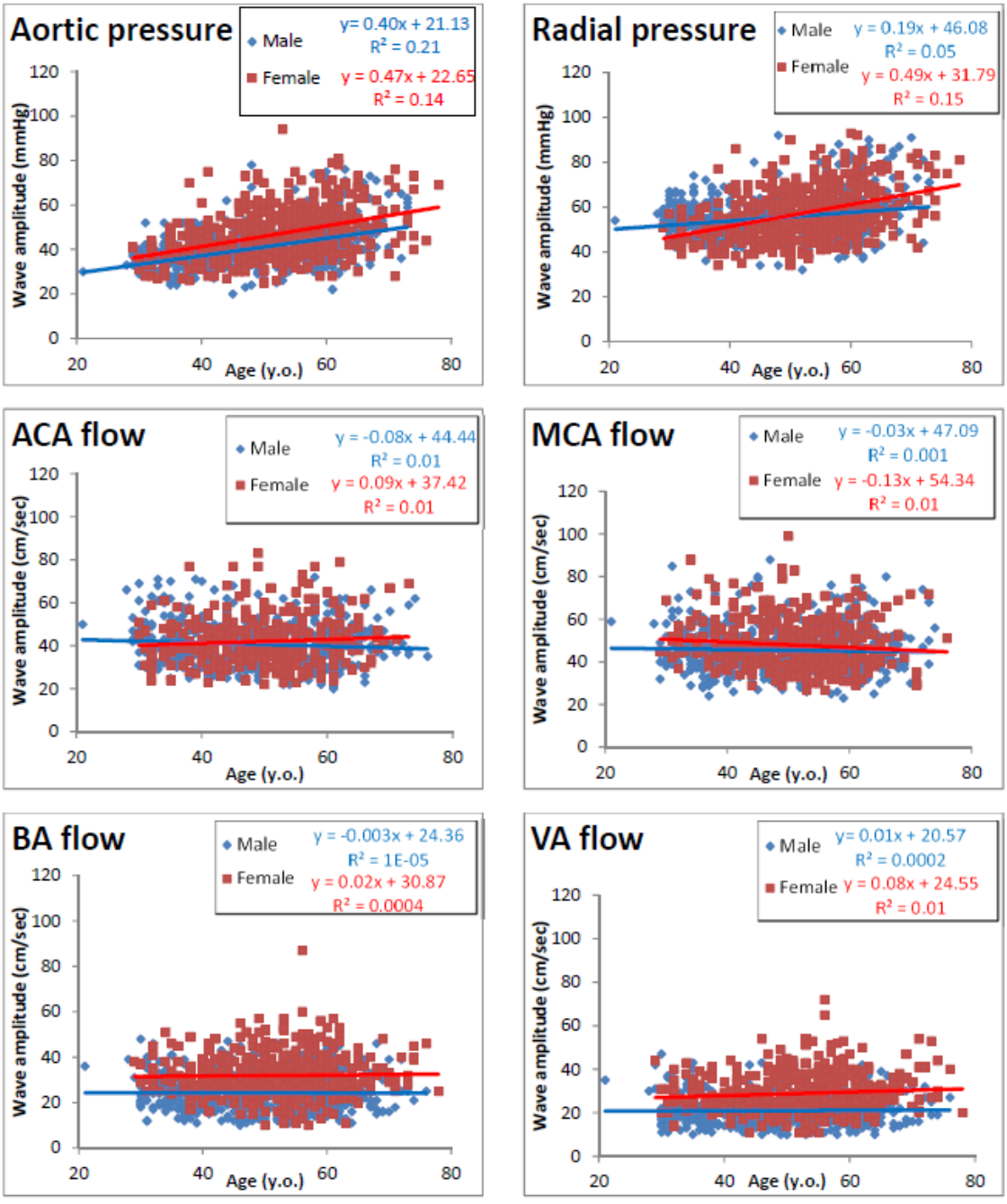


Figure 6. The effect of age and gender on pulsatility index (PI) for cerebral blood flow and systemic pressure pulses

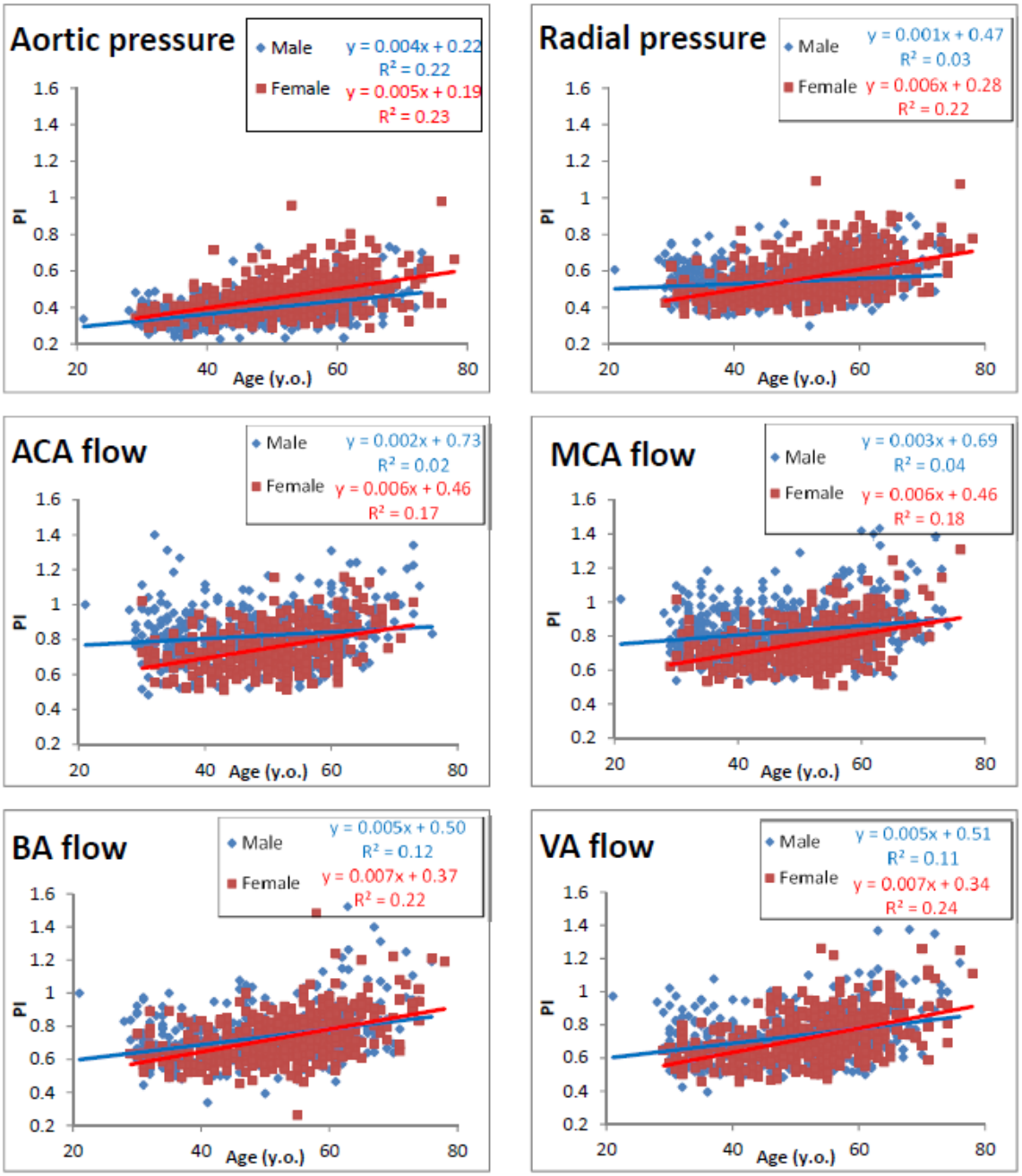


Figure 7. Cerebral vascular impedance

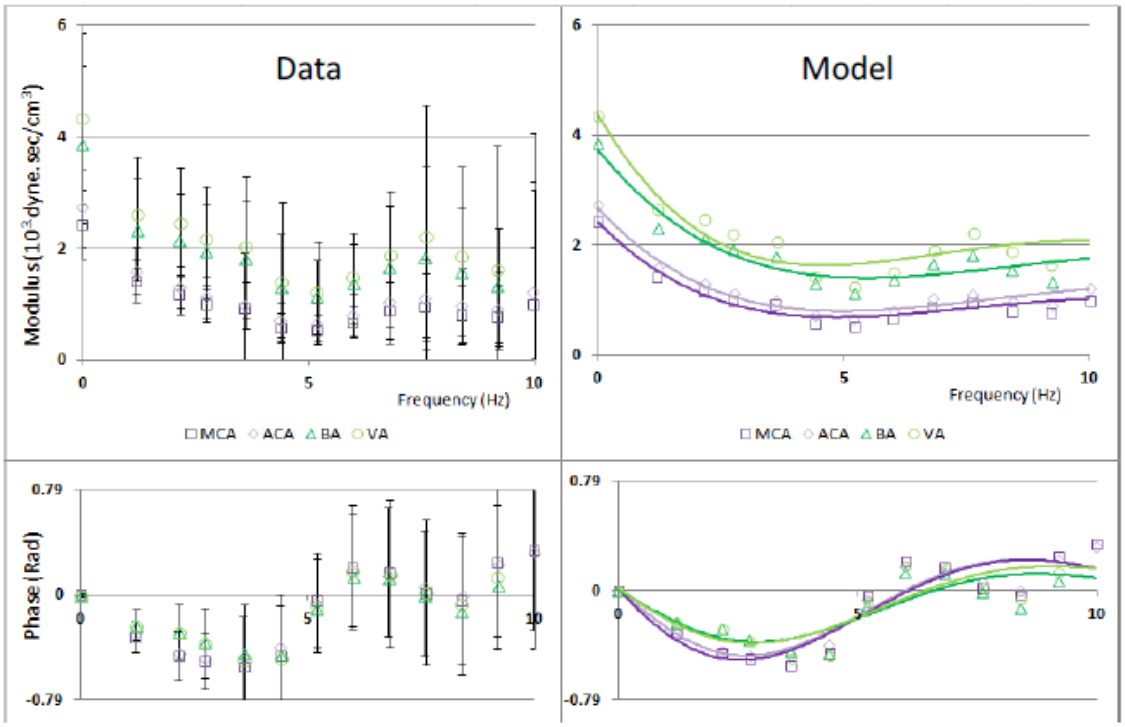


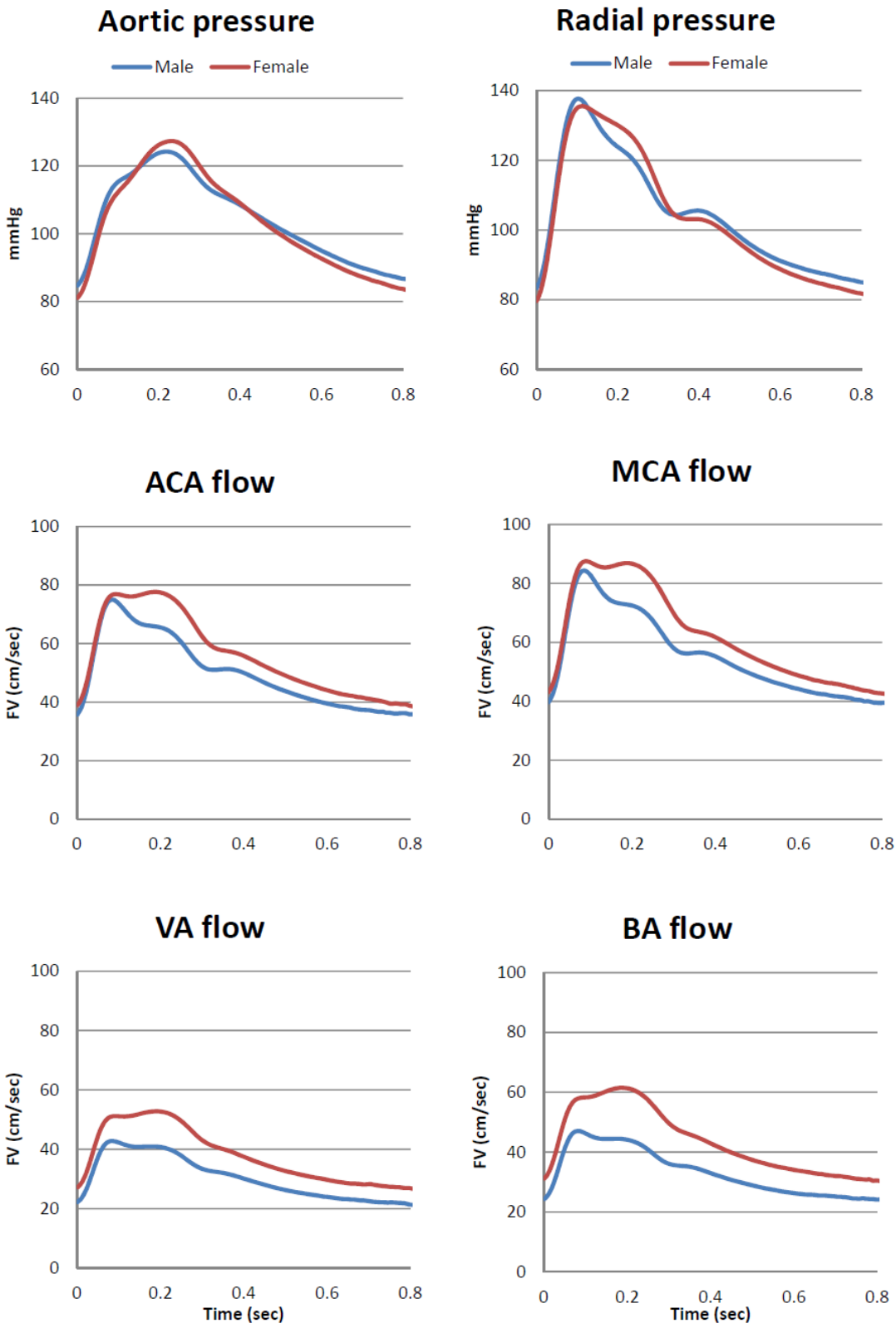
Table 1. Cohort data (mean ± 1 standard deviation)

	Women (n=523)	Men (n=497)	p-value
Anthropometric characteristics:			
Age (Years)	53±9	49±11	<0.01
Height (cm)	160±5	172±6	<0.01
Weight (kg)	60±9	74±11	<0.01
Body Mass Index	24±3	25±4	<0.01
Blood pressure and heart rate:			
Heart rate	69±10	70±10	0.68
Brachial systolic	137±14	139±14	0.05
Brachial diastolic	79±9	83±9	<0.01
Mean pressure	102±10	103±11	0.09
Central systolic	128±14	125±14	<0.01
Central diastolic	81±9	84±9	<0.01
Brachial pulse amplitude	57±12	55±10	<0.01
Central pulse amplitude	47±11	41±10	<0.01

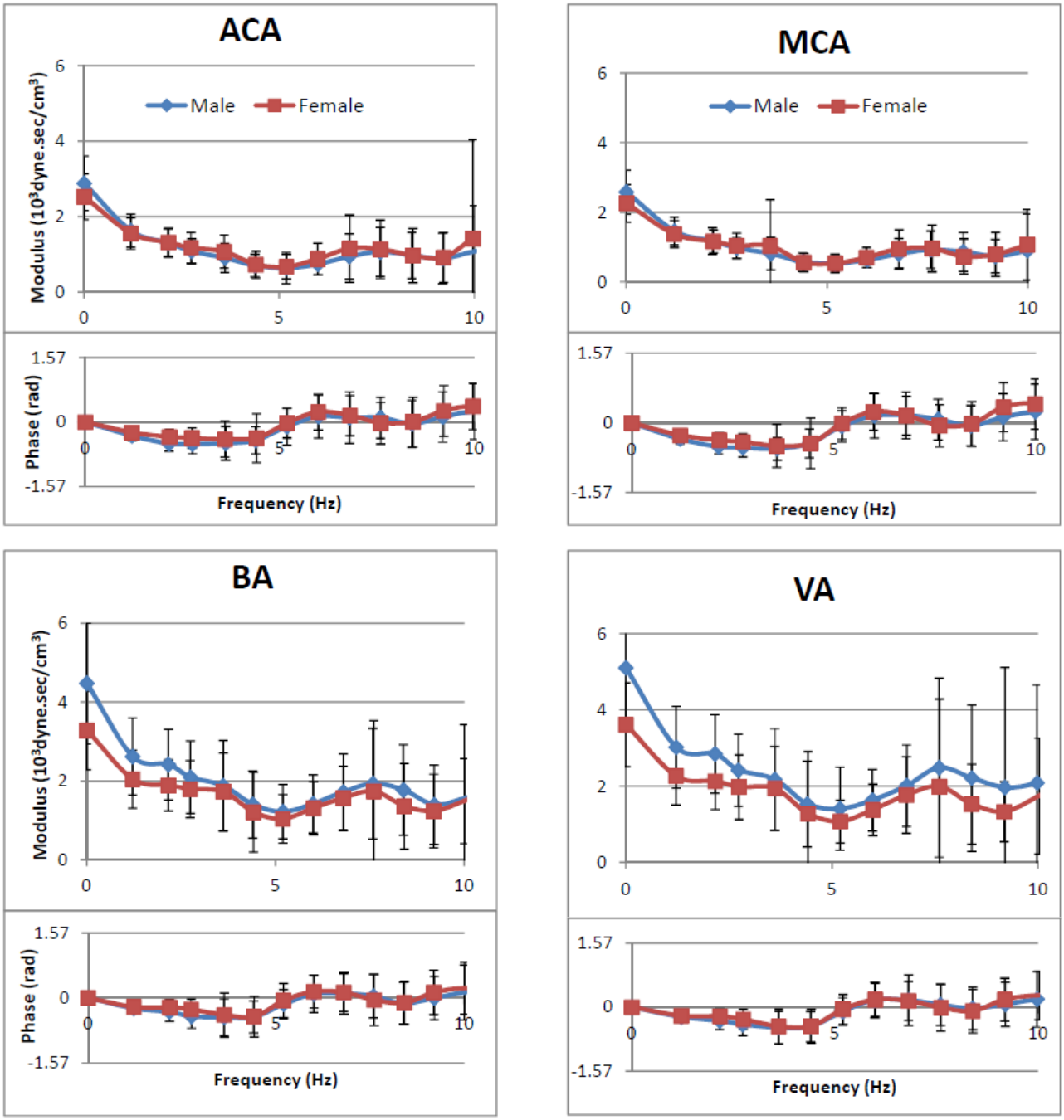
Table 2. Details of T1, T2 and ED. Time (msec) from foot of the wave to first peak (T1), second peak (T2) and to dicrotic notch (ED) is computed from flow and arterial pressure pulse waveforms by using SphygmoCor process. Although, pressure and flow pulses were measured one at a time, T1, T2 and ED are in the statistically acceptable ranges (p=0.8-0.9).

	Central BP		Radial BP		MCA		ACA		BA		VA	
(m-sec)	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
T1	94.8	9.4	98.7	14.5	89.3	10.9	90.4	13.7	87.1	10.8	88.3	11.3
T2	217.3	21.2	209.4	21.8	196.7	23.7	196.4	24.8	192.4	25.4	194.5	25.8
ED	311.7	21.5	311.9	21.9	311.6	22.4	307.5	22.1	299.7	24.2	298.9	23.8

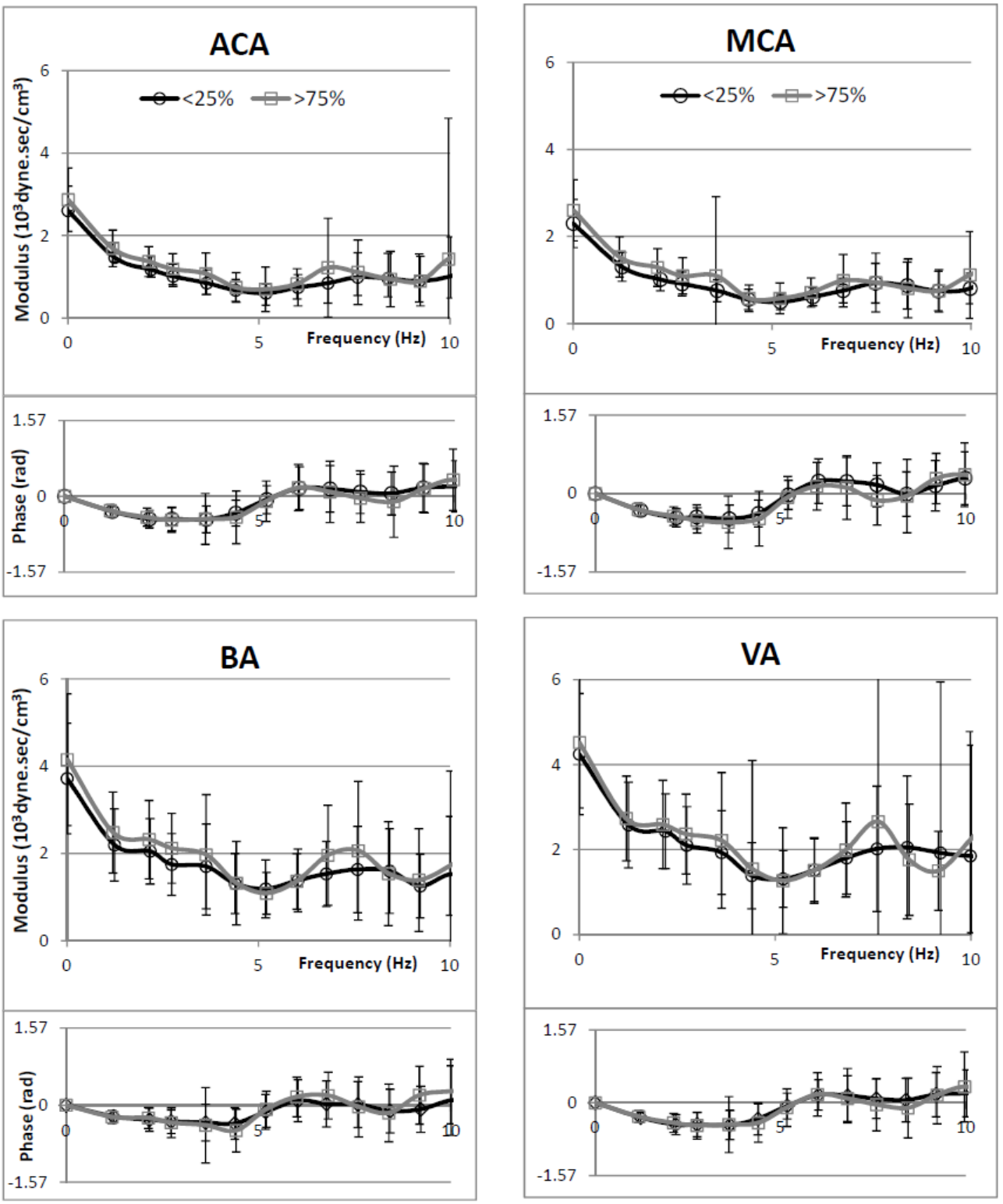
Supplemental Figure 1. Gender difference in arterial pressure (top) and cerebral arterial blood flow pulses (middle and bottom). Red and blue pulses are the ensemble-averaged waveform from 523 females and 497 males, respectively. Females show higher secondary augmented pulse in both pressure and flow pulses than males.



