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Amendments

Page 20 line 21:	References should include Van Bortel, L. M., Doprez, D., Starmans-Kool, M. J., Safar, M. E., Giannattasio, C., Cockcroft, J., Kaiser, D. R., Thuillez, C. Clinical Applications of arterial stiffness, Task Force III: Recommendations for user procedures. Am J Hypertension 2002;15:445-452.
Page 36 line 4:	site should read sight.
Page 40 paragraph 3 line5:	References should include Lehmann, E. D. Regarding the accuracy of generalized transfer functions for estimating central aortic blood pressure. J Hypertens 1999;17:1225-1227, and Lehmann, E. D. Where is the evidence that radial artery tonometry can be used to accurately and non-invasively predict central aortic blood pressure in patients with diabetes? Diabetes Care 2000;23:869-871.
Page 57 Aims of the Thesis:	The aims of the studies presented in this thesis are to explore the relationships between the arterial pressure waveform at different sites within the arterial system in both the time and frequency domains. Understanding these relationships may permit the prediction, or reconstruction, of features of the central aortic pressure waveform which have been proposed to be of greater value in the understanding and monitoring of the progression and treatment of cardiovascular disease than the measurement of peripheral arterial pressures alone. The aims include the prospective exploration and evaluation of this potential.
Page 68 line 9:	Coefficients of variability for measured diastolic blood pressure of 3.4% for central aortic pressure using the Millar catheter and 4.8% for radial tonometry are based upon an average of 26 measurements in 30 subjects. Equivalent data for central aortic diastolic pressure using a fluid filled catheter (average of 24 measurements from 10 subjects) yields similar results with a coefficient of variability of 2.7%.
Page 131 paragraph 4.2.2:	Prior to the commencement of the study all subjects were randomised 1:1 to contribute to either the derivation or validation of an ensemble average transfer function. There was an *a priori* intention to review the ensemble average transfer function obtained from the first 30 subjects randomised to contribute to the derivation.
Page 261:	Insert Kelly, R., Hayward, C., Ganis, J., Daley, J., Avolio, A., O'Rourke, M. Non-invasive registration of the arterial pressure pulse waveform using high fidelity applanation tonometry. Journal of Vascular Medicine and Biology 1989b;1:142-149.
Page 114 lines 20 and 23:	Kelly, *et al.* 1989 should read Kelly, *et al.* 1989b.
Page 115 line 7:	Kelly, *et al.* 1989 should read Kelly, *et al.* 1989b.

Arterial pressure waves: waveform characteristics, their associations and factors influencing their propagation

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THESIS

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The circulation is not everywhere and always the same

William Harvey 1578-1657

Table of Contents

CHAPTERS

Summary

Although effective preventive strategies exist, cardiovascular disease remains the leading cause of death in Western societies. Therefore substantial benefit may be gained by the identification of individuals at increased risk. Elevated blood pressure has long been recognised as a risk factor, yet the arterial pulse may be described by parameters other than systolic and diastolic pressure which may be of independent prognostic value. The augmentation index, thought to represent the influence of a pressure wave reflected from the periphery on the pressure wave resulting from cardiac contraction has been of particular interest. Since the morphology of the pulse varies throughout the arterial system it has been proposed that assessment of features of the central aortic pressure waveform may be of greatest value. Interest has therefore been directed towards non-invasive methods for the prediction of central aortic waveform features from peripheral arterial waveforms, most commonly the radial, particularly using transfer function techniques.

Individual and generalised arterial transfer functions were derived from 78 subjects, and their potential accurately to reconstruct central aortic waveform parameters from radial waveforms evaluated. Significant errors were demonstrated in reconstructed central aortic waveform parameters, particularly augmentation index, and exploration of the impact of subject gender and the presence of diabetes mellitus suggests that such factors may contribute.

Potential limitations of the frequency response characteristics of the fluid-filled catheter system and retrospective evaluation of the generalised arterial transfer functions in the above study were addressed by the use of high fidelity transducer-tipped catheters and a prospective design in a larger cohort. The results were similar, suggesting that the errors

may be inherent to the technique rather than to theoretical limitations of the fluid-filled catheter system.

The potential impact of different physiological perturbations, such as a Valsalva manoeuvre or isometric handgrip exercise, on the arterial transfer function and capacity for a generalised arterial transfer function to reconstruct central aortic waveforms was explored in the latter cohort. Similar errors were demonstrated as under baseline conditions for all parameters except the augmentation index and time to the inflection point, for which errors were increased.

Results in both cohorts strongly support the contention that for the non-invasive estimation of central aortic waveform parameters transfer function techniques offer no advantage over assessment of brachial artery blood pressures and parameters of the untransformed radial waveform. Specifically transfer functions appear inferior for the prediction of central aortic augmentation index.

Having established this I turned my attention to the determinants of augmentation by exploration of time and frequency domain relationships between arterial waveforms at 5 aortic sites, using pressure transducer tipped catheters. Contrary to general beliefs, the results suggest that apparent augmentation may result from frequency dispersion with only limited influence of reflected waves.

The relationship between pressure waveforms at different arterial sites is determined by intervening arterial properties. The findings in this thesis suggest that for the non-invasive prediction of central aortic waveform parameters in individuals, transfer function techniques offer no practical benefit for clinical management. Whether analysis of alternative waveforms, for example the carotid, might offer additional advantages remains to be explored.

Declaration

The work presented in this thesis was derived from studies performed by me in the Cardiovascular Research Centre, Monash Medical Centre and Monash University, Melbourne, Australia. This thesis contains no material which has been accepted for the award of any other degree or diploma in any university or other institution, and to the best of my knowledge and belief contains no material previously published or written by another person, except where due reference is made in the text.

..[redacted]....

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Publications

PUBLICATIONS ARISING FROM THIS THESIS

Hope SA, Tay DB, Meredith IT, Cameron JD. Comparison of Generalised and Gender-Specific Transfer Functions for the Derivation of Aortic Waveforms. Am J Physiol Heart Circ Physiol 2002;283:H1150-H1156.

Hope SA, Tay DB, Meredith IT, Cameron JD. Use of Arterial Transfer Functions for the Derivation of Aortic Waveform Characteristics. J Hypertension 2003;21:1299-1305.

RELATED PUBLICATIONS

Hope SA, Meredith IT, Farouque HMO, Worthley SG, Plunkett JC, Balazs ND. Time Course of Plasma Adhesion Molecules in Acute Coronary Syndromes. Coronary Artery Disease 2002;13:215-221.

Hope SA, Meredith IT. Cellular adhesion molecules and cardiovascular disease. Part I. Their expression and role in atherogenesis. Internal Medicine Journal 2003;33:380-6.

Hope SA, Meredith IT. Cellular adhesion molecules and cardiovascular disease. Part II. Their association with conventional and emerging risk factors, acute coronary events and cardiovascular risk prediction. Internal Medicine Journal. Accepted for publication 12/09/02.

Hope SA. Real or apparent ethnic differences in cellular adhesion molecule activity? Clin Sci 2003;104:559-60.

SUBMITTED MANUSCRIPTS ARISING FROM THIS THESIS

Hope SA, Tay DB, Meredith IT, Cameron JD. Use of arterial transfer functions for the derivation of central aortic waveform characteristics in subjects with Type 2 diabetes mellitus.

Hope SA, Meredith IT, Cameron JD. Non-invasive calibration of radial waveforms increases error in transfer function-derived central aortic waveform characteristics.

Hope SA, Tay DB, Meredith IT, Cameron JD. Central aortic pressure augmentation: a product of wave reflection or frequency dispersion?

CONFERENCE ABSTRACT PUBLICATIONS

Hope SA, Meredith IT, Cameron JD. A comparison of systolic blood pressure and other parameters between aortic and radial blood pressure waveforms. Poster for the 49th annual scientific meeting of the Cardiac Society of Australia and New Zealand 2001. Heart Lung and Circulation 2001;10:A117

Hope SA, Tay DB, Meredith IT, Cameron JD. Validity of Fourier domain arterial transfer functions for the estimation of aortic systolic BP from radial BP waveforms. Poster for the 49th annual scientific meeting of the Cardiac Society of Australia and New Zealand 2001. Heart Lung and Circulation 2001;10:A83

Hope SA, Meredith IT, Cameron JD. Comparing the pressure and time characteristics of aortic and radial blood pressure waveforms. Poster presentation at the High Blood Pressure Research Council of Australia annual meeting 2001.

Hope SA, Tay DB, Meredith IT, Cameron JD. The application of Fourier domain arterial transfer functions for the estimation of aortic systolic BP from radial BP waveforms. Poster presentation at the High Blood Pressure Research Council of Australia annual meeting 2001.

Hope SA, Meredith IT, Cameron JD. A comparison of pressure and time characteristics between aortic and radial pressure waveforms. Poster presentation at the American College of Cardiology 51st annual scientific meeting 2002. J Am Coll Cardiol 2002;39(Supplement A):243A.

Hope SA, Tay DB, Meredith IT, Cameron JD. Application of Fourier domain arterial transfer functions for the estimation of aortic waveform characteristics from radial blood pressure waveforms. Oral presentation for the World Congress of Cardiology and 50th annual scientific meeting of the Cardiac Society of Australia and New Zealand 2002. J Am Coll Cardiol 2002;39(Supplement B):338B.

Hope SA, Tay DB, Meredith IT, Cameron JD. A comparison of gender-specific and generalised arterial transfer functions for the derivation of aortic waveform characteristics from radial blood pressure waveforms. Oral presentation for the World Congress of Cardiology and 50th annual scientific meeting of the Cardiac Society of Australia and New Zealand 2002. J Am Coll Cardiol 2002;39(Supplement B):338B.

Hope SA, Tay DB, Meredith IT, Cameron JD. Application of Fourier domain arterial transfer functions for the estimation of aortic waveform characteristics from radial blood pressure waveforms. Poster presentation for the International Society of Hypertension/European Society of Hypertension meeting 2002.

Hope SA, Tay DB, Meredith IT, Cameron JD. Gender-specific and generalised arterial transfer functions in the derivation of aortic waveform characteristics from radial blood pressure waves. Poster presentation for the International Society of Hypertension/European Society of Hypertension meeting 2002.

Hope SA, Meredith IT, Tay DB, Cameron JD. Type II diabetes mellitus is associated with greater error in non-invasive transfer function derivation of central aortic systolic pressure. Poster presentation for the Australian Health and Medical Research Congress 2002.

Hope SA, Meredith IT, Cameron JD. Is central aortic systolic augmentation solely due to pressure wave reflection? Poster presentation for the American College of Cardiology 52nd annual scientific meeting 2003. J Am Coll Cardiol 2003;41(Supplement A):246A.

Hope SA, Meredith IT, Tay DB, Cameron JD. Greater error in non-invasive transfer function derived central aortic systolic pressure in type II diabetes mellitus. Poster presentation for the American College of Cardiology 52nd annual scientific meeting 2003. J Am Coll Cardiol 2003;41(Supplement A):246A.

Hope SA, Meredith IT, Cameron JD. Aortic systolic pressure augmentation: solely attributable to pressure wave reflection or influenced by wave propagation? Poster presentation for 51st annual scientific meeting of the Cardiac Society of Australia and New Zealand 2003.

Hope SA, Meredith IT, Cameron JD. Method of calibration of non-invasive blood pressure waveforms determines the accuracy of transfer function-derived central aortic pressures. Poster presentation for 51st annual scientific meeting of the Cardiac Society of Australia and New Zealand 2003.

Selected Abbreviations

SBP	Systolic blood pressure
DBP	Diastolic blood pressure
MAP	Mean arterial pressure
PP	Pulse pressure
Ad	Diastolic pressure time integral
As	Systolic pressure time integral
Tp	Time to peak pressure
Ts	Time to end of systole
Ti	Time to inflection point
Pi	Pressure at the inflection point
AP	Augmentation point
AI	Augmentation index
SVI	Subendocardial viability index
PWV	Pulse wave velocity
FFT	Fast Fourier Transformation
TF	Transfer function

Chapter 1

Literature review

TABLE OF CONTENTS

1.1 ELEMENTS OF THE STRUCTURE AND FUNCTION OF THE VASCULAR SYSTEM RELATING TO LARGE ARTERY MECHANICAL PROPERTIES

The mechanical properties of arteries have been subject to increasing interest over the last decade following wider recognition of their associations with the presence and future risk of symptomatic cardiovascular disease, since cardiovascular disease remains the leading cause of mortality in Western societies, and is projected to become the leading cause of death on a global scale by the year 2020.(Australian Institute of Health and Welfare 2001) This has led to the demonstration that, contrary to previous beliefs, the large arteries are not simply inert conduits for blood, but are highly biologically active, and that the development and progression of atherosclerosis is associated not only with structural but also functional changes in these vessels. Furchgott and Zawadzki first reported that the endothelium was essential for vasorelaxation to occur in response to acetylcholine, and was dependent upon the production of a diffusible endothelially derived substance, which was subsequently demonstrated to be nitric oxide, generated from L-arginine by the action of nitric oxide synthase.(Furchgott and Zawadzki 1980, Ignarro, *et al.* 1987, Palmer, *et al.* 1987, Palmer, *et al.* 1988) The functional changes *in vivo* that are associated with atherosclerosis appear to be due to endothelial dysfunction and although a number of endothelially derived vasoactive substances have been described, most demonstrable endothelial dysfunction relates largely to the bioavailability of nitric oxide.(Celermajer, *et al.* 1992, Joannides, *et al.* 1995, Meredith, *et al.* 1993) However, although related to the extent of atherosclerotic disease demonstrable by imaging techniques (Neunteufl, *et al.* 1997, Hashimoto, *et al.* 1999), the functional changes are not confined to arteries with overt disease, but are systemic (Anderson, *et al.* 1995a, Anderson, *et al.* 1995b), and may be detectable before

there is any demonstrable alteration of structure.(Celermajer, *et al.* 1992, Celermajer, *et al.* 1994, Clarkson, *et al.* 1997, Skyrme-Jones, *et al.* 2000)

1.1.1 Arterial structure

The wall of a normal artery is composed of three layers, the intima, the media and the adventitia (Figure 1-1), including both cellular, endothelial and smooth muscle cells, and extracellular matrix components, particularly fibrillar types I, III and V, and amorphous type IV collagen and elastin.(Ross 1992, Dingemans, *et al.* 2000) In arteries with no atherosclerotic disease the intima is composed only of endothelial cells, although occasional isolated smooth muscle cells may be found, resting on their basement membrane, containing largely amorphous type IV collagen. The media is bounded by both the internal and external elastic laminae, reticulate structures formed largely of elastin. In muscular arteries, such as the renal arteries, the media is dominated by smooth muscle cells, together with types I, III and V collagen. In larger elastic arteries, such as the aorta and its larger branches, the media is composed of several concentric lamellae of smooth muscle cells each separated by a further elastic lamina which is less distinct than the internal elastic lamina, and collagen of types I, III and V.(Dingemans, *et al.* 2000) The adventitia is composed of connective tissue in which the *vasa vasorum* are dispersed in those larger elastic arteries in which they are present.(Ross 1992) Changes in any of these layers, which may be seen with the development of atherosclerotic lesions or the presence of other disease processes, may lead to functional changes in the vessels, and particularly to changes in arterial stiffness which may be reflected by features of the arterial pulse as discussed in *Section 1.2.*

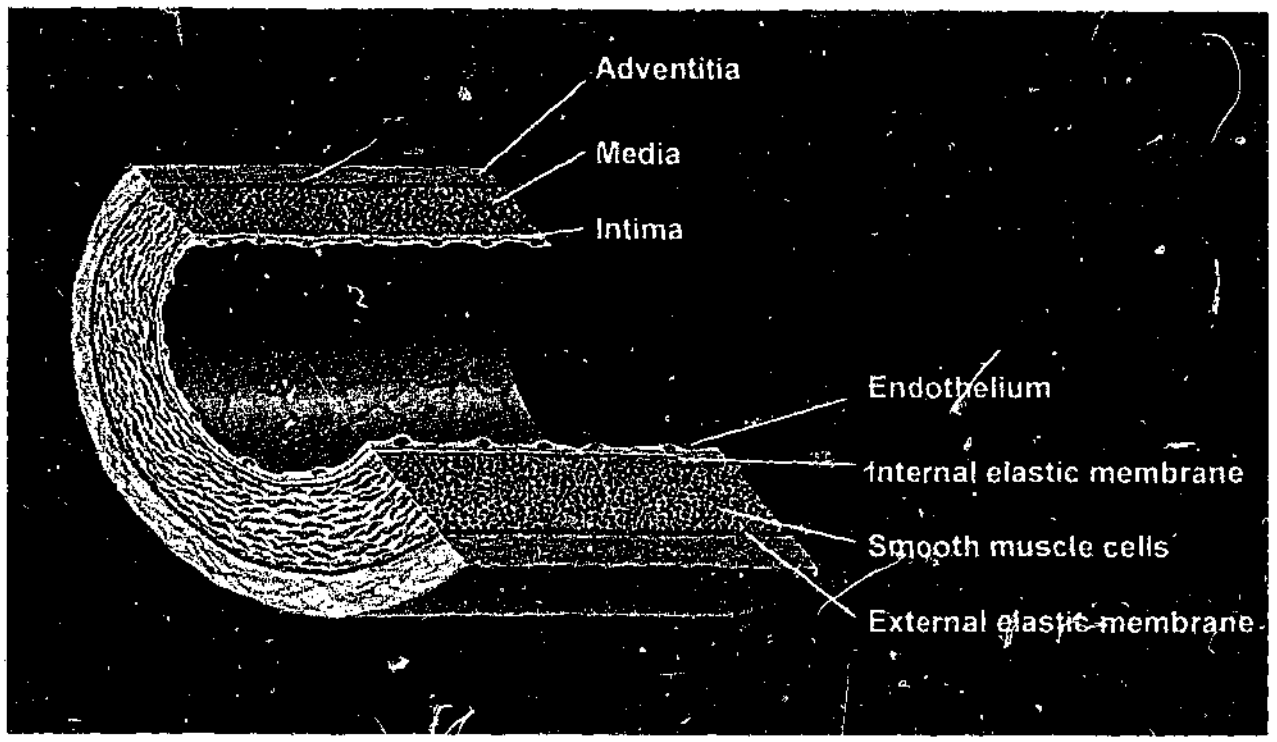


Figure 1-1. Components of the arterial wall

1.1.2 Atherosclerosis

Atherosclerosis is now recognised as an inflammatory disease involving endothelial injury consequent upon any one of a number of causes, including recognised cardiovascular risk factors such as hypercholesterolaemia, elevated plasma homocysteine levels and hypertension. This results in a number of functional abnormalities, mostly caused by, or associated with, abnormalities of endothelial nitric oxide bioavailability. Injury leads to the expression of cellular adhesion molecules by the endothelium and the recruitment of leukocytes to the developing intimal atherosclerotic lesion. This area has been extensively reviewed by a number of authors including Ross, Jang *et al*, Price and Loscalzo, Kriegelstein and Granger and others.(Ross 1986, Ross 1993, Ross 1999, Jang *et al.* 1994, Price and Loscalzo 1999, Krieglstein and Granger 2001) Macrophages become foam cells by the accumulation of lipid, and macrophage activation results in the release of cytokines and growth factors

which promote the migration of smooth muscle cells to and proliferation within the developing atherosclerotic lesion, as well as the production of extracellular matrix proteins.(Ross 1993, Ross 1999) Even if not associated with significant luminal changes due to positive remodelling of the artery, the accumulation of atheromatous plaque is likely to be associated with changes in the mechanical properties of the vessel wall and altered arterial distensibility, or stiffness, which might be associated with changes in the morphology of the arterial pressure waveform. Such changes may be more marked with the presence of calcium within the plaque, although this has not been explored. It is interesting to note, however, that observations regarding the changes in aortic stiffness associated with the conversion of the aorta "into a pipe-like bone" helped to shape the thoughts of William Harvey culminating in his 1628 landmark publication of *Exercitatio Anatomica De Motu Cordis Et Sanguinis In Animalibus* (Figure 1-2).(Harvey 1963)

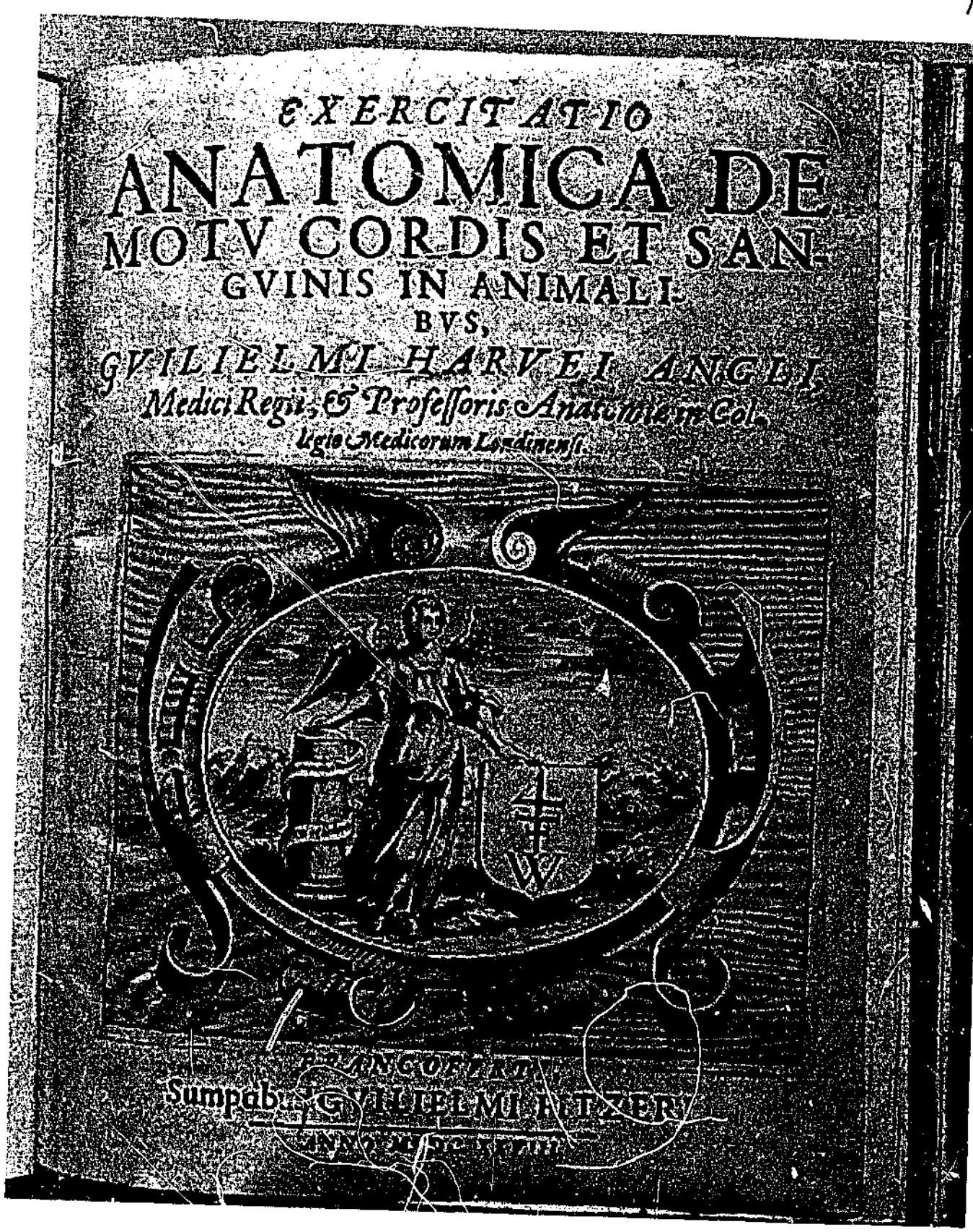


Figure 1-2. Frontice page of William Harvey's 1628 publication On The Movement of the Heart and Blood in Animals

1.1.3 Molecular factors and vascular tone

Elements of the arterial walls undergo structural changes on a molecular level with increasing age and particularly in the presence of diabetes mellitus which contribute to an increase in arterial stiffness. These include the fragmentation of elastin in the media, the first description of which is attributed to Erdheim in 1929 (Parums 1992), and recently reviewed by Robert *et al* (Robert, *et al.* 1998, Robert and Labat-Robert 2000), and also the glycation of both collagen and elastin reviewed by Paul and Bailey. (Paul and Bailey 1996) The glycation of fibrillar collagen is associated with less flexibility *in vivo* and of the amorphous basement membrane type IV collagen with both increased stiffness and increased permeability.(Paul and Bailey 1996) The effects are thought to be due to cross-linking of collagen molecules by advanced glycation end products.(Paul and Bailey 1996) The glycation of elastin is also thought to contribute to the increase in aortic stiffness associated with aging or diabetes mellitus.(Paul and Bailey 1996)

It is possible that changes in arterial tone associated either with an alteration in endothelial function and nitric oxide bioavailability or under the influence of the autonomic nervous system, or both (Nabel, *et al.* 1988, Dubois-Rande, *et al.* 1995) may also be associated with structurally independent changes in arterial stiffness. This might be due to the changes in arterial dimensions that are associated with changes in arterial tone, the influence of which on pulse wave velocity is discussed in *Section 1.2.2*, or by a transfer of stress between elastic and collagenous components of the vessel wall by changes in smooth muscle tone.(Bank, *et al.* 1996)

Thus structural and functional changes in the arteries, both in health and disease, may contribute to changes in the mechanical properties of the walls of these vessels. Since wall properties influence the propagation of energy within a conduit vessel, any such

changes will be manifest in changes in arterial pulse wave propagation and pressure waveform morphology. Terminal conditions reflecting changes in distal vessels may alter any pressure wave reflection and thereby also influence pressure waveform morphology. Thus the analysis of the arterial pressure waveform has the potential to provide information on both the structural and functional status of the arterial system which might be of clinical value.

1.2 THE PULSE IN HEALTH AND DISEASE

It has long been recognised that features of the arterial pulse may change during various disease states, and indeed that features of the pulse during health might predict the risk of cardiovascular disease in future years. Identification of individuals at high risk of future symptomatic cardiovascular disease may permit therapeutic interventions to be undertaken which have proven value for the prevention of future acute cardiovascular complications and death. The challenge arising from this therefore is the accurate identification, not only of groups, but particularly of individuals at increased cardiovascular risk. Analysis of the arterial pulse may contribute much towards the achievement of this aim.

The morphology of the arterial pulse varies between different sites within the arterial system, and it is suggested that features of the central aortic pressure waveform, and particularly the augmentation index, might be of greater clinical value in the prediction of future cardiovascular risk than the assessment of peripheral arterial pressures alone.(O'Rourke 1990, O'Rourke 1992) Whereas some investigators have used carotid artery pressure waveforms as a surrogate for aortic waveforms, having demonstrated a linear relationship between the carotid artery and aortic augmentation index (Chen, *et al.* 1996), others have preferred to attempt the accurate reconstruction of the central

aortic pressure waveform from the radial artery waveform by the application of a generalised arterial transfer function, describing the frequency domain relationship between the pressure waveforms at the 2 sites.(Karamanoglu, *et al.* 1993, Chen, *et al.* 1997, Sugimachi, *et al.* 1997, Fetics, *et al.* 1999) Despite considerable enthusiasm for this approach, the published data evaluating the validity of the technique, particularly for purely non-invasive use, remains modest. The studies presented in this thesis will explore the relationship between pressure waveforms at different sites within the arterial system, concentrating on the relationship between the central aorta and radial artery, and will evaluate the application of a generalised arterial transfer function to radial artery waveform data for the accurate reconstruction of features of the central aortic pressure waveform. Firstly, however, the relevant background will be considered.

Features of the arterial pulse will be described prior to considering the evidence that links these features with either the presence of, or risk of future, cardiovascular disease. Following this the data will be reviewed relating to the derivation and analysis of the frequency domain relationship between the arterial pulse at different arterial sites, and the potential for the understanding of this relationship to permit the reconstruction of central aortic pressure waveforms, features of which potentially contribute more to cardiovascular risk than those of more peripheral arterial pressure waveforms.