Supplemental Figure 2. Gender effect on cerebral vascular impedance. Data presented with mean and 1 SD computed from females (red) and males (blue) separately.



Supplemental Figure 3. Age effect on cerebral vascular impedance. Data from the lowest age quartile (black) are compared to that of the highest age quartile (grey).



6.4 Study: Cerebral Hemodynamics when Intracranial Pressure is Raised

A study published as:

Kim MO, **Adji A**, O'Rourke MF, Avolio AP, Smielewski P, Pickard JD, Czosnyka M. **Principles of Cerebral Hemodynamics when Intracranial Pressure is Raised: Lessons from the Peripheral Circulation**. *Journal of Hypertension* 2015; 33:1233-1241.

The normal brain is highly vascular and richly perfused, but it normally does not pulsate. The brain is unique that it is contained in a closed skull with limited connection to the exterior and to the rest of the circulation. It has been over 250 years since the Monro-Kellie doctrine was introduced (Monro 1783, Kellie 1824, Mokri 2001), of implications arising from a constant intracranial/ vertebral space occupying Brain, Cerebro-Spinal Fluid, Venous Blood, and Arterial Blood, that is an increase in one intracranial component must reduce volume of another component. Therefore we sought to better understand the mechanism of the cerebral hemodynamics, especially in the situation where intracranial pressure is raised, in this study, due to head trauma.

Data on arterial and intracranial pressure were analysed, as well as cerebral flow velocity from 8 patients with traumatic brain injury. In particular, these patients showed episodes of marked spontaneous increase of intracranial pressure, or "plateau waves". This study concluded that the rise in intracranial pressure caused no consistent change in arterial pressure, while the cerebral perfusion pressure reduced significantly. Additionally, mean flow velocity recorded from middle cerebral artery decreased and its pulsatility increased. These changes are explicable using the Monro-Kellie doctrine and emphasise the importance of reducing intracranial pressure. The central pulsatile hemodynamic indices measured in this

study have relationships with pressure inside the cranium, and could provide ways to estimate intracranial pressure noninvasively through continuous monitoring in the intensive care ward.

The findings have been presented at the Intracranial and Brain Monitoring conference in 2013, and the full manuscript is has been published in Journal of Hypertension. I performed majority of data processing, data analysis and was actively involved in manuscript preparation. From this study, we hope to open up the possibility for better use of vasodilators or vasoconstrictors to supplement present protocols of patients management, as well as use of diuretic agents or hemicraniectomy in patients with head injury. The link between central pulsatility and the pressure and flow inside the brain established from this study can be applied in clinical situations where significant pressure and/or flow wave changes occur inside the cranium.

Kim, M. O., Adji, A., O'Rourke, M.F., Avolio, A.P., Smielewski, P., Pickard, J.D., & Czosnyka, M. (2015) Principles of cerebral hemodynamics when intracranial pressure is raised: lessons from the peripheral circulation. *Journal of Hypertension.* 33(6) p. 1233-1241.

DOI: 10.1097/HJH.0000000000000539

6.5 Study: Aortic Pressure Waveform Changes during Spontaneously Raised Intracranial Pressure

A study published as:

Kim MO, **Adji A**, O'Rourke MF, Avolio AP, Smielewski P, Pickard JD, Czosnyka M. **Change in Pulsatile Cerebral Arterial Pressure and Flow Waves as a Therapeutic Strategy?** (*Acta Neurochirurgica Supplement*) **(2016)**

From the same data as published in Journal of Hypertension in section 6.4, other findings have been presented at the Intracranial and Brain Monitoring conference in 2013, and the expanded abstract on this study has just been published. I performed the initial data processing, data analysis and was actively involved in manuscript preparation.

Change in Pulsatile Cerebral Arterial Pressure and Flow Waves as a Therapeutic Strategy?

Mi Ok Kim[1], **Audrey Adji**[1,2], Michael F O'Rourke[2,3], Alberto P Avolio[1], Peter Smielewski[4], John D Pickard[4], Marek Czosnyka[4]

[1]Australian School of Advanced Medicine, Macquarie University, Sydney, Australia

[2]St Vincent's Clinic, Sydney, Australia

[3]University of New South Wales/ VCCRI, Sydney, Australia

[4]Academic Neurosurgical Unit, Addenbrooke's Hospital, Cambridge University, United Kingdom

Abstract

Background: While intracranial pressure (ICP), arterial pressure, and transcranial middle-cerebral-artery flow velocity (MCAFV) are often monitored in unconscious patients following stroke or head injury, the value of waveform indices has not been fully established.

Methods: We retrospectively analysed data of 8 adults (age 19-36 years) with closed head injury who had spontaneous and repeated episodes of elevated ICP (i.e. "plateau waves"). MCAFV was measured with transcranial Doppler, ICP with Codman catheter and radial artery pressure by cannulation. Ascending aortic pressure (AAP) was generated from radial artery using SphygmoCor^{TM}. Cerebral perfusion pressure (CPP) was calculated as AAP – ICP in the time domain.

Results: During plateau waves, ICP and cerebral flow velocity amplitude increased significantly compared to basal condition, while cerebral mean flow decreased. Amplitude of the secondary peak in ICP, AAP and MCAFV waveform became dominant.

Conclusion: Increase in amplitude of ICP, AAP and MCAFV waves can be attributed to greater prominence of reflected waves from the lower body, apparent in pulse waveform analysis. Hypothetically, arterial vasodilators such as nitrates reduce reflected pressure waves from the lower body, and through decreasing amplitude of AAP, ICP and MCAFV, may be as beneficial for the cerebral circulation as they are for the left ventricle of the heart.

Keywords: Central aortic pressure pulse, intracranial pressure, waveform analysis, pressure wave reflection

6.5.1 Introduction

The relationship between pulsatile pressure and flow entering the brain is generally considered by neurological researchers in terms of arterial "Windkessel" compliance and resistive properties, with analysis in the time domain only [1,2]. Full understanding of this subject is important to optimize treatment of such acute conditions as stroke and cerebral trauma, and long-term, to delay progression of the microvascular damage with aging and hypertension, which over decades leads to dementia. Our main interest was interpretation of the middle cerebral artery flow velocity waveform with the waveform of arterial pressure entering the skull (as ascending aortic pressure) or the brain (as cerebral perfusion pressure). We ultimately aim to establish mechanisms that explain progression of microvascular damage which leads to intellectual deterioration and dementia in later life.

6.5.2 Material and Methods

The study was performed retrospectively, and eight patients (2 women, 6 men, age 19-36 y) were selected out of 187 patients admitted to Neurocritical Care Unit of Addenbrooke's Hospital (1992 to 1998) following head injury. These patients had characteristic transient spontaneous elevations in intracranial pressure (ICP) which satisfied criteria of Lundberg's "A waves" or "plateau waves". High fidelity radial artery blood pressure (RAP) waveforms were recorded with an indwelling cannula, short, stiff connecting tubes and external pressure transducer (Edwards Lifesciences, Irvine, CA). Middle cerebral artery flow velocity (MCAFV) waveforms were recorded by transcranial Doppler technique from the left and/or right middle cerebral artery through a trans-temporal "window". ICP was recorded using intraparenchymal Codman transducers. RAP recordings were converted to ascending aortic pressure (AAP) waves using the SphygmoCor® system and validated generalised transfer function [3].

Cerebral perfusion pressure (CPP) was calculated as difference between digitised AAP and ICP waves. Pulsatility index was calculated as ratio between pulse amplitude and mean of the pulse.

Recorded pulses of RAP, AAP, ICP and MCAFV were selected over at least one respiratory cycle (about 10-second duration) during baseline and ICP plateau period in each patient (Fig. 1). These series of waveforms were ensemble-averaged to obtain representative waveform of each RAP, AAP, ICP and MCAFV pulse in each subject for further analysis.

6.5.3 Results

ICP plateau waves lasted for between 3–30 minutes in all patients. The plateau waves occurred independently of systemic arterial pressure, but created a substantial reduction in the gradient of CPP which maintains flow (Table 1). MCAFV usually showed increased amplitude during the periods of elevated ICP, but mean flow velocity decreased significantly (Fig. 1, Fig.2 and Table 1). Pulsatile ICP was significantly increased during plateau wave (Table 1). ICP pulse wave contour resembles AAP waves during plateau wave and secondary peak of the ICP, AAP, MCAFV became more prominent during ICP plateau waves (Fig.2, arrows)

6.5.4 Discussion

The rise in ICP during plateau wave period must have compressed, narrowed and unloaded all vessels within the brain including the middle cerebral artery. During the period of raised ICP, AAP remained relatively steady, but pulsatile middle cerebral artery flow did not. Simultaneous changes in pulsatile phenomena included increase in amplitude of ICP fluctuations and change in the ICP waveform to resemble the aortic pressure wave. This

demonstrated that the smallest arteries throughout the brain became exposed to high secondary pulsations which were not seen when ICP was normal. High pulsations may be attributable to wave reflection from the lower body [3], or a decrease in cerebrospinal compliance at elevated ICP In a first scenario, reduction in wave reflection from the lower body is as logical a target for vasodilator agents (nitrates, CCBs, ACEIs, and ARBs) as for the left ventricle and for other systemic arteries. Cerebral ffindings are exaggerated through compression and narrowing of brain blood vessels by rising ICP.

The major relevance of our study is to young persons with head injury, and to the possibility that late hospital complications including cerebral arterial narrowing and occlusion may be a consequence of raised pulsatility of pressure and flow in cerebral vessels. These findings should assist in monitoring and management. They open the possibility to better use of arterial dilating (nitrates, calcium channel blockers) or constricting agents (epinephrine, dopamine, norepinephrine) to supplement present protocols of ventilation, and use of diuretic agents or hemicraniectomy in patients with head injury.

References

1. Eide PK, Czosnyka M, Sorteberg W, Pickard JK, Smielewski P (2007). Association between intracranial, arterial pulse pressure amplitudes and cerebral autoregulation in head injury patients. Neurol Res 29:578-582.

2. Eide PK, Park EH, Madsen JR (2010) Arterial blood pressure vs intracranial pressure in normal pressure hydrocephalus. Acta Neurol Scand 122:262-269.

3. Nichols WW, O'Rourke MF, Vlachopoulos C. McDonald's Blood Flow in Arteries. 6th ed. London; Arnold Hodder 2011, pp 595-638.

Table. Hemodynamic indices during baseline and raised ICP "plateau waves". Significant differences (p-value is ≤ 0.01) for each index between baseline and during plateau period were represented as "*".

	Baseline	Raised ICP (Plateau waves)
Mean AAP (mmHg)	89.7	89.3
Mean CPP (mmHg)	61.1	36.1 *
Mean ICP (mmHg)	28.8	52.8 *
Pulsatile ICP (mmHg)	8.1	20.4 *
Mean MCAFV (cm/s)	53.2	40.0 *
Peak MCAFV (cm/s)	107.9	116.8
Pulsatile MCAFV (cm/s)	74.7	95.2 *
MCAFV pulsatility index	1.58	2.56 *

Figures and Legends

Figure 1. Representative recordings of intracranial pressure (ICP), cerebral arterial blood flow velocity (MCAFV), radial blood pressure (RAP) and central aortic blood pressure (AAP) are shown from one subject.

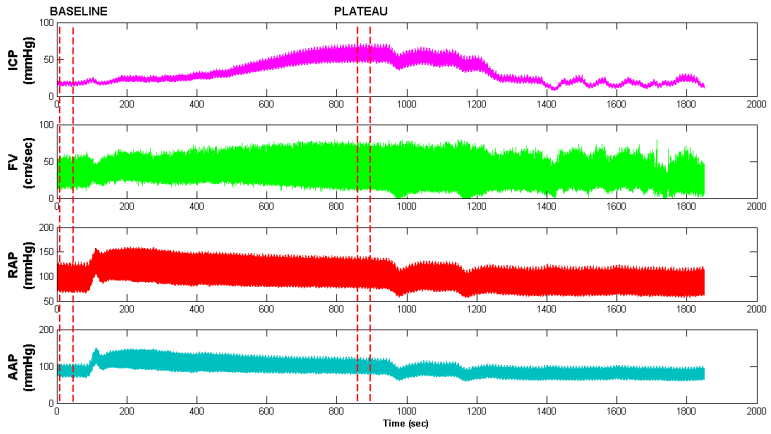
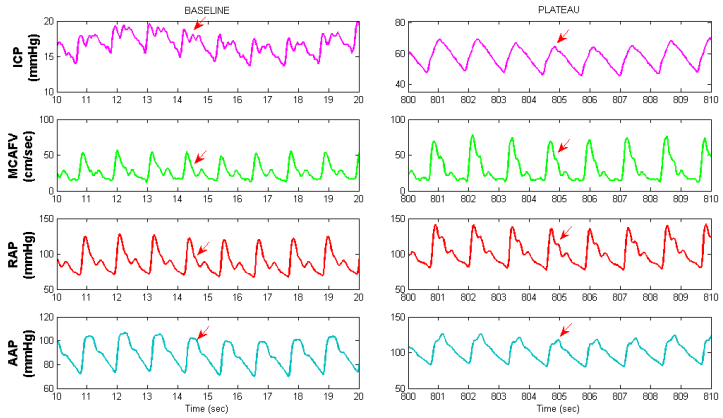


Figure 2. Series of ICP, MCAFV, RAP and AAP waveforms at baseline (left) and during raised ICP (right) are shown. Arrows indicates increased reflected wave during raised ICP period.



6.6 Morphological Similarities between the Central Aortic Pressure Waveform and the Intracranial Pressure Waveform

A study published as:

Kim MO, Eide PK, O'Rourke MF, **Adji A**, Avolio AP. **Intracranial Pressure Waveforms are More Closely Related to Central Aortic than Radial Pressure Waveforms: Implications to Pathophysiology and Therapy** (*Acta Neurochirurgica Supplement*) **(2016)**

To date, it has been the routine practice in most neurosurgery department to analyse intracranial pressure waveforms in relation to invasively-monitored radial artery waveforms. This practice has been questioned, because of pressure amplification between the heart and upper limb, and change in wave contour during travel of pressure waves to the periphery. Hence this study was to compare the relationship between intracranial pressure waveforms and waveform recorded invasively in the radial artery at the wrist, and central aortic pressure waveform derived from radial artery.

From the pilot study of 10 patients with idiopathic normal pressure hydrocephalus, the intracranial pressure was found to be more closely related to aortic pressure in their contour, and the intracranial pressure amplitude is normally 10% of the amplitude of central pressure. Further analysis is ongoing, including additional analysis between patients who undergo shunting as a therapeutic management of their hydrocephalus and those with no shunting. The findings have been presented at the Intracranial and Brain Monitoring conference in 2013, and the expanded abstract on this study has just been published. I conducted part of the data analysis, actively participated in study protocols and in manuscript preparation. The research is ongoing with a total of 26 patients' data processed to date.

Intracranial Pressure Waveforms are More Closely Related to Central Aortic than Radial Pressure Waveforms: Implications to Pathophysiology and Therapy

Mi Ok Kim[1], Per K Eide[2], Michael F O'Rourke[3,4], **Audrey Adji**[1,3], Alberto P Avolio[1]

[1]Australian School of Advanced Medicine, Macquarie University, Sydney, Australia

[2]Deparment of Neurosurgery, Rikshospitalet, Oslo, Norway

[3]St Vincent's Clinic, Sydney, Australia

[4]University of New South Wales/ VCCRI, Sydney, Australia

Abstract

Background: In patients with subarachnoid haemorrhage, pulsatile intracranial pressure (ICP) is more strongly associated with adverse events than mean ICP. Furthermore, patients with idiopathic normal pressure hydrocephalus (iNPH), and pulsatile ICP of 5 mmHg or more, gain more benefit of cerebrospinal fluid (CSF) shunting than those whose pulsatile ICP is lower than 5 mmHg.

Our study aims to investigate the morphological relationship between ICP pulsations, aortic pressure pulsations, and radial artery pulsations. Central aortic pulse pressure has been known as the best predictor of adverse cardiac events, while radial artery pulse pressure is generally measured and displayed in intensive care environments.

Methods: We studied ten iNPH patients and each of their ICP, aortic and radial pressures were digitised, ensemble-averaged and compared in time and frequency domain.

Results: The ICP wave contour was quite different to the radial pressure waveform. In contrast, the ICP waveform was similar to the aortic pressure wave contour. The ICP amplitude averaged < 10% of aortic pulse pressure. In the frequency domain, relative amplitude of the first three harmonics was similar for the ICP and aortic pressure.

Conclusion: These observations suggest that monitoring of central aortic pressure through derivation from the radial pressure wave is superior to measurement of radial pressure in studies regarding cerebral circulation.

Keywords: Intracerebral pressure waveform, central aortic pressure waveform, pressure waveform analysis

6.6.1 Introduction

Pulsations of pressure in the brain or in the aorta are directly related to cardiovascular and cerebrovascular adverse events. Central aortic pulse pressure is the best blood pressure predictor of cardiac events [1]. For the brain, pulsatile intracerebral pressure is more closely related to adverse events than mean pressure level following subarachnoid hemorrhage or head injury [2,3]. In patients with idiopathic normal pressure hydrocephalus (iNPH), more benefit is gained from cerebrospinal fluid (CSF) shunting in those with higher (> 5 mmHg) than lower (≤ 5 mmHg) pulsatile intracranial pressure (ICP) [4].

Persons whose carotid arterial pressure or flow waves show greater late systolic augmentation have higher prevalence of lacunar infarcts [5-7]. Patients with lower aortic pressure augmentation during systole have better survival prospects following head injury than those with high augmentation [3]. High pressure augmentation is the most common cause of isolated systolic hypertension in older persons, and the most common cause of cardiac failure, and of stroke [1]. Both flow and pressure augmentation are markedly reduced by the systemic arterial vasodilator nitroglycerine, with little effect on mean pressure or flow [3,6,8].

This study seeks to clarify the relationship between ICP pulsations, central aortic pressure pulsations, and pulsations in the radial artery where pressure is most conveniently measured in intensive care situations.

6.6.2 Materials and Methods

Ten patients with iNPH had ICP measured by Codman catheter system, simultaneously with radial pressure prior to therapeutic CSF shunting to the peritoneal cavity. The central aortic pressure waveform was estimated from the radial pressure waveform using a FDA-validated

generalised transfer function [3]. The three pressure waveforms were digitised, ensemble-averaged then compared in the time and frequency domain. Details of patients are given in table 1.

6.6.3 Results

In these iNPH patients, mean ICP was within the normal range (-7.1 to 9.9 mmHg), and pressure pulsations were of low amplitude (2.9 to 12.0 mmHg), and on average <10% of aortic pulse pressure. The ICP wave contour was quite different to the radial pressure wave contour. In all radial waveforms, the initial systolic peak, some 100 msec after the foot of the wave, was lower than the second systolic peak, whereas the ICP second systolic peak was dominant in all patients, averaging 35% of total waveform height. In contrast to the radial waveform, the central aortic pressure waveform was almost identical to the ICP waveform, at least during the period of systole, and augmentation index (height of the secondary wave ÷ amplitude of the wave) was 30%, and similar to that of ICP (figure 1). In the frequency domain relative amplitude of the first to third harmonics was similar for the aortic and ICP waveforms ($p=0.55$; modulus, $p=0.14$; phase).

6.6.4 Discussion

There are many reasons why the central aortic pressure wave is preferred to the radial pressure wave for monitoring cerebral vascular hemodynamics. These include:-

1. The radial aortic pressure wave is normally amplified by up to 70% in the upper limb (figure 1), so the radial artery pulse pressure may be 5-25 mmHg greater than central aortic pulse pressure. Amplification depends on the shape of the aortic and radial waveforms, and is corrected through use of the generalised transfer function process [3].

2. The aortic pressure waveform is similar to that in the carotid and vertebral arteries [3], and is the waveform which dilates the cerebral arteries with each beat of the heart, and so generates the ICP waveform.

3. The pressure (and flow) waveforms which perfuse the brain have two components; the first an impulse generated by ventricular ejection, with a peak some 100 msec after the foot of the wave, and the second a broader, wider wave which boosts (augments) pressure during the latter part of systole and contributes at least in these patients, almost half of the pressure wave amplitude. The importance of this wave, caused by wave reflection from the lower part of the body, is not apparent in the radial artery tracing since (at least in these older subjects) it is not as high as the initial pressure wave. The aortic pressure waveform gives a better guide to the stresses that are applied to the cerebral vasculature than the radial wave.

4. Reduction in wave reflection from the lower body is readily achieved with arterial (in contrast to arteriolar) vasodilators such as nitroglycerine. This can reduce wave reflection from the lower body by 60% or more (figure 2), and so markedly reduce pressure and flow pulsations in the aorta and cerebral arteries [9]. The ill-effects of central pressure pulsations on the cerebral vasculature are readily apparent from contour of the aortic waveform. Hypothetically, there is a reason to believe that reducing wave reflection from the lower body with drugs such as nitroglycerine will improve recovery from cerebral insults as has already been shown for the heart [6,8]. This has yet to be confirmed for the brain, but it is a definite possibility, and one that can be readily monitored by measurement of intracranial and central aortic pressure in routine intensive care.

In conclusion, monitoring of central aortic pressure through use of radial pressure wave convolution is superior to radial pressure wave monitoring in cerebral haemodynamic studies, since (i) it eliminates the variable amplification between aorta and radial artery under different conditions and in different subjects, (ii) it closely corresponds to contour of the ICP, at least during systole, (iii) it identifies a surge of pressure with each heart beat which is potentially injurious to vasculature of a damaged brain, and (iv) it can be used to monitor potentially beneficial effects of drugs which reduce wave reflection.

References

1. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, Christiaens T, Cifkova R, DeBacker G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F (2013) 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 31:1281-1357.

2. Eide PK, Sorteberg A, Bentsen G, Marthinsen PB, Stubhaug A, Sorteberg W (2012) Pressure-derived versus pressure wave amplitude-derived indices of cerebrovascular pressure reactivity in relation to early clinical state and 12-month outcome following aneurysmal subarachnoid hemorrhage. J Neurosurg 116:961-971.

3. Nichols WW, O'Rourke MF, Vlachopoulos C (2011) McDonald's Blood Flow in Arteries. 6th edition. London; Arnold Hodder, pp 595-638.

4. Eide PK, Park EH, Madsen JR (2010) Arterial blood pressure vs intracranial pressure in normal pressure hydrocephalus. Acta Neurol Scand 122:262-269.

5. Hirata K, Yaginuma T, O'Rourke MF, Kawakami M (2006) Age-related change in the carotid artery flow and pressure pulses implications to cerebral microvascular disease. Stroke 37:2552-2556.

6. Hirata K, O'Rourke MF, Momomura S (2007) Favourable effect of sublingual nitrate on carotid flow and pressure augmentation index. J Clin Hypertens 9(suppl A):A29.

7. Hirata K, O'Rourke MF, Momomura S (2008) Flow augmentation index as a major risk factor for silent lacunar infarction. J Hypertens 26(Suppl 1):S395.

8. Pauca AL, O'Rourke MF, Kon ND (2001) Prospective evaluation of a method for estimating ascending aortic pressure from the radial artery pressure waveform. Hypertension 38:932-937.

9. Pauca AL, Kon ND, O'Rourke MF. Benefits of nitroglycerine on arterial stiffness is directly due to effects on peripheral arteries. Heart 2005;91:1428-32.

Table. Subjects' characteristics

iNPH ID	Gender	Age	Radial pressure			Central pressure			Mean pressure	ICP			
			Systolic	Diastolic	Pulse	Systolic	Diastolic	Pulse		Peak	Trough	Pulse	Mean
1	F	77	152.8	35.3	117.5	128.7	37.5	91.2	73.9	5.7	-6.3	12.0	-1.3
2	M	82	144.7	63.5	81.2	123.1	66.0	57.1	90.8	7.6	0.9	6.7	4.4
3	M	74	114.0	61.6	52.4	108.5	62.7	45.8	80.6	15.4	4.8	10.6	9.9
4	M	73	127.0	63.5	63.5	116.4	65.3	51.1	86.8	7.4	1.5	6.0	4.3
5	F	75	143.9	69.2	74.8	137.7	71.0	66.7	98.3	5.6	-2.0	7.6	1.4
6	M	71	146.3	65.4	80.9	135.3	67.6	67.7	91.3	5.1	-2.0	7.2	1.2
7	F	83	134.8	54.9	79.9	109.5	56.1	53.4	79.1	-3.8	-6.7	2.9	-5.2
8	M	74	155.7	77.6	78.2	135.6	78.3	57.3	102.2	-4.8	-9.3	4.5	-7.1
9	M	75	150.1	66.4	83.7	123.7	68.1	55.6	89.1	7.3	3.3	4.1	5.3
10	M	74	148.1	60.5	87.6	119.7	63.2	56.5	86.9	6.1	0.1	6.0	3.1
Mean		75.8	141.7	61.8	80.0	123.8	63.6	60.2	87.9	5.2	-1.6	6.7	1.6
SD		3.9	12.9	11.0	16.8	10.5	10.8	12.7	8.6	5.8	4.6	2.8	5.1

Figures and Legends

Figure 1. Representative radial, aortic and intracranial pressures from one patient (left); pressure pulses scaled to the same amplitude (right).

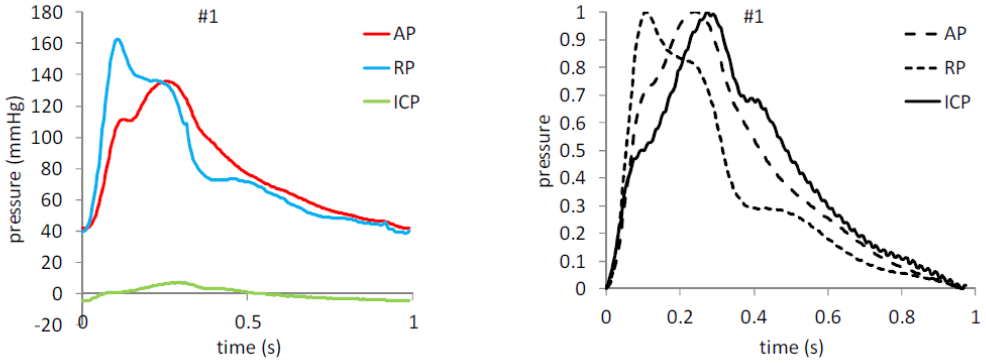
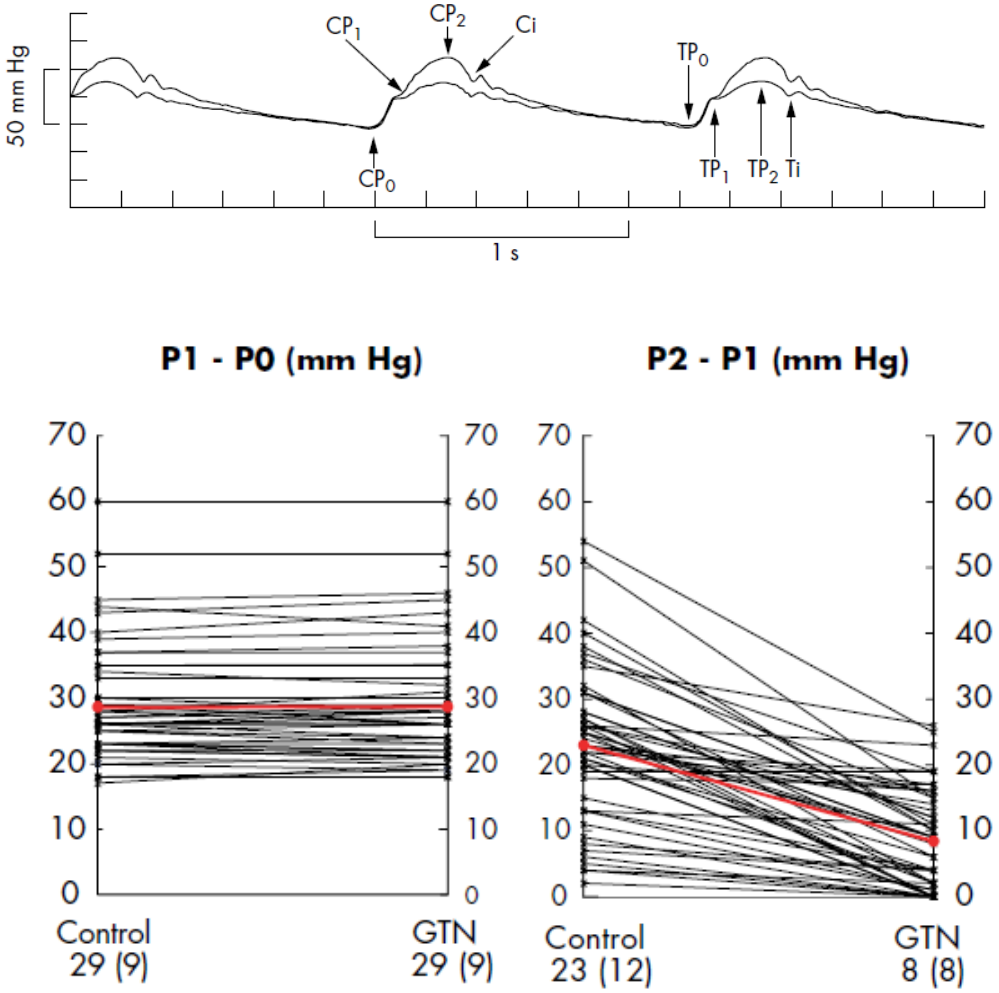


Figure 2. Effect of nitroglycerine on pressure waveforms as published in [9].



6.7 Chapter Overview

The latest hypothesis proposes that the development of dementia and kidney failure in the aging population is linked to large arterial disease. This chapter describes the means to relate the cerebral hemodynamics and circulatory system in different cohorts. In particular, the studies in this chapter demonstrate that the cerebral circulation is dependent on the heart and affected by stiffening of the arteries with aging, and there is similarity between the aortic pressure and the intracranial pressure contour. I actively participated in data analysis and manuscript preparation.

Chapter 7

Published Reviews, Editorials and Commentaries Pertaining to the Thesis Topic

This Chapter includes all of the published reviews, editorials and commentaries in which I was a co-author and that are related to the topic of this thesis. My specific contribution is detailed in each section.

7.1 Reviews

7.1.1 Noninvasive Studies of Central Aortic Pressure.

A paper by:

O'Rourke MF, **Adji A. Noninvasive Studies of Central Aortic Pressure**. *Current Hypertension Research* 2012;14:8-20.

Recently, we have described non-invasive methods of the measurement of central aortic pressure, including estimation of aortic pressure from the radial artery using transfer function, pressure equivalence, moving average and late systolic shoulder methods; from brachial site using applanation or cuff; and from carotid artery using direct tonometry or calibration using the Form Factor. We also compared the pressure amplification difference between different measurement techniques. Based on our findings, we suggested the use of radial applanation tonometry to be superior for estimation of central aortic pressure. I performed all the literature searches for related publications on this issue, as well as computation for the pressure amplification difference analysis.

O'Rourke, M. F., & Adji, A. (2012). Noninvasive studies of central aortic pressure. *Current Hypertension Research.* 14(1) p.8-20.

DOI: 10.1007/s11906-011-0236-5

7.1.2 Basis for Use of Central Blood Pressure Measurement in Office Clinical Practice.

A paper by:

O'Rourke MF, **Adji A**. **Basis for Use of Central Blood Pressure Measurement in Office Clinical Practice**. *Journal of the American Society of Hypertension* 2008;2:28-38.

Non-invasive determination of aortic pressure is now largely accepted and performed more frequently, particularly in the clinic setting and for research purposes. Cheng et al (Cheng et al. 2013) reported that central blood pressure of 130/90 mm Hg was determined to be the cut-off limit for normal pressure and hypertension. Their study emphasises the importance of measuring central blood pressure non-invasively, including cardiovascular risk assessment, rather than relying entirely in brachial pressure. I have been involved in writing papers on central blood pressure and performed various analysis with central pressure data, and these will be detailed here.

We published a review based on our clinical database to describe our experience in application of radial artery tonometry in clinical practice and emphasise the clinical value of measuring central aortic pressure non-invasively. As Dr O'Rourke's practice has a readily available database of over 1,500 subjects and patients with just under 10,000 records, I was able to organise and analyse this, and found that aortic systolic pressure was consistently lower than in the arm (average 13 mmHg). This is consistent with those taken with invasive procedure in a normal cohort (O'Rourke et al. 2001). This difference, however, was more often seen in the younger group, and became less as the subjects become older. We found a good correspondence between aortic systolic pressure estimated using the transfer function method and the late systolic shoulder method (mean difference of 1 mmHg), however, showed that the latter method was inapplicable in around 9% of cases. Differences between

aortic and peripheral pressure values were predictable on the basis of waveform patterns at either site. The result from this analysis supports radial tonometry method in characterising aging change, identified spurious systolic hypertension of youth, and greater hemodynamic benefit of “new” over “old” antihypertensive drugs, as well as improving management of patients with hypertension, cardiac failure, and angina.

O'Rourke, M.F., & Adji, A. (2008) Basis for use of central blood pressure measurement in office clinical practice. *Journal of the American Society of Hypertension.* 2(1) p.28-38.

DOI: 10.1016/j.jash.2007.08.006

7.1.3 Arterial Stiffness, Its Assessment, Prognostic Value, and Implications for Treatment.

A paper by:

Adji A, O'Rourke MF, Namasivayam M. **Arterial Stiffness, Its Assessment, Prognostic Value, and Implications for Treatment**. *American Journal of Hypertension* 2011;24:5-17.

Our State-of-the-Art review evaluated different techniques to measure arterial stiffness non-invasively, how stiffening of the arteries causes cardiac dysfunction which can be treated with drugs, how increasing pulsatility of the flow and pressure caused damage to the brain and kidneys, and finally, how the appropriate treatment can delay or prevent further damage to the heart and other highly perfused organs. I have dealt with this issue for about 10 years up to this time, and have written papers together with Dr O'Rourke and other more senior authors. Hence I have many background papers and illustrations to support measurement techniques, validating the use of radial arterial tonometry and application of generalised transfer function to derive central aortic pressure non-invasively. At the time this review was written, I had started my collaboration with other groups on the effect of arterial stiffening on the cardiac ejection pattern (through flow velocity measurement) and brain (through pressure and flow wave recording).

Adji, A., O'Rourke, M.F., & Namasivayam, M. (2011) Arterial stiffness, its assessment, prognostic value, and implications for treatment. *American Journal of Hypertension.* 24(1) p. 5-17.

DOI: 10.1038/ajh.2010.192

7.1.4 Arterial Aging: A Review of the Pathophysiology and Potential for Pharmacological Intervention.

A paper by:

O'Rourke MF, **Adji A**, Namasivayam M, Mok J. **Arterial Aging: A Review of the Pathophysiology and Potential for Pharmacological Intervention**. *Drugs and Aging* 2011;28:779-795.

The issue of arterial aging in section 7.1.3 was further emphasised in another review, written about the same time with the former, where our view supported early wave reflection as a target of therapeutic intervention.

O'Rourke, M.F., Adji, A., Namasivayam, M., & Mok, J. (2011) Arterial aging: a review of the pathophysiology and potential for pharmacological intervention. *Drugs and Aging.* 28(10) p. 779-795.

DOI: 10.2165/11592730-000000000-00000

7.2 Editorials

7.2.1 Noninvasive Generation of Aortic Pressure from Radial Pressure Waveform by Applanation Tonometry, Brachial Cuff Calibration, and Generalized Transfer Function.

A paper by:

O'Rourke MF, **Adji A**. **Noninvasive Generation of Aortic Pressure from Radial Pressure Waveform by Applanation Tonometry, Brachial Cuff Calibration, and Generalized Transfer Function**. *American Journal of Hypertension* 2014;27:143-145.

The application of a generalised transfer function to estimate central pressure waveform from the radial artery can likewise be used in confidence in diabetics, supporting the findings of Laugesen et al (Laugesen et al. 2014) where they compared the values derived from SphygmoCor and measured direct invasively. Dr O'Rourke and I have earlier written 4 reviews on this issue and I have been involved in many validation studies on the use of generalised transfer function to derive aortic from radial pressure, thus we both made similar scientific contribution in writing this editorial.

O'Rourke, M. F., & Adji, A. (2014) Noninvasive generation of aortic pressure from radial pressure waveform by applanation tonometry, brachial cuff calibration, and generalized transfer function. *American Journal of Hypertension.* 27(2) p. 143-145.

DOI: 10.1093/ajh/hpt226

7.2.2 Guidelines on Guidelines: Focus on Isolated Systolic Hypertension in Youth.

A paper by:

O'Rourke MF, **Adji A**. **Guidelines on Guidelines: Focus on Isolated Systolic Hypertension in Youth**. *Journal of Hypertension* 2013;31:649-654.

Recent large scale epidemiological studies on arterial blood pressure from the Framingham Heart Study show progressive increase in brachial systolic pressure measured by sphygmomanometer cuff from age 40 to age 80 and beyond (see **Figure 3-1**) (Franklin et al. 1997, Cheng et al. 2012). In the same paper, Framingham investigators also showed gender differences with higher systolic pressure in men than women from 20 to at least 70 years (Cheng et al. 2012). Meanwhile, studies in children have also shown gender differences, but these are relatively small up until age 14 when SP in males continues to rise while that in girls tends to rise less quickly (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004, Kulaga et al. 2012). This gender differences is associated with differences in height, and we have shown this in our commentary to the mentioned paper.

There are only a few studies of brachial systolic pressure in adolescents as adult studies usually include subjects from age 20 and older. The lowest age in the Framingham study was 25 years (Cheng et al. 2012). There is evidence of a localised peak and plateau of brachial systolic and pulse pressure (**Figure 3-1**), mainly in males at around 20-30 years of age in population studies, yet its mechanism is not fully understood. It is mentioned in the European Society of Hypertension/ European Society of Cardiology guidelines (Mancia et al. 2013) as a possible reason for determining central aortic SP in young persons, particularly those with high brachial systolic pressure to exclude "Spurious Systolic Hypertension". This condition can be found in tall young (sometimes athletic) males, due to the extreme amplification of

pressure in the upper limb, since their aortic pressure is usually within normal limits. This has been discussed in Chapter 4. The purpose is to distinguish those with hypertension due to "pure" amplification of pressure between aorta and brachial and those with "true hypertension". Our invited Editorial on Guidelines, anticipating the 2013 European Society of Hypertension/ European Society of Cardiology (ESH/ ESC) guidelines in management of hypertension, emphasised our view on the use of central pressure measurement to exclude treatment in those with suspected systolic hypertension in youth. In writing this commentary, I performed all literature searches and gathered all the published values on the systolic pressure related to this issue, and conducted further analysis on the relevance of these data to the younger population. The current guidelines on isolated systolic hypertension suggest the same treatment to patients of all ages, while no data show adverse outcome or benefit of drug therapy in this particular group. If the exaggerated pressure amplification is demonstrated in young persons, it is possible to spare them from being labelled as 'hypertensive', from inappropriate investigation, and from treatment that may induce symptoms of hypotension.

O'Rourke, M. F., & Adji, A. (2013) Guidelines on guidelines: focus on isolated systolic hypertension in youth. *Journal of Hypertension.* 31(4) p. 649-654.

DOI: 10.1097/HJH.0b013e32835d8230

7.2.3 Clinical Use of Applanation Tonometry: Hope Remains in Pandora's Box.

A paper by:

O'Rourke MF, **Adji A. Clinical Use of Applanation Tonometry: Hope Remains in Pandora's Box**. *Journal of Hypertension* 2010;28:229-233.

United States Food and Drug Administration approved the use of SphygmoCor® in 2001, a commercially-available device that employs radial applanation tonometry to derive aortic pressure waveform using generalised transfer function (Chen et al. 1997, Pauca et al. 2001).

As the pressure is usually recorded from a peripheral artery, i.e. radial, there is an issue of pressure amplification along the upper limb where the pressure is taken and ascending aorta. Regarding the current recommendation of measuring brachial cuff pressure and applying this to radial tonometry is based on invasive studies of arterial pressure waves, which showed that amplification between brachial and radial artery is very small in comparison to that between aorta and brachial artery (O'Rourke 1970, Karamanoglu et al. 1993). Verbeke et al (Verbeke et al. 2005) studied the amplification of pressure non-invasively between the brachial, where the cuff sphygmomanometry pressure values are taken, and the radial, where the applanation tonometry is normally performed. They suggested that the present method of calibrating radial tonometry to brachial-cuff systolic and diastolic pressure may be inaccurate, due to apparent pressure amplification between the two sites. Hence, they performed brachial tonometry using brachial cuff pressures (the pressure equivalence method was introduced by Kelly and Fitchett (Kelly et al. 1992)), where systolic pressure was extrapolated on the assumption that diastolic and mean pressures were identical throughout the arterial tree. Our group performed a pilot study of 20 subjects where we repeated the protocols of Verbeke et al study, and confirmed their findings of pressure amplification between brachial and radial

pressure waveforms. Nevertheless, during the study, we became aware of a crucial technical flaw that caused their results to be inaccurate.

Yet, the issue of pressure amplification between brachial and radial artery (when recorded non-invasively) remains debated for around 10 years, and many papers have been published with conflicting results. Two recent major studies have found different values for amplification; the ACCT II study reported an amplification ratio of ≈1.36 between central-to-peripheral (McEniery et al. 2008, Segers et al. 2008), while the Asklepios study found a ratio of ≈1.04 (O'Rourke et al. 2009, Segers et al. 2009). Mahieu et al (Mahieu et al. 2010), from the Asklepios Investigator group, examined the effect of calibration methods to estimation of central arterial pressure waveforms. One of their critics was the present application of brachial systolic and diastolic cuff pressure to calibrate radial artery (Mahieu et al. 2010). Based on our experience in using radial artery tonometry method and generalised transfer function to derive central aortic pressure, we have expressed our concern that there was a technical flaw on the brachial tonometry technique and warranted the brachial artery to be unsuitable for applanation tonometry, due to its location – the brachial artery is located deeper in the upper limb, is not supported by any bone, unlike the radial artery, and is covered by the brachial aponeurosis superficially. The Asklepios study's practice of using brachial tonometry calibrated to brachial cuff pressure values stood in contrast to the current practice of calibrating radial pressure waves to brachial (or radial) cuff values. For this editorial, I was actively involved in the manuscript preparation and calculation of pressure amplification values, and conducted the pilot study 5 years prior to this publication (during my candidature).

O'Rourke, M. F., & Adji, A. (2010) Clinical use of applanation tonometry: hope remains in Pandora's box. *Journal of Hypertension.* 28(2) p. 229-233.

DOI: 10.1097/HJH.0b013e328334cb2a

7.2.4 Aortic Augmentation Index and Aging: Mathematical Resolution of a Physiological Dilemma?

A paper by:

Namasivayam M, **Adji A**, O'Rourke MF. **Aortic Augmentation Index and Aging: Mathematical Resolution of a Physiological Dilemma?** *Hypertension* 2010;56:e9-e10.

The effect of aging on central pressure wave contour can be determined by the magnitude of the reflected wave, calculated as the ratio of this to the central pulse pressure. Result from the ACCT and other studies from different populations (McEniery et al. 2005, Wojciechowska et al. 2012) have shown the increase of augmentation index with age in a (curvi-)linear fashion. This phenomena has been explained in various ways; that the aging process and stiffening of the arteries causes the reflected pulse wave to occur earlier with higher magnitude (as frequently mentioned in this thesis), while Framingham investigators (Mitchell et al. 2004) interpreted this to represent decreased and delayed wave reflection attributable to proximal aortic stiffness. A mathematical approach was applied to investigate if the curvilinear increase in aortic augmentation index with age is due solely to a numerical phenomenon; that is a curvilinear relationship will arise from ratio of 2 positively sloped linear equations, i.e. increase in augmented pressure with age and increase in pulse pressure with age. We tested this approach in our database of cardiology outpatients (the same database utilised in the JASH 2008 paper cited in section 7.1.2), and our finding supported those of the ACCT and others (McEniery et al. 2005, Wojciechowska et al. 2006, Wojciechowska et al. 2012). The interpretation of increase in aortic augmentation index with age is limited by the mathematical phenomenon discussed in this paper. The flattening of augmentation index beyond 60 years can be explained, at least partly, by the fact that the parameters used to derive it (namely, augmentation pressure and aortic pulse pressure) rise in a similar and approximately linear

fashion across the life span. This is particularly important in interpretation of aortic augmentation index as a parameter of wave reflection magnitude.