1.2.1 Characterisation of the arterial pulse

The importance of the circulatory system has been recognised since antiquity, with the second century Greek physician Galen teaching that blood provided nourishment to the tissues. However, he taught that this was achieved by blood moving to and fro along the veins from the right side of the heart, whilst vital spirits ebbed and flowed in the arteries from the left side of the heart.(Green 1978) Little further progress was made in the

understanding of the circulation until the landmark work of William Harvey, *De Motu Cordis*, was published in 1628, in which evidence was first presented for the continuity of the vascular system, with blood flowing from the heart via the arteries and from there passing into the venous system and thus returning to the heart.(Harvey 1963) Although over the subsequent centuries it was appreciated that alterations in the arterial pulse were associated with certain disease states, it was not until towards the end of the 19th century that quantitative methods of assessing features of the pulse other than the rate were developed. The first development was the sphygmogram, attributed to Marey in the mid 1860's, and improved to permit quantitative representations of the arterial pulse by Mahomed in the early 1870's. The contributions of Mahomed were reviewed by O'Rourke in 1992.(O'Rourke 1992) The sphygmogram provided a graphical representation of the pulse contour, and Mohamed subsequently described features of the pulse contour in a number of disease states including fever and acute glomerulonephritis. He was thereafter the first to describe differences in the pulse contour between the carotid, brachial and radial arteries, and noted similarities between the pulse contours associated with age related arterial degeneration and hypertension. The technique was subsequently employed to provide the first description of the effects upon the pulse contour at the radial artery of nitroglycerin, used as a remedy for angina pectoris.(Murrell 1879)

In 1896 the sphygmomanometer was first introduced by Riva-Rocci, and following the description by Korotkov in 1905 of the identification of both the systolic and diastolic arterial pressures by auscultation of the brachial artery during release of pressure from the inflatable cuff, the method rapidly gained popularity and eclipsed the sphygmogram, which fell into disuse.(Green 1978, O'Rourke 1992) However, despite its merits and its considerable contribution to the understanding and determination of risk of cardiovascular disease, the sphygmomanometer provides data on only 2 discrete

features of the arterial pulse, the highest and lowest pressures, and over the last decade there has been an increasing appreciation that the arterial waveform may also be described in terms of a number of other parameters, any or all of which have the potential to provide data of independent prognostic value for cardiovascular risk. This has rekindled interest in sphygmographic techniques and the analysis of the arterial waveform for a number of features other than systolic and diastolic pressures, particularly the augmentation index, and to a lesser extent the subendocardial viability index (Figure 1-3).(Murgo, *et al.* 1980, Hayward and Kelly 1997) The augmentation index is thought to result from the superimposition on the forward travelling pressure wave resulting from cardiac contraction of a pressure wave that has been reflected back from the periphery. As such, the inflection point is thought to mark the onset of influence of the reflected wave, and the inflection point of the central aortic pressure waveform is often regarded as a surrogate measure of the rate of pulse wave propagation, or pulse wave velocity. The augmentation index has been defined in the literature in a number of different ways; originally described by Murgo *et al* as the (secondary peak pressure – the primary peak pressure)/pulse pressure *x* 100% (that is the augmentation pressure/pulse pressure *x* 100%) (Murgo, *et al.* 1980), it has also been described as the secondary peak pressure/primary peak pressure/systolic pressure (Takazawa, *et al.* 1995), as the secondary peak pressure/primary peak pressure *x* 100% (Takazawa, *et al.* 1996), and as the (secondary peak – diastolic pressure)/pulse pressure *x* 100% (Hayward, *et al.* 2002). Although closely related, the values derived by the different calculations will differ significantly, and cannot easily be equated, however, increasing values derived by one method will largely be associated with increasing values derived by any other method. The original definition of Murgo *et al* will be used throughout this thesis for all arterial waveforms.(Murgo, *et al.* 1980) The significance of the augmentation index and the inflection point will be discussed further in *Section*

1.2.2.3. In youth and in the presence of healthy compliant arteries the inflection point occurs later than the peak pressure and the putative reflected wave augments diastolic pressure.(Murgo, *et al.* 1980) However, with stiffening of the arteries the inflection point occurs earlier in the pressure waveform and results in augmentation of the systolic pressure.(Murgo, *et al.* 1980) This has the effect of increasing left ventricular hydraulic load thereby increasing myocardial workload and therefore oxygen requirement and will be associated with an increase in intramyocardial pressure during systole.(Nichols, *et al.* 1985, Heineman and Grayson 1985) Additionally, with the loss of augmentation of central aortic diastolic pressure, diastolic coronary artery blood flow is potentially impaired. This further impairs the balance between myocardial oxygen demand and supply, and given the distribution of diastolic coronary artery blood flow within the myocardium may have a particularly detrimental effect on the subendocardial region.(Hoffman, *et al.* 1985, Hoffman 1987) It is through such mechanisms that an increased augmentation index is thought to be associated with cardiovascular risk.

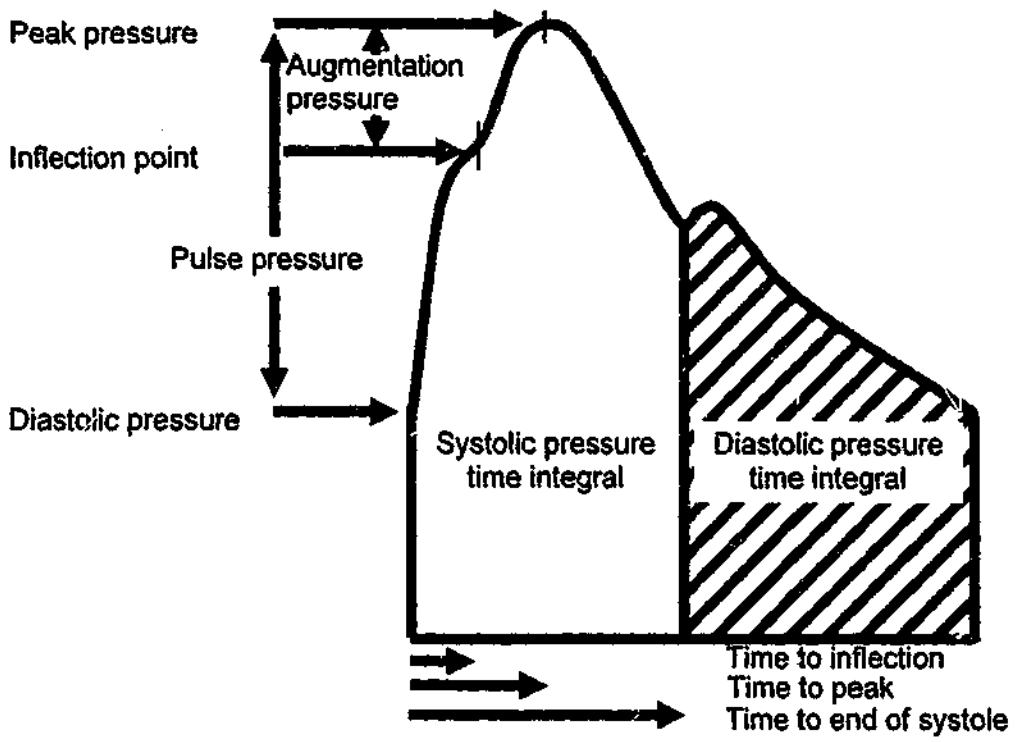


Figure 1-3. Representation of central aortic pressure waveform.

Augmentation index is described by the augmentation pressure as a proportion of the pulse pressure expressed as a percentage. Subendocardial viability index is defined as the diastolic pressure time integral/systolic pressure time integral.

1.2.2 Pulse wave propagation

The transmission of a change in pressure in an incompressible fluid in a conduit system to other parts of the system is influenced by the mechanical properties of the conduits. In a system where the conduits are rigid the change in pressure occurs simultaneously at all sites, whereas if the conduits are distensible, as is the case in the arterial system, an increase in pressure proximally will be associated with initial distension of proximal vessels and a delay in the transmission of the pressure to more peripheral sites, commonly expressed in terms of the pulse wave velocity (distance between the 2 sites/delay in transmission). With pressure wave propagation there is also the potential for wave reflection to occur at any point of discontinuity in the system, such as vascular divisions.

These phenomena, which may result not only in delay between the pressure waveform at different sites, but also in changes in the pressure waveform contour, and their assessment will be discussed further in this section.

1.2.2.1 Spectral analysis and the derivation of a transfer function

Whilst the delay in pressure wave transmission between 2 sites may be relatively easily measured, differences in the contour of complex waveforms are more difficult to characterise. The most widely adopted approach is the description of the waveforms in the frequency domain by spectral analysis and the derivation of a transfer function which describes the properties of the intervening arteries.

Spectral analysis applied to the cardiovascular system using Fourier analysis has been undertaken for many years, with its initial introduction attributed to Frank in 1926.(Attinger, *et al.* 1966) With the increasing computing power which has become available since that time the technique has become easier to apply, and has contributed substantially to the understanding of the cardiovascular system. Many investigators have used the technique to explore such diverse issues as relationships between heart rate variability and cardiovascular risk, and the relationships between blood flow and pressure within various parts of the arterial system (vascular impedance) including changes with aging, cardiovascular disease and the effects of vasoactive drugs.(Malek, 1996, Bigger, *et al.* 1992, La Rovere, *et al.* 2003, Gabe 1964, Patel, *et al.* 1965, Murgo, *et al.* 1980, Nichols, *et al.* 1985, Nichols, *et al.* 1986, Laskey and Kussmaul 1987, Brin and Yin 1984, Yaginuma, *et al.* 1986) Other investigators have applied the approach to the analysis of the transmission of the pressure pulse through the arterial system by exploring the relationship between pressure waveforms at different sites, and it is this aspect which is of relevance to this thesis.(Lasance, *et al.* 1968, O'Rourke 1970,

Karamanoglu, *et al.* 1993, Chen, *et al.* 1997, Sugimachi, *et al.* 1997, Karamanoglu and Feneley 1997, Fetics, *et al.* 1999, Segers, *et al.* 2000, Fitchett 1993) In particular, there has been substantial interest in the potential for knowledge of the relationship between the spectra of arterial pressure waveforms at 2 arterial sites, expressed as a transfer function, to permit the reconstruction of one of the waveforms from data acquired from the other arterial site. If this technique were to permit the accurate reconstruction of such a waveform it would enable the analysis of characteristics of the arterial pressure waveform at sites that are not routinely accessible. Given the suggestion that knowledge of characteristics of the central aortic pressure waveform could be of potential clinical value (O'Rourke 1990, O'Rourke 1994, O'Rourke, *et al.* 2001, O'Rourke 2002), most interest has revolved around the reconstruction of this waveform from non-invasively accessible peripheral arterial pressure waveforms, most commonly acquired from the radial artery.

Spectral analysis reduces a complex waveform to a series of simple sine and cosine waves of differing frequency, amplitude and phase, the sum of which will reproduce the original waveform. The relationship between waveforms at 2 different sites, or alternatively at the same site at 2 different times, may then be expressed in the form of a complex transfer function calculated as the quotient (output/input) of the spectra at these sites. However, the process requires that the system be both linear and time-invariant.(Bendat and Piersol 1986) The arterial system is known to be non-linear, and the use of this approach was questioned on this basis.(Attinger, *et al.* 1966) However, Attinger *et al* explored the errors attributable to the non-linearity of the arterial system and to variations in the length of the cardiac cycle and demonstrated that the errors were within the range of measurement errors.(Attinger, *et al.* 1966) The technique has therefore been considered appropriate to the vascular system despite the acknowledged departure from the assumptions.

The spectrum of the output of a system, and consequently the output itself, may be estimated by the product of the transfer function and the spectrum of the input of the system. Thus the arterial pressure waveform at 1 site might be estimated from the arterial pressure waveform at a second site provided that the arterial transfer function between the 2 sites was known. The accuracy of this process will also be influenced by the assumption of time-invariance. It has, however, been suggested that the transfer function relationship between arterial pressure waveforms at different sites does not vary under differing physiological conditions and therefore the assumption of time invariance may be met. (Karamanoglu, *et al.* 1993, O'Rourke 1994) Although it is possible to express them in other formats, arterial transfer functions are usually expressed in terms of their magnitude and phase, and will be presented in this format throughout this thesis. The first example presented in this thesis can be seen in Figure 3-4.

1.2.2.1.1 Magnitude

The magnitude of an arterial transfer function simply describes the ratio of the amplitudes of the waveform at the 2 sites at specified frequencies. For example, if the amplitude of each frequency at the output was half that at the input, the magnitude would be 0.5 at all frequencies, whereas if it were doubled at 1 frequency and tripled at a second, the magnitude at the first frequency would be 2.0 and at the second 3.0. It is relevant to note that the magnitude of a transfer function at any frequency is independent of the magnitude at all other frequencies.

1.2.2.1.2 Phase

The phase of the transfer function represents the difference in the phase of each frequency at the 2 sites and as such encodes data on the time between the acquisition of the 2 waveforms which, when data acquisition is from 2 sites separated in space, enables the estimation of either the phase velocities, pulse wave velocities of the individual frequencies, or distance between the 2 acquisition sites if the other of these variables is known. Phase velocities estimated in this way are usually referred to as apparent phase velocities, since the measurement is not direct, and the values will be distorted by the presence of reflected waves.

If the transfer function is calculated from waveforms at 2 sites a given distance apart, and the velocities of wave transmission, or phase velocities, are equal across the frequency range of interest, then the gradient of the phase diagram will be linear with a gradient which is proportional to the distance between the 2 sites.(Bendat and Piersol 1986) The gradient is not zero, since higher frequencies are associated with shorter wavelengths and will therefore have moved through a different proportion of their wavelength over the same distance. The gradient will be linear since a doubling in frequency will be associated with a halving of the wavelength and therefore a doubling of the proportion of wavelength through which the wave has travelled, or a doubling of the difference in phase shift. Additionally, when data are acquired from 2 arterial sites, since the distance between the 2 sites is constant, the gradient will also be proportional to the transit time for the different frequencies between the 2 points. Thus, it is also inversely proportional to the phase velocities. A higher phase velocity will be associated with a shorter transit time, and therefore a shallower gradient. It may therefore be seen, given the constant distance between points of measurement, that a non-linear phase diagram for an arterial transfer function is associated with differences in apparent phase velocities. This type of phase diagram might be explained by wave reflection or

alternatively be associated with frequency dispersion (differing true phase velocities at different frequencies), and therefore with distortion of the waveform with time, or distance travelled.

1.2.2.2 Pulse wave velocity

The time delay between a pressure waveform at 2 sites is described by the concept of pulse wave propagation from proximal to distal sites. The speed of propagation, or pulse wave velocity, is dependent upon both the mechanical properties and dimensions of the vessels in addition to properties of the incompressible fluid, or blood, within the vessel, and may be described by either the Moens-Korteweg equation, or the equation derived from this by Bramwell and Hill in which pulse wave velocity is expressed in terms of variables which are more easily measured in an intact organism.(Cameron 1999, Bramwell and Hill 1922)

$$c = \sqrt{\frac{E.h}{\rho.2.R}} \qquad c = \sqrt{\frac{V.dP}{\rho.dV}}$$

Moens-Korteweg equation **Bramwell Hill equation**

c is pulse wave velocity, and E represents Young's modulus of elasticity of the walls of a vessel of volume V, radius R and wall thickness h with distending pressure of P and containing blood of density ρ. dV is the change in volume associated with change of pressure dP.

As can be seen from the Moens-Korteweg equation, the pulse wave velocity is directly related to the Young's modulus of elasticity of the vessel wall, and consequently the stiffer the vessel the greater will be the pulse wave velocity.

As an indication of arterial mechanical properties, the measurement of pulse wave velocity has a number of potential advantages over other methods including the apparent simplicity of performance and, but for the potential problem of frequency dispersion, its independence of the wave properties of arterial pressure propagation.(Cameron 1999) It can also be measured equally well using either pressure or flow waves. However, the measurement is potentially complicated by the change in waveform morphology with distal progression and therefore possible difficulties in the identification of a constant point on the waveform at different sites.(Nichols and O'Rourke 1990) Although different waveform features have been suggested, since the foot of the wavefront will be little affected by any reflected waves this point has been most commonly utilised.(Nichols and O'Rourke 1990) It has also been suggested that additional difficulties are associated with the accurate identification of the foot of the wavefront since, although readily recognisable at low sampling rates, at the higher sampling rates which are necessary for the estimation of pulse wave velocity over short distances it becomes more difficult to define with precision, although this view is not universally held.(Nichols and O'Rourke 1990) Additional drawbacks include the inherent inaccuracies in estimating the distance travelled over any given arterial segment when measurements are acquired non-invasively and the dependence of pulse wave velocity on blood pressure, which potentially complicates comparisons between measurements in different subjects, or indeed in the same subject acquired on different occasions or before and after an intervention.(Bramwell and Hill 1923, Cameron 1999, Callaghan, *et al.* 1986, Blacher, *et al.* 1998a, Ngim, *et al.* 1999, Mackey, *et al.* 2002, Amar, *et al.* 2001, Millasseau, *et al.* 2002) Pulse wave velocity has also been demonstrated to be associated with spontaneous heart rate and influenced by heart rate changes resulting from ventricular pacing.(Albaladejo, *et al.* 2000, Albaladejo, *et al.* 2003, Amar, *et al.* 2001, Mackey, *et al.* 2002, Lantelme, *et al.* 2002, McGrath, *et al.*

2001, Liang *et al.* 1999) Some authors have suggested that there is no physiological rationale for the reported change with heart rate, and have suggested that the findings of Albaladejo *et al*, and by inference those of others using the same method, were related to the method used to measure pulse wave velocity, namely a device which identifies a large part of the pressure upstroke rather than simply foot-to-foot delay.(Albaladejo, *et al.* 2003, O'Rourke and Hayward 2003) This suggestion might be supported by the findings of Callaghan *et al* who described no relationship between pulse frequency and pulse wave velocity in *in vitro* studies of dog carotid arteries.(Callaghan, *et al.* 1984) However, these authors investigated a wide range of frequencies, mostly well in excess of any physiological rate. If the 2 rates that might be seen under physiological conditions are considered, the data suggest that the pulse wave velocity may be higher at the higher of these 2 frequencies.(Callaghan, *et al.* 1984) Additionally, by analogy with a perfectly elastic tube, there is a theoretical expectation that pulse wave velocity should increase with increasing frequency.(McDonald and Taylor 1959) It should also be noted that others have demonstrated similar findings to those of Albaladejo *et al* with increased pulse wave velocity, not explained by changes in blood pressure, associated with increased heart rate resulting from ventricular pacing when the pulse wave velocity was assessed by the classical foot-to-foot method, suggesting that the findings are indeed correct.(Liang, *et al.* 1999)

It has been suggested that the dependence of pulse wave velocity on more fundamental properties, such as elastic modulus or distensibility, as described in the Moens-Korteweg and Bramwell Hill equations, and on vessel geometry, which varies continuously throughout the arterial tree, might also be considered disadvantageous.(Cameron 1999) However, since even such apparently simple measurements as arterial pressure are also potentially influenced by the same mechanical and geometric factors, in addition to other factors such as peripheral

vascular resistance, these issues merit recognition, but probably should not be considered to detract significantly from the technique.

With the dependence of pulse wave velocity on vessel wall properties and dimensions, it is predictable that the pulse wave velocity differs significantly in different arterial segments, with increased pulse wave velocity in smaller and more muscular peripheral arteries than the central aorta.(McDonald 1968, Latham, *et al.* 1985) Indeed, some authors have reported regional differences in the changes observed in pulse wave velocity associated with disease processes such as diabetes mellitus.(Kimoto, *et al.* 2003) In addition to the previously mentioned limitations on comparisons between different subjects therefore, any direct comparison between subject groups is also only valid if made over the same arterial segment.

Despite all the potential limitations described above, the pulse wave velocity has been widely investigated for its associations with the presence of cardiovascular disease and its potential to contribute to the prediction of risk of future cardiovascular disease. The findings from these studies will be reviewed in *Section 1.2.3.3*.

1.2.2.3 Pressure wave reflection

There is the potential for wave reflection to occur in any wave guiding system at any point of discontinuity (or impedance change) in the system, such as vascular divisions, or potentially just changes in vascular dimensions or wall properties.(McDonald and Taylor 1959) The introduction of the concept of wave reflections in the vascular system is attributed to Grashey (1881) and Von Kries (1892).(Nichols and O'Rourke 1990) As discussed in *Section 1.2.1*, the inflection point and systolic pressure augmentation are generally believed to result from the superimposition of a reflected pressure wave on the forward travelling wave. Such reflected waves are believed to result in an increase in

cardiac afterload which may not be appreciated from sphygmomanometric measurement of peripheral artery blood pressures, yet may have a significant detrimental effect on the balance between cardiac workload and myocardial blood supply. The site of the predominant reflection point has been debated with some authors suggesting it to be at the renal arteries, or at the aortic bifurcation or femoral arteries, and others suggesting that the reflection point has no physical reality, but simply represents the combined effects of reflection from many peripheral sites.(Hamilton and Dow 1939, Hamilton 1944, McDonald and Taylor 1959, Latham, *et al.* 1985)

Although it is generally accepted that such reflected waves exist, and contribute to the phenomenon of the augmentation index, not all studies have been supportive. Karamanoglu *et al* suggest that systolic pressure augmentation is determined largely by left ventricular outflow characteristics rather than by arterial properties.(Karamanoglu and Feneley 1999) It has also been reported that a large pressure wave created by a rapid injection of blood retrogradely into a femoral artery was associated with no detectable effect on the pressure waveform recorded at the aortic root.(Nichols and O'Rourke 1990)

The concept of wave reflection has also been explored in the frequency domain. As discussed in *Section 1.2.2.1.2* the apparent phase velocities, or pulse wave velocity of individual frequency components, can be derived from the phase diagram of a transfer function. Such analysis reveals that the apparent phase velocities for pressure waves in the arterial system for the lower frequencies are higher than those of the higher frequencies, and also that there is fluctuation in the apparent phase velocities of the higher frequencies.(Porje 1946, Taylor 1957) Both of these phenomena are believed to result from pressure wave reflection since there is a theoretical expectation that phase velocity should increase with increasing frequency.(Porje 1946, Taylor 1957, McDonald and Taylor 1959) The foot-to-foot pulse wave velocity has been found

closely to approximate the average of the phase velocities of the higher frequencies.(McDonald 1968, Gabe 1964, Latham, *et al.* 1985) However, as in the time domain, not all findings are entirely consistent with the theory of wave reflection since, as McDonald and Taylor comment, neither the magnitude nor apparent phase velocities derived from transfer functions in the presence of occlusion of a major artery demonstrate the fluctuations that would be expected to result from reflection from the site of occlusion.(McDonald and Taylor 1959) It has however been suggested that reflection from multiple sites at different distances from the heart may explain some of these discrepancies.(McDonald and Taylor 1959)

1.2.3 Associations with cardiovascular risk

As previously alluded to, it has been recognised over a number of centuries that features of the arterial pulse might distinguish individuals with cardiovascular disease and at risk of cardiovascular complications or death. However, it was not until features of the pulse could be measured in absolute terms that this risk could be formally evaluated and quantified. The initial drive towards this aim came from the insurance industry seeking actuarial statistics against which they could evaluate risk for the purposes of assessing life insurance. This ultimately resulted in the birth and development of the science of epidemiology. More recently the quantitative assessment of cardiovascular risk has been employed for medical rather than actuarial purposes to identify individuals likely to benefit from various therapeutic interventions. With this has come the appreciation of the value of large population based studies, and recognition of the additional confidence to be obtained from meta-analyses, preferably considering all available data, both previously published and unpublished. By necessity such meta-analyses can only be

performed after a significant body of data is available, and therefore usually some considerable time after the first evidence is published.

Features of the arterial pulse that have been most widely assessed as markers of cardiovascular risk are measurements of pressure, including systolic and diastolic pressures, pulse pressure (systolic –diastolic pressure), mean arterial pressure and most recently average arterial pressure ((systolic + diastolic pressure)/2).(Lewington, *et al.* 2002) Other features which have been assessed and found to be associated with cardiovascular risk include both the augmentation index of central pressure waveforms and pulse wave velocity. The evidence linking these features to cardiovascular risk, which provides the rationale for their measurement, will be reviewed briefly in this section.

1.2.3.1 Blood pressure

It has long been recognised that elevated blood pressure is associated with increased cardiovascular risk, which undoubtedly increases with age.(Australian Institute of Health and Welfare 2001) There are substantial changes in usual blood pressure with age in Western societies, with blood pressure increasing from infancy, and systolic blood pressure continuing to increase throughout adult life.(Franklin, *et al.* 1997) However, whereas diastolic and mean arterial pressures increase until the age of around 50 to 60 years, following this diastolic blood pressure declines, associated with a sharp increase in pulse pressure, and mean arterial pressure stabilises.(Franklin, *et al.* 1997)

In accordance with teachings of the early 20th century, elevated diastolic pressure was traditionally regarded as the most important marker of increased cardiovascular risk, and supported by relatively early meta-analyses.(Kannel, *et al.* 1971, MacMahon, *et al.* 1990) However, as remarked by the Prospective Studies Collaboration group,

epidemiological studies are subject to appreciable random error, and as a result many studies have produced very different results.(Lewington, *et al.* 2002) Such is the case even for some of the large population based studies and even larger meta-analyses. Subsequently interest has been directed towards the assessment of systolic pressure as a stronger indicator of cardiovascular risk (Fisher 1985, Wittenberg 1985), particularly with the recognition of the risk associated with isolated systolic hypertension, that is an elevated systolic pressure associated with a normal or low diastolic pressure.(Gubner 1962, Antikainen, *et al.* 1998) This type of hypertension is most prevalent in the elderly, and is thought largely to result from increased arterial stiffness, reviewed by Oliver and Webb.(Oliver and Webb 2003) This understanding led further to the recognition that increases in arterial stiffness are responsible for the increase in pulse pressure that is observed in later life, with 2 potential adverse effects on the heart; namely an increase in cardiac work load associated with the increased systolic pressure, combined with a potential decrease in myocardial blood supply due to a fall in diastolic blood pressure.(Oliver and Webb 2003) Subsequently interest was directed to the potential for pulse pressure to be an independent marker of cardiovascular risk, which has been supported by the findings of a number of studies, with the suggestion that it may be an even stronger predictor of risk than systolic pressure.(Franklin, *et al.* 1999, Franklin, *et al.* 2001)

Increased pulse pressure has been associated with both the presence of cardiovascular disease and risk of future disease, including primary or recurrent acute coronary syndromes and cardiovascular mortality.(Scuteri, *et al.* 1995, Zakopoulos, *et al.* 2001, Nishijima, *et al.* 2001, Benetos, *et al.* 1998, Franklin, *et al.* 1997, Franklin, *et al.* 1999, Franklin, *et al.* 2001, Asmar, *et al.* 2001b, Madhavan, *et al.* 1994, Millar, *et al.* 1999, Blacher, *et al.* 2000, Benetos, *et al.* 1997, Fang, *et al.* 1995, Mitchell, *et al.* 1997, Darne, *et al.* 1989, Safar, *et al.* 2002, Domanski, *et al.* 1999a, Domanski, *et al.* 1999b,

Domanski, *et al.* 2001, Benetos, *et al.* 2000, Alderman, *et al.* 1998) Differences in the progression of pulse pressure with age have been noted between men and women, and increased pulse pressure is also associated with the presence of diabetes, the performance of physical strength training and with the occurrence of restenosis following percutaneous coronary intervention for coronary artery stenosis.(Smulyan, *et al.* 2001, Aoun, *et al.* 2001, Bertovic, *et al.* 1999) Of greater potential interest is the finding that the regression of atherosclerotic disease, as represented by carotid artery intima media thickness, which is observed with the treatment of hypertension, is associated with the fall in pulse pressure in response to treatment, rather than the fall in mean arterial pressure.(Boutouyrie, *et al.* 1999, Boutouyrie, *et al.* 2000) Increased pulse pressure is also associated with increased left ventricular mass and exercise induced myocardial ischaemia (Jokiniitty, *et al.* 2001, Kozakova, *et al.* 2003). It may be that these, and the other associations with pulse pressure that have been described, result from the direct relationship between pulse pressure and cardiac work ($r = 0.86$).(Starr 1957)

More recently, however, a further large meta-analysis including data from more than 1 million adults, suggests that although systolic, diastolic, mean arterial and pulse pressures, in addition to average pressure (systolic + diastolic pressure/2) are all predictive of cardiovascular risk, the average pressure is most informative, followed by systolic and diastolic pressures, with much less information on risk provided by the pulse pressure.(Lewington, *et al.* 2002) These authors also demonstrated that there was no threshold of systolic and diastolic blood pressure below which there was no longer an association with cardiovascular risk.

It is widely appreciated that differences are observed between blood pressures measured non-invasively by different methods. It is possible that some of the differences between studies might be related to differences in the method employed. Pressures measured

using a conventional sphygmomanometer are usually regarded as the gold standard (White, *et al.* 1993), although it has been demonstrated that this method both underestimates systolic and overestimates diastolic blood pressure with respect to simultaneous invasively measured brachial artery pressures.(Breit and O'Rourke 1974) A number of studies have found that oscillometric devices have a tendency to overestimate systolic and underestimate diastolic pressures compared with a conventional sphygmomanometer.(van Popele, *et al.* 2000) However, van Popele *et al*, using the same Dinamap® model as used in the studies presented in this thesis, demonstrated very similar systolic pressures but significantly lower diastolic pressures compared with a conventional sphygmomanometer. Given the previous findings with respect to the overestimation of true diastolic pressure with a conventional sphygmomanometer this suggests that the Dinamap® diastolic pressures may closely approximate the true values. It is also relevant to note that the differences between the Dinamap® and conventional sphygmomanometer measurements are influenced by measures of arterial stiffness.(van Popele, *et al.* 2000) However, whether this alters which method more closely approximates the true values is not known.