Namasivayam, M., Adji, A., & O'Rourke, M.F. (2010) Aortic augmentation index and aging: mathematical resolution of a physiological dilemma? *Hypertension.* 56(1) p. e9-e10.

DOI: 10.1161/HYPERTENSIONAHA.110.153742

Chapter 8

Conclusion

Aging is an inevitable physiological change which occurs in all individuals. A consequence of aging is an increase in blood pressure, due to stiffening of the major arteries, and this is known to be a key risk of cardiovascular-related disease. Management of cardiovascular disease involves monitoring of blood pressure, since arterial stiffness alters the propagation of the pressure (and flow) wave generated by the beating heart. The main focus of this research was to characterise the age-related changes in aortic pressure and cardiac flow ejection pattern non-invasively. The research objectives were achieved through the investigation of aortic pressure pulse waveform features, which derived from radial pressure waveform, and of cardiac flow ejection pattern, to provide signs of normal and abnormal arterial function. The following conclusions were reached after taking all necessary steps to achieve the objectives of the thesis:

i. The principal effect of stiffening of arteries with aging is the increase in "aortic" (carotid femoral) pulse wave velocity. Studies have shown that it is currently the 'gold standard' measure of the arterial stiffness. However, the inaccuracy of measuring distance on the surface of the body can confound the estimation of aortic pulse wave velocity. The subtraction method (the distance between carotid to suprasternal notch from the distance from suprasternal notch to femoral site) is found to have the best correspondence with the invasive measurement.

ii. As aortic pulse wave velocity increases, central aortic systolic and pulse pressure will be higher. Arterial stiffening will cause alteration of central aortic pressure and flow contour and change in pressure amplification between ascending aorta and peripheral arteries. Three methods of estimating central aortic pressure from radial pressure investigated, and all were acceptable in accuracy. The radial site for measuring pulse wave is confirmed to be superior to carotid due to the less variability in indices.

iii. The use of central aortic pressure to measure reduction in wave reflection with therapy is confirmed, thus endorsing its application in clinical studies.

iv. The inappropriate use of the brachial artery to measure the pressure wave is attributed to lower pressure amplification between central and upper limb (the "Popeye" phenomenon), thus results in the inaccuracy of central aortic pressure calculation.

v. The measurement of central aortic pressure and pressure amplification is particularly valuable in identification of those young subjects with suspected hypertension due to pressure exaggeration in the upper limb from the true hypertensive.

vi. With aging, the ascending aortic impedance pattern changes. Non-invasive determination of impedance requires accurate measurements of aortic pressure and

aortic flow. The non-invasive method for measuring aortic flow (using cardiac magnetic resonance imaging) and aortic pressure is employed to estimate ascending aortic impedance. The current practice of estimating the cardiac load with blood flow measured by Doppler echocardiography is insensitive to changes due to the aging process, and the ascending aortic flow measurement by cardiac magnetic resonance imaging is more accurate.

vii. It is feasible to characterise the ascending aortic impedance non-invasively using aortic pressure and flow, and to show the adverse effects of aortic stiffening in humans with age.

viii. The physical relationship between pressure, flow and impedance is exploited to derive aortic flow wave from aortic pressure and impedance. The initial study found this to be achievable, but further work is warranted.

ix. The reflected pressure pulse wave continues to increase with age across the life span and is associated with higher aortic systolic pressure in the older persons. This has been shown through investigations of wave reflection indices and aortic triangulation method. Thus, the changes to the pressure wave propagation associated with arterial stiffening can also predispose individuals, especially women, to cardiac ischemia.

x. With stiffening of the arteries with age, the elastic aorta cannot cushion the pulsation generated by every beat of the heart, and these pulsations extend into the brain. These pulsations can be gauged from non-invasive measurement of brain flow velocity. The brain pressure wave is found to be similar to the aortic pressure contour with smaller amplitude, and it is affected by the wave reflection from the periphery.

xi. Future work includes development of a simple, realistic model to characterise aging change in cardiac ejection pattern and its progress with cardiovascular

disease by utilisation of the known changes in vascular impedance with age, and compare this with the current routine method of measuring aortic flow waves. Further implication of the arterial stiffening to the damage in the brain vasculature due to higher flow pulsation will also be further investigated.

References

Abhayaratna, W. P., Srikusalanukul, W.,Budge, M. M. (2008). "Aortic stiffness for the detection of preclinical left ventricular diastolic dysfunction: pulse wave velocity versus pulse pressure." Journal of Hypertension **26**(4): 758-764

Agabiti-Rosei, E., Mancia, G., O'Rourke, M. F., Roman, M. J., Safar, M. E., Smulyan, H., Wang, J.-G., Wilkinson, I. B., Williams, B.,Vlachopoulos, C. (2007). "Central Blood Pressure Measurements and Antihypertensive Therapy: A Consensus Document." Hypertension **50**(1): 154-160.

Agnoletti, D., Lieber, A., Zhang, Y., Protogerou, A. D., Borghi, C., Blacher, J.,Safar, M. E. (2013). "Central hemodynamic modifications in diabetes mellitus." Atherosclerosis **230**(2): 315-321.

Agnoletti, D., Zhang, Y., Salvi, P., Borghi, C., Topouchian, J., Safar, M. E.,Blacher, J. (2012). "Pulse pressure amplification, pressure waveform calibration and clinical applications." Atherosclerosis **224**(1): 108-112.

Ainstie, F. E. (1868). "On certain modifications of Marey's sphygmograph." Lancet **1868**: 91.

Aird, W. C. (2011). "Discovery of the Cardiovascular System: from Galen to William Harvey." Journal of Thrombosis and Haemostasis **9**(Supplement 1): 118-129.

Allen, N., Berry, J. D., Ning, H., Van Horn, L., Dyer, A.,Lloyd-Jones, D. M. (2012). "Impact of Blood Pressure and Blood Pressure Change During Middle Age on the Remaining Lifetime Risk for Cardiovascular Disease: The Cardiovascular Lifetime Risk Pooling Project." Circulation **125**(1): 37-44.

Apéria, A. (1940). "Haemodynamical studies." Scandinavian Archives of Physiology **83**(Suppl 1): 1-230.

Aquaro, G. D., Cagnolo, A., Tiwari, K. K., Todiere, G., Bevilacqua, S., Di Bella, G., Ait-Ali, L., Festa, P., Glauber, M.,Lombardi, M. (2013). "Age-dependent changes in elastic properties of thoracic aorta evaluated by magnetic resonance in normal subjects." Interactive CardioVascular and Thoracic Surgery **17**(4): 674-679.

Asmar, R. G., London, G. M., O'Rourke, M. E., Safar, M. E.,for the REASON Project coordinators investigators (2001). "Improvement in Blood Pressure, Arterial Stiffness and Wave Reflections With a Very-Low-Dose Perindopril/Indapamide Combination in Hypertensive Patient: A Comparison With Atenolol." Hypertension **38**(4): 922-926.

Attinger, E. O., Anne, A.,McDonald, D. A. (1966). "Use of Fourier series for the analysis of biological system." Biophysical Journal **6**: 291-304.

Avolio, A., Westerhof, B. E., Siebes, M.,Tyberg, J. V. (2009). "Arterial hemodynamics and wave analysis in the frequency and time domains: an evaluation of the paradigms." Medical & Biological Engineering & Computing **47**(2): 107-110.

Avolio, A. P. (1976). Hemodynamic studies and modeling of the mammalian arterial system. PhD, University of New South Wales.

Avolio, A. P., Butlin, M.,Walsh, A. (2010). "Arterial blood pressure measurement and pulse wave analysis—their role in enhancing cardiovascular assessment." Physiological Measurement **21**: R1-47.

Avolio, A. P., Chen, S. G., Wang, R. P., Zhang, C. L., Li, M. F.,O'Rourke, M. F. (1983). "Effects of aging on changing arterial compliance and left ventricular load in a northern Chinese urban community." Circulation **68**(1): 50-58.

Avolio, A. P., Deng, F. Q., Li, W. Q., Luo, Y. F., Huang, Z. D., Xing, L. F.,O'Rourke, M. F. (1985). "Effects of aging on arterial distensibility in populations with high and low prevalence of hypertension: comparison between urban and rural communities in China." Circulation **71**(2): 202-210.

Avolio, A. P., Van Bortel, L. M., Boutouyrie, P., Cockcroft, J. R., McEniery, C. M., Protogerou, A. D., Roman, M. J., Safar, M. E., Segers, P.,Smulyan, H. (2009). "Role of Pulse Pressure Amplification in Arterial Hypertension: Experts' Opinion and Review of the Data." Hypertension **54**(2): 375-383.

Avramovski, P., Janakievska, P., Sotiroski, K., Zafirova-Ivanovska, B.,Sikole, A. (2014). "Aortic pulse wave velocity is a strong predictor of all – cause and cardiovascular mortality in chronic dialysis patients." Renal Failure **36**(2): 176-186.

Baksi, A. J., Treibel, T. A., Davies, J. E., Hadjiloizou, N., Foale, R. A., Parker, K. H., Francis, D. P., Mayet, J.,Hughes, A. D. (2009). "A meta-analysis of the mechanism of blood pressure change with aging." J Am Coll Cardiol **54**(22): 2087-2092.

Bargainer, J. D. (1967). "Pulse Wave Velocity in the Main Pulmonary Artery of the Dog." Circulation Research **20**(6): 630-637.

Bargiotas, I., Bollache, E., Mousseaux, E., Giron, A., de Cesare, A., Redheuil, A.,Kachenoura, N. (2015). "MR and applanation tonometry derived aortic impedance: association with aging and left ventricular remodeling." Journal of Magnetic Resonance Imaging **41**(3): 781-787.

Barodka, V. M., Joshi, B. L., Berkowitz, D. E., Hogue, C. W. J.,Nyhan, D. (2011). "Implications of Vascular Aging." Anesthesia & Analgesia **112**(5): 1048-1060

Bateman, G. A. (2004). "Pulse wave encephalopathy: a spectrum hypothesis incorporating Alzheimer's disease, vascular dementia and normal pressure hydrocephalus." Medical Hypotheses **62**(2): 182-187.

Baumann, M., Wassertheurer, S., Suttmann, Y., Burkhardt, K.,Heemann, U. (2014). "Aortic pulse wave velocity predicts mortality in chronic kidney disease stages 2–4." Journal of Hypertension **32**(4): 899-903

Bedford, D. E. (1951). "The Ancient Art of Feeling the Pulse." British Heart Journal **13**(4): 423-437.

Ben-Shlomo, Y., Spears, M., Boustred, C., May, M., Anderson, S. G., Benjamin, E. J., Boutouyrie, P., Cameron, J., Chen, C.-H., Cruickshank, J. K., Hwang, S.-J., Lakatta, E. G., Laurent, S., Maldonado, J., Mitchell, G. F., Najjar, S. S., Newman, A. B., Ohishi, M., Pannier, B., Pereira, T., Vasan, R. S., Shokawa, T., Sutton-Tyrell, K., Verbeke, F., Wang, K.-L., Webb, D. J., Willum Hansen, T., Zoungas, S., McEniery, C. M., Cockcroft, J. R.,Wilkinson, I. B. (2014). "Aortic Pulse Wave Velocity Improves Cardiovascular Event Prediction: An Individual Participant Meta-Analysis of Prospective Observational Data From 17,635 Subjects." Journal of the American College of Cardiology **63**(7): 636-646.

Benetos, A., Gautier, S., Labat, C., Salvi, P., Valbusa, F., Marino, F., Toulza, O., Agnoletti, D., Zamboni, M., Dubail, D., Manckoundia, P., Rolland, Y., Hanon, O., Perret-Guillaume, C., Lacolley, P., Safar, M. E.,Guillemin, F. (2012). "Mortality and Cardiovascular Events Are Best Predicted by Low Central/Peripheral Pulse Pressure Amplification But Not by High Blood Pressure Levels in Elderly Nursing Home Subjects: The PARTAGE (Predictive Values of Blood Pressure and Arterial Stiffness in Institutionalized Very Aged Population) Study." Journal of the American College of Cardiology **60**(16): 1503-1511.

Benetos, A., Thomas, F., Joly, L., Blacher, J., Pannier, B., Labat, C., Salvi, P., Smulyan, H.,Safar, M. E. (2010). "Pulse Pressure Amplification: A Mechanical Biomarker of Cardiovascular Risk." Journal of the American College of Cardiology **55**(10): 1032-1037.

Bollache, E., Kachenoura, N., Bargiotas, I., Giron, A., De Cesare, A., Bensalah, M., Lucor, D., Redheuil, A.,Mousseaux, E. (2015). "How to estimate aortic characteristic impedance from magnetic resonance and applanation tonometry data?" Journal of Hypertension **33**(3): 575-583.

Bonapace, S., Rossi, A., Cicoira, M., Targher, G., Valbusa, F., Benetos, A.,Vassanelli, C. (2013). "Increased Aortic Pulse Wave Velocity as Measured by Echocardiography Is Strongly Associated with Poor Prognosis in Patients with Heart Failure." Journal of the American Society of Echocardiography **26**(7): 714-720.

Booth, J. (1977). "A Short History of Blood Pressure Measurement." Proceedings of Royal Society of Medicine **70**: 793-799.

Bramwell, J. C. (1924). "Arterial elasticity in man." Quarterly Journal of Medicine **17**: 225-243.

Bramwell, J. C.,Hill, A. V. (1922). "The velocity of the pulse wave in man." Proceedings of the Royal Society of London **23**: 298-306.

Bramwell, J. C.,Hill, A. V. (1922). "Velocity of transmission of the pulse-wave and elasticity of arteries." Lancet **199**: 891-892.

Brandts, A., van Elderen, S. G., Westenberg, J. J., van der Grond, J., van Buchem, M. A., Huisman, M. V., Kroft, L. J., Tamsma, J. T.,de Roos, A. (2009). "Association of aortic arch pulse wave velocity with left ventricular mass and lacunar brain infarcts in hypertensive patients: assessment with MR imaging." Radiology **253**(3): 681-688.

Breit, S. N.,O'Rourke, M. F. (1974). "Comparison of direct and indirect arterial pressure measurements in hospitalized patients." Australian New Zealand Journal of Medicine **4**(5): 485-491.

Broadbent, W. H. (1890). The Pulse. Philadelphia, Lea Brothers.

Burdon-Sanderson, J. (1867). Handook of the Sphygmograph. London, Robert Hardwicke.

Burton, A. C. (1952). Laws of physics and flow in blood vessels. London, Churchill.

Byrom, F. B. (1969). The Hypertensive Vascular Crisiss: an Experimental Study. London, Heinemann.

Cavalcante, J. L., Lima, J. A. C., Redheuil, A.,Al-Mallah, M. H. (2011). "Aortic Stiffness: Current Understanding and Future Directions." Journal of the American College of Cardiology **57**(14): 1511-1522.

Cecelja, M., Jiang, B., McNeill, K., Kato, B., Ritter, J., Spector, T.,Chowienczyk, P. (2009). "Increased Wave Reflection Rather Than Central Arterial Stiffness Is the Main Determinant of Raised Pulse Pressure in Women and Relates to Mismatch in Arterial Dimensions: A Twin Study." Journal of the American College of Cardiology **54**(8): 695-703.

Cecelja, M., Jiang, B., Spector, T. D.,Chowienczyk, P. (2012). "Progression of Central Pulse Pressure Over 1 Decade of Aging and its Reversal by Nitroglycerin: A Twin Study." Journal of the American College of Cardiology **59**(5): 475-483.

Chen, C.-H., Nevo, E., Fetics, B., Pak, P. H., Yin, F. C. P., Maughan, W. L.,Kass, D. A. (1997). "Estimation of Central Aortic Pressure Waveform by Mathematical Transformation of Radial Tonometry Pressure: Validation of Generalized Transfer Function." Circulation **95**(7): 1827-1836.

Cheng, H. M., Chuang, S. Y., Sung, S. H., Yu, W. C., Pearson, A., Lakatta, E. G., Pan, W. H.,Chen, C. H. (2013). "Derivation and validation of diagnostic thresholds for central blood pressure measurements based on long-term cardiovascular risks." Journal of the American College of Cardiology **62**(19): 1780-1787.

Cheng, S., Xanthakis, V., Sullivan, L. M.,Vasan, R. S. (2012). "Blood Pressure Tracking Over the Adult Life Course: Patterns and Correlates in the Framingham Heart Study." Hypertension **60**(6): 1393-1399.

Chester, R., Sander, G., Fernandez, C., Chen, W., Berenson, G.,Giles, T. (2013). "Women have significantly greater difference between central and peripheral arterial pressure compared with men: The Bogalusa Heart Study." Journal of the American Society of Hypertension **7**(5): 379-385.

Chirinos, J. A., Kips, J. G., Jacobs Jr, D. R., Brumback, L., Duprez, D. A., Kronmal, R., Bluemke, D. A., Townsend, R. R., Vermeersch, S.,Segers, P. (2012). "Arterial Wave Reflections and Incident Cardiovascular Events and Heart Failure: MESA (Multiethnic Study of Atherosclerosis)." Journal of the American College of Cardiology **60**(21): 2170-2177.

Chirinos, J. A., Kips, J. G., Roman, M. J., Medina-Lezama, J., Li, Y., Woodiwiss, A. J., Norton, G. R., Yasmin, Van Bortel, L., Wang, J.-G., Cockcroft, J. R., Devereux, R. B., Wilkinson, I. B., Segers, P.,McEniery, C. M. (2011). "Ethnic Differences in Arterial Wave Reflections and Normative Equations for Augmentation Index." Hypertension **57**(6): 1108-1116.

Chirinos, J. A., Rietzschel, E. R., De Buyzere, M. L., De Bacquer, D., Gillebert, T. C., Gupta, A. K., Segers, P.,on behalf of the Asklepios investigators (2009). "Arterial Load and Ventricular-Arterial Coupling: Physiologic Relations With Body Size and Effect of Obesity." Hypertension **54**(3): 558-566.

Chirinos, J. A.,Segers, P. (2010). "Noninvasive Evaluation of Left Ventricular Afterload: Part 1: Pressure and Flow Measurements and Basic Principles of Wave Conduction and Reflection." Hypertension **56**(4): 555-562.

Chirinos, J. A.,Segers, P. (2010). "Noninvasive Evaluation of Left Ventricular Afterload: Part 2: Arterial Pressure-Flow and Pressure-Volume Relations in Humans." Hypertension **56**(4): 563-570.

Cho, S. W., Kim, B. K., Kim, J. H., Byun, Y. S., Goh, C. W., Rhee, K. J., Ahn, H. S., Lee, B. K.,Kim, B. O. (2013). "Non-invasively measured aortic wave reflection and pulse pressure amplification are related to the severity of coronary artery disease." Journal of Cardiology **62**(2): 131-137.

Choi, C. U., Kim, E. J., Kim, S. H., Shin, S. Y., Choi, U.-J., Kim, J. W., Lim, H. E., Rha, S.-W., Park, C. G., Seo, H. S.,Oh, D. J. (2010). "Differing effects of aging on central and peripheral blood pressures and pulse wave velocity: a direct intraarterial study." Journal of Hypertension **28**(6): 1252-1260.

Coutinho, T., Bailey, K. R., Turner, S. T.,Kullo, I. J. (2014). "Arterial Stiffness is Associated with Increase in Blood Pressure Over Time in Treated Hypertensives." Journal of the American Society of Hypertension **8**: 414-421.

Coutinho, T., Borlaug, B. A., Pellikka, P. A., Turner, S. T.,Kullo, I. J. (2013). "Sex Differences in Arterial Stiffness and Ventricular-Arterial Interactions." Journal of the American College of Cardiology **61**(1): 96-103.

Cullen, K. M., Kocsi, Z.,Stone, J. (2005). "Pericapillary haem-rich deposits: evidence for microhaemorrhages in aging human cerebral cortex." J Cereb Blood Flow Metab **25**(12): 1656-1667.

Cullen, K. M., Kocsi, Z.,Stone, J. (2006). "Microvascular pathology in the aging human brain: evidence that senile plaques are sites of microhaemorrhages." Neurobiology of Aging **27**: 1786-1796.

Davies, J. E., Alastruey, J., Francis, D. P., Hadjiloizou, N., Whinnett, Z. I., Manisty, C. H., Aguado-Sierra, J., Willson, K., Foale, R. A., Malik, I. S., Hughes, A. D., Parker, K. H.,Mayet, J. (2012). "Attenuation of wave reflection by wave entrapment creates a "horizon effect" in the human aorta." Hypertension **60**(3): 778-785.

Davies, J. E., Baksi, J., Francis, D. P., Hadjiloizou, N., Whinnett, Z. I., Manisty, C. H., Aguado-Sierra, J., Foale, R. A., Malik, I. S., Tyberg, J. V., Parker, K. H., Mayet, J.,Hughes, A. D. (2010). "The arterial reservoir pressure increases with aging and is the major determinant of the aortic augmentation index." Am J Physiol Heart Circ Physiol **298**(2): H580-586.

Dawber, T. R., Thomas, H. E., Jr,McNamara, P. M. (1973). "Characteristics of the dicrotic notch of the arterial pulse wave in coronary heart disease." Angiology **24**: 244-256.

Denardo, S. J., Nandyala, R., Freeman, G. L., Pierce, G. L.,Nichols, W. W. (2010). "Pulse Wave Analysis of the Aortic Pressure Waveform in Severe Left Ventricular Systolic Dysfunction." Circulation: Heart Failure **3**(1): 149-156.

Devos, D. G. H., Rietzschel, E., Heyse, C., Vandemaele, P., Van Bortel, L., Babin, D., Segers, P., Westenberg, J. M.,Achten, R. (2015). "MR pulse wave velocity increases with age faster in the thoracic aorta than in the abdominal aorta." Journal of Magnetic Resonance Imaging **41**(3).

Dogui, A., Redheuil, A., Lefort, M., DeCesare, A., Kachenoura, N., Herment, A.,Mousseaux, E. (2011). "Measurement of aortic arch pulse wave velocity in cardiovascular MR: Comparison of transit time estimators and description of a new approach." Journal of Magnetic Resonance Imaging **33**(6): 1321-1329.