1.2.3.2 Augmentation index

As described earlier, the augmentation index is thought to represent the influence of a pressure wave reflected from the periphery on the forward travelling pressure wave which results from cardiac contraction. It is suggested that in health and in youth, when the arteries are compliant and the pulse wave velocity low, that the reflected wave returns to the ascending aorta during diastole and results in augmentation of diastolic blood pressure, in a manner which is mimicked by the technique of intra-aortic balloon counterpulsation in the treatment of myocardial failure.(Avolio, *et al.* 1984, Nichols and

O'Rourke 1990) However, with increasing age or in the presence of arteriosclerosis the pulse wave velocity is increased, and the reflected wave arrives in the ascending aorta prior to the completion of systole. This is associated not only with increased cardiac afterload, by the augmentation of systolic blood pressure, but also potentially detrimentally affects coronary artery blood supply through the loss of the augmentation of diastolic pressure, and it is through these mechanisms that the central aortic augmentation index is thought potentially to influence cardiovascular risk. The data reviewed in this section will be limited to studies in which the augmentation index has been measured either from waveforms acquired invasively from the central aorta or non-invasively by applanation tonometry of the carotid artery.

In keeping with the theoretical increase in cardiac afterload with increased augmentation index is the association between carotid augmentation index and indices of left ventricular mass in healthy subjects, and in those with hypertension or end stage renal disease.(Marchais, *et al.* 1993, Saba, *et al.* 1993, Kohara, *et al.* 1999, Peterson, *et al.* 2003) Also in keeping with the theory of wave reflection is the inverse relationship between augmentation index and both pulse wave velocity and height, an association which has been proposed to explain the association of increased augmentation index in women and also potentially the increased cardiovascular mortality observed in women with symptomatic cardiovascular disease.(London, *et al.* 1995, Marchais, *et al.* 1993, Smulyan, *et al.* 1998, Hayward and Kelly 1997, McGrath, *et al.* 2001) Increased augmentation index is also associated with increased age, blood pressure and the presence of microalbuminuria or end stage renal disease.(Hayward and Kelly 1997, Chen, *et al.* 1995, Smulyan, *et al.* 1998, Saba, *et al.* 1999, Tsioufis, *et al.* 2003, London, *et al.* 1992)

Increased augmentation index is associated with the presence of angiographic coronary artery disease, and predicts the ischaemic threshold in such patients.(Hayashi, *et al.*

2002, Kingwell, *et al.* 2002) It is also associated with both cardiovascular and all cause mortality in patients with end stage renal disease.(London, *et al.* 2001) It is however interesting to note, particularly with reference to findings of reconstructed central aortic waveforms that will be discussed in *Section 1.3.3*, that no change in augmentation index was observed in postmenopausal women who commenced hormone replacement therapy either in healthy women or women with diabetes mellitus.(Hayward, *et al.* 2001, Tanaka, *et al.* 1998b) Nor was any difference observed in augmentation index between groups of hypertensive subjects with and without hypercholesterolaemia.(Saba, *et al.* 1999) Furthermore, although augmentation index is lower in habitually physically active compared with sedentary postmenopausal women, an exercise training regime in postmenopausal women resulted in no change in augmentation index.(Tanaka, *et al.* 2000, Seals, *et al.* 2001)

A change in augmentation index has been demonstrated in association with drug treatments known to be of value in reducing cardiovascular risk. A reduction in augmentation index is consistently associated with the use of angiotensin converting enzyme (ACE) inhibitor therapy.(London, *et al.* 1994, Chen, *et al.* 1995, London, *et al.* 1996b, Pannier, *et al.* 2001, Asmar, *et al.* 2001) A similar reduction is also seen with a calcium channel blocker.(London, *et al.* 1994, Guerin, *et al.* 1992) However, when either of these 2 drug classes was compared with a β blocker, little or no change in augmentation index was observed with the latter.(Guerin, *et al.* 1992, Chen, *et al.* 1995, Pannier, *et al.* 2001, Asmar, *et al.* 2001c) It should also be noted that the augmentation index appears to be inversely related to heart rate (Stefanadis, *et al.* 1998, McGrath, *et al.* 2001, Gatzka, *et al.* 2001a), and the differences between the effect of a β blocker and other drug classes has been largely attributed to the heart rate differences following therapy.(Dart, *et al.* 2001, Dart, *et al.* 2002)

Both the theoretical factors and associations presented above have contributed to the belief that knowledge of the central aortic augmentation index, which may differ significantly between subjects that have similar brachial artery blood pressures, may help to direct the treatment of cardiovascular disease and risk factors in a clinically advantageous manner. Although most of the data presented relates to direct non-invasive measurements of carotid artery augmentation index by applanation tonometry, it is the belief that central aortic augmentation may be even more clinically useful that has fuelled the enthusiasm to reconstruct central aortic waveforms from peripherally accessible waveforms, most commonly the radial. The techniques involved in this process will be discussed further in *Section 1.3*.

1.2.3.3 Pulse wave velocity

As discussed earlier, the pulse wave velocity is directly related to arterial stiffness, and therefore has the potential to distinguish individuals with arterial degeneration or those at risk of cardiovascular disease. As such it has been extensively investigated in subjects with, or at risk of, cardiovascular disease, and for its associations with recognised cardiovascular risk factors.

The associations between the increase in pulse wave velocity and both heart rate and blood pressure have been discussed in *Section 1.2.2.2.*(Albaladejo, *et al.* 2000, Albaladejo, *et al.* 2003, Amar, *et al.* 2001, Mackey, *et al.* 2002, Lantelme, *et al.* 2002, McGrath, *et al.* 2001, Liang, *et al.* 1999, Bramwell and Hill 1923, Cameron 1999, Callaghan, *et al.* 1986, Blacher, *et al.* 1998a, Ngim, *et al.* 1999, Millasseau, *et al.* 2002) As might be expected, given the association with arterial stiffness, pulse wave velocity has been demonstrated by a number of investigators to increase with age.(Bramwell, *et al.* 1923, Laogun and Gosling 1982, Avolio, *et al.* 1983, Asmar, *et al.* 1995, Blacher, *et*

al. 1998a, Amar, *et al.* 2001, Smulyan, *et al.* 2001, Cheung, *et al.* 2002a, Mackey, *et al.* 2002, Millasseau, *et al.* 2002, Tomiyama, *et al.* 2003) Although pulse wave velocity increases throughout both childhood and adulthood in both men and women, it is lower in women between the ages of around 10 years and the menopause, when it increases more rapidly to become very similar to that in men.(Laogun and Gosling 1982, Rajzer, *et al.* 1999, Staessen, *et al.* 2001, McGrath, *et al.* 2001, Amar, *et al.* 2001, Mackey, *et al.* 2002, Tomiyama, *et al.* 2003) It is worthy of note that hormone replacement therapy is associated with a lower pulse wave velocity, which increases with withdrawal of therapy.(Rajkumar, *et al.* 1997b, Waddell, *et al.* 1999) Pulse wave velocity is also positively associated with left ventricular mass.(London, *et al.* 1996a, Cheung, *et al.* 2002b)

Increased pulse wave velocity is also associated with the presence of other cardiovascular risk factors including chronic, but not acute, smoking (Mahmud and Feely 2003), diabetes mellitus (Blacher, *et al.* 1998a, Aoun, *et al.* 2001, Mackey, *et al.* 2002, Kimoto, *et al.* 2003), renal function (Mourad, *et al.* 2001, Aoun, *et al.* 2001) and plasma homocysteine levels (Blacher, *et al.* 1998a, Bortolotto, *et al.* 1999). Pulse wave velocity is also associated with both gestational age, negatively, and birth weight, positively.(Oren, *et al.* 2003) The birth weight association might be surprising, but the investigators comment that the associations are explained largely by prematurity with regards to gestational age, and the prevalence of maternal diabetes in the infants of high birth weight.(Oren, *et al.* 2003)

Not only is increased pulse wave velocity associated with the presence of cardiovascular risk factors, but also with the integrity of endothelial function assessed non-invasively and the presence or extent of atherosclerosis.(Ramsey, *et al.* 1995a, Ramsey, *et al.* 1995b, Zureik, *et al.* 2002, Cheung, *et al.* 2002b, Kidawa, *et al.* 2003) Pulse wave velocity is predictive of exercise capacity and the ischaemic threshold in patients with

known cardiac disease (Bonapace, *et al.* 2003, Kingwell, *et al.* 2002), and there is some evidence that it is associated with the type of atherosclerotic plaque in the carotid arteries, suggesting that it may have potential to distinguish patients at higher or lower risk of acute cardiovascular events.(Zureik, *et al.* 2003) In keeping with this potential is the strong association with risk of future acute cardiovascular events and mortality.(Lebrun, *et al.* 2002, Blacher, *et al.* 1998b, Blacher, *et al.* 1999a, Blacher, *et al.* 1999b, London, *et al.* 2001, Laurent, *et al.* 2001, Shoji, *et al.* 2001, Safar, *et al.* 2002, Cruickshank, *et al.* 2002, Boutouyrie, *et al.* 2002, Laurent, *et al.* 2003)

Drug treatments of value in the treatment of cardiovascular disease, and associated with reduction of cardiovascular risk, are also associated with a fall in pulse wave velocity. Most, but not all (Pannier, *et al.* 2001), studies have demonstrated a fall in pulse wave velocity with the administration of either an ACE inhibitor or angiotensin receptor blocker.(London, *et al.* 1994, London, *et al.* 1996b, Asmar, *et al.* 2001a, Vuurmans, *et al.* 2002, Asmar 2001c) However, some authors have suggested that the fall in pulse wave velocity is entirely attributable to the fall in blood pressure.(London, *et al.* 1996b) It is interesting to note also that increased pulse wave velocity has also been described in patients with polymorphisms of the ACE gene and ACE receptor gene that are associated with an increased risk of myocardial infarction.(Benetos, *et al.* 1996b, Taniwaki, *et al.* 1999, Lajemi, *et al.* 2001) Similar reductions in pulse wave velocity have been observed with both β blocker and calcium channel blocker therapy (London, *et al.* 1994, Asmar, *et al.* 2001c, Pannier, *et al.* 2001), and response to treatment is influenced by ACE and ACE receptor polymorphisms.(Benetos, *et al.* 1996a) The evidence relating to the effect of lipid lowering therapy with statin treatment and changes in pulse wave velocity are conflicting. Two small double blind placebo controlled trials describe opposite findings, with pulse wave velocity increased over a

12 week treatment period in one study (Raison, *et al.* 2002), but decreased over a 6 month treatment period in the second.(Ichihara, *et al.* 2002)

Similarly to the findings relating to augmentation index as previously described, habitual physical activity in postmenopausal women is associated with a lower pulse wave velocity, although pulse wave velocity did not change with a short term aerobic training program.(Tanaka, *et al.* 1998a, Seals, *et al.* 2001) Conversely, increased pulse wave velocity is associated with habitual strength training.(Bertovic, *et al.* 1999)

It has thus been demonstrated that various features of the arterial pulse are strongly associated both with the presence and risk of cardiovascular disease, and that their assessment may therefore be of clinical value. It should be remembered that all the waveform parameters that have been described to be associated with cardiovascular risk are closely interrelated, which probably explains the very similar associations with cardiovascular risk and risk factors. Such close relationships may complicate the identification of waveform parameters of greatest significance for the evaluation of cardiovascular risk. Very small differences between groups may result in the entry of different waveform characteristics into any statistical model, and may explain the differences between many studies. The close relationship also complicates the interpretation of a change in any parameter, since changes in other parameters will occur simultaneously and should also be considered. It therefore remains extremely difficult, for instance, to separate and establish the relative contributions to cardiovascular risk of blood pressure measurements, augmentation of central aortic systolic pressure and pulse wave velocity.

1.3 ARTERIAL TRANSFER FUNCTIONS

As alluded to earlier, there has been great interest in the possibility of reconstructing central aortic waveforms from non-invasively accessible peripheral arterial waveforms. The radial artery has generally been the preferred peripheral site, since optimal applanation is easier to achieve than at the carotid artery and a satisfactory level of expertise in the technique can be achieved with less experience.(Chen, *et al.* 1997) The process of reconstruction of the central aortic pressure waveform has involved the use of arterial transfer functions, as discussed in *Section 1.2.2.1*, and studies in which arterial transfer functions have been derived or validated and studies which have utilised the technique for the reconstruction of central aortic pressure waveforms will be discussed in this section.

1.3.1 Previous studies deriving arterial transfer functions

Arterial transfer functions have been derived by a number of investigators to describe the relationship between the pressure pulse at different arterial sites since the late 1960's.(Lasance, *et al.* 1968, O'Rourke 1970, Karamanoglu, *et al.* 1993, Karamanoglu and Feneley 1996, Chen, *et al.* 1997, Sugimachi, *et al.* 1997, Karamanoglu and Feneley 1997, Fetics, *et al.* 1999, Segers, *et al.* 2000, Fitchett 1993) The derived arterial transfer functions have subsequently been used to reconstruct central aortic waveforms from peripheral waveforms for the estimation of cardiac output (Lasance, *et al.* 1968), the estimation of aortic valve gradients in aortic stenosis (Fitchett 1993), or for the characterisation of features of the central aortic pressure waveform itself.(O'Rourke 1970, Karamanoglu, *et al.* 1993, Chen, *et al.* 1997, Sugimachi, *et al.* 1997,

Karamanoglu and Feneley 1997, Fetics, *et al.* 1999, Segers, *et al.* 2000) Of relevance when comparing the transfer functions and results from the different studies is consideration of the technical differences between the studies which, although at first site may not appear significant, may potentially be of substantial importance. Different investigators have derived transfer functions by different methods, either in the time domain (Karamanoglu and Feneley 1997), or the frequency domain, by either non-parametric, Fast Fourier Transform (FFT) based methods (Lasance, *et al.* 1968, O'Rourke 1970, Karamanoglu, *et al.* 1993, Chen, *et al.* 1997, Sugimachi, *et al.* 1997, Fetics, *et al.* 1999, Segers, *et al.* 2000, Fitchett 1993), or parametric, autoregressive exogenous (ARX) methods (Chen, *et al.* 1997, Fetics, *et al.* 1999). Most investigators have derived arterial transfer functions for the relationship between the pressure waveforms in the ascending aorta and a peripheral artery, including the brachial (Lasance, *et al.* 1968, O'Rourke 1970, Karamanoglu, *et al.* 1993), radial (Karamanoglu, *et al.* 1993, Chen, *et al.* 1997, Sugimachi, *et al.* 1997, Fetics, *et al.* 1999), carotid (Karamanoglu and Feneley 1996), femoral (Fitchett 1993) or finger (Karamanoglu and Feneley 1997), whereas others have derived relationships between 2 peripheral arterial sites, the carotid and radial arteries (Segers, *et al.* 2000). As expected, transfer functions derived between different sites differ significantly.(Karamanoglu, *et al.* 1993, Nichols and O'Rourke 1998) In addition to this, arterial waveforms have been acquired by different methods. Although central aortic waveforms have been acquired invasively in all studies, some investigators have used fluid-filled catheter systems (Lasance, *et al.* 1968, O'Rourke 1970), and others pressure transducer-tipped catheters (Karamanoglu, *et al.* 1993, Chen, *et al.* 1997, Sugimachi, *et al.* 1997, Karamanoglu and Feneley 1997, Fetics, *et al.* 1999). Concerns have been expressed regarding the adequacy of the frequency response characteristics of fluid-filled catheter systems for this purpose. Peripheral waveforms have been acquired either invasively using fluid-filled catheter

systems (Lasance, *et al.* 1968, O'Rourke 1970), or non-invasively, either by applanation tonometry (Karamanoglu, *et al.* 1993, Chen, *et al.* 1997, Sugimachi, *et al.* 1997, Fetics, *et al.* 1999) or finger photoplethysmography (Karamanoglu and Feneley 1997). Waveforms acquired non-invasively by applanation tonometry require to be calibrated to known arterial pressures. Some investigators have calibrated waveforms to the mean and diastolic blood pressures of the invasively measured central aortic waveform (Chen, *et al.* 1997, Fetics, *et al.* 1999), whereas others have calibrated to invasively measured brachial artery systolic and diastolic pressures.(Karamanoglu, *et al.* 1993) In addition, some investigators have also used partly or wholly model-based approaches (Karamanoglu and Feneley 1996, Karamanoglu and Feneley 1997, Segers, *et al.* 2000). Each of these methodological variations may have a substantial impact on the capacity for a given arterial transfer function accurately to reconstruct central aortic waveform parameters from peripheral arterial waveforms acquired by the same, or a different, method to that used in the transfer function derivation. The possible permutations are presented diagrammatically in Figure 1-4. This highlights the limitations of attempting to generalise the findings of one study to different transfer functions and different methods of waveform acquisition.

In the studies presented in this thesis transfer functions are derived between measured central aortic pressure waveforms, and waveforms acquired non-invasively from the radial artery by applanation tonometry. Further detailed discussion will therefore be limited to those studies which have derived similar transfer functions. These comprise 4 studies, those of Karamanoglu *et al*, Chen *et al*, Sugimachi *et al* and Fetics *et al* (Karamanoglu, *et al.* 1993, Chen, *et al.* 1997, Sugimachi, *et al.* 1997, Fetics, *et al.* 1999). These studies have all involved relatively small numbers of subjects, and between them have presented data using 4 different methods of transfer function derivation. Karamanoglu *et al* used a non-parametric FFT method to derive waveform

spectra from 14 subjects (1 female) before calculating a generalised aortic-radial transfer function. This transfer function was then inverted to yield a radial-aortic transfer function for the reconstruction of central aortic waveforms from radial artery data.(Karamanoglu, *et al.* 1993) Chen *et al* used a parametric technique for the derivation of waveform spectra from 20 subjects (4 female), the linear autoregressive-exogenous method (ARX), and calculated an aortic-radial transfer function which was again inverted to yield a radial-aortic transfer function.(Chen, *et al.* 1997) Although these authors also derived a transfer function using an FFT based method from the same data, the results were not presented. However, the authors commented that the transfer functions were similar although they found that the ARX method yielded a smaller variance.(Chen, *et al.* 1997) The authors also commented that the approach of inverting an aortic-radial transfer function to obtain the radial-aortic transfer function is limited by the amplification of high frequency noise.(Chen, *et al.* 1997) Although, as they note, this may be ameliorated by the application of a low pass filter, other authors have explored the derivation of direct radial-aortic transfer functions to avoid this problem. Sugimachi *et al* used an FFT method, involving a windowing procedure to minimise spectral leakage together with the averaging of overlapping spectral estimates to retrieve the data lost by windowing, to derive waveform spectra from 8 patients in atrial fibrillation (6 female), before direct calculation of a generalised radial-aortic transfer function.(Sugimachi, *et al.* 1997) Fetics *et al* used both FFT and ARX methods to derive spectra from 20 subjects (unknown gender mix) and calculated both aortic-radial and radial-aortic transfer functions from both spectral data sets.(Fetics, *et al.* 1999) In addition to these studies there is currently available a commercial system for the reconstruction of central aortic waveforms from either radial or carotid artery waveform data, SphygmoCor® (AtCor Medical (previously PWV Medical), West Ryde, Australia).

However, neither the transfer functions utilised by the system, nor details of their methods of derivation, are in the public domain.

The authors of the first 3 studies above have evaluated their transfer functions for the reconstruction of the central aortic waveform by applying the generalised transfer function only to the radial data of the subjects from whom the transfer function was derived.(Karamanoglu, *et al.* 1993, Chen, *et al.* 1997, Sugimachi, *et al.* 1997) They have all reported reasonable reconstruction of central aortic systolic pressure, although the manner in which this has been reported is variable. Karamanoglu *et al* report a mean overestimation of 2.4mmHg, Sugimachi *et al* report a coefficient of determination (r^2) of 0.937, and Chen *et al* a mean difference of 0 ± 3.7 mmHg under baseline conditions.(Karamanoglu, *et al.* 1993, Sugimachi, *et al.* 1997, Chen, *et al.* 1997) Chen *et al* also reported reconstructed central aortic augmentation index, and found a mean underestimate of 7 ± 9%.(Chen, *et al.* 1997) These authors did not however report any measure of correlation between the measured and reconstructed augmentation indices, but found the quality of the reconstruction to be dependent upon the higher frequency components of the transfer function.(Chen, *et al.* 1997)

It is interesting to note that, although the numerical values of no transfer function have been published, those comparable generalised arterial transfer functions that have been presented in graphical form in the literature appear very similar, although all have wide confidence intervals.(Karamanoglu, *et al.* 1993, Chen, *et al.* 1997, Fetics, *et al.* 1999)

It has been suggested that the frequency domain relationship between the aortic and radial pressure waveforms does not differ significantly under different conditions, and therefore that a single generalised arterial transfer function might be equally applicable for the reconstruction of central aortic waveforms from radial waveforms under widely varying physiological conditions.(Karamanoglu, *et al.* 1993, O'Rourke 1994) It is suggested that the transmission of the pressure wave in the upper limb is little affected

by such factors as age, blood pressure or vasodilator therapy.(O'Rourke 1994) However, considering the graphical representations of aortic-radial transfer functions in the literature, it does appear that the aortic-radial arterial transfer function may differ from baseline following the administration of sublingual or intravenous glyceryl trinitrate (Karamanoglu, *et al.* 1993, Chen, *et al.* 1997), and it is reported that the transfer function is markedly altered by localised disturbance to the hand, such as the application of pressure or reactive hyperaemia.(Nichols and O'Rourke 1998)

The individual arterial transfer function is determined by the mechanical properties of the arterial system between the 2 sites of pressure waveform acquisition. Thus it would also be expected that subjects with shorter arms or smaller arteries would have different individual arterial transfer functions from those with longer arms or larger arteries. Additionally, differences in mechanical properties of the brachial artery have been demonstrated to be associated with, for example, age and the presence of diabetes mellitus, and these factors might also be expected to alter the individual arterial transfer function.(Kimoto, *et al.* 2003, Henry, *et al.* 2003) It is possible that such factors are responsible for the wide confidence intervals for the generalised arterial transfer function seen by all investigators, although differences in heart rate may also contribute.(Karamanoglu, *et al.* 1993, Chen, *et al.* 1997, Fetics, *et al.* 1999)

It must be remembered that the data presented above regarding the accuracy of reconstruction of central aortic waveform parameters were acquired from those subjects who contributed to the derivation of the transfer function being evaluated. This procedure simply validates the applied mathematical transformations, and cannot validate the transfer functions for use in other subject groups.(Lehmann 1998) Therefore, before the technique could be considered to be of value for the reconstruction of central aortic waveforms in individual subjects, appropriate prospective validation studies are indicated.

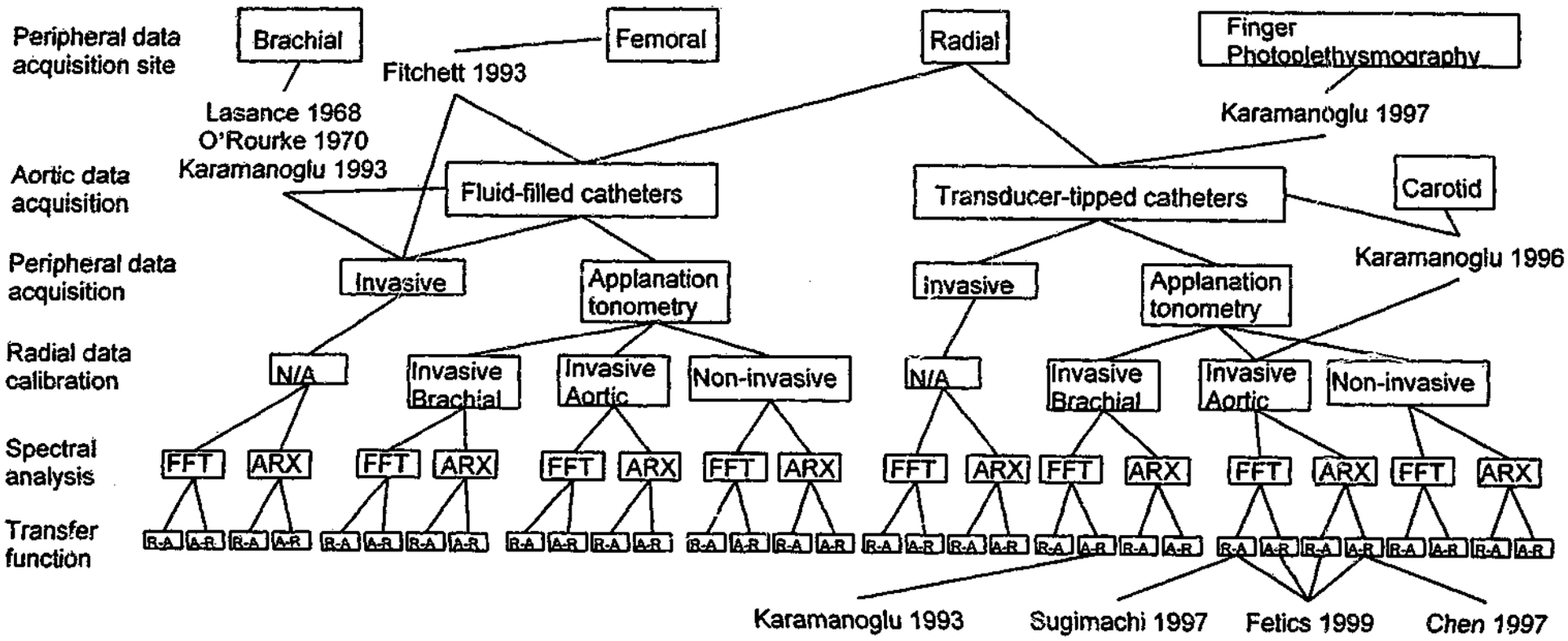


Figure 1-4. Diagrammatic representation of possible techniques for the derivation of an arterial transfer function and those which have been utilised

N/A is not applicable, FFT Fast Fourier Transformation, ARX autoregressive exogenous method, R-A radial to aortic and A-R aortic to radial.

1.3.2 Prospective validation of transfer function techniques for the reconstruction of central aortic waveform characteristics

The data in the literature contributing to the prospective validation of arterial transfer functions for the reconstruction of central aortic pressure waveform characteristics from radial waveform data remains extremely modest. In considering the available data, it must also be recognised that there are important, if apparently subtle, differences between the methods of data acquisition used in some of the studies which may impact significantly on the general applicability of the findings to other subject groups. These differences relate mainly to the acquisition (invasive or applanation tonometry) and calibration (to invasively or non-invasively acquired blood pressures) of the radial waveforms, but also to the acquisition of the aortic waveforms (transvascularly in spontaneously breathing patients at the time of cardiac catheterisation, or transmurally in patients who were ventilated with an open chest at the time of cardiac surgery). Studies will be presented according to the generalised arterial transfer function that was evaluated, but the above factors will also be noted.

The study of Takazawa *et al* is one of 3 in which central aortic waveforms were reconstructed from radial waveforms acquired by applanation tonometry which were calibrated to non-invasively measured brachial artery pressures.(Takazawa, *et al.* 1996) These authors reconstructed central aortic waveforms in 20 subjects undergoing cardiac catheterisation using a computational algorithm derived from the generalised transfer function of Karamanoglu *et al.*(Takazawa, *et al.* 1996, Karamanoglu, *et al.* 1993) These investigators found central aortic systolic pressure to be underestimated by 11mmHg under baseline conditions, suggesting that this algorithm may not be applicable to other

subject groups. The authors also reported a strong relationship between the augmentation index of the measured and reconstructed central aortic waveforms (r = 0.75, $P < 0.001$), but did so using a data set including repeated measurements from each individual which will falsely strengthen the underlying statistical relationship. The exact relationship between the computational algorithm used by these investigators and either the generalised transfer function of Karamanoglu *et al* or that used in the commercial SphygmoCor® system is unknown.(Takazawa, *et al.* 1996, Karamanoglu, *et al.* 1993)

Fetics *et al* evaluated their own transfer functions prospectively in a further group of 19 subjects undergoing cardiac catheterisation for the derivation of central aortic waveforms from non-invasively acquired radial waveforms calibrated to measured central aortic pressures.(Fetics, *et al.* 1999) These authors derived 4 different generalised arterial transfer functions, but found the direct radial-aortic transfer function derived by the ARX method to yield the best reconstruction of the central aortic waveform.(Fetics, *et al.* 1999) Using this transfer function they found the reconstruction of the central aortic systolic pressure to be good, mean error 0.4 ± 2.9 mmHg, but reconstruction of AI was disappointing, with a mean percentage error of -54 ± 232%.(Fetics, *et al.* 1999) These authors did not report the degree of correlation between the measured and reconstructed parameters, but the error in the reconstructed AI suggests that the correlation between this parameter of the reconstructed and measured waveforms is likely to be small.