Dow, P.,Hamilton, W. F. (1938). "An experimental study of the velocity of the pulse wave propagated through the aorta." American Journal of Physiology **125**: 60-65.

Drzewiecki, G. M., Melbin, J.,Noordergraaf, A. (1983). "Arterial tonometry: Review and analysis." Journal of Biomechanics **16**(2): 141-152.

Fisher, J. W. (1914). "The Diagnostic Value of the Sphygmomanometer in Examinations for Life Insurance." JAMA **58**: 1752-1754.

Fitchett, D. H., Simkus, G., Genest, J., Marpole, D.,Beaudry, P. (1988). "Effect of nitroglycerin on left ventricular hydraulic load." Canadian Journal of Cardiology **4**(2): 72-75.

Fok, H., Guilcher, A., Li, Y., Brett, S., Shah, A., Clapp, B.,Chowienczyk, P. (2014). "Augmentation pressure is influenced by ventricular contractility/relaxation dynamics: novel mechanism of reduction of pulse pressure by nitrates." Hypertension **63**(5): 1050-1055.

Frank, O. (1899). "Die Grundform des Arteriellen Pulses." Zeitschrift for Biologie **37**: 483–526.

Frank, O. (1905). "Der Puls in den Arterien." Zeitschrift for Biologie **46**: 441-553.

Frank, O. (1926). "Die Theorie der Pulswellen." Zeitschrift for Biologie **85**: 91-130.

Frank, O. (1930). "Schatzung des Schlagvolumens des menschlichen Herzens auf Grund der Wellen und Windkesseltheorie." Zeitschrift fGr Biologie **90**: 405-409.

Franklin, S. S., Gustin, W., Wong, N. D., Larson, M. G., Weber, M. A., Kannel, W. B.,Levy, D. (1997). "Hemodynamic Patterns of Age-Related Changes in Blood Pressure: The Framingham Heart Study." Circulation **96**(1): 308-315.

Franklin, S. S., Khan, S. A., Wong, N. D., Larson, M. G.,Levy, D. (1999). "Is Pulse Pressure Useful in Predicting Risk for Coronary Heart Disease?: The Framingham Heart Study." Circulation **100**(4): 354-360.

Franklin, S. S., Larson, M. G., Khan, S. A., Wong, N. D., Leip, E. P., Kannel, W. B.,Levy, D. (2001). "Does the Relation of Blood Pressure to Coronary Heart Disease Risk Change With Aging?: The Framingham Heart Study." Circulation **103**(9): 1245-1249.

Franklin, S. S., Lopez, V. A., Wong, N. D., Mitchell, G. F., Larson, M. G., Vasan, R. S.,Levy, D. (2009). "Single Versus Combined Blood Pressure Components and Risk for Cardiovascular Disease: The Framingham Heart Study." Circulation **119**(2): 243-250.

Freis, E. D. (1960). "Hemodynamics of hypertension." Physiological Reviews **40**: 27-53.

Fry, D. L., Mallos, A. J.,Casper, A. G. T. (1956). "A Catheter Tip Method for Measurement of the Instantaneous Aortic Blood Velocity." Circulation Research **4**(5): 627-632.

Fry, D. L., Noble, F. W.,Mallos, A. J. (1957). "An Electric Device for Instantaneous and Continuous Computation of Aortic Blood Velocity." Circulation Research **5**(1): 75-78.

Fujita, M., Takazawa, K., Tanaka, H.,Ibukiyama, C. (1999). "Effects of nicorandil on aortic input impedance." Japanese Circulation Journal **63**: 111-116.

Fye, W. B. (1990). "William Henry Broadbent." Clinical Cardiology **13**: 62-64.

Fye, W. B. (1997). "Thomas Young." Clinical Cardiology **20**: 87-88.

Fye, W. B. (2006). "Ernest Henry Starling." Clinical Cardiology **29**: 181-182.

Gabe, I. T., Gault, J. H., Ross, J., Jr., Mason, D. T., Mills, C. J., Schillingford, J. P.,Braunwald, E. (1969). "Measurement of instantaneous blood flow velocity and pressure in conscious man with a catheter-tip velocity probe." Circulation **40**: 603-614.

Gabe, I. T., Karnell, J., Porjé, I. G.,Rudewald, B. (1964). "The Measurement of Input Impedance and Apparent Phase Velocity in the Human Aorta." Acta Physiologica Scandinavica **61**(1-2): 73-84.

Garrison, F. H. (1931). "An Outline of the History of the Circulatory System." Bulletin of the New York Academy of Medicine **7**(10): 781-806.

Gąsecki, D., Rojek, A., Kwarciany, M., Kowalczyk, K., Boutouyrie, P., Nyka, W., Laurent, S.,Narkiewicz, K. (2012). "Pulse wave velocity is associated with early clinical outcome after ischemic stroke." Atherosclerosis **225**(2): 348-352.

Gąsecki, D., Rojek, A., Kwarciany, M., Kubach, M., Boutouyrie, P., Nyka, W., Laurent, S.,Narkiewicz, K. (2012). "Aortic Stiffness Predicts Functional Outcome in Patients After Ischemic Stroke." Stroke **43**(2): 543-544.

Ghasemzadeh, N.,Zafari, A. M. (2011). "A Brief Journey into the History of the Arterial Pulse." Cardiology Research and Practice **2011**(164832): 14.

Gordin, D., Wadén, J., Forsblom, C., Thorn, L., Rosengård-Bärlund, M., Tolonen, N., Saraheimo, M., Harjutsalo, V., Groop, P.-H.,for the FinnDiane Study Group (2011). "Pulse Pressure Predicts Incident Cardiovascular Disease but Not Diabetic Nephropathy in Patients With Type 1 Diabetes (The FinnDiane Study)." Diabetes Care **34**(4): 886-891.

Greenfield, J. C.,Fry, D. L. (1965). "Relationship Between Instantaneous Aortic Flow and the Pressure Gradient." Circulation Research **17**(4): 340-348.

Greenfield, J. C., Jr., Harley, A., Thompson, H. K.,Wallace, A. G. (1968). "Pressure-flow studies in man during atrial fibrillation." The Journal of Clinical Investigation **47**(10): 2411-2421.

Greenfield, J. C., Starmer, C. F.,Walston, A. (1971). Measurement of aortic blood flow in man by the computed pressure derivative method.

Gurven, M., Blackwell, A. D., Rodríguez, D. E., Stieglitz, J.,Kaplan, H. (2012). "Does Blood Pressure Inevitably Rise With Age?: Longitudinal Evidence Among Forager-Horticulturalists." Hypertension **60**(1): 25-33.

Hale, J. F., McDonald, D. A.,Womersley, J. R. (1955). "Velocity profiles of oscillating arterial flow, with some calculations of viscous drag and the Reynolds number." The Journal of Physiology **128**(3): 629-640.

Hales, S. (1733). Statical Essays: Containing Haemastaticks.

Hamilton, W. F. (1944). "The patterns of the arterial pressure pulse." American Journal of Physiology **141**: 235-241.

Hamilton, W. F., Brewer, G.,Brotman, I. (1934). "Pressure pulse contours in the intact animal." American Journal of Physiology **107**(2): 427-435.

Hamilton, W. F.,Dow, P. (1938). "An experimental study of the standing waves in the pulse propagated through the aorta." American Journal of Physiology **125**: 48-59.

Hamilton, W. F.,Remington, J. W. (1947). "The measurement of the stroke volume from the pressure pulse." American Journal of Physiology **148**(1): 14-24.

Hamilton, W. F., Remington, J. W.,Dow, P. (1945). "The determination of the propagation velocity of the arterial pulse wave." American Journal of Physiology **144**(4): 521-535.

Harvey, W. (1628). Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus. Frankfurt.

Hashimoto, J.,Ito, S. (2010). "Pulse Pressure Amplification, Arterial Stiffness, and Peripheral Wave Reflection Determine Pulsatile Flow Waveform of the Femoral Artery." Hypertension **56**(5): 926-933.

Hashimoto, J.,Ito, S. (2011). "Central pulse pressure and aortic tiffness determine renal hemodynamics." Hypertension **58**: 839-846.

Hashimoto, J.,Ito, S. (2013). "Aortic Stiffness Determines Diastolic Blood Flow Reversal in the Descending Thoracic Aorta: Potential Implication for Retrograde Embolic Stroke in Hypertension." Hypertension **62**(3): 542-549.

Hashimoto, J.,Ito, S. (2015). "Aortic blood flow reversal determines renal function." Hypertension **66**: 61-67.

Hashimoto, J., Nichols, W. W., O'Rourke, M. F.,Imai, Y. (2008). "Association Between Wasted Pressure Effort and Left Ventricular Hypertrophy in Hypertension: Influence of Arterial Wave Reflection." American Journal of Hypertension **21**(3): 329-333.

Heffernan, K. S., Jae, S. Y., Wilund, K. R., Woods, J. A.,Fernhall, B. (2008). "Racial differences in central blood pressure and vascular function in young men." American Journal of Physiology **295**(6): H2380-H2387.

Helps, E. P. W.,McDonald, D. A. (1954). "Arterial blood flow calculated from pressure gradients." Journal of Physiology **124**(Supplements): 30P-31P.

Henry Feugeas, M. C., De Marco, G., Peretti, I. I., Godon-Hardy, S., Fredy, D.,Claeys, E. S. (2005). "Age-related cerebral white matter changes and pulse-wave encephalopathy: observations with three-dimensional MRI." Magnetic resonance imaging **23**(9): 929-937.

Henskens, L. H. G., Kroon, A. A., van Oostenbrugge, R. J., Gronenschild, E. H. B. M., Fuss-Lejeune, M. M. J. J., Hofman, P. A. M., Lodder, J.,de Leeuw, P. W. (2008). "Increased Aortic Pulse Wave Velocity Is Associated With Silent Cerebral Small-Vessel Disease in Hypertensive Patients." Hypertension **52**(6): 1120-1126.

Herbert, A., Cruickshank, J. K., Laurent, S.,Boutouyrie, P. (2014). "Establishing reference values for central blood pressure and its amplification in a general healthy population and according to cardiovascular risk factors." Eur Heart J **35**(44): 3122-3133.

Herisson, J. (1835). The Sphygmometer: an Instrument which Renders the Action of the Arteries Apparent to the Eye. London, Longmans.

Herment, A., Kachenoura, N., Lefort, M., Bensalah, M., Dogui, A., Frouin, F., Mousseaux, E.,De Cesare, A. (2010). "Automated segmentation of the aorta from phase contrast MR images: validation against expert tracing in healthy volunteers and in patients with a dilated aorta." Journal of Magnetic Resonance Imaging **31**(4): 881-888.

Hickson, S. S., Butlin, M., Graves, M., Taviani, V., Avolio, A. P., McEniery, C. M.,Wilkinson, I. B. (2010). "The Relationship of Age With Regional Aortic Stiffness and Diameter." JACC: Cardiovascular Imaging **3**(12): 1247-1255.

Hickson, S. S., Butlin, M., Mir, F. A., Graggaber, J., Cheriyan, J., Khan, F., Brace, A. A., Cockcroft, J. R., Wilkinson, I. B., McEniery, C. M.,on behalf of the Anglo-Cardiff Collaboration Trial Investigators (2009). "The accuracy of central SBP determined from the second systolic peak of the peripheral pressure waveform." Journal of Hypertension **27**: 1784-1788.

Hirata, K., Yaginuma, T., O'Rourke, M. F.,Kawakami, M. (2006). "Age-Related Changes in Carotid Artery Flow and Pressure Pulses: Possible Implications for Cerebral Microvascular Disease." Stroke **37**(10): 2552-2556.

Hope, S. A., Meredith, I. T., Tay, D.,Cameron, J. D. (2007). "'Generalizability' of a radial-aortic transfer function for the derivation of central aortic waveform parameters." Journal of Hypertension **25**(9): 1812-1820

Hope, S. A., Tay, D. B., Meredith, I. T.,Cameron, J. D. (2005). "Waveform dispersion, not reflection, may be the major determinant of aortic pressure wave morphology." Am J Physiol Heart Circ Physiol **289**(6): H2497-2502.

Huan, Y.,Townsend, R. (2011). "Is There a Role for Measuring Central Aortic Pressure?" Current Cardiology Reports **13**(6): 502-506.

Huang, C.-M., Wang, K.-L., Cheng, H.-M., Chuang, S.-Y., Sung, S.-H., Yu, W.-C., Ting, C.-T., Lakatta, E. G., Yin, F. C. P., Chou, P.,Chen, C.-H. (2011). "Central versus ambulatory blood pressure in the prediction of all-cause and cardiovascular mortalities." Journal of Hypertension **29**(3): 454-459.

Huffman, M. D., Capewell, S., Ning, H., Shay, C. M., Ford, E. S.,Lloyd-Jones, D. M. (2012). "Cardiovascular Health Behavior and Health Factor Changes (1988–2008) and Projections to 2020: Results From the National Health and Nutrition Examination Surveys." Circulation **125**(21): 2595-2602.

Hughes, T. M., Kuller, L. H., Barinas-Mitchell, E. M.,et al. (2014). "Arterial stiffness and β-amyloid progression in nondemented elderly adults." JAMA Neurology.

Hughes, T. M., Kuller, L. H., Barinas-Mitchell, E. M., Mackey, R. H., McDade, E. M., Klunk, W. E., Aizenstein, H. J., Cohen, A. D., Snitz, B. E., Mathis, C. A., Dekosky, S. T.,Lopez, O. L. (2013). "Pulse wave velocity is associated with β-amyloid deposition in the brains of very elderly adults." Neurology **81**: 1711-1718.

James, W. (1956). The Will to Believe, Human Immortality, and Other Essays in Popular Philosophy, Dover Publication.

Janner, J. H., Godtfredsen, N. S., Ladelund, S., Vestbo, J.,Prescott, E. (2013). "High aortic augmentation index predicts mortality and cardiovascular events in men from a general population, but not in women." European Journal of Preventive Cardiology **20**(6).

Jones, W. B., Hefner, L. L., Bancroft, W. H., Jr.,Klip, W. (1959). "Velocity of blood flow and stroke volume obtained from the pressure pulse." The Journal of Clinical Investigation **38**(11): 2087-2090.

Jones, W. B.,Reeves, T. J. (1968). "Total cardiac output response during four minutes of exercise." American Heart Journal **76**(2): 209-216.

Jones, W. B., Russell, R. O., Jr.,Dalton, D. H., Jr. (1966). "An evaluation of computed stroke volume in man." Am Heart J **72**(6): 746-750.

Kaess, B. M., Rong, J., Larson, M. G., Hamburg, N. M., Vita, J. A., Levy, D., Benjamin, E. J., Vasan, R. S.,Mitchell, G. F. (2012). "Aortic stiffness, blood pressure progression, and incident hypertension." JAMA **308**(9): 875-881.

Kannel, W. B., Dawber, T. R., Kagan, A., Revotskie, N.,Stokes, I. J. (1961). "Factors of Risk in the Development of Coronary Heart Disease—Six-Year Follow-up ExperienceThe Framingham Study." Annals of Internal Medicine **55**(1): 33-50.

Kannel, W. B., Gordon, T.,Schwartz, M. J. (1971). "Systolic versus diastolic blood pressure and risk of coronary heart disease: The Framingham study." The American Journal of Cardiology **27**(4): 335-346.

Kar, S.,Sharma, R. (2015). "Current assessment of mitral regurgitation." Journal of the American College of Cardiology **65**: 1089-1091.

Karamanoglu, M., Gallagher, D. E., Avolio, A. P.,O'Rourke, M. F. (1994). "Functional origin of reflected pressure waves in a multibranched model of the human arterial system." American Journal of Physiology **267**(5): H1681-H1688.

Karamanoglu, M., Gallagher, D. E., Avolio, A. P.,O'Rourke, M. F. (1995). "Pressure wave propagation in a multibranched model of the human upper limb." American Journal of Physiology **269**(4): H1363-H1369.

Karamanoglu, M., O'Rourke, M. F., Avolio, A. P.,Kelly, R. P. (1993). "An analysis of the relationship between central aortic and peripheral upper limb pressure waves in man." European Heart Journal **14**(2): 160-167.

Karras, A., Haymann, J.-P., Bozec, E., Metzger, M., Jacquot, C., Maruani, G., Houillier, P., Froissart, M., Stengel, B., Guardiola, P., Laurent, S., Boutouyrie, P., Briet, M.,on behalf of the Nephro Test Study Group (2012). "Large Artery Stiffening and Remodeling Are Independently Associated With All-Cause Mortality and Cardiovascular Events in Chronic Kidney Disease." Hypertension **60**(6): 1451-1457.

Katz, A. M. (1990). "Cardiomyopathy of overload." New England Journal of Medicine **322**: 100-110.

Katz, A. M. (2002). "Ernest Henry Starling, his predecessors, and the "Law of the Heart"." Circulation **106**: 2986-2992.

Kearney, P. M., Whelton, M., Reynolds, K., Muntner, P., Whelton, P. K.,He, J. (2005). "Global burden of hypertension: analysis of worldwide data." The Lancet **365**(9455): 217-223.

Kellie, G. (1824). "Appearance observed in the dissection of two individuals; death from cold and congestion of the brain." Transaction Medicine Chirurgica Society of Edinburgh **1**: 84.

Kelly, R.,Fitchett, D. (1992). "Noninvasive determination of aortic input impedance and external left ventricular power output: A validation and repeatability study of a new technique." Journal of the American College of Cardiology **20**(4): 952-963.

Kelly, R., Hayward, C., Avolio, A.,O'Rourke, M. (1989). "Noninvasive determination of age-related changes in the human arterial pulse." Circulation **80**(6): 1652-1659.

Kelly, R., Hayward, C., Ganis, J., Daley, J., Avolio, A.,O'Rourke, M. (1989). "Noninvasive registration of the arterial pressure pulse waveform using high-fidelity applanation tonometry." Journal of Vascular Medicine and Biology **1**: 142-149.

Korotkov, N. S. (1905). "K voprosu o metodoach eesldovania krovyanovo davlenia." Imperatoor Vorenno JzV Med Akad **11**: 365-367.

Korteweg, D. J. (1878). ""Ueber die Fortpflanzungsgeschwindigkeit des Schalles in elastischen Röhren." ("On the velocity of propagation of sound in elastic tubes.")." Annalen der Physik und Chemie, New Series **5**(12): 525-542.

Kroeker, E. J.,Wood, E. H. (1955). "Comparison of Simultaneously Recorded Central and Peripheral Arterial Pressure Pulses During Rest, Exercise and Tilted Position in Man." Circulation Research **3**(6): 623-632.

Kroeker, E. J.,Wood, E. H. (1956). "Beat-to-Beat Alterations in Relationship of Simultaneously Recorded Central and Peripheral Arterial Pressure Pulses During Valsalva Maneuver and Prolonged Expiration in Man." Journal of Applied Physiology **8**(5): 483-494.

Kulaga, Z., Litwin, M., Grajda, A., Kulaga, K., Gurzkowska, B., Gózdz, M., Pan, H.,The OLAF Study Group (2012). "Oscillometric blood pressure percentiles for Polish normal-weight school-aged children and adolescents." Journal of Hypertension **30**(10): 1942-1954

Landis, E. (1976). "Carl John Wiggers." Biographical Memoirs: National Academy of Sciences **48**: 363-397.

Laskey, W. K., Kussmaul, W. G., Martin, J. L., Kleaveland, J. P., Hirshfeld, J. W.,Shroff, S. (1985). "Characteristics of vascular hydraulic load in patients with heart failure." Circulation **72**(1): 61-71.

Latson, T. W., Hunter, W. C., Katoh, N.,Sagawa, K. (1988). "Effect of nitroglycerin on aortic impedance, diameter, and pulse-wave velocity." Circulation Research **62**(5): 884-890.

Laugesen, E., Høyem, P., Stausbøl-Grøn, B., Mikkelsen, A., Thrysøe, S., Erlandsen, M., Christiansen, J. S., Knudsen, S. T., Hansen, K. W., Kim, W. Y., Hansen, T. K.,Poulsen, P. L. (2013). "Carotid-Femoral Pulse Wave Velocity Is Associated With Cerebral White Matter Lesions in Type 2 Diabetes." Diabetes Care **36**(3): 722-728.

Laugesen, E., Rossen, N. B., Peters, C. D., Mæng, M., Ebbehøj, E., Knudsen, S. T., Hansen, K. W., Bøtker, H. E.,Poulsen, P. L. (2014). "Assessment of central blood pressure in patients with type 2 diabetes: a comparison between SphygmoCor and invasively measured values." American Journal of Hypertension **27**: 169-176.

Laurent, S., Cockcroft, J., Van Bortel, L., Boutouyrie, P., Giannattasio, C., Hayoz, D., Pannier, B., Vlachopoulos, C., Wilkinson, I.,Struijker-Boudier, H. (2006). "Expert consensus document on arterial stiffness: methodological issues and clinical applications." European Heart Journal **27**(21): 2588-2605.

Lawes, C. M. M., Hoorn, S. V.,Rodgers, A. (2008). "Global burden of blood-pressure-related disease, 2001." The Lancet **371**(9623): 1513-1518.

Lawrence, C. (1978). "Physiological apparatus in the Wellcome museum: 1. The Marey sphygmograph." Medical History **22**: 196-200.

Lawrence, C. (1979). "Physiological apparatus in the Wellcome museum: 2. The Dudgeon sphygmograph and its descendants." Medical History **23**: 96-101.

Lewis, T. T., Sutton-Tyrrell, K., Penninx, B. W., Vogelzangs, N., Harris, T. B., Vaidean, G. D., Ayonayon, H. N., Kim, L., Lakatta, E. G.,Newman, A. B. (2010). "Race, Psychosocial Factors, and Aortic Pulse Wave Velocity: The Health, Aging, and Body Composition Study." The Journals of Gerontology Series A: Biological Sciences and Medical Sciences **65A**(10): 1079-1085.

Lewis, W. H., Jr (1941). "The evolution of clinical sphygmomanometry." Bulletin of the New York Academy of Medicine **17**: 871-881.

Li, Y., Staessen, J. A., Sheng, C.-S., Huang, Q.-f., O'Rourke, M.,Wang, J.-G. (2012). "Age dependency of peripheral and central systolic blood pressures: cross-sectional and longitudinal observations in a Chinese population." Hypertension Research **35**: 115-122.

Liao, J.,Farmer, J. (2014). "Arterial Stiffness as a Risk Factor for Coronary Artery Disease." Current Atherosclerosis Reports **16**(2): 1-7.