Segers *et al* digitised the published aortic-radial transfer function of Chen *et al*, and calculated the corresponding complex transfer function.(Segers, *et al.* 2000) This transfer function, which may differ slightly from the original derived by Chen *et al*, was applied to invasively acquired radial waveforms, therefore requiring no calibration procedure, from 45 patients anaesthetised prior to cardiac procedures.(Segers, *et al.* 2001) Although not explicitly stated, it seems that the measured aortic waveforms were

acquired transmurally with the chest opened prior to surgery. The potential impact of the change in the normal physical external constraints upon the aorta on the aortic waveform morphology under these conditions is unknown. These authors found the reconstructed AI to underestimate the measured by 4 ± 16% under baseline conditions, and 2 ± 15% during the intravenous administration of glyceryl trinitrate, with correlation coefficients of just 0.66 and 0.46 at baseline and during the intravenous administration of glyceryl trinitrate respectively.

Four groups of investigators have published studies using the commercial SphygmoCor® device.(Pauca, *et al.* 2001, Söderström, *et al.* 2002, Davies, *et al.* 2003, Smulyan, *et al.* 2003) The former 2 groups have reconstructed central aortic pressure waveforms from invasively measured radial waveforms, hence requiring no calibration procedure.(Pauca, *et al.* 2001, Söderström, *et al.* 2002) Only the latter 2 groups of investigators have used radial waveforms acquired by applanation tonometry calibrated to non-invasively measured brachial artery pressures, as is required for the purely non-invasive application of this device.(Davies, *et al.* 2003, Smulyan, *et al.* 2003) Whereas Pauca *et al* demonstrated very close reproduction of central aortic systolic and diastolic pressures in 62 patients anaesthetised with an open chest prior to cardiac surgery, with aortic pressures acquired transmurally, (errors 0 ± 4 and 1 ± 2 mmHg, SBP and DBP respectively), Söderström *et al*, in 12 patients undergoing cardiac catheterisation, Davies *et al*, in 28 patients undergoing cardiac catheterisation, and Smulyan *et al*, in 50 patients undergoing cardiac catheterisation, found the reconstructed waveforms to underestimate central aortic systolic pressure and overestimate diastolic pressure (SBP underestimate 8 ± 2 mmHg, 7 ± 10 mmHg and 2 ± 11mmHg, and DBP overestimate 4 ± 2 mmHg, 12 ± 7 mmHg and 10 ± 13mmHg, Söderström *et al*, Davies *et al* and Smulyan *et al* respectively).(Pauca, *et al.* 2001, Söderström, *et al.* 2002, Davies, *et al.* 2003, Smulyan, *et al.* 2003) It is possible that the differences between the study of Pauca *et al*

and the other 3 studies may relate, at least in part, to the differences in the measured aortic pressures between the groups (significantly lower in the group of Pauca *et al*).(Pauca, *et al.* 2001, Söderström, *et al.* 2002, Davies, *et al.* 2003, Smulyan, *et al.* 2003) Only Söderström *et al* reported the reconstruction of central aortic augmentation index, with a mean underestimate of 5 ± 8%.(Söderström, *et al.* 2002) No data on correlation was presented, but significant deficiencies were evident, since an augmentation index was identified on the reconstructed waveforms of 4 subjects for whom no augmentation index was identified on the original measured waveforms. The same investigators also reported, from a similar group of 12 patients, that 45/49 waveforms were classified to the correct Murgo classification of augmentation index (A > 12%, B > 0 and ≤ 12% and C ≤ 0%).(Söderström, *et al.* 1998) No further details are available, however. The group of Pauca *et al* reported a correct Murgo classification in just 32/50 waveforms reconstructed from 35 patients prior to cardiac surgery.(O'Rourke, *et al.* 1999)

Despite the paucity of data validating the use of arterial transfer functions for the reconstruction of central aortic waveforms, summarised diagrammatically in Figure 1-5, the technique has gained popularity for non-invasive use, and an increasing number of manuscripts have been published describing studies in which central aortic waveform parameters have been reconstructed with the use of the SphygmoCor® system. The increasing popularity of the technique is probably attributable at least in part to its simplicity and to the minimal training and experience required before central aortic waveforms can be reconstructed with a high degree of reproducibility both in healthy subjects, and subjects with chronic renal failure.(Wilkinson, *et al.* 1998, Siebenhofer, *et al.* 1999, Covic, *et al.* 2000, Savage, *et al.* 2002, Filipovsky, *et al.* 2000)

Given the disappointing results from the 3 relevant studies regarding the accuracy of reconstruction of central aortic pressures from radial waveforms acquired by

applanation tonometry and calibrated to non-invasively measured arterial pressures, and the limited, and discouraging, data regarding the reconstruction of the central aortic augmentation index, the results of the non-invasive application of the technique should perhaps be interpreted with caution. However, the findings of the studies which have used this technique will be discussed in the following section.

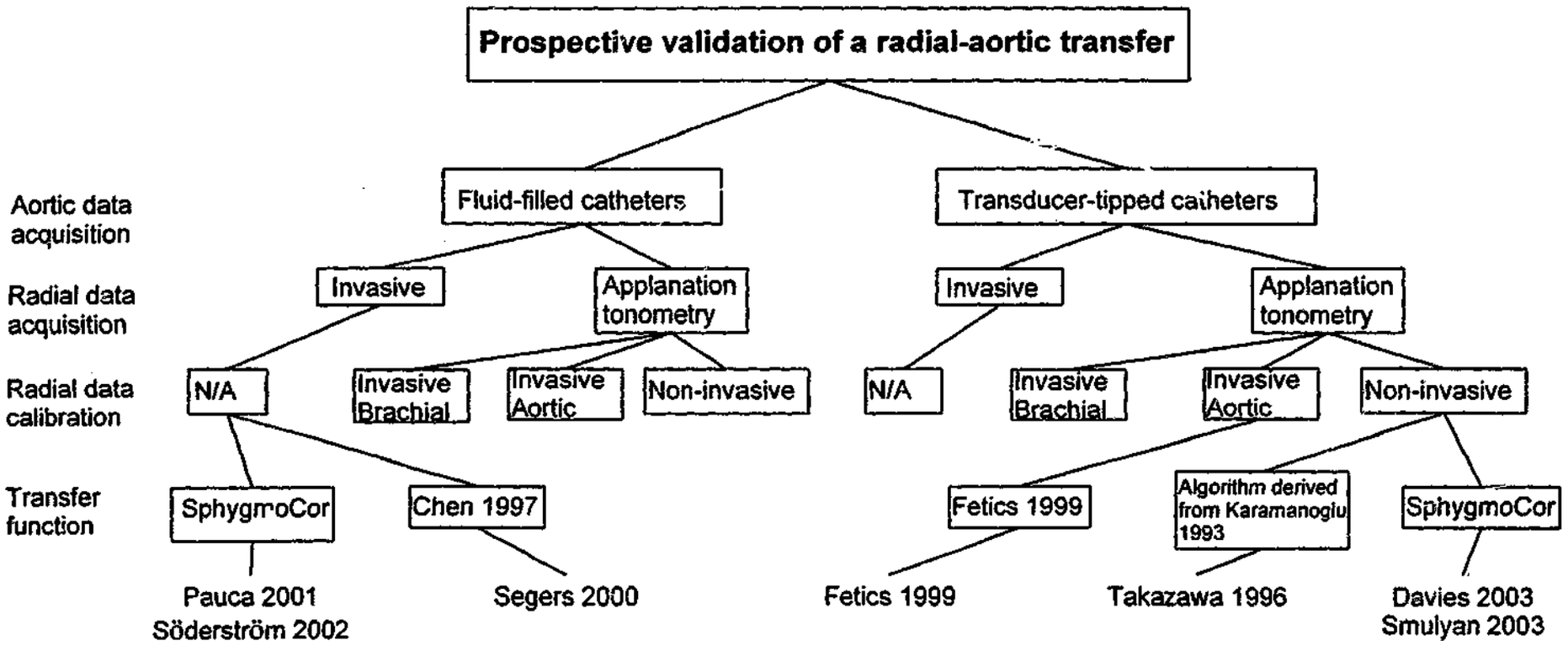


Figure 1-5. Diagrammatic summary of radial-aortic transfer functions that have been prospectively validated and the techniques adopted

N/A is not applicable

1.3.3 The analysis of central aortic waveforms reconstructed using the SphygmoCor® device from non-invasively acquired radial artery pressure waveforms

Central aortic waveforms have been reconstructed from non-invasively acquired radial artery waveforms from many different subject groups, both healthy and diseased, by different investigators. Associations have been analysed between reconstructed waveform parameters, particularly the augmentation index, and various subject characteristics, cardiovascular risk factors, other disease states and drug effects. It must however be remembered that these reconstructed waveform parameters may differ significantly from those of the true central aortic waveform.

1.3.3.1 Subject demographic characteristics

In a classical twin study, reconstructed central aortic augmentation index has been demonstrated to have a heritable component (37%) which was largely independent of the heritability of blood pressure, heart rate or height.(Snieder, *et al.* 2000) It has also been demonstrated to have an inverse relationship with both height and heart rate and a positive relationship with age and blood pressure, as might be expected (Yasmin and Brown 1999, Cameron, *et al.* 1998, Wilkinson, *et al.* 2000a, Ferro, *et al.* 2002), and by some investigators to be associated with gender.(Ferro, *et al.* 2002) It is conceivable that some of these associations, particularly the association with gender, may be explained if the generalised arterial transfer function was not equally appropriate for all

individuals. Reconstructed central aortic augmentation index is also positively associated with left ventricular mass in both normal healthy volunteers and subjects undergoing haemodialysis for chronic renal failure.(Deague, *et al.* 2001, Covic, *et al.* 2000) Reconstructed central aortic pulse pressure has been demonstrated to be positively associated, and therefore pulse pressure peripheral amplification negatively associated, with increasing age (Wilkinson, *et al.* 2001a), a finding which is proposed to explain the phenomenon of so-called spurious systolic hypertension of youth.(O'Rourke, *et al.* 2000, O'Rourke, *et al.* 2001)

1.3.3.2 Conventional cardiovascular risk factors

The magnitude of the reconstructed central aortic augmentation index has been found to be associated with smoking, hypercholesterolaemia, birth weight and the presence of diabetes mellitus or insulin resistance.

Reconstructed central aortic augmentation index is chronically increased in smokers, but acutely increased further following the smoking of a single cigarette.(Mahmud and Feely 2003, Fennessy, *et al.* 2003) The latter investigators also explored the effect of a cold pressor test on the reconstructed central aortic augmentation index in smokers and non-smokers, and found no difference between the groups.(Fennessy, *et al.* 2003) However, the radial artery tonometry was carried out on the same limb as was immersed in cold water for the cold pressor test, and it is therefore possible, since the arterial transfer function can be substantially altered by local influences on the hand, that these results were largely influenced by local effects and may not be related to any true central differences between the groups.(Nichols and O'Rourke 1998) Both reconstructed central aortic augmentation index and pulse pressure are increased in subjects with hypercholesterolaemia.(Wilkinson, *et al.* 2002b) Whereas this might be expected, it is

interesting to contrast this with the finding for the carotid artery augmentation index which demonstrated no association with hypercholesterolaemia in a group with hypertension.(Saba, *et al.* 1999)

The association between reconstructed central aortic augmentation index and birth weight is interesting. The J-shaped relationship between birth weight and risk of subsequent mortality from cardiovascular disease (the Barker hypothesis), with decreasing risk with increasing birth weight except in those of highest birth weight, likely to be influenced by maternal diabetes, has emerged and become accepted over the last 15 years.(Barker, *et al.* 1989, Barker, *et al.* 1990, Launer, *et al.* 1993, Osmond, *et al.* 1993, Barker, *et al.* 1993, Barker 1995, Stein, *et al.* 1996, Jarvelin 2000) It is therefore interesting to note that associations between the reconstructed central aortic augmentation index and birth weight are apparent during childhood (mean age 11 years).(Lurbe, *et al.* 2003) It must be remembered, in the interpretation of these findings, that generalised arterial transfer functions have only been derived from fully grown adults and, even if valid for use in adults, are very unlikely to be valid for use in children with smaller stature and different body proportions.(O'Rourke, *et al.* 2001) However, since the mean age was similar in each of the birth weight categories examined, the conclusion that differences exist between the groups is valid, although the differences may relate to factors other than true central aortic waveform parameters.

Published findings relating to the effects of insulin and the presence of diabetes mellitus on the reconstructed central aortic augmentation index vary slightly. Although most investigators have demonstrated an increased reconstructed central aortic augmentation index in subjects with diabetes mellitus, Brooks *et al* demonstrated the association only in men, with both type I and type II diabetes mellitus.(Brooks, *et al.* 1999, Brooks, *et al.* 2001, Wilkinson, *et al.* 2000b) In contrast, Siebenhofer *et al* demonstrated no difference in augmentation index between subjects with longstanding type I diabetes mellitus and

control subjects.(Siebenhofer, *et al.* 2000) It is possible that these differences may be explained by differences in either plasma insulin levels, or the degree of insulin resistance, since Westerbacka *et al* have demonstrated that insulin decreases reconstructed central aortic augmentation index both in healthy volunteers and subjects with type I diabetes mellitus, although the effect was blunted, and the blunting of the effect was associated with insulin resistance both in those with diabetes mellitus and in the healthy volunteers.(Westerbacka, *et al.* 1999a, Westerbacka, *et al.* 1999b, Westerbacka, *et al.* 2000, Westerbacka, *et al.* 2001)

1.3.3.3 Other disease states

Reconstructed central aortic waveform parameters have been the subject of interest in subjects with a range of disease states, most of which are associated with increased cardiovascular risk.

The association between cardiovascular risk and renal impairment is well established, and as discussed in *Section 1.2.3.2*, associated with central aortic augmentation index, measured non-invasively in the carotid artery.(London, *et al.* 1992) It is therefore not surprising that the reconstructed central aortic waveform parameters of this group of patients have been of particular interest. Reconstructed central aortic augmentation index is increased in patients with chronic renal failure.(Vuurmans, *et al.* 2002) However, the findings for the acute impact of fluid-reduction during haemodialysis on reconstructed central aortic augmentation index vary, with some investigators showing no change (Covic, *et al.* 2000), whereas others have demonstrated significant reduction in most subjects.(Vuurmans, *et al.* 2002) The discrepancy may be explained by differences in drug therapy, since Vuurmans *et al* demonstrated that, although they had seen no change in augmentation index under baseline conditions, following treatment

with enalapril haemodialysis was associated with a fall in the reconstructed central aortic augmentation index to levels comparable to a control group.(Vuurmans, *et al.* 2002) In a group that had undergone renal transplantation, reconstructed central aortic augmentation index was also associated with the total period of renal replacement therapy, an immunosuppression regime including cyclosporine therapy and the persistence of an arteriovenous fistula.(Ferro, *et al.* 2002) The association with the presence of an arteriovenous fistula was interpreted as identifying this as a potentially reversible contributing factor to the increased cardiovascular risk in this population.(Ferro, *et al.* 2002) However, it is equally conceivable that the altered haemodynamic conditions associated with the fistula render the generalised arterial transfer function inappropriate in this population, and that the differences in the reconstructed waveform may not be matched by similar differences in the true central aortic waveform.

The effects of replacement of various hormones in groups with demonstrable deficiency on the reconstructed central aortic augmentation index have also been evaluated. Adult subjects with growth hormone deficiency have an increased reconstructed central aortic augmentation index, which falls with growth hormone replacement therapy.(Smith, *et al.* 2002, Irving, *et al.* 2002) However, apparently paradoxically, the reconstructed central aortic augmentation index of patients with acromegaly was found not to differ from controls.(Irving, *et al.* 2002) This latter anomaly may be explained by the very small numbers of acromegalic subjects studied (5), all of whom had undergone transsphenoidal surgery for treatment, by which 2 had been completely cured prior to the assessment of reconstructed waveforms.(Irving, *et al.* 2002) Similarly, combined oestrogen progestogen hormone replacement therapy in women with Turner's syndrome is associated with a fall in the reconstructed central aortic augmentation index, which is in contrast to the findings for carotid artery augmentation index in postmenopausal

women (Elsheikh, *et al.* 2000, Hayward, *et al.* 2001, Tanaka, *et al.* 1998b), and thyrotoxicosis is associated with a decreased augmentation index, not explained by heart rate, which increases following treatment.(Obuobie, *et al.* 2002)

Klocke *et al* demonstrated increased reconstructed central aortic augmentation index in patients with rheumatoid arthritis compared with a control group. They also demonstrated increased reconstructed mean arterial pressure in those with rheumatoid arthritis, together with an increased radial systolic and mean arterial pressures in the control group.(Klocke, *et al.* 2003) This latter is worthy of comment, since available data suggests that mean arterial pressure varies little throughout the arterial system (Hamilton and Dow 1939, Simkus and Fitchett 1990), therefore it is intriguing that the reconstructed waveforms seem to deviate from this.(Klocke, *et al.* 2003)

Patients with intracranial aneurysms have been demonstrated to have greater reconstructed central aortic augmentation index than a control population.(Turner, *et al.* 2001) However, it should again be considered whether different arterial properties in this patient group, as indicated by the propensity to aneurysm formation, might render the generalised arterial transfer function inappropriate to this population.

Other investigators have made simple observations in different populations, namely that different reconstructed central waveform parameters may be observed in subjects with similar brachial artery pressures (Schofield, *et al.* 2002), and that such differences will result in different values for calculated distensibility of an abdominal aortic aneurysm (Wilson, *et al.* 2001).

1.3.3.4 Drug actions

The effects of many drugs, and combinations of drugs, on reconstructed central aortic waveform parameters, mainly augmentation index, have been investigated. These

include the effects of nitrates, β blockers, angiotensin, ACE inhibitors and angiotensin receptor blockade, endothelin and endothelin receptor blockade, caffeine and alcohol, amongst others.

Nitrate drugs have long been known to change the shape of the radial artery waveform.(Murrell 1879) It is perhaps not surprising therefore that nitrate administration is also associated with changes in the reconstructed central aortic waveform. These changes take the form of a decrease in reconstructed central aortic blood pressures, with or without a change in brachial artery blood pressures, and also a decrease in reconstructed central aortic augmentation index.(Stokes, *et al.* 2003, Jiang, *et al.* 2002, O'Rourke and Nichols 2002, Kelly, *et al.* 2001) The administration of sildenafil, or co-administration with nitrate therapy, also decreases reconstructed central aortic augmentation index and central blood pressures to an extent not recognisable from simple brachial artery sphygmomanometry.(Mahmud, *et al.* 2001, O'Rourke and Nichols 2002) That changes are evident in the reconstructed central aortic waveforms with the administration of nitrate therapy which cannot be recognised from brachial artery sphygmomanometry has been proposed to provide strong evidence for the potential value of pulse wave analysis of reconstructed central aortic waveforms.(O'Rourke, *et al.* 2001, Nichols and Singh 2002)

Most, but not all (Stokes, *et al.* 2003), investigators have demonstrated a fall in reconstructed central aortic augmentation index with the administration of either an ACE inhibitor or an angiotensin receptor blocker, or indeed a greater decrease with co-administration of the 2.(Dart, *et al.* 2001, Asmar, *et al.* 2001a, Mahmud and Feely 2002b, Asmar 2001d, Spratt, *et al.* 2001) Conversely, the administration of angiotensin is associated with an increase in reconstructed central aortic augmentation index.(Kelly, *et al.* 2001, Wilkinson, *et al.* 2001b) It may be that the beneficial effects of ACE inhibitor therapy, or angiotensin receptor blockade, on cardiovascular risk may be

explained in part by these effects on central aortic waveform features, and particularly the augmentation index. The effects of ACE inhibitors have also been compared with those of β blockers, and although ACE inhibitors were found to have a greater effect on reconstructed central aortic augmentation index, the difference has been entirely attributed to the difference in heart rate, lower on β blocker therapy, associated with the 2 treatments. (Dart, *et al.* 2001, Asmar, *et al.* 2001d) Omapatrilat administration, a vasopeptidase inhibitor which inhibits both angiotensin converting enzyme and neutral endopeptidase, is associated with a fall in reconstructed central aortic augmentation index in patients with chronic cardiac failure.(McClean, *et al.* 2001)

Other drug effects which have been evaluated include the effect of endothelin-1 administration and consumption of both caffeine and alcohol, the vasoactive substances to which the population is most commonly exposed. Endothelin-1 administration, which resulted in no change in brachial systolic pressure, was associated with an increase in both reconstructed central aortic systolic pressure and augmentation index, effects which were abolished by the co-administration of an endothelin-1 receptor blocker.(Vuurmans, *et al.* 2003) The effects of chronic and acute consumption of alcohol were found to be divergent, with the former associated with an increase in reconstructed central aortic augmentation index and blood pressure, and the latter with a fall in both these reconstructed waveform parameters.(Mahmud and Feely 2002a) The consumption of caffeine is also associated with increases in reconstructed central aortic pressures and augmentation index.(Vlachopoulos, *et al.* 2001, Vlachopoulos, *et al.* 2003)

As discussed earlier, the inflection point is thought to mark the onset of influence of the reflected pressure wave that is responsible for the phenomenon of the augmentation index, and as such the time to the inflection point is usually closely related to, and often adopted as a surrogate measure of, pulse wave velocity. It is therefore interesting to note

that the time to the inflection point may be dissociated from the pulse wave velocity under some conditions.(Mahmud and Feely 2002b, Deary, *et al.* 2002, Vlachopoulos, *et al.* 2003) This may be explained either by differing errors in the reconstructed central aortic waveform parameters under differing conditions, or alternatively may provide evidence that the inflection point and augmentation index are not entirely explained by pressure wave reflection.

1.3.3.5 Assessment of endothelial function

As discussed in *Section 1.1*, impaired endothelial function, manifest particularly by a reduced bioavailability of endothelially derived nitric oxide, is associated with the presence of atherosclerotic disease, but may also be identified in those at risk of development of symptomatic cardiovascular disease prior to any clinical manifestations.(Celermajer, *et al.* 1992, Celermajer, *et al.* 1994, Clarkson, *et al.* 1997, Skyrme-Jones, *et al.* 2000, Neunteufl, *et al.* 1997, Hashimoto, *et al.* 1999)

The analysis of reconstructed central aortic pressure waveforms has also been used for the assessment of vascular function.(Wilkinson, *et al.* 2002a) Some vasoactive substances, such as β_2-receptor agonists, or vascular interventions, such as reactive hyperaemia, result in arterial vasodilation through an endothelial-dependant mechanism involving the L-arginine-nitric oxide pathway.(Chowienczyk, *et al.* 1999, Meredith, *et al.* 1996) Reconstructed central aortic augmentation index is reduced by the administration of inhaled albuterol by a mechanism which is inhibited by the administration of N^G-monomethyl-L-arginine, which inhibits the L-arginine-nitric oxide pathway.(Wilkinson, *et al.* 2002a) The reduction in reconstructed central aortic augmentation index in response to inhaled albuterol is reduced in subjects with hypercholesterolaemia compared with healthy controls, and correlated with the

endothelial-dependent control of forearm blood flow as assessed by the intra-arterial administration of acetylcholine.(Wilkinson, *et al.* 2002a) There was no difference in the change in augmentation index in response to sublingual nitroglycerin, which acts by an endothelial-independent mechanism, in the same subjects.(Wilkinson, *et al.* 2002a) The administration of N^G-monomethyl-L-arginine has also been shown to cause an increase in baseline reconstructed central aortic augmentation index in healthy subjects, suggesting that the differences seen in augmentation index in subjects with cardiovascular risk factors may reflect differences in endothelial function.(Wilkinson, *et al.* 2002a) It should however be noted that blood pressure increased and heart rate fell following the administration of N^G-monomethyl-L-arginine, both of which would be expected to increase reconstructed central aortic augmentation index, however it was felt that the magnitude of changes could not be explained by these factors.(Wilkinson, *et al.* 2002a) Not surprisingly, similar findings have been demonstrated for the assessment of untransformed radial artery waveforms under similar conditions.(Hayward, *et al.* 2002, Lind, *et al.* 2003)

1.4 AIMS OF THE THESIS

The aims of the studies presented in this thesis are to explore the relationships between the arterial pressure waveform at different sites within the arterial system in both the time and frequency domains, and to explore by prospective evaluation the potential for a greater understanding of these relationships to permit the prediction, or reconstruction, of features of the central aortic pressure waveform which have been proposed to be of greater value in the understanding and monitoring of the progression and treatment of cardiovascular disease than the measurement of peripheral arterial pressures alone.

1.4.1 Specific aims of the thesis

1) To derive a generalised arterial transfer function for the relationship between the central aortic and radial pressure waveforms.

2) To determine the number of individual transfer functions necessary for the derivation of a generalised arterial transfer function which is representative of the population.

3) To determine the capacity of a generalised arterial transfer function, when applied to non-invasively acquired radial artery waveforms, accurately to reconstruct central aortic waveform parameters.

4) To determine the impact of subject demographic features, specifically gender and the presence of diabetes mellitus, and physiological interventions, specifically isometric handgrip exercise and the Valsalva manoeuvre, on the arterial transfer function and the capacity for the generalised arterial transfer function accurately to reconstruct central aortic pressure waveform parameters.

5) To determine whether the frequency domain analysis and generalised arterial transfer function offers any advantage for the prediction of central aortic waveform features over simple time domain analysis of untransformed radial artery waveforms.

6) To characterise the progressive changes in aortic pressure waveform features with transmission of the pulse wave from the central aorta to the aortic bifurcation.

Chapter 2

General description of methods

TABLE OF CONTENTS

2.1 STUDY SUBJECTS

2.1.1 Subject recruitment

Patients were recruited from those referred to the Cardiac Catheterisation Laboratory of Monash Medical Centre for elective coronary angiography or percutaneous coronary procedures. All such patients were considered eligible for inclusion. Patients were excluded in the absence of informed consent, if there was a known positive viral hepatitis or HIV status, if there were symptoms or clinical evidence of peripheral vascular disease affecting brachial artery blood pressure or the radial pulse, or if there was a procedural complication prior to the acquisition of data.

Patients were fasted and prepared for cardiac catheterisation in accordance with normal clinical practice. A personal and family history was obtained from all study participants. A history of hypertension was defined as a blood pressure of greater than 140/90 mmHg on more than one reading, or treatment with oral antihypertensive agents for a previous clinical indication. A history of hypercholesterolaemia was defined as a total serum cholesterol of greater than 5.5mmol/L, or current treatment with lipid lowering agents for a previous clinical indication. This definition therefore also encompasses subjects for whom lipid lowering therapy was indicated for secondary prevention but who may not have had a cholesterol level of greater than 5.5mmol/L. A history of diabetes mellitus was defined as a previous diagnosis of diabetes mellitus according to standard clinical diagnostic criteria. A family history of cardiovascular disease was defined as a history of cardiovascular disease in a first degree relative younger than 60 years of age.

2.1.2 Ethics approval and consent

The studies performed and presented in this thesis were approved by the Southern Health Human Research Ethics Committee A of Monash Medical Centre (Project Number 01063A). Written information was provided, and the procedures discussed with the subjects prior to the acquisition of written consent. The studies were carried out in accordance with the National Statement on Ethical Conduct in Research Involving Humans (June 1999) produced by the National Health and Medical Research Council of Australia.

2.2 ACQUISITION OF PRESSURE WAVEFORMS

Non-invasive radial and measured central aortic pressure waveforms were acquired simultaneously, together with an electrocardiographic record, in all subjects. All data were acquired to a personal computer using Chart® for Powerlab® (ADInstruments, Castle Hill, NSW, Australia). All central aortic pressure and electrocardiographic data were acquired through the Horizon 9000WS Cathlab System (Mennen Medical, Tel Aviv, Israel). Data from patients in whom the central aortic pressure waveforms were recorded using fluid-filled catheters were acquired at 200Hz. Data from patients in whom the central aortic pressure waveforms were recorded using Millar Mikro-tip® catheter transducers were acquired at either 200Hz or 2000Hz. All data acquired at 2000Hz were re-sampled at 200Hz for waveform analysis and transfer function derivation. 2000Hz data were used only for estimation of pulse wave velocities. At least 30 seconds of continuous optimal quality data were acquired from each subject.

2.2.1 Aortic waveforms

Central aortic pressure waveforms were acquired from 78 subjects using the standard fluid-filled catheter system, and subsequently from 93 subjects using Millar Mikro-tip® catheter transducers (Millar Instruments Inc, Houston, Texas, USA).

2.2.1.1 Fluid-filled catheters

Central aortic pressure waveforms were acquired via 6 French low compliance diagnostic fluid-filled catheters (Impulse™ angiographic catheter, Boston Scientific Scimed Inc, Maple Grove, MN, USA) positioned in the ascending aorta, via a DPT 6000 Pressure Transducer (Surgicare, Braeside, Victoria, Australia). Although data were acquired through the Mennen Cathlab System, the pressure output recorded to the computer was independently calibrated to 0 and 100mmHg using a Delta-Cal™ Transducer Simulator/Tester (Utah Medical Products Inc, Midvale, Utah, USA). It is recognised that the accuracy of pressure measurements acquired via a fluid-filled catheter system may be influenced by the frequency response and damping characteristics of the system. This issue can be addressed by a direct comparison between the fluid-filled catheter system and a solid state intravascular micromanometer. The comparison was made with a RADI pressure wire (frequency response 500Hz) (RADI Medical Systems, Uppsala, Sweden) in 5 subjects, and the frequency response characteristics found to be similar over the frequency range of interest (Figure 3-7). The clinical system was therefore felt to be adequate for the proposed study, however the issue is discussed in greater detail in *Chapter 3*, and addressed further by the use of Millar Mikro-tip® catheters in the subsequent study.

2.2.1.2 *Millar catheters*

Two French Millar Mikro-tip® catheter transducers (Millar Instruments Inc, Houston, Texas, USA) (diffused semiconductor sensor, pressure range -50 to 300mmHg with a natural frequency of > 20kHz) were used for the acquisition of central aortic pressure waveforms. Factory calibration of the catheters was verified according to the manufacturer's instructions prior to initial sterilisation. During pressure waveform acquisition, the catheter was attached to an appropriate Millar Control Box (Model TCB-500, Millar Instruments Inc, Houston, Texas, USA), in accordance with the manufacturer's instructions, the output from which was passed through the Mennen Cathlab System to ensure patient electrical isolation prior to acquisition to a personal computer. The output was calibrated to the 0, 20 and 100mmHg output of the Millar Control Box. Prior to invasive pressure waveform acquisition, the catheter tip was placed in saline solution and zeroed by adjusting the balance on the Millar Control Box according to the manufacturer's instructions.

Central aortic pressure waveforms were acquired by positioning a 6 French right coronary guiding catheter (Mach1™ guide catheter, Boston Scientific Scimed Inc, Maple Grove, MN, USA) in the ascending aorta, and passing the Millar catheter through this, under fluoroscopic control, until the tip was positioned 1cm distal to the tip of the guiding catheter.

2.2.2 Radial waveforms

Radial waveforms were acquired by applanation tonometry. According to the theory of tonometry, the flattening (applanation) of the curved surface of a pressure-containing structure permits direct measurement of the pressure within.(Drzewiecki, *et al.* 1983) The technique requires the use of a force sensor of appropriate dimensions in relation to

vessel size, coplanar with a larger non-sensing surface, and positioned accurately over the vessel of interest. Optimal applanation eliminates distortion of the sensed pressure by the circumferential stresses in the curved vessel wall by rendering them tangential to the force sensor, and is essential for accurate representation of intravascular pressures (see Figure 2-1). Although it is recognised that distortion of the sensed pressure waveform is associated with the application of excessive, as well as too little, force to the tonometer during waveform acquisition, and that there is no direct indicator of optimal applanation, optimal applanation is generally accepted to be indicated by the acquisition of a waveform that has a stable baseline, maximal amplitude and an appropriate configuration (Chen, *et al.* 1996, Kelly, *et al.* 1989). Optimal applanation can be achieved most easily in superficial arteries that are well supported by bony tissue. (Chen, *et al.* 1997) The radial artery fits this description well, and since optimal applanation can be achieved with relative ease following minimal training and experience, it has long been a popular site, and has been proposed as the artery of choice for this purpose.(Drzewiecki, *et al.* 1983, Chen, *et al.* 1997, Wilkinson, *et al.* 1998)

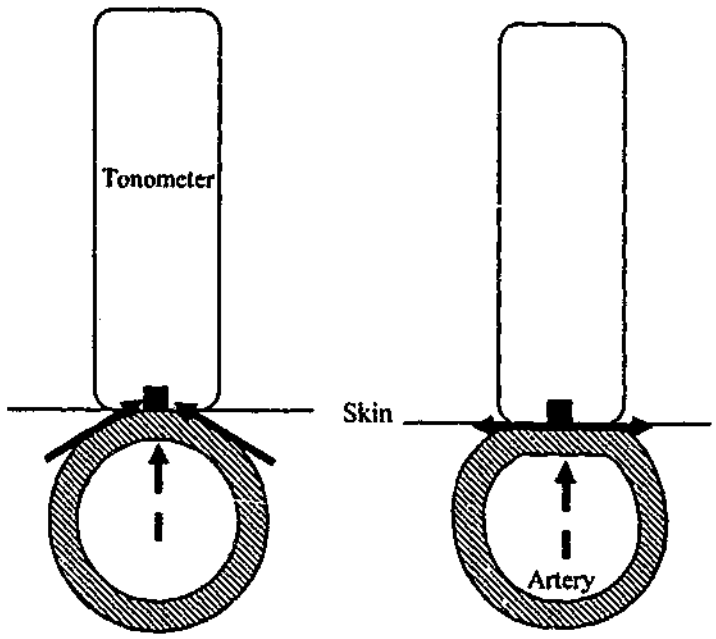


Figure 2-1. Diagrammatic representation of arterial applanation tonometry

▬ ▬ ► Represents intravascular pressure forces, ⟶ represents circumferential forces. Flattening of the arterial wall eliminates the registration by the tonometer of arterial wall circumferential stresses.

For the studies presented in this thesis non-invasive radial waveforms were acquired by applanation tonometry using a Millar® Mikro-tip® tonometer (Model SSD-713, Millar Instruments Inc, Houston, Texas, USA) by appropriately trained and experienced personnel. The tonometer incorporates a high fidelity piezoresistive pressure transducer (diffused semiconductor sensor, pressure range 0 to 300mmHg, nominal natural frequency 35 kHz) coplanar with a larger flat area which is in contact with the skin overlying the area of maximal arterial pulsation. The tonometer was attached to a Millar Control Box (Model TCB-500, as above), in accordance with the manufacturer's instructions, the output from which was acquired to a personal computer. Waveforms were acquired from the left radial artery, except in patients who had no left radial artery following harvesting for coronary artery bypass surgery, or who had a left arteriovenous fistula.

2.3 CALIBRATION OF RADIAL PRESSURE WAVEFORMS

Pressure waveforms acquired non-invasively by applanation tonometry are acquired as a voltage output resulting from the deformation of the piezoresistive tonometer sensor. Since the absolute voltage output may vary substantially dependent upon the manual pressure applied to the tonometer, a given voltage output cannot simply be equated with a given pressure. In addition, although the nominal output from the Millar control box is 200mV/100mmHg, this output is achieved only when the pressure is applied directly to the transducer, whereas the interposition of tissues between the radial artery lumen and the transducer results in a lower output. Therefore to provide absolute pressure data, the waveforms must be calibrated using 2 components of a known blood pressure. This practice requires the adoption of certain assumptions. Whereas it has long been recognised that there are potentially large differences in systolic pressure in different parts of the arterial tree, due to peripheral amplification of systolic pressure, available data support an assumption that the diastolic and mean arterial pressures are similar throughout.(Hamilton and Dow 1939, Simkus and Fitchett 1990) This assumption was therefore adopted, and non-invasive radial pressure waveforms were scaled to mean and diastolic arterial pressures, either invasively measured central aortic or non-invasively measured brachial artery depending on the proposed application, by linear interpolation. This approach is consistent with the practice of some, but not all, authors who have previously investigated this technique.(Fetics, *et al.* 1999, Chen, *et al.* 1997) Other authors have assumed equivalence of brachial and radial artery systolic and diastolic pressures, although the evidence supporting this approach is less clear.(Sato, *et al.* 1993, Takazawa, *et al.* 1996, Karamanoglu, *et al.* 1993)

Whereas when the above procedure is applied to single cardiac cycles the associated error is due only to the error in the underlying assumption of the equivalence of mean and diastolic pressures, when applied to a continuous data set containing more than 1 cardiac cycle more potential sources of error are apparent. The potential increase in error is largely due to variability between waveforms from different cardiac cycles and to baseline variability. The source of the variability is twofold: firstly artifactual variability due to variations in the pressure applied to the tonometer during waveform acquisition, and secondly due to genuine biological variation between cardiac cycles. Provided appropriate care has been taken to achieve optimal arterial applanation the former is minimised (coefficient of variability of central aortic diastolic pressures 3.4% and of radial diastolic pressures 4.8% (data from study presented in *Chapter 4*)). However, the source of the variability cannot be identified by examination of the radial waveform alone, and further assumptions must be adopted to enable calibration. Depending on the application (*vide infra*), the radial waveforms were calibrated to either invasively measured central aortic pressure waveforms or non-invasively acquired brachial artery pressures. When calibrating to measured aortic waveforms, the pressures used were the average of all the identified aortic diastolic pressures in the data set together with the mean pressure of the entire aortic data set. During derivation of spectra of the waveforms, as described in *Section 2.5.1*, the minimum value in each 256 point segment of data, containing at least 1 diastole, was equated with the measured diastolic pressure, and the mean with the measured mean pressure, and the waveform calibrated by linear interpolation. Whereas this procedure will minimise the error associated with artifactual baseline variability, it will introduce some error when any baseline variability is due to true biological variability of pressure.

2.4 WAVEFORM ANALYSIS

All arterial pressure waveforms were analysed for standard waveform features and for other parameters which have been proposed to be of potential clinical value, as well as those parameters of importance in their calculation; these include the peak systolic pressure (SBP), time interval to peak pressure (Tp) and to the end of systole (Ts), diastolic (Ad) and systolic (As) pressure time integrals, and the ratio of these (Ad/As) known as the subendocardial viability index (SVI). An inflection point on the systolic pressure wave was identified when present, together with the time to this inflection point (Ti), the pressure at the inflection point (Pi), the augmentation pressure (AP) (SBP – Pi), and augmentation index (AI) (AP/pulse pressure x100%) (Figure 1-3). Time intervals were measured from the onset of the systolic pressure upstroke of each waveform, as depicted.

All analysis software was purpose written using either Visual C++ 5.0® (Microsoft Corporation, Seattle, USA) or Matlab® v6R12 (MathWorks Inc, Natick, USA). Software was written to identify the above parameters of both radial and aortic waveforms recorded at 200Hz, as well as the delay between waveforms, whilst permitting scaling of the radial waveform to either invasively or non-invasively measured mean and diastolic pressures. Individual cardiac cycles were analysed, thus restricting the errors in calibration to those of the assumption of equivalence of mean and diastolic pressures, using trend removal techniques to minimise artifactual baseline variability of the tonometry-acquired radial waveform. The beginning of each cardiac cycle was identified by the maximum rate of change of the first derivative of the pressure waveform, equivalent to the peak of the second derivative (Figure 2-2). The inflection point was identified as the first zero crossing (positive to negative) of the third derivative (Figure 2-3). Other authors have used the fourth derivative (Kelly, *et al.*

1989), however the third derivative was chosen for 2 reasons: firstly, this method appeared more robust in its capacity to identify all appropriate inflection points, and secondly the point identified is that point where the pressure begins its secondary rise, and therefore corresponds more appropriately to the point which might represent the onset of influence of a reflected wave on the measured pressure waveform. The dichrotic notch was identified by extreme low pass filtering the waveform, and subtracting this from the original. The resultant waveform represents the contribution from high frequency pressure waveform components, and the peak of this waveform reliably identified the dichrotic notch.

Average parameters of both radial and aortic waveforms were derived by averaging the waveform parameters from up to a maximum of 10 typical individual cardiac cycles. When ventricular ectopic beats were present, pre-ectopic, ectopic and post-ectopic beats were excluded from analysis. Representative waveforms were derived as an ensemble average of the selected cardiac cycles in the time domain, truncated to the length of the shortest cardiac cycle (Figure 2-4). The representative waveforms were used in both the derivation of transfer functions and for the reconstruction of aortic waveforms by the application of an arterial transfer function to the radial data, as described in *Section 2.6.*

Also analysed was the delay between either the peak of the R, or nadir of the S, wave of the electrocardiogram and the upstroke of the aortic pressure waveform for data recorded at 2000Hz. Delay was measured from the nadir of the S wave in those patients with very poor R waves. However, since all comparisons were made within individuals, any constant point on the electrocardiogram could have been selected. Measured delays were used in the subsequent calculation of pulse wave velocities.

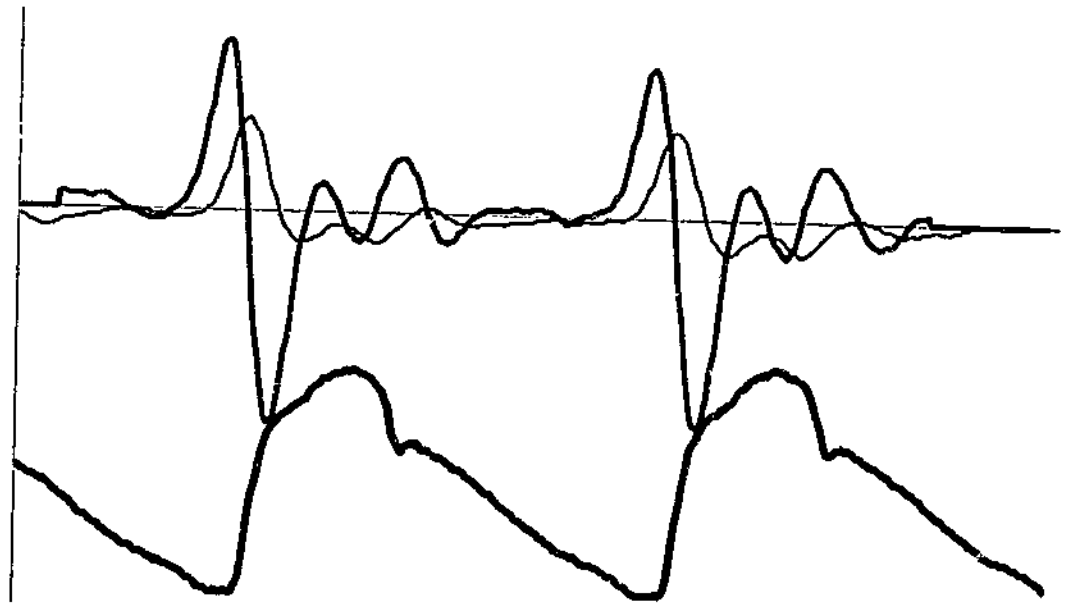


Figure 2-2. Central aortic pressure waveforms and the first and second derivatives

——— represents central aortic pressure waveform, ——— represents the first derivative of the pressure waveform and ——— the second derivative.

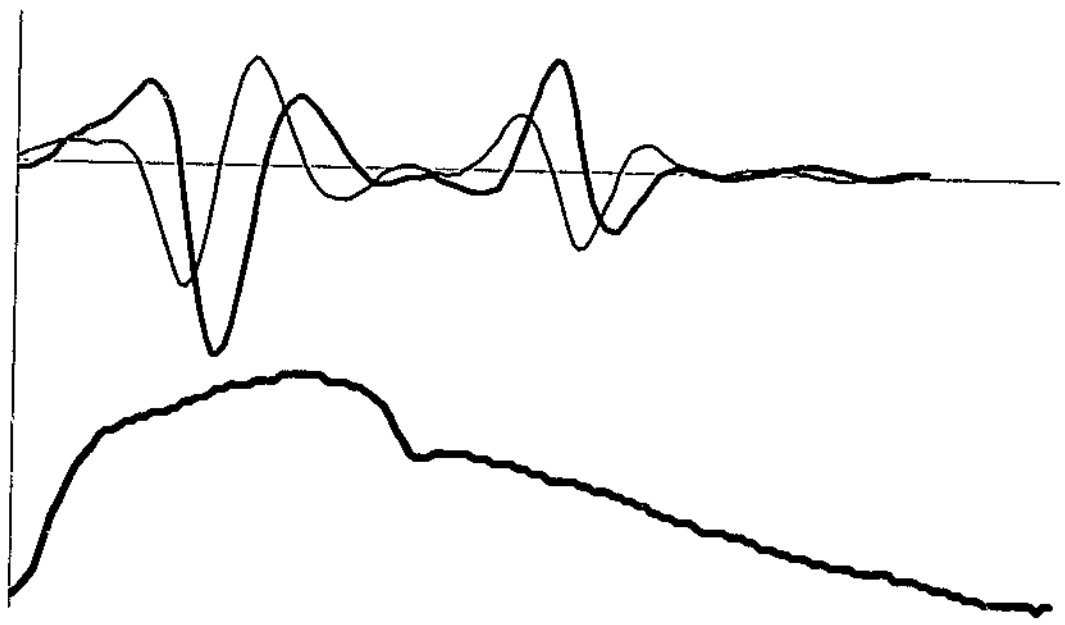


Figure 2-3. Individual central aortic pressure waveform and third and fourth derivatives

——— represents central aortic pressure waveform, ——— represents the third derivative of the pressure waveform and ——— the fourth derivative.

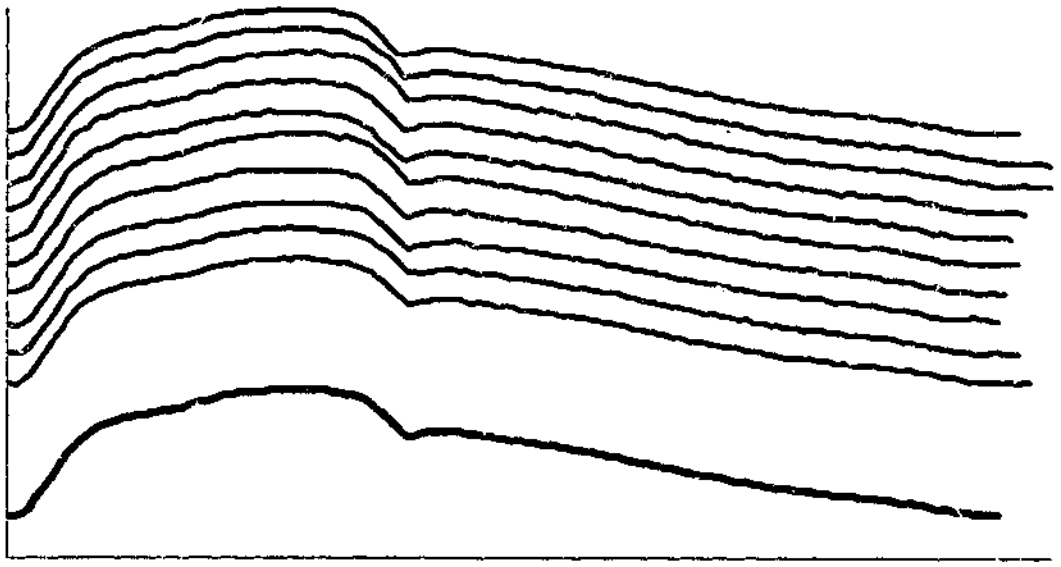


Figure 2-4. Representative aortic waveform.

——— is the representative aortic waveform derived as the average of the individual waveforms truncated to the length of the shortest cycle. ——— represents the individual aortic waveforms.

2.5 DERIVATION OF TRANSFER FUNCTIONS

All transfer functions were derived from data acquired, or re-sampled, at 200Hz. A non-parametric single-input/single-output model was adopted to calculate 256 point linear time-invariant transfer functions between applanated radial and directly measured central aortic blood pressure waveforms. Complex radial-aortic transfer functions were derived as the quotient of the aortic spectrum over the radial spectrum and expressed in terms of magnitude (amplification) and phase. All calculations were done in Matlab® with only the first 14 harmonics (10Hz) included in the final spectra. This frequency range is consistent with that used by previous authors.(Chen, *et al.* 1997, Fetics, *et al.* 1999, Karamanoglu, *et al.* 1993) Throughout this thesis 0Hz will be referred to as the 1st harmonic. Thus the second harmonic will represent the fundamental frequency of 0.78Hz.

The radial-aortic, rather than the more physiologically correct aortic-radial, transfer function was derived. This approach was adopted since, following the findings of Fetics *et al*, it was felt likely to be associated with less error in the reconstructed central aortic waveforms by avoiding the necessity to invert an aortic-radial transfer function, with potential inappropriate amplification of frequencies of small amplitude.(Fetics, *et al.* 1999)

The best approach to the derivation of individual arterial transfer functions has not been established. Whereas in principle the most representative estimate of the spectrum of a waveform, and therefore the transfer function between sites, is obtained by averaging a number of spectra, the most representative arterial waveforms in the time domain are obtained by averaging a number of arterial waveforms. Whether the calculation of a single arterial transfer function between single representative central aortic and radial waveforms might yield a better estimate of the true individual transfer function has not been investigated. Two methods are explored in this thesis for the derivation of transfer functions, methods 1 and 2 yielding transfer functions TF_1 and TF_2 respectively.

2.5.1 Transfer function 1 – Method 1

A 4096 point data sequence was selected with due regard for artifactual baseline variability of the radial waveform. Aortic and radial spectra were calculated by Fast Fourier Transformation (FFT) using a 256 point Hanning window with 128 point overlap to obtain ensemble average spectra for waveforms for each individual (Welch's averaged periodogram method). Individual complex transfer functions were calculated as the quotient of the output spectrum (aortic) over the input spectrum (radial). Thus each individual transfer function represented the average of 31 separate, but overlapping, transfer functions derived from the original 4096 point data sequence. This

practice of averaging a large number of transfer functions for each individual is likely to produce a better estimate of the true individual transfer function than the calculation of a single individual transfer function, or the averaging of only a very small number of transfer functions, as has been the practice in some studies.(Fetics, *et al.* 1999) Ensemble average transfer functions for groups were obtained by averaging the individual transfer functions.

2.5.2 Transfer function 2 – Method 2

Representative radial and aortic waveforms were initially aligned at identical start-systolic points (local maxima of the first derivative). These time domain averaged representative pressure waveforms were extended to 256 points by constant extension at the end diastolic pressure. A single 256 point FFT was performed on these average waveforms, and individual complex transfer functions calculated as the quotient of the output spectrum (aortic) over the input spectrum (radial). Ensemble average transfer functions for groups were obtained by averaging the individual transfer functions.

2.6 RECONSTRUCTION OF CENTRAL AORTIC PRESSURE WAVEFORMS

Individual central aortic pressure waveforms were reconstructed by the multiplication of the 256 point complex radial-aortic transfer function (TF_1 or TF_2 as appropriate) by the FFT-derived spectrum of a time domain average representative scaled radial waveform from each individual in the cohort under consideration.

2.7 STATISTICAL ANALYSES

Categorical data are presented as numbers and percentages, and continuous variables as their mean and standard deviation. Differences between categorical characteristics of subject groups were assessed by χ^2 or Fisher's Exact test, if numbers in any category were too small for the χ^2 test. Differences between continuous characteristics of subject groups were assessed by unpaired t-tests. Differences between corresponding characteristics of different waveforms within subjects were assessed by paired t-tests or repeated measures analysis of variance as appropriate. Within subjects contrasts were explored to identify the source of differences revealed by repeated measures analysis of variance. Between-subjects factors were entered to explore the impact of categorical variables such as gender of the presence of diabetes mellitus. The relationships between corresponding parameters of measured central aortic and reconstructed or radial waveforms were explored by simple linear regression and Pearson's correlation. Errors in reconstructed waveform parameters were further evaluated using the method of Bland and Altman for assessing agreement between 2 methods of clinical measurement.(Bland and Altman 1986) The correlation was explored first since the method of Bland and Altman was designed for the analysis only of variables that are related.(Bland and Altman 1986) Relationships between measured central aortic pressure waveform parameters and subject demographic characteristics were explored by linear regression and correlation techniques. Differences between regression relationships were explored as described in Biostatistical Analysis (Zar 1984), and between correlation coefficients by Fisher's Z transformation.(Zar 1984) Significance was taken as a two tailed $P < 0.05$, and statistical analyses were performed using SPSS 10.0 or 11.0 for Windows (SPSS Inc, Chicago, IL, USA) and Microsoft Excel 2000 (Microsoft Corporation). Specific statistical analyses are presented in individual chapters.

Chapter 3

The use of arterial transfer functions for the derivation of aortic pressure waveform characteristics

TABLE OF CONTENTS

3.1 INTRODUCTION

The association between arterial blood pressure and cardiovascular risk is well established, with reduction in risk with the effective treatment of hypertension.(Chalmers 1999) However, the reduction in risk is less than might be predicted from observational epidemiological studies.(MacMahon, *et al.* 1990, Collins, *et al.* 1990) This finding has fuelled interest in the properties of the arterial system which might explain this discrepancy, and in methods which might enable more accurate estimation of the likely impact of treatment on cardiovascular risk in the individual. In this respect, interest has been directed towards the analysis of mechanical properties of the arterial system and characteristics of the central aortic pressure waveform. A number of interrelated parameters reflecting vascular stiffness have been associated with increased cardiovascular risk.(Kelly, *et al.* 1989, Cameron 1999, Marchais, *et al.* 1993, Mohiaddin, *et al.* 1989, Martin, *et al.* 2000, Leeson, *et al.* 2000, O'Rourke 1990, Salomaa, *et al.* 1995, Berry, *et al.* 1999) Much interest has surrounded the assessment of the central aortic augmentation index since, with equivalent non-invasively measured peripheral blood pressure, a higher central augmentation index is associated with increased left ventricular afterload, which probably explains the association with left ventricular hypertrophy, and offers the potential to refine the assessment of cardiovascular risk in patients with similar brachial artery blood pressures.(Nichols, *et al.* 1985, Marchais, *et al.* 1993, O'Rourke 1990)

Since the direct measurement of central aortic pressure waveforms is invasive, if the analysis of central waveform characteristics is to be of widespread clinical value a non-invasive method of estimation of these characteristics is essential. Although the assessment of waveforms acquired non-invasively by applanation tonometry of arteries close to the central aorta provides acceptable estimates of central aortic waveform

characteristics (carotid (Cameron and Dart 1994, Chen, *et al.* 1996), subclavian (Aakhus, *et al.* 1993)), the radial artery is often proposed as the preferred site for applanation tonometry since it is well supported by bony tissue making optimal applanation theoretically easier to achieve, and reproducible results are attainable after minimal training.(Chen, *et al.* 1997, Wilkinson, *et al.* 1998) However, since the radial and central pressure waveforms differ significantly in morphology this approach requires that the radial waveform be further manipulated before adequately representing the central aortic. The use of transfer functions has been proposed for this purpose. However, the data validating their use is modest. The aims of this study were therefore to explore the utility of arterial transfer functions for the derivation of central aortic pressure waveforms, to explore the impact of differing methods of transfer function derivation, and the impact of gender and the presence of Type 2 diabetes mellitus on the accuracy of central aortic waveform reconstruction.

3.2 METHODS

3.2.1 Subjects and data acquisition

Subjects were recruited from amongst those referred to the coronary catheterisation laboratory for elective coronary angiography or percutaneous coronary interventional procedures. Inclusion and exclusion criteria were as described in *Section 2.1.1*. The study was approved by the Southern Health Human Research Ethics Committee and subjects gave written consent to participate in the study.

Data were acquired from 78 subjects, 61 male, the characteristics of whom are presented in Table 3-1. Drug treatments were typical of a group with established coronary artery disease (Table 3-2). Central aortic pressure waveforms were recorded

invasively via a low-compliance fluid-filled catheter positioned in the ascending aorta simultaneously with non-invasively obtained radial artery waveform data acquired via a Millar® Mikro-tip® tonometer (Millar Instruments) as described in *Section 2.2*. The comparative frequency response characteristics of the fluid-filled catheter system with a transducer-tipped pressure wire over the frequency range of interest are presented in Figure 3-7, and are discussed later in the chapter. The peripheral tonometric waveforms were scaled to measured aortic mean and diastolic pressures by linear interpolation as described in *Section 2.3*.

Table 3-1. Subject characteristics

Male gender	61 (78%)	**Current smoking**	7 (9%)
Age (years)	63 ± 10	**Diabetes Mellitus**	19 (24%)
Height (m)	1.70 ± 0.10	**Hypertension**	43 (55%)
Weight (kg)	78 ± 13	**Hypercholesterolaemia**	66 (85%)
Body Mass Index (kg/m^2)	28 ± 4	**Obesity (BMI>30)**	24 (31%)
Heart Rate (bpm)	65 ± 11	**Family History**	34 (44%)

BMI is body mass index, bpm is beats per minute. Hypertension defined as blood pressure > 140/90 mmHg or anti-hypertensive drug therapy, hypercholesterolaemia as total cholesterol > 5.5 mmol/L or cholesterol lowering therapy.

Table 3-2. Subject drug treatments

β Blocker	54 (69%)	Statin	59 (76%)
Ca^{2+} Channel Blocker	28 (36%)	ACE inhibitor	29 (37%)
Aspirin	62 (79%)	AR Blocker	4 (5%)
Nitrate	36 (46%)	Diuretic	15 (19%)

ACE is angiotensin converting enzyme, AR is angiotensin receptor.

3.2.2 Comparison of 2 methods of transfer function derivation

Individual transfer functions were derived for each subject by 2 methods as described in *Section 2.5*. The individual transfer functions were averaged for the entire group to yield 2 ensemble average transfer functions (TF_1 and TF_2, Method 1 and Method 2 respectively).