Lieber, A., Millasseau, S., Bourhis, L., Blacher, J., Protogerou, A., Levy, B. I.,Safar, M. E. (2010). "Aortic wave reflection in women and men." American Journal of Physiology **299**(1): H236-H242.

Lim, S. S., Vos, T., Flaxman, A. D., Danaei, G., Shibuya, K., Adair-Rohani, H., AlMazroa, M. A., Amann, M., Anderson, H. R., Andrews, K. G., Aryee, M., Atkinson, C., Bacchus, L. J., Bahalim, A. N., Balakrishnan, K., Balmes, J., Barker-Collo, S., Baxter, A., Bell, M. L., Blore, J. D., Blyth, F., Bonner, C., Borges, G., Bourne, R., Boussinesq, M., Brauer, M., Brooks, P., Bruce, N. G., Brunekreef, B., Bryan-Hancock, C., Bucello, C., Buchbinder, R., Bull, F., Burnett, R. T., Byers, T. E., Calabria, B., Carapetis, J., Carnahan, E., Chafe, Z., Charlson, F., Chen, H., Chen, J. S., Cheng, A. T.-A., Child, J. C., Cohen, A., Colson, K. E., Cowie, B. C., Darby, S., Darling, S., Davis, A., Degenhardt, L., Dentener, F., Des Jarlais, D. C., Devries, K., Dherani, M., Ding, E. L., Dorsey, E. R., Driscoll, T., Edmond, K., Ali, S. E., Engell, R. E., Erwin, P. J., Fahimi, S., Falder, G., Farzadfar, F., Ferrari, A., Finucane, M. M., Flaxman, S., Fowkes, F. G. R., Freedman, G., Freeman, M. K., Gakidou, E., Ghosh, S., Giovannucci, E., Gmel, G., Graham, K., Grainger, R., Grant, B., Gunnell, D., Gutierrez, H. R., Hall, W., Hoek, H. W., Hogan, A., Hosgood Iii, H. D., Hoy, D., Hu, H., Hubbell, B. J., Hutchings, S. J., Ibeanusi, S. E., Jacklyn, G. L., Jasrasaria, R., Jonas, J. B., Kan, H., Kanis, J. A., Kassebaum, N., Kawakami, N., Khang, Y.-H., Khatibzadeh, S., Khoo, J.-P., Kok, C., Laden, F., Lalloo, R., Lan, Q., Lathlean, T., Leasher, J. L., Leigh, J., Li, Y., Lin, J. K., Lipshultz, S. E., London, S., Lozano, R., Lu, Y., Mak, J., Malekzadeh, R., Mallinger, L., Marcenes, W., March, L., Marks, R., Martin, R., McGale, P., McGrath, J., Mehta, S., Memish, Z. A., Mensah, G. A., Merriman, T. R., Micha, R., Michaud, C., Mishra, V., Hanafiah, K. M., Mokdad, A. A., Morawska, L., Mozaffarian, D., Murphy, T., Naghavi, M., Neal, B., Nelson, P. K., Nolla, J. M., Norman, R., Olives, C., Omer, S. B., Orchard, J., Osborne, R., Ostro, B., Page, A., Pandey, K. D., Parry, C. D. H., Passmore, E., Patra, J., Pearce, N., Pelizzari, P. M., Petzold, M., Phillips, M. R., Pope, D., Pope Iii, C. A., Powles, J., Rao, M., Razavi, H., Rehfuess, E. A., Rehm, J. T., Ritz, B., Rivara, F. P., Roberts, T., Robinson, C., Rodriguez-Portales, J. A., Romieu, I., Room, R., Rosenfeld, L. C., Roy, A., Rushton, L., Salomon, J. A., Sampson, U., Sanchez-Riera, L., Sanman, E., Sapkota, A., Seedat, S., Shi, P., Shield, K., Shivakoti, R., Singh, G. M., Sleet, D. A., Smith, E., Smith, K. R., Stapelberg, N. J. C., Steenland, K., Stöckl, H., Stovner, L. J., Straif, K., Straney, L., Thurston, G. D., Tran, J. H., Van Dingenen, R., van Donkelaar, A., Veerman, J. L., Vijayakumar, L., Weintraub, R., Weissman, M. M., White, R. A., Whiteford, H., Wiersma, S. T., Wilkinson, J. D., Williams, H. C., Williams, W., Wilson, N., Woolf, A. D., Yip, P., Zielinski, J. M., Lopez, A. D., Murray, C. J. L.,Ezzati, M. (2012). "A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010." The Lancet **380**(9859): 2224-2260.

Lin, M.-M., Cheng, H.-M., Sung, S.-H., Liao, C.-F., Chen, Y.-H., Huang, P.-H.,Chen, C.-H. (2012). "Estimation of central aortic systolic pressure from the second systolic peak of the peripheral upper limb pulse depends on central aortic pressure waveform morphology." Journal of Hypertension **30**(3): 581-586.

Lloyd-Jones, D. M. (2010). "Cardiovascular risk prediction: basic concepts, current status, and future directions." Circulation **121**: 1768-1777.

Ludwig, C. (1847). "Beitrage zur Kenntniss des Einflusses der Respirationsbewegungen auf den Blutlauf im Aortensysteme." Muller Archiv Anat Physiol Wissensch Med: 242-302.

Mackenzie, J. (1902). The Study of the Pulse. Arterial, Venous, and Hepatic and of the Movements of the Heart. Edinburgh, Young J Pentland.

Mahieu, D., Kips, J., Rietzschel, E. R., De Buyzere, M. L., Verbeke, F., Gillebert, T. C., De Backer, G. G., De Bacquer, D., Verdonck, P., Van Bortel, L. M., Segers, P.,on behalf of the Asklepios investigators (2010). "Noninvasive assessment of central and peripheral arterial pressure (waveforms): implications of calibration methods." Journal of Hypertension **28**(2): 300-305.

Mahomed, F. A. (1872). "The physiology and clinical use of the sphygmograph." Medical Times Gazette **1**: 62.

Mancia, G., Fagard, R., Narkiewicz, K., Redón, J., Zanchetti, A., Böhm, M., Christiaens, T., Cifkova, R., De Backer, G., Dominiczak, A., Galderisi, M., Grobbee, D. E., Jaarsma, T., Kirchhof, P., Kjeldsen, S. E., Laurent, S., Manolis, A. J., Nilsson, P. M., Ruilope, L. M., Schmieder, R. E., Sirnes, P. A., Sleight, P., Viigimaa, M., Waeber, B.,Zannad, F. (2013). "2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)." Journal of Hypertension **31**(7): 1281-1357

Mansour, A. S., Yannoutsos, A., Majahalme, N., Agnoletti, D., Safar, M. E., Ouerdane, S.,Blacher, J. (2013). "Aortic stiffness and cardiovascular risk in type 2 diabetes." Journal of Hypertension **31**(8): 1584-1592.

Marey, E.-J. (1860). "Recherches sur le pouls au moyen d'un nouvel appareil enregistreur, le sphygmographe." Société de Biologie : Journal of Physiology.

Marey, E.-J. (1863). Physiologie médicale de la circulation du sang, basée sur l'étude graphique des mouvements du coeur et du pouls artériel, avec application aux maladies de l'appareil circulatoire. Paris, Delahaye.

Marey, E.-J. (1881). Le circulation du sang a´ l'e´tat physiologique et dans des maladies. . Paris, Masson.

Martin, C., Sun, W., Primiano, C., McKay, R.,Elefteriades, J. (2013). "Age-dependent ascending aortic mechanics assessed through multiphase CT." Annals of Biomedical Engineering **41**: 2565-2574.

Mazzaro, L., Almasi, S. J., Shandas, R., Seals, D. R.,Gates, P. E. (2005). "Aortic Input Impedance Increases With Age in Healthy Men and Women." Hypertension **45**(6): 1101-1106.

McDonald, D. A. (1952). "The occurrence of turbulent flow in the rabbit aorta." The Journal of Physiology **118**(3): 340-347.

McDonald, D. A. (1955). "The relation of pulsatile pressure to flow in arteries." The Journal of Physiology **127**(3): 533-552.

McDonald, D. A. (1960). Blood Flow in Arteries. London, American Physiological Society.

McDonald, D. A. (1974). Blood Flow in Arteries. London, Edward Arnold.

McDonald, D. A.,Nichols, W. W. (1973). "Cardiac output derived from the time derivative and phase velocities of aortic pressure waves." Medical and Biological Enigneering **11**: 678-690.

McDonald, D. A.,Taylor, M. G. (1959). "The hydrodynamics of the arterial circulation." Progress in Biophysics **9**: 107-173.

McEniery, C. M., Cockcroft, J. R., Roman, M. J., Franklin, S. S.,Wilkinson, I. B. (2014). "Central blood pressure: current evidence and clinical importance." European Heart Journal **35**: 1719-1725.

McEniery, C. M., Yasmin, Hall, I. R., Qasem, A., Wilkinson, I. B.,Cockcroft, J. R. (2005). "Normal Vascular Aging: Differential Effects on Wave Reflection and Aortic Pulse Wave Velocity: The Anglo-Cardiff Collaborative Trial (ACCT)." Journal of the American College of Cardiology **46**(9): 1753-1760.

McEniery, C. M., Yasmin, Maki-Petaja, K. M., McDonnell, B. J., Munnery, M., Hickson, S. S., Franklin, S. S., Cockcroft, J. R., Wilkinson, I. B.,on behalf of the Anglo-Cardiff Collaboration Trial Investigators (2010). "The

Impact of Cardiovascular Risk Factors on Aortic Stiffness and Wave Reflections Depends on Age: The Anglo-Cardiff Collaborative Trial (ACCT III)." Hypertension **56**(4): 591-597.

McEniery, C. M., Yasmin, McDonnell, B., Munnery, M., Wallace, S. M., Rowe, C. V., Cockcroft, J. R., Wilkinson, I. B.,on Behalf of the Anglo-Cardiff Collaborative Trial Investigators (2008). "Central Pressure: Variability and Impact of Cardiovascular Risk Factors: The Anglo-Cardiff Collaborative Trial II." Hypertension **51**(6): 1476-1482.

Mehrabian, S., Raycheva, M., Gateva, A., Todorova, G., Angelova, P., Traykova, M., Stankova, T., Kamenov, Z.,Traykov, L. (2012). "Cognitive dysfunction profile and arterial stiffness in type 2 diabetes." Journal of the Neurological Sciences **322**(1–2): 152-156.

Merillon, J. P., Fontenier, G., Lerallut, J. F., Jaffrin, M. Y., Chastre, J., Assayag, P., Motte, G.,Gourgon, R. (1984). "Aortic input impedance in heart failure: comparison with normal subjects and its changes during vasodilator therapy." European Heart Journal **5**(6): 447-455.

Merillon, J. P., Fontenier, G. J., Lerallut, J. F., Jaffrin, M. Y., Motte, G. A., Genain, C. P.,Gourgon, R. R. (1982). "Aortic input impedance in normal man and arterial hypertension: its modification during changes in aortic pressure." Cardiovascular Research **16**(11): 646-656.

Merillon, J. P., Lebras, Y., Chastre, J., Lerallut, J. F., Motte, G., Fontenier, G., Huet, Y., Jaffrin, M. Y.,Gourgon, R. (1983). "Forward and backward waves in the arterial system, their relationship to pressure waves form." European Heart Journal **4**(suppl G): 13-20.

Merillon, J. P., Motte, G., Fruchaud, J., Masquet, C.,Gourgon, R. (1978). "Evaluation of the elasticity and characteristic impedance of the ascending aorta in man." Cardiovascular Research **12**(7): 401-406.

Merillon, J. P., Motte, G., Masquet, C., Azancot, I., Guiomard, A.,Gourgon, R. (1982). "Relationship between physical properties of the arterial system and left ventricular performance in the course of aging and arterial hypertension." European Heart Journal **3**(suppl A): 95-102.

Milan, A., Tosello, F., Naso, D., Avenatti, E., Leone, D., Magnino, C.,Veglio, F. (2013). "Ascending aortic dilatation, arterial stiffness and cardiac organ damage in essential hypertension." Journal of Hypertension **31**(1): 109-116.

Mills, C. J. (1966). "A catheter tip electromagnetic velocity probe." Physics in Medicine and Biology **11**: 323-324.

Mills, C. J., Gabe, I. T., Gault, J. H., Mason, D. T., Ross, J., Braunwald, E.,Shillingford, J. P. (1970). "Pressure-flow relationships and vascular impedance in man." Cardiovascular Research **4**(4): 405-417.

Milnor, W. R. (1975). "Arterial impedance as ventricular afterload." Circulation Research **36**(5): 565-570.

Milnor, W. R. (1989). Hemodynamics. Baltimore, Williams Wilkins.

Milnor, W. R., Conti, C. R., Lewis, K. B.,O'Rourke, M. F. (1969). "Pulmonary Arterial Pulse Wave Velocity and Impedance in Man." Circulation Research **25**(6): 637-649.

Mitchell, A., Saez, A., Kos, M., Witzke, O., Kribben, A.,Nurnberger, J. (2010). "Pulse wave velocity predicts mortality in renal transplant patients." European Journal of Medical Research **15**(10): 452 - 455.

Mitchell, G. F., Hwang, S.-J., Vasan, R. S., Larson, M. G., Pencina, M. J., Hamburg, N. M., Vita, J. A., Levy, D.,Benjamin, E. J. (2010). "Arterial Stiffness and Cardiovascular Events: The Framingham Heart Study." Circulation **121**(4): 505-511.

Mitchell, G. F., Parise, H., Benjamin, E. J., Larson, M. G., Keyes, M. J., Vita, J. A., Vasan, R. S.,Levy, D. (2004). "Changes in Arterial Stiffness and Wave Reflection With Advancing Age in Healthy Men and Women: The Framingham Heart Study." Hypertension **43**(6): 1239-1245.

Mitchell, G. F., van Buchem, M. A., Sigurdsson, S., Gotal, J. D., Jonsdottir, M. K., Kjartansson, Ó., Garcia, M., Aspelund, T., Harris, T. B., Gudnason, V.,Launer, L. J. (2011). "Arterial stiffness, pressure and flow pulsatility

and brain structure and function: the Age, Gene/Environment Susceptibility – Reykjavik Study." Brain **134**(11): 3398-3407.

Mitchell, G. F., Wang, N., Palmisano, J. N., Larson, M. G., Hamburg, N. M., Vita, J. A., Levy, D., Benjamin, E. J.,Vasan, R. S. (2010). "Hemodynamic Correlates of Blood Pressure Across the Adult Age Spectrum: Noninvasive Evaluation in the Framingham Heart Study." Circulation **122**(14): 1379-1386.

Mitchell, J. R.,Wang, J.-J. (2014). "Expanding application of the Wiggers diagram to teach cardiovascular physiology." Advances in Physiology Education **38**(2): 170-175.

Miyashita, H. (2012). "Clinical Assessment of Central Blood Pressure." Current Hypertension Reviews **8**: 80-90.

Miyashita, H., Aizawa, A., Hashimoto, J., Hirooka, Y., Imai, Y., Kawano, Y., Kohara, K., Sunagawa, K., Suzuki, H., Tabara, Y., Takazawa, K., Takenaka, T., Yasuda, H.,Shimada, K. (2010). "Cross-Sectional Characterization of all Classes of Antihypertensives in Terms of Central Blood Pressure in Japanese Hypertensive Patients." American Journal of Hypertension **23**(3): 260-268.

Miyashita, H., Ikeda, U., Tsuruya, Y., Sekiguchi, H., Shimada, K.,Yaginuma, T. (1994). "Noninvasive evaluation of the influence of aortic wave reflection on left ventricular ejection during auxotonic contraction." Heart Vessels **9**(1): 30-39.

Moens, A. I. (1878). Die Pulscurve. Leiden, E J Brill.

Mokri, B. (2001). "The Monro-Kellie hypothesis: applications in CSF volume depletion." Neurology **56**: 1746-1748.

Monro, A. (1783). Observations on Structure and Function of the Nervous System. Edinburgh, Creech and Johnson.

Morris, A. A., Patel, R. S., Binongo, J. N. G., Poole, J., Mheid, I., Ahmed, Y., Stoyanova, N., Vaccarino, V., Din-Dzietham, R., Gibbons, G. H.,Quyyumi, A. (2013). "Racial Differences in Arterial Stiffness and Microcirculatory Function Between Black and White Americans." Journal of the American Heart Association **2**(2).

Murgo, J. P., Westerhof, N., Giolma, J. P.,Altobelli, S. A. (1980). "Aortic input impedance in normal man: relationship to pressure wave forms." Circulation **62**(1): 105-116.

Murgo, J. P., Westerhof, N., Giolma, J. P.,Altobelli, S. A. (1981). "Effects of exercise on aortic input impedance and pressure wave forms in normal humans." Circulation Research **48**(3): 334-343.

Murgo, J. P., Westerhof, N., Giolma, J. P.,Altobelli, S. A. (1981). "Manipulation of ascending aortic pressure and flow wave reflections with the Valsalva maneuver: relationship to input impedance." Circulation **63**(1): 122-132.

Murray, C. J. L., Richards, M. A., Newton, J. N., Fenton, K. A., Anderson, H. R., Atkinson, C., Bennett, D., Bernabé, E., Blencowe, H., Bourne, R., Braithwaite, T., Brayne, C., Bruce, N. G., Brugha, T. S., Burney, P., Dherani, M., Dolk, H., Edmond, K., Ezzati, M., Flaxman, A. D., Fleming, T. D., Freedman, G., Gunnell, D., Hay, R. J., Hutchings, S. J., Ohno, S. L., Lozano, R., Lyons, R. A., Marcenes, W., Naghavi, M., Newton, C. R., Pearce, N., Pope, D., Rushton, L., Salomon, J. A., Shibuya, K., Vos, T., Wang, H., Williams, H. C., Woolf, A. D., Lopez, A. D.,Davis, A. (2013). "UK health performance: findings of the Global Burden of Disease Study 2010." The Lancet **381**(9871): 997-1020.

Mynard, J. P., Smolich, J. J.,Avolio, A. (2015). "The ebbing tide of the reservoir-wave model." J Hypertens **33**(3): 461-464.

Najjar, S. S., Scuteri, A., Shetty, V., Wright, J. G., Muller, D. C., Fleg, J. L., Spurgeon, H. P., Ferrucci, L.,Lakatta, E. G. (2008). "Pulse Wave Velocity Is an Independent Predictor of the Longitudinal Increase in Systolic Blood Pressure and of Incident Hypertension in the Baltimore Longitudinal Study of Aging." Journal of the American College of Cardiology **51**(14): 1377-1383.

Nakano, T., Munakata, A., Shimaura, N., Asano, K.,Ohkuma, H. (2012). "Augmentation index is related to white matter lesions." Hypertension Research **35**(7): 729-732.

Narayan, O., Casan, J., Szarski, M., Dart, A. M., Meredith, I. T.,Cameron, J. D. (2014). "Estimation of central aortic blood pressure: a systematic meta-analysis of available techniques." Journal of Hypertension **32**(9): 1727-1740.

National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents (2004). "The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents." Pediatrics **114**(Supplement 2): 555-576.

Neil, E. (1961). "Carl Ludwig and his pupils." Circulation Research **9**: 971-978.

Nelson, A. J., Worthley, S. G., Cameron, J. D., Willoughby, S. R., Piantadosi, C., Carbone, A., Dundon, B. K., Leung, M. C., Hope, S. A., Meredith, I. T.,Worthley, M. I. (2009). "Cardiovascular magnetic resonance-derived aortic distensibility: validation and observed regional differences in the elderly." Journal of Hypertension **27**(3): 535-542.

Nelson, M. R., Stepanek, J., Cevette, M., Covalciuc, M., Hurst, R. T.,Tajik, A. J. (2010). "Noninvasive Measurement of Central Vascular Pressures With Arterial Tonometry: Clinical Revival of the Pulse Pressure Waveform?" Mayo Clinic Proceedings **85**(5): 460-472.

Nichols, W. W., Avolio, A. P.,Kelly, R. P. (1993). Effects of age and of hypertension on wave travel and reflections. In: Arterial Vasodilation: Mechanism and Therapy. O'Rourke, M. F., Safar, M. E.,Dzau, V. London, Edward Arnold.

Nichols, W. W., Conti, C. R., Walker, W. E.,Milnor, W. R. (1977). "Input impedance of the systemic circulation in man." Circulation Research **40**(5): 451-458.

Nichols, W. W.,O'Rourke, M. F. (1990). McDonald's Blood Flow in Arteries. 3rd ed. London, Hodder Arnold.

Nichols, W. W., O'Rourke, M. F., Avolio, A. P., Yaginuma, T., Murgo, J. P., Pepine, C. J.,Conti, C. R. (1985). "Effects of age on ventricular-vascular coupling." The American Journal of Cardiology **55**(9): 1179-1184.

Nichols, W. W., O'Rourke, M. F., Avolio, A. P., Yaginuma, T., Pepine, C. J.,Conti, C. R. (1986). "Ventricular/vascular interaction in patients with mild systemic hypertension and normal peripheral resistance." Circulation **74**(3): 455-462.

Nichols, W. W., O'Rourke, M. F.,Vlachopoulos, C. (2011). McDonald's Blood Flow in Arteries. London, Hodder Arnold.

Nichols, W. W., Pepine, C. J., Geiser, E. A.,Conti, C. R. (1980). "Vascular load defined by the aortic input impedance spectrum." Federation Proceedings **39**(2): 196-201.

Nilsson, P. M., Boutouyrie, P., Cunha, P., Kotsis, V., Narkiewicz, K., Parati, G., Rietzschel, E., Scuteri, A.,Laurent, S. (2013). "Early vascular ageing in translation: from laboratory investigations to clinical applications in cardiovascular prevention." Journal of Hypertension **31**(8): 1517-1526.

Nilsson, P. M., Khalili, P.,Franklin, S. S. (2014). "Blood pressure and pulse wave velocity as metrics for evaluating pathologic ageing of the cardiovascular system." Blood Pressure **23**(1): 17-30.

O'Rourke, M. F. (1965). "Dynamic accuracy of the electromagnetic flowmeter." Journal of Applied Physiology **20**: 142-147.

O'Rourke, M. F. (1967). "Pressure and flow waves in systemic arteries and the anatomical design of the arterial system." Journal of Applied Physiology **23**(2): 139-149.

O'Rourke, M. F. (1967). "Steady and pulsatile enerly losses in the systemic circulation under normal conditions and in simulate arterial diseases." Cardiovascular Research **1**: 313-328.