Reconstructed central aortic pressure waveforms were derived by the application of each ensemble average transfer function to a representative radial artery waveform for each subject, as described in *Section 2.6*. All waveforms, both measured and derived, were analysed using purpose-written software as described in *Section 2.4*.

3.2.3 Comparison of gender-specific and generalised transfer functions

Subject characteristics, cardiovascular risk factors and drug treatments for the men and women separately are shown in Table 3-3, Table 3-4 and Table 3-5. The menopausal

status of the women in this study was not documented. Individual transfer functions derived by both methods were averaged for each gender individually (male: mTF_1, mTF_2, female: fTF_1 and fTF_2, by Methods 1 and 2 respectively), and central aortic waveforms were reconstructed by the application of both the gender-appropriate and gender-inappropriate transfer functions, in addition to the generalised ensemble average transfer functions to the representative radial artery data for each subject.

Waveform analysis was undertaken and parameters of waveforms reconstructed using both generalised and gender-specific transfer functions were compared with the measured central aortic.

A secondary analysis was undertaken comparing the reconstructed central waveforms of the female group with a subgroup of males matched for measured central aortic systolic blood pressure to assess whether differences between generalised and gender-specific transfer functions could be explained simply by the difference in blood pressure between the genders.

Table 3-3. Subject characteristics and differences between genders

	Males	Females	*P* value
Age (years)	63 ± 11	65 ± 8	NS
Height (m)	1.72 ± 0.09	1.59 ± 0.03	< 0.001
Weight (kg)	79 ± 13	76 ± 12	NS
Body Mass Index (kg/m^2)	27 ± 4	30 ± 5	< 0.05
Heart Rate (bpm)	68 ± 12	73 ± 12	NS
SBP (mmHg)	127 ± 21	147 ± 20	< 0.001
DBP (mmHg)	68 ± 10	72 ± 10	NS
MAP (mmHg)	91 ± 13	101 ± 13	< 0.01
PP (mmHg)	59 ± 18	74 ± 17	< 0.01

Variables are presented as mean ± standard deviation. NS is not significant, SBP systolic blood pressure, DBP diastolic blood pressure, MAP mean arterial pressure, PP pulse pressure.

Table 3-4. Subject cardiovascular risk factors and differences between genders

Risk Factor	Males	Females	*P* value
Current smoking	5 (8%)	2 (12%)	NS
Diabetes Mellitus	14 (23%)	5 (29%)	NS
Hypertension	29 (48%)	14 (82%)	< 0.05
Hypercholesterolaemia	51 (84%)	15 (88%)	NS
Obesity (BMI>30)	13 (21%)	11 (65%)	< 0.001
Family History	23 (38%)	11 (65%)	< 0.05

Hypertension defined as blood pressure > 140/90 mmHg or anti-hypertensive drug therapy, hypercholesterolaemia as total cholesterol > 5.5 mmol/L or cholesterol lowering drug therapy. BMI is body mass index (kg/m^2). NS is not significant.

Table 3-5. Subject drug treatments and differences with gender

Drug Class	Males	Females	*P* value
β Blocker	44 (66%)	10 (59%)	NS
Ca^{2+} Channel Blocker	20 (33%)	8 (47%)	NS
Aspirin	46 (75%)	16 (94%)	NS
Nitrate	26 (43%)	10 (59%)	NS
Statin	45 (74%)	14 (82%)	NS
ACE inhibitor	23 (38%)	6 (35%)	NS
AR Blocker	3 (5%)	1 (6%)	NS
Diuretic	12 (20%)	3 (18%)	NS
Nicorandil	2 (3%)	1 (6%)	NS
Other	41 (67%)	13 (76%)	NS

ACE is angiotensin converting enzyme. AR is angiotensin receptor. NS is not significant.

3.2.4 Impact of Type 2 diabetes on the use of arterial transfer functions

Nineteen of the subjects studied had diabetes mellitus. All 19 had Type 2 diabetes, 9 using oral hypoglycaemic agents alone, 2 using insulin alone, 3 using both oral hypoglycaemic agents combined with insulin, and the remainder treated by diet. Mean interval since diagnosis of diabetes was 9.5 ± 10.7 years. In no subject was the diabetes considered to be uncontrolled at the time of the coronary procedure, although no objective measure of control was available. 13 subjects had suffered a previous acute coronary syndrome, and all were suspected to have coronary artery disease. 38 age and sex-matched subjects without diabetes, but a similar burden of coronary artery disease,

were selected for comparison. Subject characteristics, cardiovascular risk factors and drug treatments are presented in Table 3-6, Table 3-7 and Table 3-8.

A diabetes-specific transfer function was derived by averaging the individual transfer functions, derived by Method 1, of the subjects with diabetes mellitus. Central aortic waveforms were reconstructed by the application of this transfer function to the representative radial artery data for each subject with diabetes mellitus, and by the application of TF_1 to the representative radial data for all subjects, both with and without diabetes.

Waveform analysis was undertaken, and measured aortic waveform parameters were compared with those of waveforms reconstructed using the generalised transfer function in subjects with and without diabetes mellitus. The impact of the use of a diabetes-specific transfer function was evaluated in the group with diabetes mellitus.

Table 3-6. Characteristics of subjects with and without diabetes mellitus

	Diabetes	No diabetes	*P* value
Number	19	38	
Age (years)	66 ± 11	65 ± 10	NS
Height (m)	1.69 ± 0.09	1.69 ± 0.09	NS
Weight (kg)	81 ± 15	79 ± 12	NS
Body Mass Index (kg/m^2)	28.4 ± 5.3	27.9 ± 4.0	NS
Heart Rate (bpm)	72 ± 10	69 ± 12	NS
SBP (mmHg)	134 ± 22	135 ± 25	NS
DBP (mmHg)	68 ± 11	70 ± 10	NS
MAP (mmHg)	93 ± 13	95 ± 14	NS
PP (mmHg)	66 ± 20	65 ± 20	NS

Variables are presented as mean ± standard deviation. NS is not significant, SBP systolic blood pressure, DBP diastolic blood pressure, MAP mean arterial pressure, PP pulse pressure.

Table 3-7. Cardiovascular risk factors of subjects with and without diabetes mellitus

Risk Factor	Diabetes	No diabetes	*P* value
Male gender	14 (74%)	28 (74%)	NS
Current smoking	4 (21%)	1 (3%)	< 0.05
Hypertension	11 (58%)	22 (58%)	NS
Hypercholesterolaemia	17 (89%)	32 (84%)	NS
Obesity (BMI>30)	9 (47%)	9 (24%)	NS
Family History	9 (47%)	14 (37%)	NS
Coronary artery disease on angiography	16 (84%)	33 (87%)	NS

Hypertension defined as blood pressure > 140/90 mmHg or anti-hypertensive drug therapy, hypercholesterolaemia as total cholesterol > 5.5 mmol/L or cholesterol lowering drug therapy. BMI is body mass index. NS is not significant.

Table 3-8. Drug treatments of subjects with and without diabetes mellitus

Drug Class	Diabetes	No diabetes	*P* value
β Blocker	12 (63%)	26 (68%)	NS
Ca^{2+} Channel Blocker	10 (53%)	12 (32%)	NS
Aspirin	13 (68%)	31 (82%)	NS
Nitrate	10 (53%)	18 (47%)	NS
Statin	15 (79%)	29 (76%)	NS
ACE inhibitor	9 (47%)	11 (29%)	NS
AR Blocker	0 (0%)	3 (8%)	NS
Diuretic	7 (37%)	3 (8%)	< 0.01
Nicorandil	3 (16%)	0 (0%)	< 0.05
Other	17 (89%)	27 (71%)	NS

ACE is angiotensin converting enzyme. AR is angiotensin receptor. NS is not significant.

3.2.5 Assessment of burden of coronary artery disease

The burden of coronary artery disease was assessed from the clinical angiographic study performed at the time of data collection, and categorized into 5 groups: 1) angiographically smooth arteries, 2) minor irregularities only, 3) single vessel disease, with a stenosis of ≥ 70% in one vessel, 4) double vessel disease, with a stenosis of ≥ 70% in one vessel and a stenosis of ≥ 50% in a second vessel, 5) triple vessel disease, with a stenosis of ≥ 70% in one vessel and a stenosis of ≥ 50% in both other major coronary arteries. When considering the prevalence of coronary artery disease, subjects

were considered to have coronary artery disease if they had single, double or triple vessel disease.

3.2.6 Statistical analysis

Relationships between waveform parameters and subject demographic features were explored using both simple and stepwise multiple linear regression techniques. Mean values of measured aortic and reconstructed waveforms were compared by repeated measures analysis of variance. 95% limits of agreement were calculated according to the method of Bland and Altman.(Bland and Altman 1986) Comparisons were made between Pearson's correlation coefficients for the relationships between the measured aortic parameters and reconstructed waveforms (Fisher's Z transformation). Regression slopes were compared with the line of unity. Differences between groups were compared using unpaired t tests.

3.3 RESULTS

3.3.1 Central aortic waveform parameters

Parameters of the measured central aortic waveforms are presented in Table 3-9. By simple linear regression, all time intervals were associated with heart rate ($P < 0.001$). Both increased AP and AI were associated with shorter Ti, consistent with an increased pulse wave velocity. These relationships were retained in multiple stepwise linear regression models including heart rate (AP only $P < 0.001$, $r^2 = 0.35$, AP and heart rate $P < 0.001$, $r^2 = 0.56$, AI only $P < 0.001$, r^2 0.46, AI and heart rate $P < 0.001$, $r^2 = 0.65$). Larger As was associated with longer Ts, but was additionally independently associated

with increased heart rate (Ts only $P < 0.001$, $r^2 = 0.36$, Ts and heart rate $P < 0.001$, $r^2 = 0.45$). Increased Ad was associated with slower heart rate ($P < 0.001$, $r^2 = 0.63$), but not associated with Ts. Higher SVI was significantly associated with a slower heart rate ($P < 0.001$, $r^2 = 0.45$). In this group AI was not associated with either heart rate or height. The presence of coronary artery disease was weakly correlated with a shorter Ti ($P < 0.05$, $r^2 = 0.06$), and the burden of coronary artery disease with increased pulse pressure ($P < 0.05$, $r^2 = 0.05$) only.

3.3.2 Comparison of 2 methods of transfer function derivation

Simple visual inspection revealed that, although the morphology of the scaled radial waveform differed significantly from that of the directly measured central aortic waveform, after the application of either ensemble average arterial transfer function to the radial data the output bore a much closer resemblance to the measured central aortic waveform than to the radial (Figure 3-1).

Although present on each measured aortic waveform, no inflection point could be identified on 14 TF_1 and 5 TF_2-derived waveforms. These waveforms were therefore excluded from analyses of AI, Ti, AP and Pi. All other waveform characteristics were appropriately identified on all reconstructed waveforms.

The mean measured central aortic values and relationships between the different parameters of the measured central aortic waveform and TF_1 and TF_2-derived waveforms are presented in Table 3-9 and Table 3-10 respectively. Although most derived parameters were correlated with the respective measured central aortic parameters, transfer function-derived AI was not correlated with the measured aortic for

either transfer function, and although the correlation between derived and measured Ti just reached statistical significance for TF_2, no correlation was seen for TF_1. This reflects the finding that the derived AI for both transfer functions remains closely related to the radial AI ($r^2 = 0.51$) which, in this group of subjects, is not related to the measured aortic (Figure 3-2). There was no significant difference between the TF_1 and TF_2-associated correlation coefficients for any parameter. There were significant differences between these correlation coefficients and those between the measured aortic and radial parameters in the same subjects for SBP ($P < 0.05$ TF_1 and $P < 0.01$ TF_2, closer relationship with transfer function-derived parameters), Ts ($P < 0.05$ TF_2, closer relationship with radial parameters) and Pi ($P < 0.001$ TF_1 and $P < 0.01$ TF_2, closer relationship with radial parameters) only.

Despite the significant relationships between most derived and respective measured parameters, there were statistically significant differences in the mean values of most parameters and considerable individual scatter, as reflected by the Bland Altman 95% limits of agreement (Table 3-9, Table 3-10 and Figure 3-3).

Regression slopes for the relationships between the derived and respective measured aortic parameters were compared with the line of unity to assess any change in the error between the derived and measured parameters across their range. With the exception of Ad, the regression slopes all differed significantly from 1 ($P < 0.001$), suggesting that a correction is required which differs at different physiological values. This is supported by a positive relationship between the magnitude of the errors in the derived parameters and the respective measured parameters for all parameters except Ad (both TF_1 and TF_2) and DBP (TF_2 only).

Figure 3-1. Example of radial, aortic and TF_2-derived waveforms in the same subject

Table 3-9. Relationships between measured aortic and TF_1-derived waveform parameters

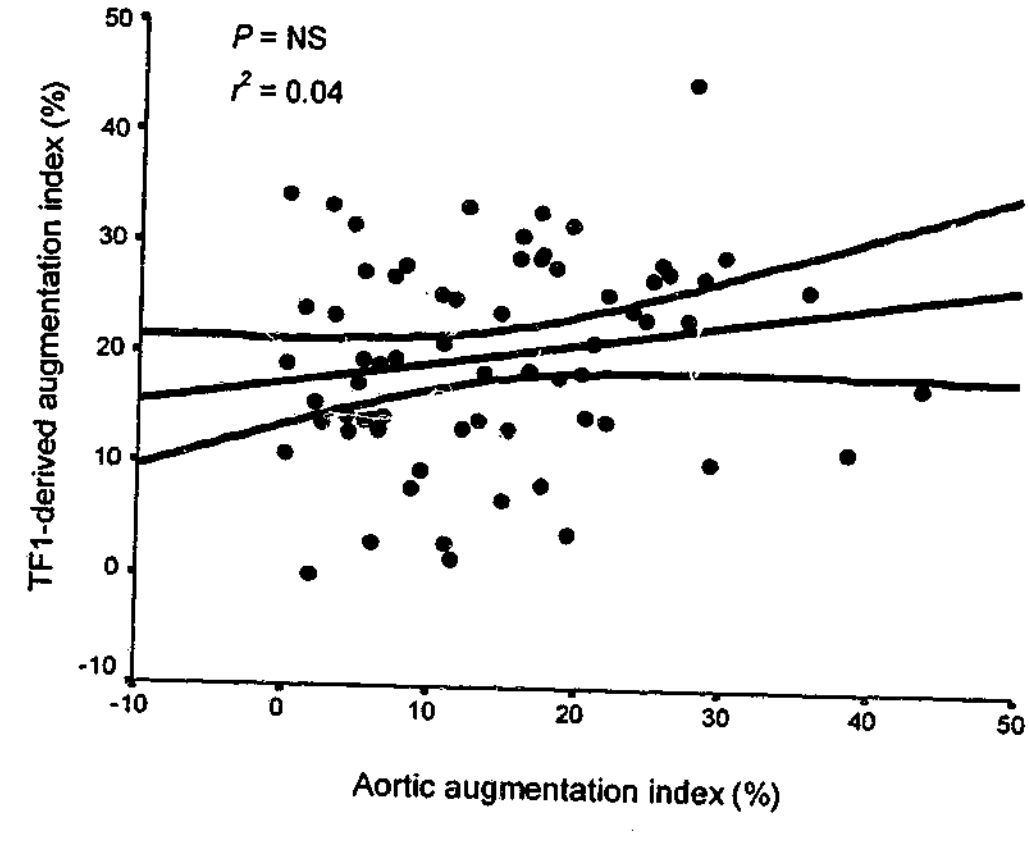
Parameter	Measured aortic	Mean difference (aortic – TF_1)	95% limits of agreement	Pearson's *r*
SBP (mmHg)	131 ± 22	3 ***	± 15	0.94 ***
DBP (mmHg)	69 ± 10	8 ***	± 5	0.97 ***
PP (mmHg)	62 ± 19	-5 ***	± 16	0.91 ***
As (mmHg.s)	35.95 ± 6.79	-0.31	± 6.30	0.87 ***
Ad (mmHg.s)	47.73 ± 11.98	4.41 ***	± 6.17	0.97 ***
SVI	1.35 ± 0.31	0.14 ***	± 0.40	0.80 ***
AI (%)	14.4 ± 10.1	-5.6 ***	± 24.4	0.20
Ti (s)	0.161 ± 0.035	0.012 **	± 0.067	0.30 *
Tp (s)	0.237 ± 0.032	0.009 **	± 0.049	0.66 ***
Ts (s)	0.323 ± 0.030	0.024 ***	± 0.060	0.58 ***
AP (mmHg)	9 ± 6	5 ***	± 15	0.47 ***
Pi (mmHg)	122 ± 21	8 ***	± 21	0.86 ***

SBP is systolic blood pressure, DBP diastolic blood pressure, PP pulse pressure, As systolic pressure time integral, Ad diastolic pressure time integral, SVI subendocardial viability index, Ti time to inflection, Tp time to peak pressure, Ts time to end systole, AP augmentation pressure and Pi pressure at the inflection. * is $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$.

Table 3-10. Relationships between measured aortic and TF_2-derived waveform parameters

Parameter	Measured aortic	Mean difference (aortic – TF_2)	95% limits of agreement	Pearson's *r*
SBP (mmHg)	131 ± 22	1	± 14	0.95 ***
DBP (mmHg)	69 ± 10	1 **	± 5	0.97 ***
PP (mmHg)	62 ± 19	0	± 15	0.92 ***
As (mmHg.s)	35.95 ± 6.79	-1.81 ***	± 7.32	0.85 ***
Ad (mmHg.s)	47.73 ± 11.98	1.55 ***	± 7.39	0.96 ***
SVI	1.35 ± 0.31	0.11 ***	± 0.42	0.79 ***
AI (%)	14.4 ± 10.1	-4.3 **	± 24.3	0.18
Ti (s)	0.161 ± 0.035	0.009	± 0.081	0.13
Tp (s)	0.237 ± 0.032	-0.010 **	± 0.058	0.66 ***
Ts (s)	0.323 ± 0.030	-0.024 ***	± 0.072	0.53 ***
AP (mmHg)	9 ± 6	-3 ***	± 15	0.29 *
Pi (mmHg)	122 ± 21	4 ***	± 17	0.92 ***

SBP is systolic blood pressure, DBP diastolic blood pressure, PP pulse pressure, As systolic pressure time integral, Ad diastolic pressure time integral, SVI subendocardial viability index, Ti time to inflection, Tp time to peak pressure, Ts time to end systole, AP augmentation pressure and Pi pressure at the inflection. * is $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$.



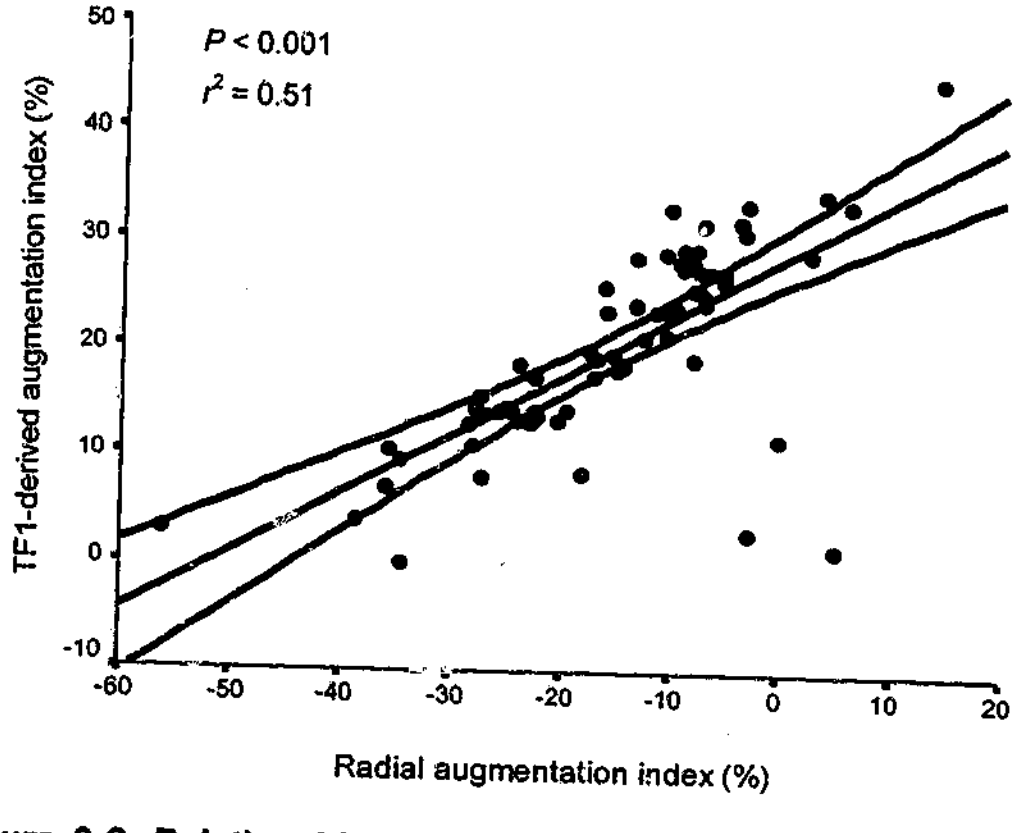
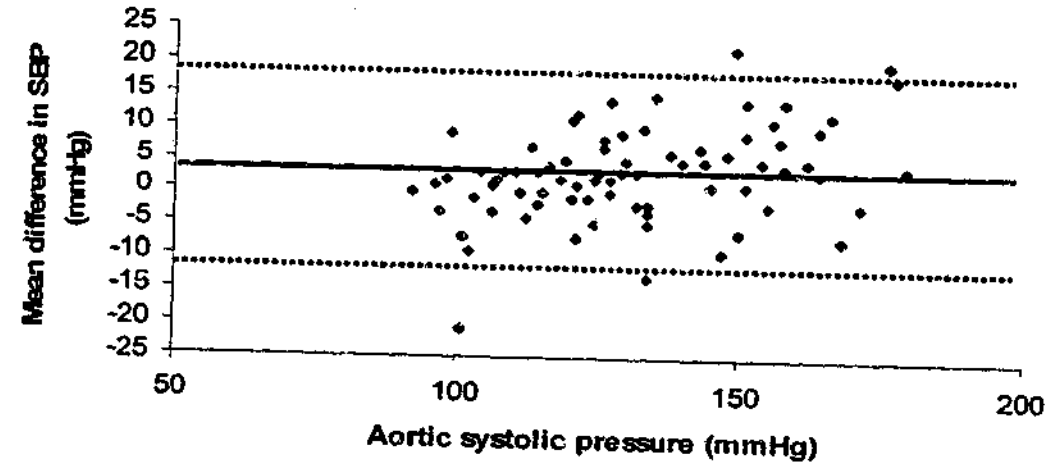
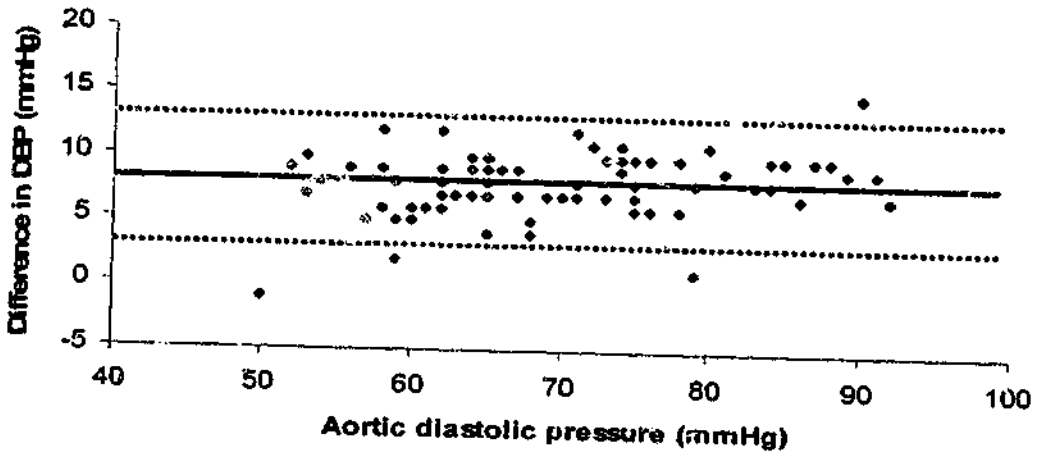


Figure 3-2. Relationships between TF_1-derived and measured aortic and radial augmentation indices

$P < 0.001$ for difference between correlation coefficients. Lines are mean regression line and 95% confidence intervals, and r Pearson's correlation coefficient.





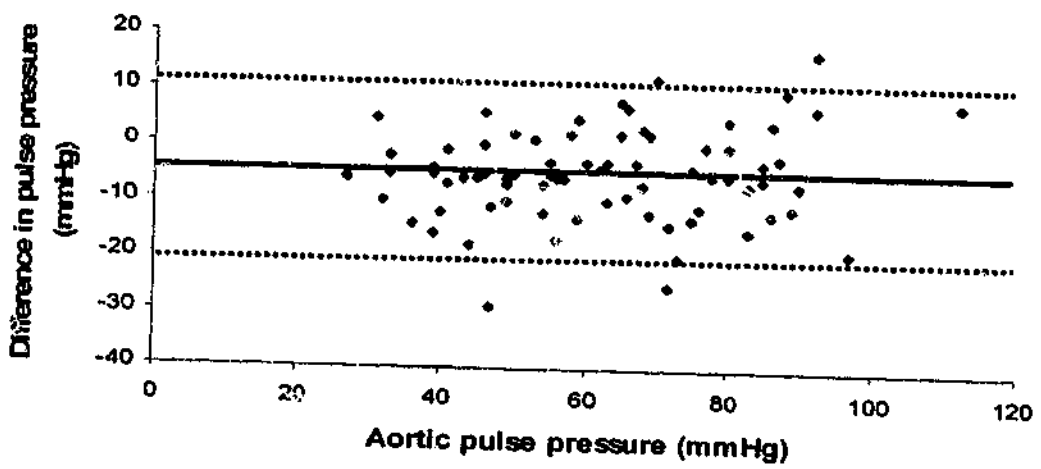


Figure 3-3. Modified Bland Altman plots for aortic and TF_1-derived systolic, diastolic and pulse pressures

——— marks mean difference, ····· 95% limits of agreement. Difference is measured aortic – transfer function-derived. SBP is systolic blood pressure and DBP diastolic blood pressure.

3.3.3 Comparison of gender-specific and generalised transfer functions

Generalised and male and female transfer functions are depicted in Figure 3-4. As can be seen, at all frequencies the magnitude of the transfer function is greater, and the slope of the transfer function phase less, in the female group.