O'Rourke, M. F. (1968). "Impact pressure, lateral pressure and impedance in the proximal aorta and pulmonary artery." Journal of Applied Physiology **25**: 533-541.

O'Rourke, M. F. (1970). "Influence of ventricular ejection on the relationship between central aortic and brachial pressure pulse in man." Cardiovascular Research **4**(3): 291-300.

O'Rourke, M. F. (1976). "Pulsatile arterial haemodynamics in hypertension." Australian and New Zealand Journal of Medicine **6**(Suppl 2): 40-48.

O'Rourke, M. F. (1982). Arterial Function in Health and Disease. Edinburgh, Churchill Livingstone.

O'Rourke, M. F. (1982). "Vascular impedance in studies of arterial and cardiac function." Physiological Reviews **62**(2): 570-623.

O'Rourke, M. F. (1984). "Starling's law of the heart: an appraisal 70 years on." Australian and New Zealand Journal of Medicine **14**: 879-887.

O'Rourke, M. F. (1992). "Frederick Akbar Mahomed." Hypertension **19**: 212-217.

O'Rourke, M. F. (2002). "From theory into practice: arterial haemodynamics in clinical hypertension." Journal of Hypertension **20**(10): 1901-1915.

O'Rourke, M. F. (2007). "Arterial aging: pathophysiological principles." Vascular Medicine **12**: 329-341.

O'Rourke, M. F. (2015). "Central aortic pressure: alive and well at 25 years." Journal of Hypertension **33**: 187-188.

O'Rourke, M. F.,Avolio, A. P. (1980). "Pulsatile flow and pressure in human systemic arteries. Studies in man and in a multibranched model of the human systemic arterial tree." Circulation Research **46**(3): 363-372.

O'Rourke, M. F., Avolio, A. P.,Kelly, R. P. (1992). The Arterial Pulse. Baltimore, Lea & Febiger.

O'Rourke, M. F., Blazek, J. V., Morreels, C. L.,Krovetz, L. J. (1968). "Pressure wave transmission along the human aorta: changes with age and in arterial degenerative disease." Circulation Research **23**(4): 567-579.

O'Rourke, M. F., Kelly, R.,Avolio, A. P. (1992). The Arterial Pulse. Philadelphia, Lea & Febiger.

O'Rourke, M. F.,Milnor, W. R. (1971). Relation between differential pressure and flow in the pulmonary artery of the dog.

O'Rourke, M. F., Nichols, W. W.,Vlachopoulos, C. (2013). "CrosssTalk: Wave reflection and the Physiological Society." Journal of Physiology **591**.

O'Rourke, M. F., Pauca, A. L.,Jiang, X. J. (2001). "Pulse wave analysis." British Journal of Clinical Pharmacology **51**: 507-522.

O'Rourke, M. F., Safar, M. E.,Dzau, V. (1993). Arterial Vasodilation: Mechanisms and Therapy. Edinburgh, Lea and Febiger.

O'Rourke, M. F., Safar, M. E.,Dzau, V. (2010). "The Cardiovascular Continuum extended: Aging effects on the aorta and microvasculature." Vascular Medicine **15**(6): 461-468.

O'Rourke, M. F.,Seward, J. B. (2006). "Central Arterial Pressure and Arterial Pressure Pulse: New Views Entering the Second Century After Korotkov." Mayo Clinic Proceedings **81**(8): 1057-1068.

O'Rourke, M. F.,Takazawa, K. (2009). "Flawed Measurement of Brachial Tonometry for Calculating Aortic Pressure?" Hypertension **54**(5): e131.

O'Rourke, M. F.,Taylor, M. G. (1966). "Vascular impedance of the femoral bed." Circulation Research **18**(2): 126-139.

O'Rourke, M. F.,Taylor, M. G. (1967). "Input impedance of the systemic circulation." Circulation Research **20**(4): 365-380.

O'Rourke, M. F., Vlachopoulos, C.,Graham, R. (2000). "Spurious systolic hypertension in youth." Vascular Medicine **5**: 141-145.

O'Rourke, M. F. S., Michel E,Dzau, V. (1993). Arterial Vasodilation: Mechanisms and Therapy. Edinburgh, Lea and Febiger.

O'Rourke, M. F.,Hashimoto, J. (2007). "Mechanical Factors in Arterial Aging: A Clinical Perspective." Journal of the American College of Cardiology **50**(1): 1-13.

O'Rourke, M. F.,Nichols, W. W. (2005). "Aortic Diameter, Aortic Stiffness, and Wave Reflection Increase With Age and Isolated Systolic Hypertension." Hypertension **45**(4): 652-658.

O'Rourke, M. F.,Safar, M. E. (2005). "Relationship Between Aortic Stiffening and Microvascular Disease in Brain and Kidney: Cause and Logic of Therapy." Hypertension **46**(1): 200-204.

Oates, C. (2001). Cardiovascular Haemodynamics and Doppler Waveforms Explained. London, Greenwich Medical Media Ltd.

Palatini, P., Casiglia, E., Gąsowski, J., Głuszek, J., Jankowski, P., Narkiewicz, K., Saladini, F., Stolarz-Skrzypek, K., Tikhonoff, V., Van Bortel, L., Wojciechowska, W.,Kawecka-Jaszcz, K. (2011). "Arterial stiffness, central hemodynamics, and cardiovascular risk in hypertension." Vascular Health and Risk Management **7**: 725-739.

Pannier, B., Guérin, A. P., Marchais, S. J., Safar, M. E.,London, G. M. (2005). "Stiffness of Capacitive and Conduit Arteries: Prognostic Significance for End-Stage Renal Disease Patients." Hypertension **45**(4): 592-596.

Parker, K. H. (2009). "A brief history of arterial wave mechanics." Medical, Biology, Engineering and Computing **47**: 111–118.

Pase, M. P., Stough, C., Grima, N. A., Harris, E., Macpherson, H., Scholey, A. B.,Pipingas, A. (2013). "Blood Pressure and Cognitive Function: The Role of Central Aortic and Brachial Pressures." Psychological Science **24**(11): 2173-2181.

Patel, D. J., de Freitas, F. M.,Fry, D. L. (1963). "Hydraulic input impedance to aorta and pulmonary artery in dogs." Journal of Applied Physiology **18**: 134-140.

Patel, D. J., Greenfield, J., J C, Austen, W. G., Morrow, A. G.,Fry, D. L. (1965). "Pressure-flow relationships in the ascending aorta and femoral artery of man." Journal of Applied Physiology **20**: 459-463.

Patel, D. J., Mason, D. J., Ross, J., J,Braunwald, E. (1965). "Harmonic analysis of pressure pulses obtained from the heart and great vessels of man." American Heart Journal **69**: 785-794.

Patterson, S., Piper, H.,Starling, E. H. (1914). "The regulation of the heart beat." Journal of Physiology **48**: 465-513.

Pauca, A. L., O'Rourke, M. F.,Kon, N. D. (2001). "Prospective Evaluation of a Method for Estimating Ascending Aortic Pressure From the Radial Artery Pressure Waveform." Hypertension **38**(4): 932-937.

Pepine, C. J., Nichols, W. W.,Conti, C. R. (1978). "Aortic input impedance in heart failure." Circulation **58**(3): 460-465.

Pepine, C. J., Nichols, W. W., Curry, R. C., Jr.,Conti, C. R. (1979). "Aortic Input Impedance during Nitroprusside Infusion." The Journal of Clinical Investigation **64**(2): 643-654.

Perkovic, V., Huxley, R., Wu, Y., Prabhakaran, D.,MacMahon, S. (2007). "The Burden of Blood Pressure-Related Disease: A Neglected Priority for Global Health." Hypertension **50**(6): 991-997.

PHG (1834). "The sphygmometer: an instrument which makes every actin of the arteries apparent to the eye." Lancet **23**: 22-27.

Pierce, G. L., Zhu, H., Darracott, K., Edet, I., Bhagatwala, J., Huang, Y.,Dong, Y. (2013). "Arterial Stiffness and Pulse-Pressure Amplification in Overweight/Obese African- American Adolescents: Relation With Higher Systolic and Pulse Pressure." American Journal of Hypertension **26**(1): 20-26.

Poels, M. M. F., Zaccai, K., Verwoert, G. C., Vernooij, M. W., Hofman, A., van der Lugt, A., Witteman, J. C. M., Breteler, M. M. B., Mattace-Raso, F. U. S.,Ikram, M. A. (2012). "Arterial Stiffness and Cerebral Small Vessel Disease: The Rotterdam Scan Study." Stroke **43**(10): 2637-2642.

Poiseuille, J. (1828). "Recherches sur la Force du Coeur aortique." Archives generales de medecine **8**: 550.

Porje, I. G. (1946). "Studies of the arterial pulse wave, particularly in the aorta." Acta Physiologica Scandinavica **13**(Suppl 42): 1-68.

Postel-Vinay, N. (1996). A Century of Hypertension: 1896-1996. Chichester, John Wiley.

Protogerou, A. D., Safar, M. E., Papaioannou, T. G., Zhang, Y., Agnoletti, D., Papadogiannis, D.,Blacher, J. (2011). "The combined effect of aortic stiffness and pressure wave reflections on mortality in the very old with cardiovascular disease: the PROTEGER Study." Hypertension Research **34**(7): 803-808.

Redheuil, A. (2014). "Cardiovascular aging: Insights from local and regional measures of aortic stiffness using magnetic resonance imaging." Artery Research.

Redheuil, A., Wu, C. O., Kachenoura, N., Ohyama, Y., Yan, R. T., Bertoni, A. G., Hundley, G. W., Duprez, D. A., Jacobs, D. R., Jr., Daniels, L. B., Darwin, C., Sibley, C., Bluemke, D. A.,Lima, J. A. (2014). "Proximal aortic distensibility is an independent predictor of all-cause mortality and incident CV events: the MESA study." Journal of the American College of Cardiology **64**(24): 2619-2629.

Redheuil, A., Yu, W.-C., Mousseaux, E., Harouni, A. A., Kachenoura, N., Wu, C. O., Bluemke, D.,Lima, J. A. C. (2011). "Age-Related Changes in Aortic Arch Geometry: Relationship With Proximal Aortic Function and Left Ventricular Mass and Remodeling." Journal of the American College of Cardiology **58**(12): 1262-1270.

Redheuil, A., Yu, W.-C., Wu, C. O., Mousseaux, E., de Cesare, A., Yan, R., Kachenoura, N., Bluemke, D.,Lima, J. A. C. (2010). "Reduced Ascending Aortic Strain and Distensibility: Earliest Manifestations of Vascular Aging in Humans." Hypertension **55**(2): 319-326.

Redon, J., Olsen, M. H., Cooper, R. S., Zurriaga, O., Martinez-Beneito, M. A., Laurent, S., Cifkova, R., Coca, A.,Mancia, G. (2011). "Stroke mortality and trends from 1990 to 2006 in 39 countries from Europe and Central Asia: implications for control of high blood pressure." European Heart Journal **32**(11): 1424-1431.

Reeve, J. C., Abhayaratna, W. P., Davies, J. E.,Sharman, J. E. (2014). "Central Hemodynamics Could Explain the Inverse Association Between Height and Cardiovascular Mortality." American Journal of Hypertension **27**(3): 392-400.

Regnault, V., Lagrange, J., Pizard, A., Safar, M. E., Fay, R., Pitt, B., Challande, P., Rossignol, P., Zannad, F.,Lacolley, P. (2014). "Opposite Predictive Value of Pulse Pressure and Aortic Pulse Wave Velocity on Heart Failure With Reduced Left Ventricular Ejection Fraction: Insights From an Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) Substudy." Hypertension **63**(1): 105-111.

Regnault, V., Thomas, F., Safar, M. E., Osborne-Pellegrin, M., Khalil, R. A., Pannier, B.,Lacolley, P. (2012). "Sex Difference in Cardiovascular Risk: Role of Pulse Pressure Amplification." Journal of the American College of Cardiology **59**(20): 1771-1777.

Remington, J. W. (1963). The Physiology of the Aorta and Major Arteries. American Physiological Society Handbook of Physiology. Section 2, Circulation. Washington DC, American Physiology Society. **2:** 799-838.

Remington, J. W.,Hamilton, W. F. (1946). "Calculation of the arterial uptake and stroke volume from the pressure pulse contour." Federation Proceedings **5**(1 Pt 2): 85.

Remington, J. W.,Hamilton, W. F. (1947). "Quantitative calculation of the time course of cardiac ejection from the pressure pulse." American Journal of Physiology **148**(1): 25-34.

Remington, J. W., Noback, C. R., Hamilton, W. F.,Gold, J. J. (1948). "Volume elasticity characteristics of the human aorta and prediction of the stroke volume from the pressure pulse." American Journal of Physiology **153**(2): 298-308.

Remington, J. W.,Wood, E. H. (1956). "Formation of Peripheral Pulse Contour in Man." Journal of Applied Physiology **9**(3): 433-442.

Reusz, G. S., Cseprekal, O., Temmar, M., Kis, É., Cherif, A. B., Thaleb, A., Fekete, A., Szabó, A. J., Benetos, A.,Salvi, P. (2010). "Reference Values of Pulse Wave Velocity in Healthy Children and Teenagers." Hypertension **56**(2): 217-224.

Riva Rocci, S. (1896). "Un sfigmomanometro nuovo." Gazette Medical di Torino **47**: 981-996.

Roman, M. J.,Devereux, R. B. (2014). "Association of Central and Peripheral Blood Pressures With Intermediate Cardiovascular Phenotypes." Hypertension **63**(6): 1148-1153.

Roman, M. J., Okin, P. M., Kizer, J. R., Lee, E. T., Howard, B. V.,Devereux, R. B. (2010). "Relations of central and brachial blood pressure to left ventricular hypertrophy and geometry: the Strong Heart Study." Journal of Hypertension **28**(2): 384-388.

Rosano, C., Watson, N., Chang, Y., Newman, A. B., Aizenstein, H. J., Du, Y., Venkatraman, V., Harris, T. B., Barinas-Mitchell, E.,Sutton-Tyrrell, K. (2013). "Aortic Pulse Wave Velocity Predicts Focal White Matter Hyperintensities in a Biracial Cohort of Older Adults." Hypertension **61**(1): 160-165.

Russo, C., Jin, Z., Palmieri, V., Homma, S., Rundek, T., Elkind, M. S. V., Sacco, R. L.,Di Tullio, M. R. (2012). "Arterial Stiffness and Wave Reflection: Sex Differences and Relationship With Left Ventricular Diastolic Function." Hypertension **60**(2): 362-368.

Safar, M. E. (2010). "Arterial aging - hemodynamic changes and therapeutic options." Nature Reviews. Cardiology **7**(8): 442-449.

Safar, M. E.,Nilsson, P. M. (2013). "Pulsatile hemodynamics and cardiovascular risk factors in very old patients: background, sex aspects and implications." Journal of Hypertension **31**(5): 848-857.

Sagawa, K., Lie, R. K.,Schaefer, J. (1990). "Translation of Otto Frank's Paper Wie Grundform des Arteriellen Pulses" Zeitschrift fGr Biologie 37: 483-526 (1899)." Journal of Molecular and Cellular Cardiology **22**: 253-277.

Sakai, T., Takazawa, K., Fujita, M., Yabe, K., Maeda, K.,Kobayashi, T. (1993). "Changes in flow velocity pattern in the left ventricular outflow tract before and after administration of nitroglycerine as assessed by Doppler echocardiography." Journal of Cardiology (Japan) **23**(S37): 25-33.

Sakai, T., Takazawa, K., Maeda, K., Yabe, K., Fujita, M.,Kobayashi, T. (1992). "Changes in flow velocity pattern in the left ventricular outflow tract after vasoconstriction and vasodilatation assessed by Doppler echocardiography." Journal of Tokyo Medical College **50**(5): 712-726.

Salvi, P., Safar, M. E., Labat, C., Borghi, C., Lacolley, P., Benetos, A.,on behalf of the Partage study investigators (2010). "Heart disease and changes in pulse wave velocity and pulse pressure amplification in the elderly over 80 years: the PARTAGE Study." Journal of Hypertension **28**(10): 2127-2133.

Schultz, M. G., Davies, J. E., Hardikar, A., Pitt, S., Moraldo, M., Dhutia, N., Hughes, A. D.,Sharman, J. E. (2014). "Aortic reservoir pressure corresponds to cyclic changes in aortic volume: physiological validation in humans." Arterioscler Thromb Vasc Biol **34**(7): 1597-1603.

Schultz, M. G., Davies, J. E., Roberts-Thomson, P., Black, J. A., Hughes, A. D.,Sharman, J. E. (2013). "Exercise central (aortic) blood pressure is predominantly driven by forward traveling waves, not wave reflection." Hypertension **62**(1): 175-182.

Scuteri, A., Tesauro, M., Guglini, L., Lauro, D., Fini, M.,Di Daniele, N. (2013). "Aortic stiffness and hypotension episodes are associated with impaired cognitive function in older subjects with subjective complaints of memory loss." International Journal of Cardiology **169**(5): 371-377.

Segers, P., Mahieu, D., Kips, J., Rietzschel, E., De Buyzere, M., De Bacquer, D., Bekaert, S., De Backer, G., Gillebert, T., Verdonck, P., Van Bortel, L.,for the Asklepios investigators (2009). "Amplification of the Pressure Pulse in the Upper Limb in Healthy, Middle-Aged Men and Women." Hypertension **54**(2): 414-420.

Segers, P., Mahieu, D., Kips, J.,Van Bortel, L. M. (2007). "The use of a generalized transfer function: different processing, different results!" Journal of Hypertension **25**(9): 1783-1787

Segers, P., Mahieu, D., Rietzschel, E. R., De Buyzere, M. L.,Van Bortel, L. M. (2008). "Impact of Radial Artery Pressure Waveform Calibration on Estimated Central Pressure Using a Transfer Function Approach." Hypertension **52**(3): e24-e25.

Segers, P., Rietzschel, E. R., De Buyzere, M. L., Vermeersch, S. J., De Bacquer, D., Van Bortel, L. M., De Backer, G., Gillebert, T. C., Verdonck, P. R.,on behalf of the Asklepios investigators (2007). "Noninvasive (Input) Impedance, Pulse Wave Velocity, and Wave Reflection in Healthy Middle-Aged Men and Women." Hypertension **49**(6): 1248-1255.

Segers, P., Taelman, L., Degroote, J., Bols, J.,Vierendeels, J. (2015). "The aortic reservoir-wave as a paradigm for arterial haemodynamics: insights from three-dimensional fluid-structure interaction simulations in a model of aortic coarctation." Journal of Hypertension **33**(3): 554-563.

Shadwick, R. E. (1999). "Mechanical design in arteries." Journal of Experimental Biology **202**(Pt 23): 3305-3313.

Sharman, J. E., Davies, J. E., Jenkins, C.,Marwick, T. H. (2009). "Augmentation index, left ventricular contractility, and wave reflection." Hypertension **54**(5): 1099-1105.

SHEP Cooperative Research Group (1991). "Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: Final results of the Systolic Hypertension in the Elderly Program (SHEP)." JAMA **265**(24): 3255-3264.

Shiburi, C. P., Staessen, J. A., Maseko, M., Wojciechowska, W., Thijs, L., Van Bortel, L. M., Woodiwiss, A. J.,Norton, G. R. (2006). "Reference Values for SphygmoCor Measurements in South Africans of African Ancestry." American Journal of Hypertension **19**(1): 40-46.

Shipley, R. E., Gregg, D. E.,Schroeder, E. F. (1943). "An experimental study of flow patterns in various peripheral arteries." American Journal of Physiology **138**: 718-731.

Singer, J., Trollor, J. N., Baune, B. T., Sachdev, P. S.,Smith, E. (2014). "Arterial stiffness, the brain and cognition: A systematic review." Ageing Research Reviews **15**(0): 16-27.

Smith, I. B. (1993). "The Impact of Stephen Hales on Medicine." Journal of the Royal Society of Medicine **86**: 349-352.

Spencer, M. P.,Denison, A. B. (1963). Pulsatile blood flow in the vascular system. Handbook of Physiology. Washington DC, American Physiology Society. **2:** 839-864.

Staessen, J. A., Wang, J.-G., Bianchi, G.,Birkenhager, W. H. (2003). "Essential hypertension." Lancet **361**: 1629-1641.

Starling, E. H. (1918). The Linacre lecture on the Law of the Heart. London, Longmans.

Stea, F., Bozec, E., Millasseau, S., Khettab, H., Boutouyrie, P.,Laurent, S. (2014). "Comparison of the Complior Analyse device with Sphygmocor and Complior SP for pulse wave velocity and central pressure assessment." Journal of Hypertension **32**(4): 873-880

Stone, J., Johnstone, D., Mitrofanis, J.,O'Rourke, M. F. (2015). "The mechanical cause of age-related dementia: the brain is destroyed by the pulse." Journal of Alzheimers Disease **44**: 355-373.

Suever, J. D., Oshinski, J., Rojas-Campos, E., Huneycutt, D., Cardarelli, F., Stillman, A. E.,Raggi, P. (2012). "Reproducibility of pulse wave velocity measurements with phase contrast magnetic resonance and applanation tonometry." International Journal of Cardiovascular Imaging **28**: 1141-1146.

Suga, H., Sagawa, K.,Shoukas, A. A. (1973). "Load Independence of the Instantaneous Pressure-Volume Ratio of the Canine Left Ventricle and Effects of Epinephrine and Heart Rate on the Ratio." Circulation Research **32**(3): 314-322.

Sugawara, J., Hayashi, K.,Tanaka, H. (2010). "Distal Shift of Arterial Pressure Wave Reflection Sites With Aging." Hypertension **56**(5): 920-925.

Takazawa, K. (1987). "A clinical study of the second component of left ventricular systolic pressure." Journal of the Tokyo Medical College **45**: 256-270.

Takazawa, K., Kobayashi, H., Kojima, I., Aizawa, A., Kinoh, M., Sugo, Y., Shimizu, M., Miyawaki, Y., Tanaka, N., Yamashina, A.,Avolio, A. (2012). "Estimation of central aortic systolic pressure using late systolic inflection of radial artery pulse and its application to vasodilator therapy." Journal of Hypertension **30**(5): 908-916.

Takazawa, K., Kobayashi, H., Shindo, N., Tanaka, N.,Yamashina, A. (2007). "Relationship between radial and central arterial pulse wave and evaluation of central aortic pressure using the radial arterial pulse wave." Hypertension Research **30**: 219-228.

Tanindi, A., Erkan, A. F., Alhan, A.,Töre, H. F. (2014). "Central pulse pressure amplification is associated with more extensive and severe coronary artery disease." Scandinavian Cardiovascular Journal **48**: 167-175.

Taviani, V., Patterson, A. J., Graves, M. J., Hardy, C. J., Worters, P., Sutcliffe, M. P. F.,Gillard, J. H. (2010). "Accuracy and repeatability of fourier velocity encoded M-mode and two-dimensional cine phase contrast for pulse wave velocity measurement in the descending aorta." Journal of Magnetic Resonance Imaging **31**(5): 1185-1194.

Taylor, M. G. (1957). "An approach to an analysis of the arterial pulse wave. I. Oscillations in an attenuating line." Physics in Medicine and Biology **1**: 258-269.

Taylor, M. G. (1957). "An approach to an analysis of the arterial pulse wave. II. Fluid oscillations in an elastic pipe." Physics in Medicine and Biology **1**: 321-329.

Taylor, M. G. (1959). "An experimental determination of the propagation of fluid oscillations in a tube with a visco-elastic wall; together with an analysis of the characteristics required in an electrial analogue." Physics in Medicine and Biology **4**: 63-82.

Taylor, M. G. (1959). "The influence of the anomalous viscosity of blood upon its oscillatory flow." Physics in Medicine and Biology **3**: 273-290.

Taylor, M. G. (1964). Wave travel in arteries and the design of the cardiovascular system. New York, McGaw-Hill.

Taylor, M. G. (1965). "Wave travel in a nonuniform transmission line, in relation to pulses in arteries." Physics in Medicine and Biology **10**: 539-550.

Taylor, M. G. (1966). "The input impedance of an assembly of randombly branching elastic tubes." Biophysical Journal **6**(1): 29–51.

Taylor, M. G. (1966). "An introduction to some recent developments in arterial haemodynamics." Australasian Annals of Medicine **15**(1): 71-86.

Taylor, M. G. (1966). "Wave transmission through an assembly of randomly branching elastic tubes." Biophysical Journal **6**(5): 697-716.

Taylor, M. G. (1967). "The elastic properties of arteries in relation to the physiological functions of the arterial system." Gastroenterology **52**: 358-363.

Taylor, M. G. (1973). "Hemodynamics." Annual Review of Physiology **35**: 87-116.

The Reference Values for Arterial Stiffness' Collaboration (2010). "Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values'." European Heart Journal **31**(19): 2338-2350.

Ting, C. T., Brin, K. P., Lin, S. J., Wang, S. P., Chang, M. S., Chiang, B. N.,Yin, F. C. (1986). "Arterial hemodynamics in human hypertension." Journal of Clinical Investigations **78**(6): 1462-1471.

Ting, C. T., Chen, J. W., Chang, M. S.,Yin, F. C. (1995). "Arterial hemodynamics in human hypertension. Effects of the calcium channel antagonist nifedipine." Hypertension **25**(6): 1326-1332.

Ting, C. T., Chou, C. Y., Chang, M. S., Wang, S. P., Chiang, B. N.,Yin, F. C. (1991). "Arterial hemodynamics in human hypertension. Effects of adrenergic blockade." Circulation **84**(3): 1049-1057.

Ting, C. T., Yang, T. M., Chen, J. W., Chang, M. S.,Yin, F. C. (1993). "Arterial hemodynamics in human hypertension. Effects of angiotensin converting enzyme inhibition." Hypertension **22**(6): 839-846.

Townsend, R. R., Wilkinson, I. B., Schiffrin, E. L., Avolio, A. P., Chirinos, J. A., Cockcroft, J. R., Heffernan, K. S., Lakatta, E. G., McEniery, C. M., Mitchell, G. F., Najjar, S. S., Nichols, W. W., Urbina, E. M.,Weber, T. (2015). "Recommendations for Improving and Standardizing Vascular Research on Arterial Stiffness: A Scientific Statement From the American Heart Association." Hypertension **66**(3): 698-722.

Tsao, C. W., Seshadri, S., Beiser, A. S., Westwood, A. J., Decarli, C., Au, R., Himali, J. J., Hamburg, N. M., Vita, J. A., Levy, D., Larson, M. G., Benjamin, E. J., Wolf, P. A., Vasan, R. S.,Mitchell, G. F. (2013). "Relations of arterial stiffness and endothelial function to brain aging in the community." Neurology **81**: 984-991.

Uebaba, K., O'Rourke, M. F., Sindone, A. P., Keogh, A. M., Siswanto, B. B., McDonald, P. S., Ishiyama, H., Amano, K.,Xu, F. (2002). "Arterial pulse wave analysis for the assessment of cardiac failure: value of non-invasive applanation tonometry of radial artery." Japanese Journal of Applied Physiology **32**: 147-157.

Uretsky, S., Gillam, L., Lang, R., Chaudhry, F. A., Argulian, E., Supariwala, A., Gurram, S., Jain, K., Subero, M., Jang, J. J., Cohen, R.,Wolff, S. D. (2015). "Discordance between echocardiography and MRI in the assessment of mitral regurgitation severity." Journal of the American College of Cardiology **65**: 1078-1088.

Vaitkevicius, P. V., Fleg, J. L., Engel, J. H., O'Connor, F. C., Wright, J. G., Lakatta, L. E., Yin, F. C.,Lakatta, E. G. (1993). "Effects of age and aerobic capacity on arterial stiffness in healthy adults." Circulation **88**(4): 1456-1462.

Van Bortel, L. M., Laurent, S., Boutouyrie, P., Chowienczyk, P., Cruickshank, J. K., De Backer, T., Filipovsky, J., Huybrechts, S., Mattace-Raso, F. U. S., Protogerou, A. D., Schillaci, G., Segers, P., Vermeersch, S., Weber, T., on behalf of the Artery Society,the European Society of Hypertension Working Group on Vascular Structure Function (2012). "Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity." Journal of Hypertension **30**(3): 445-448

van Sloten, T. T., Schram, M. T., van den Hurk, K., Dekker, J. M., Nijpels, G., Henry, R. M. A.,Stehouwer, C. D. A. (2014). "Local stiffness of the carotid and femoral artery is associated with incident cardiovascular events and all-cause mortality – The Hoorn Study –." Journal of the American College of Cardiology **63**: 1739-1747.

van Vierordt, K. (1855). Die Lehre vom Arterienpuls in gesunden und kranken Zuständen gegründet auf eine neue Methode der bildlichen Darstellung des menschlichen Pulses. Braunschweig, Vieweg und Sohn.

Vasan, R. S. (2008). "Pathogenesis of Elevated Peripheral Pulse Pressure: Some Reflections and Thinking Forward." Hypertension **51**(1): 33-36.

Verbeke, F., Maréchal, C., Van Laecke, S., Van Biesen, W., Devuyst, O., Van Bortel, L. M., Jadoul, M.,Vanholder, R. (2011). "Aortic Stiffness and Central Wave Reflections Predict Outcome in Renal Transplant Recipients." Hypertension **58**(5): 833-838.

Verbeke, F., Segers, P., Heireman, S., Vanholder, R., Verdonck, P.,Van Bortel, L. M. (2005). "Noninvasive Assessment of Local Pulse Pressure: Importance of Brachial-to-Radial Pressure Amplification." Hypertension **46**(1): 244-248.

Verbeke, F., Van Biesen, W., Honkanen, E., Wikström, B., Jensen, P. B., Krzesinski, J.-M., Rasmussen, M., Vanholder, R.,Rensma, P. L. (2011). "Prognostic Value of Aortic Stiffness and Calcification for Cardiovascular Events and Mortality in Dialysis Patients: Outcome of the Calcification Outcome in Renal Disease (CORD) Study." Clinical Journal of the American Society of Nephrology **6**(1): 153-159.

Vermeersch, S. J., Rietzschel, E. R., De Buyzere, M. L., De Bacquer, D., De Backer, G., Van Bortel, L. M., Gillebert, T. C., Verdonck, P. R., Segers, P.,on behalf of the Asklepios investigators (2008). "Age and gender

related patterns in carotid-femoral PWV and carotid and femoral stiffness in a large healthy, middle-aged population." Journal of Hypertension **26**(7): 1411-1419.

Veterans Administration Cooperative Study Group on Antihypertensive Agents (1967). "Effects of treatment on morbidity in hypertension: I. Results in patients with diastolic blood pressures averaging 115 through 129 mm hg." JAMA **202**(11): 1028-1034.

Veterans Administration Cooperative Study Group on Antihypertensive Agents (1970). "Effects morbidity of treatment on in hypertension: II. results in patients with diastolic blood pressure averaging 90 through 114 mm hg." JAMA **213**(7): 1143-1152.

Virmani, R., Avolio, A. P., Mergner, W. J., Robinowitz, M., Herderick, E. E., Cornhill, J. F., Guo, S. Y., Liu, T. H., Ou, D. Y.,O'Rourke, M. F. (1991). "Effect of aging on aortic morphology in populations with high and low prevalence of hypertension and atherosclerosis. Comparison between occidental and Chinese communities." American Journal of Pathology **139**: 1119-1129.

Vlachopoulos, C., Aznaouridis, K., O'Rourke, M. F., Safar, M. E., Baou, K.,Stefanadis, C. (2010). "Prediction of cardiovascular events and all-cause mortality with central haemodynamics: a systematic review and meta-analysis." European Heart Journal **31**(15): 1865-1871.

Vlachopoulos, C., Aznaouridis, K.,Stefanadis, C. (2010). "Prediction of Cardiovascular Events and All-Cause Mortality With Arterial Stiffness: A Systematic Review and Meta-Analysis." Journal of the American College of Cardiology **55**(13): 1318-1327.

Vlachopoulos, C., Aznaouridis, K.,Stefanadis, C. (2014). "Aortic Stiffness for Cardiovascular Risk Prediction: Just Measure It, Just Do It!" Journal of the American College of Cardiology **63**(7): 647-649.

Wakerlin, G. E. (1962). "From Bright toward light: the story of hypertension research." Circulation Research **11**: 131-136.

Wang, J. J., O'Brien, A. B., Shrive, N. G., Parker, K. H.,Tyberg, J. V. (2003). "Time-domain representation of ventricular-arterial coupling as a windkessel and wave system." Am J Physiol Heart Circ Physiol **284**(4): H1358-1368.

Wang, K. L., Cheng, H. M., Sung, S. H., Chuang, S. Y., Li, C. H., Spurgeon, H. A., Ting, C. T., Najjar, S. S., Lakatta, E. G., Yin, F. C., Chou, P.,Chen, C. H. (2010). "Wave reflection and arterial stiffness in the prediction of 15-year all-cause and cardiovascular mortalities: a community-based study." Hypertension **55**(3): 799-805.

Watson, N. L., Sutton-Tyrrell, K., Rosano, C., Boudreau, R. M., Hardy, S. E., Simonsick, E. M., Najjar, S. S., Launer, L. J., Yaffe, K., Atkinson, H. H., Satterfield, S.,Newman, A. B. (2011). "Arterial Stiffness and Cognitive Decline in Well-Functioning Older Adults." The Journals of Gerontology Series A: Biological Sciences and Medical Sciences **66A**(12): 1336-1342.

Webb, A. J. S., Simoni, M., Mazzucco, S., Kuker, W., Schulz, U.,Rothwell, P. M. (2012). "Increased Cerebral Arterial Pulsatility in Patients With Leukoaraiosis: Arterial Stiffness Enhances Transmission of Aortic Pulsatility." Stroke **43**(10): 2631-2636.

Weber, E.-H. (1850). "“Ueber die Anwendung der Wellenlehre vom Kreislaufe des Blutes und insbesondere auf die Pulslehre.” (“On the application of wave theory to the circulation of blood and in particular to the pulse.”) (in German)." Mathematical-Physical Section **2**: 164-204.

Weber, E.-H.,Weber, W. (1825). Wellenlehre auf Experimente gegrundet. Leipzig, Gerhard Fleischer.

Weber, M. A. (2015). "Interpreting blood pressure in young adults." Journal of the American College of Cardiology **65**(4): 336-338.

Weber, T., Auer, J., O’Rourke, M. F., Punzengruber, C., Kvas, E.,Eber, B. (2006). "Prolonged mechanical systole and increased arterial wave reflections in diastolic dysfunction." Heart **92**(11): 1616-1622.

Weber, T., Wassertheurer, S., O'Rourke, M. F., Haiden, A., Zweiker, R., Rammer, M., Hametner, B.,Eber, B. (2013). "Pulsatile hemodynamics in patients with exertional dyspnea: potentially of value in the diagnostic

evaluation of suspected heart failure with preserved ejection fraction." Journal of the American College of Cardiology **61**(18): 1874-1883.

Weber, W. (1866). ""“Theorie der durch Wasser oder andere incompressible Flüssigkeiten in elastischen Röhren fortgepflanzten Wellen.” (“Theory of waves propagating in water or in other incompressible liquids contained in elastic tubes.”) (in German)." Mathematical-Physical Section **18**: 353-357.

Westerhof, B. E., Guelen, I., Stok, W. J., Lasance, H. A. J., Ascoop, C. A. P. L., Wesseling, K. H., Westerhof, N., Bos, W. J. W., Stergiopulos, N.,Spaan, J. A. E. (2008). "Individualization of transfer function in estimation of central aortic pressure from the peripheral pulse is not required in patients at rest." Journal of Applied Physiology **105**(6): 1858-1863.

Westerhof, B. E., Guelen, I., Westerhof, N., Karemaker, J. M.,Avolio, A. (2006). "Quantification of Wave Reflection in the Human Aorta From Pressure Alone: A Proof of Principle." Hypertension **48**(4): 595-601.

Westerhof, N.,O'Rourke, M. F. (1995). "Haemodynamic basis for the development of left ventricular failure in systolic hypertension and for its logical therapy." Journal of Hypertension **13**(9): 943-952.

Westerhof, N., Segers, P.,Westerhof, B. E. (2015). "Wave Separation, Wave Intensity, the Reservoir-Wave Concept, and the Instantaneous Wave-Free Ratio: Presumptions and Principles." Hypertension **66**(1): 93-98.

Westerhof, N., Sipkema, P., van den Bos, G. C.,Elzinga, G. (1972). "Forward and backward waves in the arterial system." Cardiovascular Research **6**(6): 648-656.

Westerhof, N., Westerhof, B. E., Tyberg, J. V., Bouwmeester, J. C., Shrive, N. G.,Wang, J. J. (2013). "CrossTalk proposal: Forward and backward pressure waves in the arterial system do / do not represent reality." Journal of Physiology **591**: 1167-1177.

Westerhof, N..,Westerhof, B. E. (2015). "The reservoir wave paradigm discussion." Journal of Hypertension **33**(3): 458-460.

Wetterer, E. (1954). "Flow and Pressure in the Arterial System, Their Hemodynamic Relationship, and the Principles of Their Measurement." Minnesota Medicine **37**(2): 77-86.

Wiggers, C. J. (1928). The Pressure pulses in the cardiovascular system. London, Longmans, Green and Co.

Wiggers, C. J. (1938). "Physical and physiological aspects of arteriosclerosis and hypertension." Annals of Internal Medicine **6**: 12-30.

Wiggers, C. J. (1942). "Basic hemodynamic principles essential to interpretation of cardiovascular disorders." Bulletin of the New York Academy of Medicine **18**: 3-17.

Williams, B.,Lacy, P. S. (2005). "Blood pressure and outcomes in clinical trials." J Hypertens **23**(3): 487-488.

Williams, B.,Lacy, P. S. (2010). "Central haemodynamics and clinical outcomes: going beyond brachial blood pressure?" European Heart Journal **31**(15): 1819-1822.

Wohlfahrt, P., Krajcoviechova, A., Jozifova, M., Mayer, O., Vanek, J., Filipovsky, J., Laurent, S.,Cifkova, R. (2014). "Large artery stiffness and carotid flow pulsatility in stroke survivors." Journal of Hypertension **32**(5): 1097-1103

Wohlfahrt, P., Krajčoviechová, A., Seidlerová, J., Mayer, O., Filipovský, J.,Cífková, R. (2014). "Comparison of Noninvasive Assessments of Central Blood Pressure Using General Transfer Function and Late Systolic Shoulder of the Radial Pressure Wave." American Journal of Hypertension **27**(2): 162-168.

Wojciechowska, W., Staessen, J. A., Nawrot, T., Cwynar, M., Seidlerova, J., Stolarz, K., Gasowski, J., Ticha, M., Richart, T., Thijs, L., Grodzicki, T., Kawecka-Jaszcz, K.,Filipovsky, J. (2006). "Reference Values in White Europeans for the Arterial Pulse Wave Recorded by Means of the SphygmoCor Device." Hypertension Research **29**(7): 475-483.

Wojciechowska, W., Stolarz-Skrzypek, K., Tikhonoff, V., Richart, T., Seidlerová, J., Cwynar, M., Thijs, L., Li, Y., Kuznetsova, T., Filipovský, J., Casiglia, E., Grodzicki, T., Kawecka-Jaszcz, K., O'Rourke, M.,Staessen, J. A.

(2012). "Age dependency of central and peripheral systolic blood pressures: Cross-sectional and longitudinal observations in European populations." Blood Pressure **21**(1): 58-68.

Womersley, J. R. (1955). The Mathematical Analysis of the Arterial Circulation in a State of Oscillatory Motion. Dayton, OH, Wright Air Development Centre.

Womersley, J. R. (1955). "Method for the calculation of velocity, rate of flow and viscous drag in arteries when the pressure gradient is known." The Journal of Physiology **127**(3): 553-563.

Wykretowicz, A., Rutkowska, A., Krauze, T., Przymuszala, D., Guzik, P., Marciniak, R.,Wysocki, H. (2012). "Pulse pressure amplification in relation to body fatness." British Journal of Clinical Pharmacology **73**(4): 546-552.

Yaginuma, T., Avolio, A., O'Rourke, M., Nichols, W., Morgan, J. J., Roy, P., Baron, D., Branson, J.,Feneley, M. (1986). "Effect of glyceryl trinitrate on peripheral arteries alters left ventricular hydraulic load in man." Cardiovascular Research **20**(2): 153-160.

Yang, G., Wang, Y., Zeng, Y., Gao, G. F., Liang, X., Zhou, M., Wan, X., Yu, S., Jiang, Y., Naghavi, M., Vos, T., Wang, H., Lopez, A. D.,Murray, C. J. L. (2013). "Rapid health transition in China, 1990–2010: findings from the Global Burden of Disease Study 2010." The Lancet **381**(9882): 1987-2015.

Yano, Y., Stamler, J., Garside, D. B., Daviglus, M. L., Franklin, S. S., Carnethon, M. R., Liu, K., Greenland, P.,Lloyd-Jones, D. M. (2015). "Isolated Systolic Hypertension in Young and Middle-Aged Adults and 31-Year Risk for Cardiovascular Mortality: The Chicago Heart Association Detection Project in Industry Study." Journal of the American College of Cardiology **65**(4): 327-335.

Yin, F. C., Guzman, P. A., Brin, K. P., Maughan, W. L., Brinker, J. A., Traill, T. A., Weiss, J. L.,Weisfeldt, M. L. (1983). "Effect of nitroprusside on hydraulic vascular loads on the right and left ventricle of patients with heart failure." Circulation **67**(6): 1330-1339.

Young, T. (1809). "The Croonian Lecture: on the Function of the Heart and Arteries." Philosophical Transactions of the Royal Society of London **99**(1809): 1-31.

Zamani, P., Bluemke, D. A., Jacobs, D. R., Jr., Duprez, D. A., Kronmal, R., Lilly, S. M., Ferrari, V. A., Townsend, R. R., Lima, J. A., Budoff, M., Segers, P., Hannan, P.,Chirinos, J. A. (2015). "Resistive and pulsatile arterial load as predictors of left ventricular mass and geometry: the multi-ethnic study of atherosclerosis." Hypertension **65**(1): 85-92.

Zamani, P., Jacobs, D. R., Jr., Segers, P., Duprez, D. A., Brumback, L., Kronmal, R. A., Lilly, S. M., Townsend, R. R., Budoff, M., Lima, J. A., Hannan, P.,Chirinos, J. A. (2014). "Reflection magnitude as a predictor of mortality: the Multi-Ethnic Study of Atherosclerosis." Hypertension **64**(5): 958-964.

Zeki Al Hazzouri, A., Newman, A. B., Simonsick, E., Sink, K. M., Sutton Tyrrell, K., Watson, N., Satterfield, S., Harris, T., Yaffe, K.,for the Health ABC Study (2013). "Pulse Wave Velocity and Cognitive Decline in Elders: The Health, Aging, and Body Composition Study." Stroke **44**(2): 388-393.

Zhang, Y., Agnoletti, D., Protogerou, A. D., Topouchian, J., Wang, J.-G., Xu, Y., Blacher, J.,Safar, M. E. (2013). "Characteristics of pulse wave velocity in elastic and muscular arteries: a mismatch beyond age." Journal of Hypertension **31**(3): 554-559

Zhong, W., Cruickshanks, K. J., Schubert, C. R., Carlsson, C. M., Chappell, R. J., Klein, B. E. K., Klein, R.,Acher, C. W. (2014). "Pulse Wave Velocity and Cognitive Function in Older Adults." Alzheimer Disease & Associated Disorders **28**(1): 44-49

Zimmer, H.-G. (2002). "Who discovered the Frank-Starling mechanism?" News in Physiological Sciences **17**: 181-184.

Appendix A

In this appendix is the publication by the European group The Reference Values of Arterial Measurement Collaboration, which is led by Herbert A, Laurent S, Cruickshank JK, Boutouyrie P. They published the "Establishing Reference Values for Central Blood Pressure and its Amplification in a General Healthy Population and according to Cardiovascular Risk-Factors" in the European Heart Journal 2014;35:3122-3132. I and Dr O'Rourke participated in contributing our database of volunteers and patients to be included in their analysis. This paper is attached.

Appendix A of this thesis has been removed as it contains published material. Please refer to the following citation for details of the article contained in these pages.

Herbert, A., Laurent, S., Cruickshank, J. K., Boutouyrie, P., on behalf of the Reference Values of Arterial Measurements Collaboration. (2014) Establishing reference values for central blood pressure and its amplification in a general healthy population and according to cardiovascular risk-factors. *European Heart Journal.* 35(44) p. 3122-3132.

DOI: 10.1093/eurheartj/ehu293

Appendix B

In this appendix is a copy of final ethics approval letter related to studies described in chapter 5 sections 5.2 and 5.3.

Appendix B of this thesis has been removed as it may contain sensitive/confidential content