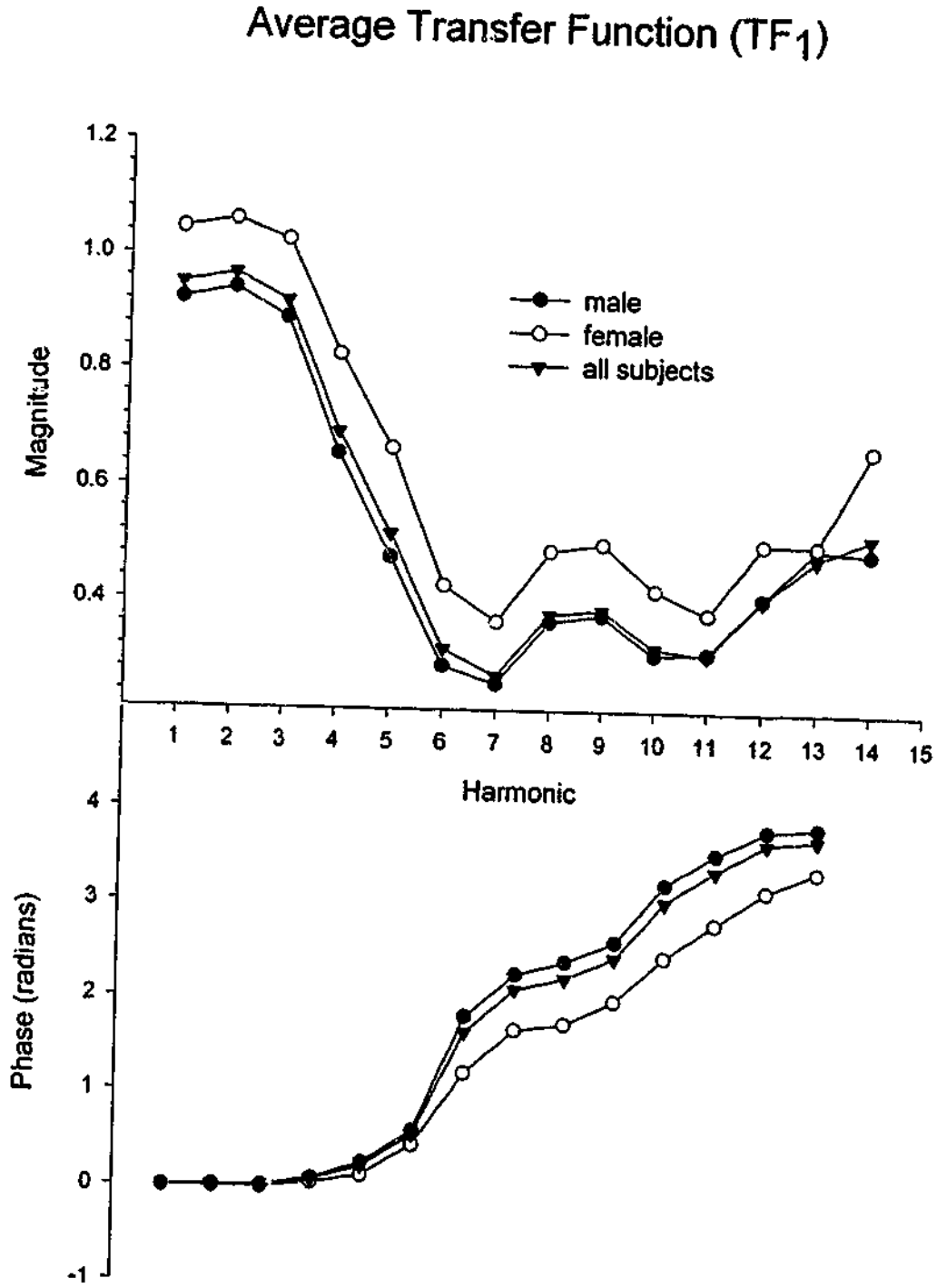


Figure 3-4. Generalised and gender-specific transfer functions (Method 1)

3.3.3.1 Measured central aortic waveform parameters and gender

Unpaired t tests comparing measured central aortic parameters in men and women revealed significantly higher SBP, Pi and As in females, with significantly lower SVI (Table 3-11). These findings remained unchanged in a multiple stepwise linear regression model when height, weight, heart rate and age were also considered. Additionally, longer Ts was significantly associated with female gender after heart rate was considered ($P < 0.05$ for gender after consideration of heart rate, total model $P < 0.001$, $r^2 = 0.46$). As already noted, larger As was associated with both longer Ts and increased heart rate, however it was also independently associated with female gender ($P < 0.05$ after consideration of Ts and heart rate, total model $P < 0.001$, $r^2 = 0.48$). Higher SVI was significantly associated with male gender ($P < 0.01$ after consideration of heart rate, total model $P < 0.001$, $r^2 = 0.51$), but this association was not independent of Ts ($P < 0.001$ after consideration of heart rate), which preferentially entered the multiple regression model (total model $P < 0.001$, $r^2 = 0.85$). AI was not associated with gender, and the previously noted inverse relationship between AI and Ti was not influenced by gender.

Table 3-11. Comparison of mean measured aortic parameters in men and women

	Mean male	Mean female
SBP (mmHg)	127 ± 21	146 ± 19 ***
Tp (s)	0.239 ± 0.031	0.231 ± 0.035
Ts (s)	0.321 ± 0.027	0.328 ± 0.038
As (mmHg.s)	34.8 ± 6.8	40.0 ± 4.9 **
Ad (mmHg.s)	48.4 ± 12.9	45.4 ± 7.8
SVI	1.4 ± 0.3	1.2 ± 0.2 **
AI (%)	15 ± 11	12 ± 7
Ti (s)	0.160 ± 0.034	0.165 ± 0.037
AP (mmHg)	9 ± 6	9 ± 6
Pi (mmHg)	118 ± 21	137 ± 18 ***
DBP (mmHg)	68 ± 10	72 ± 10

** is $P < 0.01$, *** $P < 0.001$ for difference between men and women. Data expressed as mean ± standard deviation. SBP is systolic blood pressure, Tp time to peak pressure, Ts time to end of systole, As systolic pressure time integral, Ad diastolic pressure time integral, SVI subendocardial viability index, AI augmentation index, Ti time to inflection point, AP augmentation pressure, Pi pressure at inflection point and DBP diastolic blood pressure.

3.3.3.2 Method 1

As previously noted, derived AI did not correlate with the directly measured (AI), and was therefore not further analysed. There were significant differences between the measured and derived mean values of the other parameters assessed, but no differences between the values derived by the generalised or gender appropriate transfer function (Table 3-12). There were no differences between the correlation coefficients for the

relationship between the measured and derived waveform parameters for the generalised and gender-appropriate transfer functions.

There were differences in derived mean values for most parameters when the generalised transfer function was compared with the gender-inappropriate transfer function (SBP, Tp, As, Ad, Ti, AP and Pi (all $P < 0.001$)). For some parameters the mean difference from measured was smaller with the gender-inappropriate than the generalised transfer function (Tp, Ti, AP ($P < 0.001$), but for no parameter was the correlation significantly stronger, and for SBP ($P < 0.001$), DBP ($P < 0.001$) and Pi ($P < 0.05$) the correlation was stronger with the generalised transfer function. Correlation coefficients for these parameters were also stronger with the gender-appropriate than the gender-inappropriate transfer function, but the difference did not reach statistical significance.

Comparison of the regression slopes for the relationships between gender appropriate transfer function-derived and measured aortic parameters with those for the relationships between the generalised transfer function-derived and measured aortic parameters revealed significant differences for SBP ($P < 0.05$) and Pi ($P < 0.01$) only. The gender-appropriate transfer function produced regression slopes nearer to unity for SBP and Pi, not differing from unity for SBP. Comparison of the regression slopes for the relationships between gender-inappropriate transfer function-derived and measured aortic parameters with those for the relationships between the generalised-transfer function-derived and measured aortic parameters revealed a difference only for Ad ($P < 0.05$), with that for the generalised transfer function being closer to unity.

Table 3-12. Relationships between transfer function-derived and measured aortic parameters

Parameter	Measured	TF_1		$GATF_1$		$GNTF_1$	
	Mean	Mean	*r*	Mean	*r*	Mean	*r*
SBP (mmHg)	129	128 ***	0.94 ***	128 *	0.91 ***	137 *** ‡	0.87 *** ‡
Tp (s)	0.226	0.246 **	0.66 ***	0.247 ***	0.64 ***	0.239 ‡	0.57 ***
Ts (s)	0.310	0.347 ***	0.58 ***	0.346 ***	0.57 ***	0.344 ***	0.68 ***
As (mmHg.s)	34.5	36.3	0.89 ***	36.3	0.84 ***	38.9 *** ‡	0.87 ***
Ad (mmHg.s)	52.0	43.3 ***	0.97 ***	43.3 ***	0.95 ***	46.5 ** ‡	0.96 ***
SVI	1.54	1.21 ***	0.80 ***	1.21 ***	0.79 ***	1.20 ***	0.84 ***
AI (%)	14.4	20.0 ***	0.20	19.3 **	0.16	14.5 ‡	0.14
Ti (s)	0.161	0.147 **	0.30 *	0.149 *	0.10	0.155 ‡	0.32 **
AP (mmHg)	8.8	13.8 ***	0.47 ***	12.7 ***	0.25 *	11.1 * ‡	0.51 ***
Pi (mmHg)	122	113 ***	0.86 ***	114 ***	0.82 ***	127 * ‡	0.72 *** ‡
DBP (mmHg)	69	61 ***	0.97 ***	61 ***	0.94 *** ‡	66 ***	0.90 *** ‡

GATF is gender-appropriate transfer function, GNTF gender-inappropriate transfer function, SBP systolic blood pressure, Tp time to peak pressure, Ts time to end of systole, As systolic pressure time integral, Ad diastolic pressure time integral, SVI subendocardial viability index, AI augmentation index, Ti time to inflection point, AP augmentation pressure, Pi pressure at inflection point and DBP diastolic blood pressure. *r* is Pearson's correlation coefficient between derived and measured parameters. * is $P < 0.05$, ** is $P < 0.01$, *** is $P < 0.001$ for difference between derived and measured mean values. ‡ is $P < 0.05$ for difference from TF_1 derived mean values or correlation coefficients.

3.3.3.3 Method 2

Again as previously noted, derived AI and Ti were not significantly correlated with the respective measured parameters, and were therefore not further analysed. There were statistically significant differences between the measured and derived mean values of a number of the other parameters assessed (Table 3-13). Where differences existed between values derived by the generalised and gender-appropriate transfer functions, with the exception of DBP for which the generalised transfer function was significantly better, with the mean difference from measured less than the limits of measurement, the gender-appropriate transfer function-derived parameters either did not differ from measured (AP, Pi), or the differences were less than the limits of measurement (SBP, Tp). There were significant differences between the correlation coefficients for the relationship between the measured and derived waveform parameters for the generalised and gender-appropriate transfer functions for both Ad and As, with the generalised transfer function being stronger (both $P < 0.01$). There were differences in derived mean values for all parameters when the generalised transfer function was compared with the gender-inappropriate transfer function. With the exception of AP and Pi, the mean differences were smaller with the generalised than the gender-inappropriate transfer function. For AP and Pi there were no differences in the correlation coefficients, and the mean differences from measured were still smaller with the gender-appropriate transfer function, although not reaching statistical significance.

Correlation was significantly better with the generalised than the gender-inappropriate TF for Ts ($P < 0.05$), As, Ad and SVI (all $P < 0.001$). Correlation coefficients for these parameters were also better with the gender-appropriate than the gender-inappropriate transfer function, but reached statistical significance only for As ($P < 0.05$), Ad and SVI (both $P < 0.001$).

Comparison of the regression slopes for the relationships between gender appropriate transfer function-derived with measured aortic parameters with those for the relationships between the generalised-transfer function derived and measured aortic parameters revealed significant differences for Tp and Pi only (both $P < 0.05$). The gender-appropriate transfer function produced a regression slope significantly nearer to unity for Pi. Comparison of the regression slopes for the relationships between gender-inappropriate transfer function-derived with measured aortic parameters with those for the relationships between the generalised transfer function-derived and measured aortic parameters revealed significant differences for Ad, SVI (both $P < 0.05$) and Tp ($P < 0.01$) with those for the generalised transfer function being closer to unity.

Table 3-13. Relationships between transfer function-derived and measured aortic parameters

Parameter	Measured	TF_2		$GATF_2$		$GNTF_2$	
	Mean	Mean	*r*	Mean	*r*	Mean	*r*
SBP (mmHg)	129	130	0.95 ***	130 ‡	0.95 ***	132 ‡	0.95 ***
Tp (s)	0.226	0.247 **	0.70 ***	0.231 * ‡	0.59 ***	0.221 *** ‡	0.50 ***
Ts (s)	0.310	0.346 ***	0.53 ***	0.344 **	0.32 **	0.436 *** ‡	0.16 ‡
As (mmHg.s)	34.5	37.8 ***	0.85 ***	38.2 **	0.67 *** ‡	46.8 *** ‡	0.41 *** ‡†
Ad (mmHg.s)	52.0	46.2 ***	0.96 ***	45.8 *	0.89 *** ‡	37.5 *** ‡	0.65 *** ‡†
SVI	1.54	1.24 ***	0.79 ***	1.26 *	0.70 ***	0.897 *** ‡	0.22 * ‡†
AI (%)	14.4	18.6 **	0.18	14.1 ‡	0.18	15.4 ‡	0.17
Ti (s)	0.161	0.151	0.13	0.154	0.15	0.154 *	0.37 **
AP (mmHg)	8.8	11.6 ***	0.29 *	8.4 ‡	0.21	9.8 ‡	0.42 ***
Pi (mmHg)	122	116 ***	0.92 ***	122 ‡	0.93 ***	123 ‡	0.92 ***
DBP (mmHg)	69	69 **	0.97 ***	72 *** ‡	0.98 ***	74 *** ‡	0.96 ***

GATF is gender-appropriate transfer function, GNTF gender-inappropriate transfer function, SBP systolic blood pressure, Tp time to peak pressure, Ts time to end of systole, As systolic pressure time integral, Ad diastolic pressure time integral, SVI subendocardial viability index, AI augmentation index, Ti time to inflection point, AP augmentation pressure, Pi pressure at inflection and DBP diastolic blood pressure. *r* is Pearson's correlation coefficient between derived and measured parameters. * is $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ for difference between derived and measured mean values. ‡ is $P < 0.05$ for difference from TF_2 derived mean values or correlation coefficients. † is $P < 0.05$ for difference from $GATF_2$ derived correlation coefficients.

3.3.3.4 Subgroup analysis

Matching the female group with a group of males by measured systolic blood pressure yielded groups with no difference in any measured central waveform parameters with gender. Analysis of the findings in these groups confirmed that significant differences remained between waveform parameters derived by the use of generalised and gender-specific transfer functions. Specifically, the gender-appropriate TF_1 yielded results significantly closer to the measured than did the generalised TF_1 for SBP ($P < 0.001$), DBP ($P < 0.01$), Ad ($P < 0.01$) and Pi ($P < 0.05$). Additionally, TF_2 yielded results significantly closer to the measured than the generalised TF_2 for SBP ($P < 0.001$), Ti ($P < 0.01$), Tp ($P < 0.001$), AP ($P < 0.001$) and Pi ($P < 0.001$).

3.3.4 Impact of Type 2 diabetes on the use of arterial transfer functions

3.3.4.1 Measured central aortic and radial waveforms

Measured central aortic waveform parameters were similar in subjects with and without diabetes, with a significant difference only in Ti ($P < 0.05$) (Table 3-14). Ti was shorter, with a trend to higher AP ($P < 0.08$) and AI ($P < 0.09$) in the subjects with diabetes. Central aortic and radial waveform parameters, with the exception of AI, AP and Ti, were all significantly correlated in subjects both with and without diabetes ($P < 0.05$ Tp in subjects with diabetes, $P < 0.01$ Tp in subjects without diabetes, otherwise $P < 0.001$). AI, AP and Ti were not further analysed. Correlation coefficients did not differ between those with and without diabetes. There was, however, a trend towards a smaller difference between measured central aortic and radial systolic pressure in the subjects with diabetes than those without (mean difference of 7 ± 10 mmHg and 14 ± 11 mmHg

respectively ($P < 0.07$)). Stepwise multiple regression analysis, considering subject age, gender, height, weight, body mass index, the presence of conventional cardiovascular risk factors and heart rate, revealed current smoking, heart rate and the presence of a positive family history to be associated with the difference between the radial and measured central aortic Ad ($P < 0.01$, $r^2 = 0.27$), As ($P < 0.001$, $r^2 = 0.34$) and Ts ($P < 0.01$, $r^2 = 0.28$), and diabetes mellitus with the difference between the radial and measured central aortic AP ($P < 0.05$, $r^2 = 0.08$).

Table 3-14. Central aortic waveform parameters in subjects with and without diabetes

	Diabetes	No diabetes
SBP (mmHg)	133 ± 22	134 ± 23
Ad (mmHg.s)	43.67 ± 9.97	49.26 ± 12.98
As (mmHg.s)	35.80 ± 5.75	37.13 ± 7.84
SVI	1.25 ± 0.33	1.35 ± 0.28
DBP (mmHg)	68 ± 11	70 ± 10
AI (%)	18.0 ± 10.2	13.1 ± 9.8
Ti (s)	0.144 ± 0.030 *	0.163 ± 0.033
Ts (s)	0.320 ± 0.028	0.324 ± 0.034
Tp (s)	0.229 ± 0.027	0.238 ± 0.033
AP (mmHg)	12 ± 7	8 ± 7
Pi (mmHg)	122 ± 22	126 ± 22

SBP is systolic blood pressure, As systolic pressure time integral, Ad diastolic pressure time integral, SVI subendocardial viability index, DBP diastolic blood pressure, AI augmentation index, Ti time to inflection point, Ts time to end of systole, Tp time to peak pressure, AP augmentation pressure, and Pi pressure at inflection point. * denotes $P < 0.05$ for difference between subjects with and without diabetes.

3.3.4.2 *Transfer function-derived waveforms*

Errors in the transfer function-derived parameters are presented in Table 3-15. As previously noted, despite relatively small mean errors, neither the transfer function-derived AI nor Ti correlated with the corresponding directly measured parameter using the generalised transfer function. The findings were similar with the diabetes-specific transfer function, and these parameters were therefore not further analysed. Since transfer function-derived AP correlated with measured AP only using the generalised transfer function and only in the group without diabetes it was also not further analysed. As noted in the entire study group, transfer function-derived AI, Ti and AP remained correlated with the radial parameters in this subgroup of subjects without diabetes (AI r^2 = 0.83 ($P < 0.001$), Ti r^2 = 0.13 ($P < 0.05$), AP r^2 = 0.33 ($P < 0.001$)). The findings were unchanged when the diabetes-specific transfer function was applied to those with diabetes (AI r^2 = 0.79 ($P < 0.001$), Ti r^2 = 0.52 ($P < 0.01$), AP r^2 = 0.27 ($P < 0.05$)) (Figure 3-5).

The presence of diabetes mellitus was associated with a greater error in the derivation of central systolic blood pressure using the generalised transfer function (6 ± 7 mmHg and 2 ± 8 mmHg, groups with and without diabetes respectively) ($P < 0.05$) (Figure 3-6). The presence of diabetes mellitus was not associated with a difference in error in the derivation of any other waveform parameter using the generalised transfer function. However, stepwise multiple regression analysis, considering subject age, gender, height, weight, body mass index, the presence of conventional cardiovascular risk factors and heart rate, also revealed the error in As to be associated with body mass index ($P < 0.05$, r^2 = 0.08), SVI with age ($P < 0.05$, r^2 = 0.09), DBP with current smoking, female gender and heart rate ($P < 0.01$, r^2 = 0.28), and Tp with both age and heart rate ($P < 0.05$, r^2 = 0.17) in this group. The use of the diabetes-specific transfer function yielded

a significant improvement in the error in the derived systolic pressure ($P < 0.001$) to 0 ± 7 mmHg, such that the error was no different from that using the generalised transfer function in the group without diabetes. There were also significant improvements using the diabetes-specific transfer function in the error in the derived Ad ($P < 0.01$), diastolic blood pressure ($P < 0.001$), Tp ($P < 0.001$) and Pi ($P < 0.001$) in the group with diabetes. However, as previously noted, the error in most parameters derived using the generalised transfer function was positively associated with the measured value of the parameter, for example the greater the central aortic systolic blood pressure the greater the error in the derived systolic blood pressure, (SBP $r^2 = 0.13$ ($P < 0.01$), As $r^2 = 0.19$ ($P < 0.001$), SVI $r^2 = 0.18$ ($P < 0.001$), Ts $r^2 = 0.11$ ($P < 0.05$), Tp $r^2 = 0.38$ ($P < 0.001$), Pi $r^2 = 0.51$ ($P < 0.001$)). Despite the improvements in mean error, this relationship was not altered by the substitution of the diabetes-specific transfer function-derived values in the group with diabetes. The improvements in error with the use of the diabetes-specific transfer function were not associated with statistically significant changes in the correlation between measured and transfer function-derived parameters.

Table 3-15. Error in transfer function-derived waveform parameters

	No diabetes	Diabetes	
	GTF	GTF	DTF
SBP (mmHg)	2 ± 8 *	6 ± 7	0 ± 7 ***
Ad (mmHg.s)	4.60 ± 3.18	4.41 ± 3.94	1.97 ± 2.64 ** ††
As (mmHg.s)	-0.37 ± 3.43	-0.45 ± 3.72	-0.94 ± 2.83
SVI	0.15 ± 0.22	0.15 ± 0.23	0.10 ± 0.16
DBP (mmHg)	9 ± 2	8 ± 2	5 ± 2 *** †††
AI (%)	-7.1 ± 12.9	-4.9 ± 12.9	-1.4 ± 11.6
Ti (s)	0.014 ± 0.034	-0.006 ± 0.035	-0.002 ± 0.026
Ts (s)	-0.025 ± 0.028	-0.035 ± 0.039	-0.020 ± 0.019
Tp (s)	-0.010 ± 0.026	-0.017 ± 0.023	-0.008 ± 0.021 ***
AP (mmHg)	-7 ± 8	-4 ± 7	-3 ± 7
Pi (mmHg)	9 ± 12	11 ± 11	1 ± 10 *** †

GTF is generalised transfer function, DTF is diabetes-specific transfer function. * denotes $P < 0.05$, ** $P < 0.01$, and *** $P < 0.001$ for significant differences from GTF errors in subjects with diabetes. † denotes $P < 0.05$, †† $P < 0.01$, and ††† = $P < 0.001$ for significant differences from GTF errors in subjects without diabetes. SBP is systolic blood pressure, As systolic pressure time integral, Ad diastolic pressure time integral, SVI subendocardial viability index, DBP diastolic blood pressure, AI augmentation index, Ti time to inflection point, Ts time to end of systole, Tp time to peak pressure, AP augmentation pressure, and Pi pressure at inflection point. Error is measured aortic minus respective reconstructed parameter.

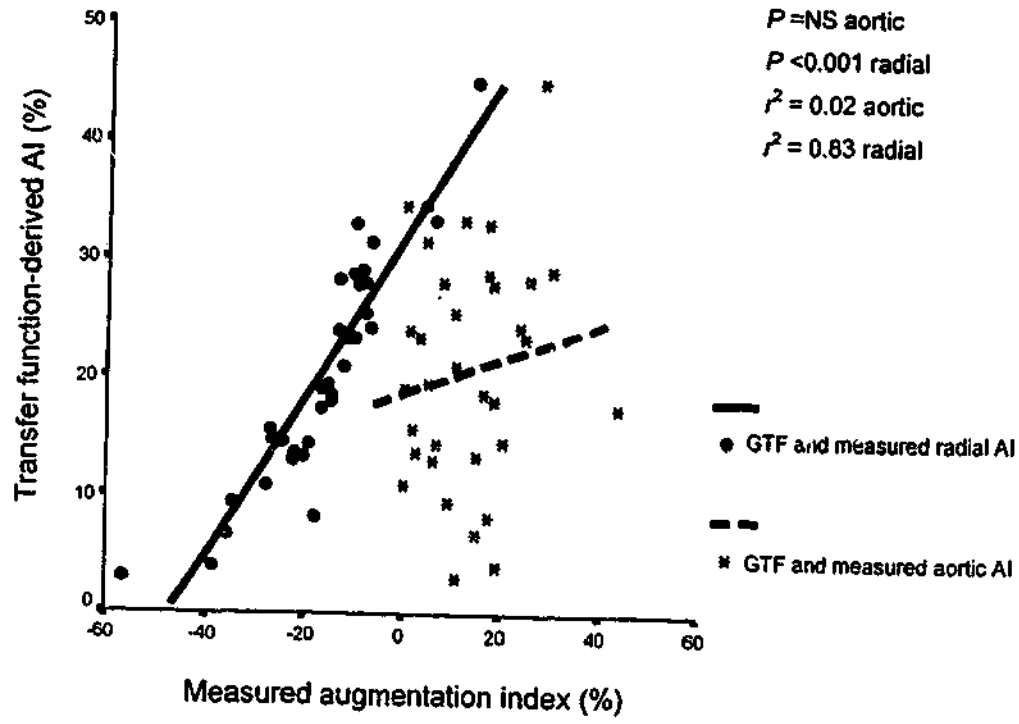


Figure 3-5. Relationship between generalised transfer function-derived and measured radial and aortic augmentation index

GTF is generalised transfer function. AI is augmentation index.

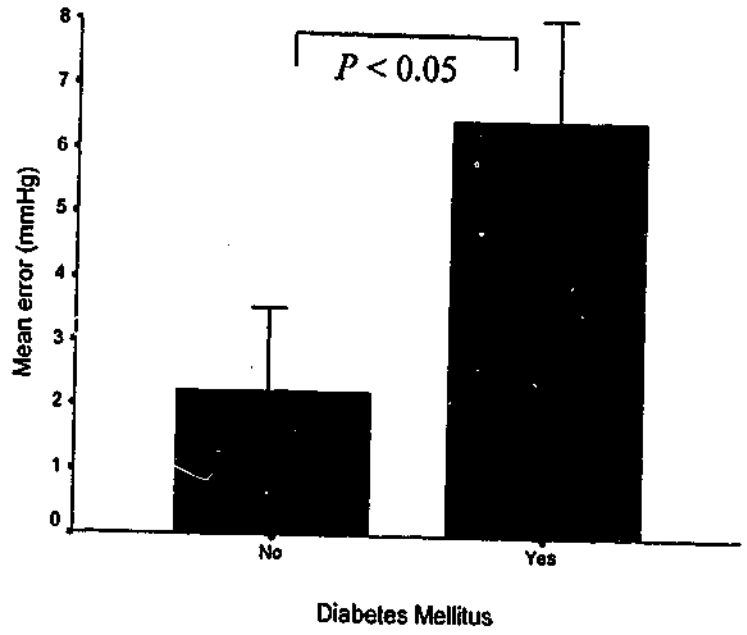


Figure 3-6. Mean error between measured and generalised transfer function-derived systolic pressure in subjects with and without diabetes

Bars represent standard error of the mean. Error is measured aortic minus reconstructed systolic blood pressure.

3.4 DISCUSSION

3.4.1 Applicability of transfer function techniques to the arterial system and technical limitations

Despite the potential departure of the arterial system from the assumptions of linearity and time invariance inherent to the parametric, or Fast Fourier Transform based, methods of derivation of a transfer function, in common with others the findings presented in this chapter demonstrate that waveforms closely resembling the central aortic pressure waveform can be derived by the application of an arterial transfer function to non-invasively acquired radial artery waveforms.(Karamanoglu, *et al.* 1993, Chen, *et al.* 1997, Fetics, *et al.* 1999, Takazawa, *et al.* 1996, Sugimachi, *et al.* 1997) However, in keeping with previous studies, the reconstructed waveform does not perfectly replicate the central aortic waveform, and a number of factors may influence the variability from the measured waveform.(Karamanoglu, *et al.* 1993, Chen, *et al.* 1997, Fetics, *et al.* 1999, Takazawa, *et al.* 1996, Sugimachi, *et al.* 1997) Firstly, there is the inherent variability between individuals which was evident in the individual transfer functions, particularly at the higher frequencies for both magnitude and phase components. Secondly, but specific to Method 1, although the theoretical value of the 1st harmonic is 1, given the assumption of equality of mean pressures, the 1st harmonic of the ensemble average transfer function was significantly less than 1. This might be explained by a number of factors, including chance. However, it is likely to have been influenced by errors in the process of calibrating the radial waveform described in *Section 2.3* or by the handling of the data in the derivation of the transfer function. Welch's method involves the spectral analysis of overlapping data segments within the

complete data set, a total of 31 in the method described, each of which has been subject to a windowing procedure, the Hanning window in this case, and the averaging of the transfer functions derived from each data segment. Although the windowing process generally improves the estimation of the spectra, the procedure itself may have resulted in a systematic loss of data resulting in the 1st harmonic differing from the theoretical value. Any such systematic error might also impact upon the calculated magnitude at other frequencies. This is not a feature of TF_2 since the transfer function derivation was performed on a pair of single pressure waveforms which had been artificially aligned. It is also possible that the number of subjects contributing to any of the transfer functions may have been insufficient to provide a good estimate of the generalised transfer function. This possibility is more likely for the gender-specific, particularly female (17 subjects), and diabetes-specific (19 subjects) transfer functions which are based on relatively small numbers. It should be acknowledged however that the generalised transfer functions presented in the previously published studies have been derived from between 8 and 20 subjects only, and thus if these numbers are insufficient it is a fault that is shared by the previous studies, and is an issue which has not been previously addressed.(Karamanoglu, *et al.* 1993, Chen, *et al.* 1997, Fetics, *et al.* 1999, Sugimachi, *et al.* 1997)

The reconstruction of the central aortic augmentation index, which is predominantly dependent upon high frequency components of the waveform, was particularly poor, as has been previously noted.(Chen, *et al.* 1997, Fetics, *et al.* 1999) It is possible that this is due to limitations in the frequency response characteristics of either the fluid-filled catheter or tonometer systems used for the acquisition of pressure waveform data in this study. Frequency response characteristics of a fluid-filled catheter system are limited compared to the pressure transducer-tipped catheters that have been used in previous studies to derive arterial transfer functions, particularly at the higher frequencies.

However, it should be remembered that the frequency range included in the transfer function is limited, and as discussed previously observations in our own laboratory (Figure 3-7) suggest that the frequency response characteristics of our fluid-filled catheter system and an intravascular micromanometer may be very similar in the clinical setting over the required frequency range. This, and the marked similarity between the transfer function derived in this chapter and that of Fetics *et al* shown in Figure 3-8, which was digitised for comparison, suggest that the frequency response characteristics of the system were adequate for the purposes of this study.(Fetics, *et al.* 1999) It is also possible that high frequency data may have been lost from the radial waveforms. Although findings have differed, it has been suggested that there may be significant loss of data acquired by applanation tonometry of the radial artery pressure waveform at frequencies above 5-6 Hz resulting from the frequency response characteristics of the intervening tissues between the radial artery and the tonometer.(Sato, *et al.* 1993) Although the findings of Kelly *et al* suggest that this may not be a significant factor with a Millar tonometer, these authors have demonstrated a difference between intravascular and tonometry acquired waveforms from the femoral arteries of dogs when the Millar tonometer was applied to the overlying intact skin rather than in direct contact with the artery, clearly demonstrating that the skin and underlying tissues may impact on the quality of pressure waveform reproduction by applanation tonometry.(Kelly, *et al.* 1989) They also found that the lower harmonics contributed relatively more to the waveform recorded by tonometry rather than measured intravascularly, again suggesting that some high frequency data may have been lost using this technique.(Kelly, *et al.* 1989) It is possible therefore that the capacity adequately to reconstruct the central aortic augmentation index from non-invasively acquired radial artery waveforms by the application of a transfer function may be limited by the inherent limitations of arterial applanation tonometry.

Alternatively, accuracy may be limited by the restricted frequency range of the arterial transfer function. Although this could be addressed by increasing the frequency range of the transfer function, all published studies in which arterial transfer functions have been derived have been limited to a similar frequency range.(Chen, *et al.* 1997, Fetics, *et al.* 1999, Karamanoglu, *et al.* 1993, Sugimachi, *et al.* 1997) This is because there is little energy in the arterial pressure waveform at higher frequencies, leading to a decreased signal to noise ratio at high frequencies of the applanated waveform.(Kelly, *et al.* 1989, Sato, *et al.* 1993) Consequently increasing the frequency range would result in inappropriate amplification of noise when waveforms are reconstructed by the application of a transfer function, and would be unlikely to improve the accuracy of reconstructed waveforms.

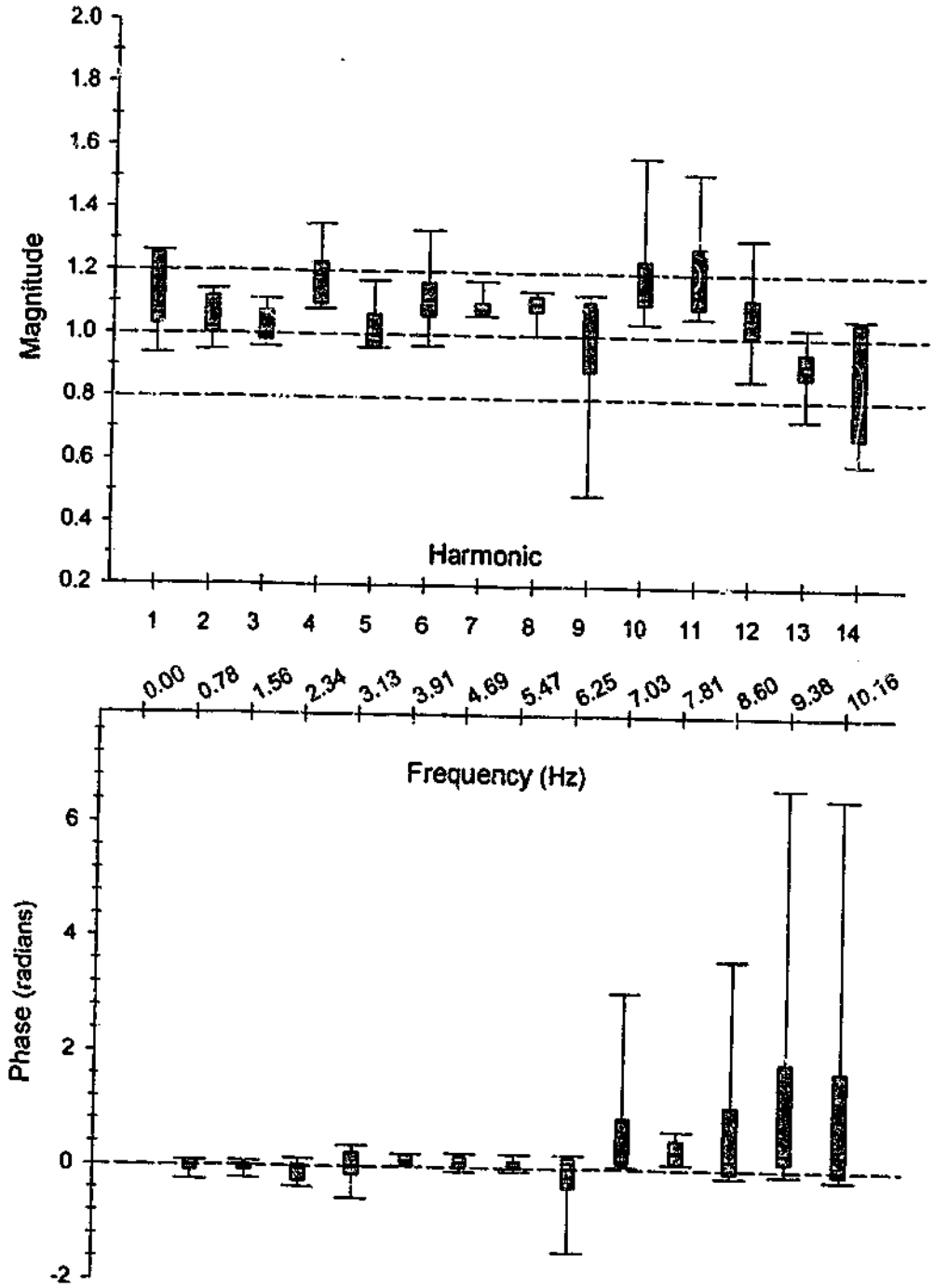


Figure 3-7. Frequency comparison (transfer function) comparing central aortic pressure measured by the fluid-filled catheter system (input) and a RADI pressure wire (output) (RADI Medical Systems, Uppsala, Sweden)

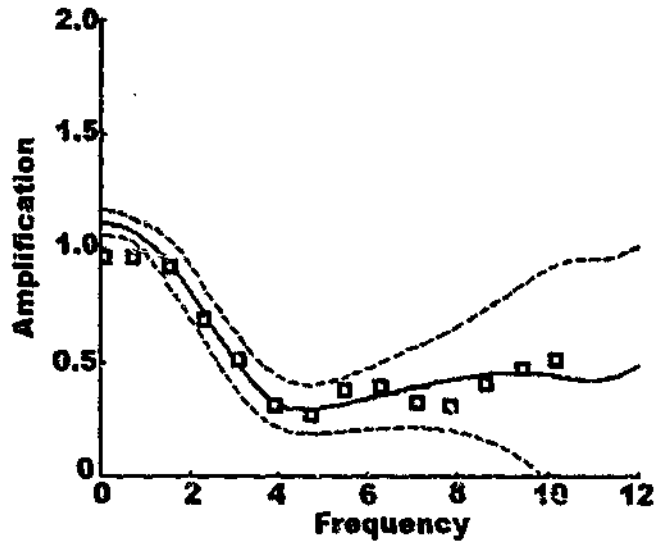


Figure 3-8. Magnitude of transfer function TF_1 compared with that of Fetics *et al*, digitised for comparison.

□ depicts TF_1. Bold line depicts mean and dotted lines the standard deviation of the transfer function of Fetics *et al.*(Fetics, *et al.* 1999) Amplification is magnitude.

3.4.2 Subject characteristics and central aortic waveform parameters

The findings with respect to measured central aortic waveform parameters are in keeping with previously published data, with significant differences in aortic waveform parameters between different subject groups. The longer Ts and lower SVI demonstrated in women have been noted previously,(Gatzka, *et al.* 2001b, Hayward and Kelly 1997), although this appeared to be related to blood pressure in this group. The lower SVI in women, felt to represent an adverse relationship between left ventricular workload and coronary blood flow, has been proposed to contribute to the relatively poorer outcomes in women with cardiovascular disease.(Hayward and Kelly 1997)

Differences were also seen between those subjects with and without diabetes mellitus, with a longer Ti and a trend towards a greater AP and AI in those with diabetes. Although there is no previously published data on measured central aortic waveform parameters in subjects with diabetes, these differences, together with the trend towards lesser peripheral amplification of systolic blood pressure in those with diabetes are as would be expected in a group with stiffer arteries and consequently a higher pulse wave velocity.

The absence of a relationship between subject height and the measured central aortic augmentation index, as has previously been described with carotid artery augmentation index, might be considered surprising. It must however be remembered that the subjects contributing to the studies described were selected by their clinical indication for cardiac catheterisation. As such it is possible that they were also essentially selected on the basis of the adverse effects of altered arterial mechanical properties, and therefore associations with subject demographic features that might be present in an unselected healthy population, or one without symptomatic cardiovascular disease, might be obscured.

3.4.3 The influence of subject characteristics on an ensemble average transfer function

As discussed above, significant differences have been demonstrated in central waveform parameters between different subject groups which may reflect differences in arterial mechanical properties. The premise that a difference in central waveform parameters does not necessarily imply a difference in the relationship between central and radial pressure waveforms has been used to support the proposition that a single

generalised arterial transfer function may be suitable for use in all individuals. However, a difference in arterial mechanical properties, either wall properties or geometry, will influence the propagation of the pressure waveform in terms of velocity, and possibly also in the damping or reflection of different frequency components, between the central aorta and the peripheral arteries, and therefore is likely to be associated with differences in individual transfer functions such that the application of a single generalised arterial transfer function to all subjects may not be appropriate.

Although there is some discrepancy in the literature, there appear to be differences in the mechanical properties of arteries between men and women.(Ahlgren, *et al.* 2001, Amar, *et al.* 2001, Asmar, *et al.* 1997, Gatzka, *et al.* 2001b, Giltay, *et al.* 1999a, Giltay, *et al.* 1999b, Hayward and Kelly 1997, London, *et al.* 1995, Rajzer, *et al.* 1999, Ryden Ahlgren, *et al.* 1995, Smulyan, *et al.* 2001, Sonesson, *et al.* 1994, van der Heijden-Spek, *et al.* 2000, Winer, *et al.* 2001, Yasmin and Brown 1999) The discrepancies are probably in part due to different study populations, the use of different methods of assessment, assessment of different parts of the arterial tree and consideration of different covariables during statistical analysis. The differences between men and women in both mechanical properties and arterial geometry may also be influenced by age, and menopausal status in women.(Karpanou, *et al.* 1996, Lanne, *et al.* 1994, London, *et al.* 1995, Rajkumar, *et al.* 1997a, Smulyan, *et al.* 2001, Sonesson, *et al.* 1993, Staessen, *et al.* 2001, van der Heijden-Spek, *et al.* 2000, Waddell, *et al.* 2001, Westendorp, *et al.* 1999) Changes in these physical properties will be responsible for changes in pulse wave velocity, with differences in different parts of the arterial tree resulting in different regional changes in pulse wave velocity which may differ between men and women.(Lanne, *et al.* 1994, London, *et al.* 1995, Sonesson, *et al.* 1993) The changes in geometry may also result in changes in the distance to any peripheral reflection sites. These factors may all contribute to important differences in the

relationship between peripheral and central pressure waveforms between men and women and are probably reflected in the differences seen in the ensemble average transfer functions derived in the 2 genders and the differences in waveforms reconstructed by the application of generalised, gender-appropriate and gender-inappropriate transfer functions.

The reconstruction of a central waveform by the application of an arterial transfer function requires knowledge of both the magnitude and phase components of the transfer function. Whereas the concept that a change in the magnitude of a transfer function may have a substantial impact on the resultant reconstructed waveform is easily grasped, as discussed earlier the influence of a change in the phase may be less intuitively understood. However, the impact may be equally as important. For example if two sine waves of the same frequency and amplitude are added in phase the resultant waveform is a sine wave of the same frequency but twice the amplitude, whereas if they are added π radians (180°) out of phase the result will be a flat line of magnitude equal to twice the mean value of the two waveforms. Whereas this is an extreme example it serves to illustrate the issue and the potential importance of factors which may influence the phase of the transfer function. If all other factors were equal, including the phase velocities, the phases of a transfer function derived by Method 1 would be linearly related to the distance between the two pressure acquisition sites, such that if transfer functions were derived between the central aorta and the radial artery and between the central aorta and a point half way between the central aorta and radial artery, the phase of the latter transfer function would be half that of the former at all frequencies. This suggests that an ensemble average transfer function derived from a group of subjects with shorter arms would be likely to have a smaller phase at all frequencies than one derived from subjects with longer arms. Although it is unlikely that all other factors will be equal, this probably explains at least in part the difference in phase seen between

male and female subjects (Figure 3-4). Although the phase data contained within the transfer functions derived by Method 2 are similar, the diagrams are less easily interpreted due to the artificial synchronisation of the foot of the pressure waveforms.

Similarly, if all other factors were equal, including the distance between pressure acquisition sites, the phase of a transfer function derived by Method 1 between the 2 sites would be inversely proportional to the phase velocities, such that if the phase velocities were doubled at all frequencies, then the phase of the transfer function would be halved at all frequencies. It has previously been demonstrated that diabetes mellitus is associated with changes in arterial mechanical properties with increased arterial stiffness early in the progression of the disease, before the presence of any discernible vascular complications.(Berry, *et al.* 1999, Salomaa, *et al.* 1995) It is thought that these changes may be caused by both structural changes in the arterial walls caused by abnormal glycation and functional changes associated with relative insulin resistance.(Salomaa, *et al.* 1995) These changes would be expected to be associated with an increase in pulse wave velocity, and are consistent with our findings of a shorter Ti and trend towards a greater AP and AI in those with diabetes. It is therefore likely that pulse wave velocity related differences in transfer function phase may explain at least in part the differences demonstrated between the reconstructed central waveforms derived using the generalised and diabetes-specific transfer functions in subjects with diabetes.

3.4.4 Comparative merits of different methods of transfer function derivation

The results of two similar methods of transfer function derivation have been explored. The methods were selected on the basis of the premise that whereas the best estimate of the average individual arterial transfer function will be obtained by averaging a number of representative transfer functions, the best estimate of the average pressure waveforms will be obtained by averaging a number of representative waveforms. A single transfer function obtained from these average waveforms may therefore ultimately provide a better estimate of the individual transfer function. It is not intuitively clear which of these methods would be most likely to yield the best reconstructed waveforms. Although both methods provide similar transfer function magnitudes, the former method (Method 1) has the advantage that it provides phase diagrams which are more easily interpreted and as discussed above have provided insight into some factors which may influence the applicability of a generalised transfer function to different subject groups. However, since the reconstructed waveforms are derived by the application of a transfer function to an average representative radial artery pressure waveform, conceptually it would seem likely that the application of a transfer function derived from similar data (Method 2) may yield better reconstructed waveforms. In support of this, no significant difference was found between SBP, PP and Ti derived using TF_2 and the measured parameters, although as noted, the relationship between measured and reconstructed Ti was weak, and the correlations between reconstructed and measured parameters did not differ with TF_1 and TF_2. Also, although an inflection point was missing from significantly fewer waveforms reconstructed using TF_2 compared with TF_1, there was no improvement in the accuracy with which the AI was reconstructed on those waveforms on which an inflection point was present. Therefore if there is an

advantage to using TF_2 it appears small on the basis of the data presented in this chapter.

The radial-aortic transfer function was derived in preference to the more mechanistically correct aortic-radial since the inversion of the latter, which is necessary for the reconstruction of aortic from radial waveforms, may be associated with inappropriate amplification of noise. This is supported by the findings of Fetics *et al* who explored the use of both aortic-radial and radial-aortic transfer functions for the reconstruction of central aortic from radial waveforms.(Fetics, *et al.* 1999) However, Fetics *et al* also compared both parametric (autoregressive exogenous) and non-parametric (Fast Fourier Transformation) methods for transfer function derivation and found significant differences between derived transfer functions and disappointing accuracy in central waveform reconstruction with the non-parametric method.(Fetics, *et al.* 1999) In contrast to this transfer function TF_1 is very similar to the parametrically derived radial-aortic transfer function of Fetics *et al.*(Fetics, *et al.* 1999) This might be explained by the better estimate of the individual transfer functions by averaging 31 transfer functions per subject in this study, rather than the averaging of only two by Fetics *et al.*(Fetics, *et al.* 1999) It appears, therefore, that provided a good estimate is obtained of individual transfer functions ensemble average transfer functions obtained from many groups are likely to be very similar.(Fetics, *et al.* 1999, Chen, *et al.* 1997, Karamanoglu, *et al.* 1993) However, it is clear from the data presented in this chapter that relatively subtle differences in transfer functions can have a significant impact on the accuracy of reconstruction of central aortic waveforms. Therefore, although the general similarity between different transfer functions is encouraging, data using one transfer function should not be accepted to validate an alternative but similar transfer function for the reconstruction of central aortic waveforms, nor should a transfer

function be accepted to be equally applicable to subject groups which differ from those in which the transfer function has been previously evaluated.

3.4.5 General validity of arterial transfer functions

The application of a generalised transfer function which is derived from a population mean would be expected to result in a low bias when applied to that population in any derived parameter, as has been demonstrated in these results. This does not however imply validity on an individual basis, as is illustrated by the marked individual scatter apparent for many parameters, despite the relatively small mean differences. This is particularly true of the reconstructed augmentation index which was not correlated with the measured central aortic, but remained closely related to the radial. This close relationship has also been demonstrated by other investigators,(Millasseau, *et al.* 2003) and raises the question as to what is really being presented by authors who have evaluated transfer function-reconstructed augmentation index in various populations.

The data presented in this chapter however cannot contribute to a discussion of the general validity of the application of these transfer functions to any other population. As has previously been noted, the application of a transfer function to data contributing to the derivation of that transfer function simply validates the applied mathematical transformations.(Lehmann 1998) The question of the general validity of any transfer function can only be addressed by the prospective application of the transfer function to a population which has not contributed to its derivation, however, it is likely that the data presented in this chapter provides an indication of the minimum error and individual scatter which might be expected in any other population.

3.5 CONCLUSIONS

Pressure waveforms resembling those in the central aorta may be reconstructed from non-invasively acquired radial waveform data by the application of a generalised arterial transfer function. However, a number of potential limitations of the methods used in this study may have contributed to the significant error and individual variability in reconstructed waveform parameters. Additionally, recognisable individual demographic factors may influence the individual transfer function in such a way that a generalised arterial transfer function may be inappropriate for all subject groups. However, the validity of a generalised arterial transfer function can only be assessed adequately in a study with a prospective design in which the transfer function is assessed in a population which has not contributed to its derivation.

Chapter 4

Prospective validation of radial aortic transfer functions for the derivation of central aortic waveform parameters

TABLE OF CONTENTS

4.1 INTRODUCTION

A number of questions have been raised by the findings and observed study limitations discussed in *Chapter 3*. Several of these are addressed in this chapter. Firstly, as discussed, the application of the transfer function only to radial data from subjects who have contributed to the derivation cannot validate the transfer function for use in other subject groups. This issue is addressed in the prospective design of the studies described in this chapter, together with an exploration of the number of subjects likely to be necessary to contribute to the derivation of a representative generalised arterial transfer function.

As demonstrated in *Chapter 3*, although the application of a generalised arterial transfer function to a non-invasively acquired radial artery pressure waveform yields a reconstructed waveform which closely resembles the measured central aortic, there are significant limitations in its capacity to reconstruct specific features of the central aortic waveform, and particularly the augmentation index. As discussed, since the augmentation index is thought to be dependent upon accurate reconstruction of high frequency components of the waveform (Chen, *et al.* 1997), this may have been due to inadequate frequency response characteristics of the central aortic fluid-filled catheter system used in acquiring the data for the derivation of the transfer function. Although the data discussed in *Chapter 3* suggests that the frequency response characteristics of the system used were adequate for this purpose, this potential limitation has been addressed in these studies by the use of high fidelity pressure transducer tipped catheters for the acquisition of the central aortic data.

Additionally, although the best estimate of both the transfer function between central aortic and radial waveforms and the reconstructed waveforms are likely to be obtained by the method used in *Chapter 3*, that is by the calibration of the radial waveforms to

the measured central aortic pressures, if the technique is to be used entirely non-invasively, the radial waveforms used for waveform reconstruction must be calibrated to non-invasively measured blood pressures, which introduces an additional source of error. The effects of this on the reconstructed waveforms are explored in this chapter, together with the effect on the transfer function of using non-invasively calibrated radial waveforms for its derivation.

4.2 METHODS

4.2.1 Subjects and data acquisition

93 subjects, 64 male, were recruited from amongst those referred to the cardiac catheterisation laboratory for elective coronary angiography or percutaneous coronary interventional procedures. Inclusion and exclusion criteria were as described in *Section 2.1.1*. The study was approved by the Southern Health Human Research Ethics Committee and subjects gave written consent to participate in the study. Subject characteristics, cardiovascular risk factors and drug treatments of the group are presented in Table 4-1 and Table 4-2.

Central aortic waveforms were recorded via a 2 French Millar Mikro-tip® catheter transducer positioned in the ascending aorta simultaneously with non-invasively obtained radial artery waveform data acquired via a Millar® Mikro-tip® tonometer as described in *Section 2.2*, together with 3 contemporaneous non-invasive brachial artery blood pressure measurements (Dinamap™ XL vital signs monitor, Johnson and Johnson Medical Inc, Tampa, Florida). Non-invasive blood pressure measurements were acquired from the contralateral arm during arterial pressure waveform acquisition except in those patients with an arterio-venous fistula for current or previous

haemodialysis, in whom measurements were obtained in the ipsilateral arm immediately following waveform acquisition (5 subjects). The radial waveforms were scaled to both measured aortic and the mean of the non-invasively measured brachial artery mean and diastolic pressures by linear interpolation as described in *Section 2.3*.

Table 4-1. Subject characteristics

Male gender	64 (69%)	**Current smoking**	10 (11%)
Age (years)	61 ± 13	**Diabetes Mellitus**	17 (18%)
Height (m)	1.71 ± 0.09	**Hypertension**	46 (49%)
Weight (kg)	80 ± 14	**Hypercholesterolaemia**	75 (81%)
Body Mass Index (kg/m^2)	28 ± 5	**Obesity (BMI>30)**	19 (20%)
Heart Rate (bpm)	66 ± 11	**Family History**	24 (26%)
SBP (mmHg)	134 ± 23	**DBP (mmHg)**	73 ± 10
MAP (mmHg)	95 ± 15	**Pulse pressure (mmHg)**	61 ± 18

BMI is body mass index, bpm beats per minute, SBP systolic blood pressure, DBP diastolic blood pressure and MAP mean arterial pressure. Blood pressures are non-invasively measured brachial artery pressures.

Table 4-2. Subject drug treatments

β Blocker	51 (55%)	**Statin**	64 (69%)
Ca^{2+} Channel Blocker	21 (23%)	**ACE inhibitor**	36 (39%)
Aspirin	71 (76%)	**AR Blocker**	12 (13%)
Nitrate	22 (24%)	**Diuretic**	13 (14%)

ACE is angiotensin converting enzyme, AR is angiotensin receptor.

4.2.2 Number of subjects required for the derivation of a generalised arterial transfer function

Prior to the commencement of the study all subjects were randomised 1:1 to contribute to either the derivation or validation of an ensemble average transfer function, with an *a priori* intention to review the transfer function obtained from the first 30 subjects randomised to contribute to the derivation. This review was planned to assess whether the inclusion of data from additional subjects was likely to contribute to further improvement in the ensemble average transfer function. Individual transfer functions were derived by Method 1 and Method 2, described in *Section 2.5*, using radial waveforms calibrated to both measured aortic and brachial artery blood pressures. Progressive numbers of transfer functions were averaged from 1 to 30, and the magnitude and phase assessed in terms of absolute values of the mean, the standard error of the mean and percentage change in the mean with increasing numbers of transfer functions included in the average.

Ensemble average transfer functions obtained by Method 1 and Method 2 for the entire group contributing to the derivation using radial waveforms calibrated to aortic blood

pressures were designated as TF_{a1} and TF_{a2} respectively, and to brachial pressures as TF_{b1} and TF_{b2}.

4.2.3 Prospective validation study

All subjects not contributing to the derivation of the transfer functions contributed to this study. Reconstructed central aortic pressure waveforms were derived for each subject by the application of both TF_{a1} and TF_{a2} to representative radial waveforms calibrated to both measured aortic and brachial artery blood pressures, and the application of both TF_{b1} and TF_{b2} to representative radial waveforms calibrated to brachial artery blood pressures. All waveforms, both measured and derived, were analysed as previously described.

4.2.4 Statistical analysis

Categorical variables are presented as number and percentage, and continuous variables as mean ± standard deviation. Differences in subject features between groups were assessed using unpaired t tests, χ^2 tests or Fisher's Exact test as appropriate.(Zar 1984) The effects of averaging increasing numbers of individual transfer functions on the ensemble average transfer function were assessed in terms of absolute mean values, standard error of the mean and percentage change. Differences between parameters of radial and measured central aortic waveforms, and between measured central aortic and reconstructed waveforms were assessed using paired t tests. The relationships between parameters of the radial and measured central aortic and between the measured central aortic and reconstructed waveforms were explored using regression techniques and

Pearson's correlation. Differences in Pearson's correlation coefficients were explored using Fisher's *Z* transformation.

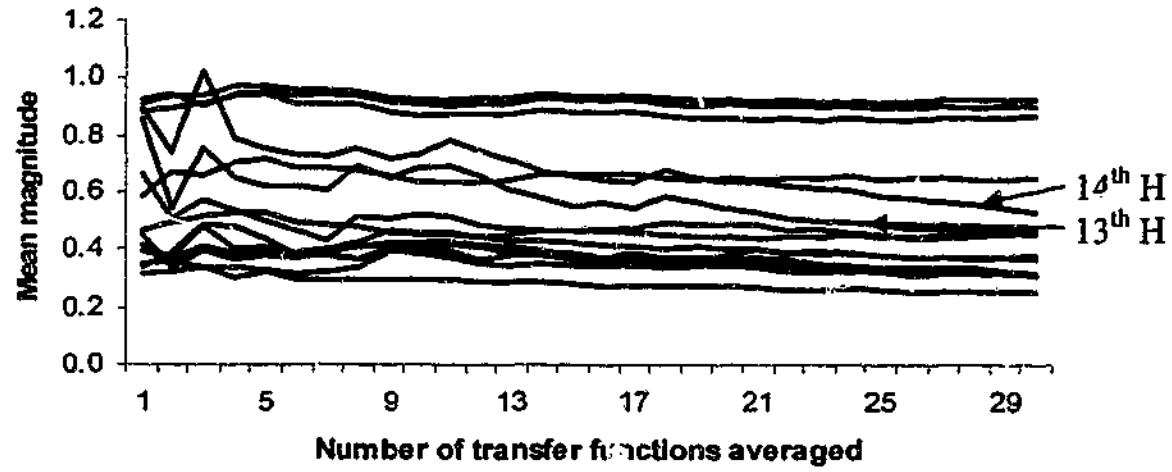
4.3 RESULTS

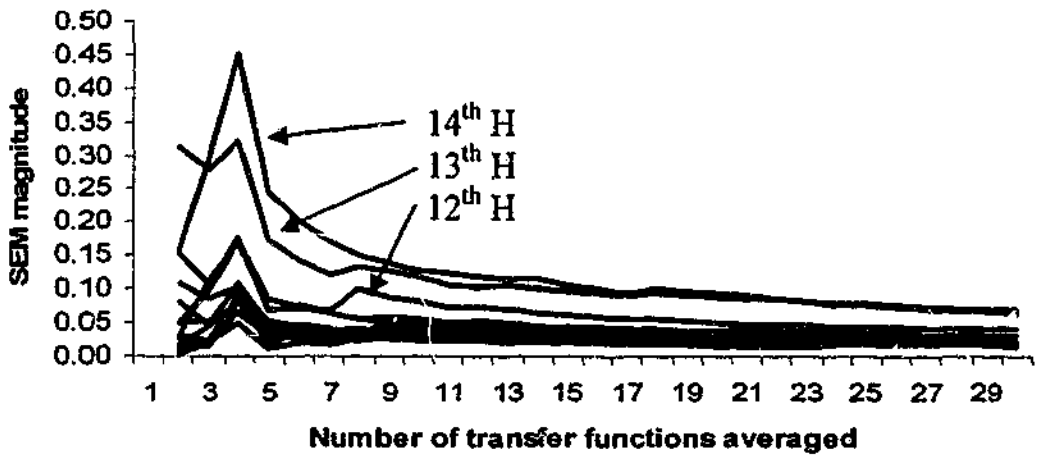
4.3.1 Number of subjects required for the derivation of an arterial transfer function

The changes in the mean magnitude and mean phase of the average transfer function at each harmonic with averaging of progressive numbers of individual transfer functions (Method 1, aortic calibration (TF_{a1})) in terms of the absolute mean, standard error of the mean and percentage change in the mean are presented in Figure 4-1 and Figure 4-2. Although the absolute values differed, particularly for phase, the pattern of change in the mean, standard error of the mean and percentage change in the mean with averaging increasing numbers of transfer functions was similar for transfer functions derived by both Method 1 and Method 2. The mean magnitude and phase of the transfer function derived by Method 2 with averaging of progressive numbers of individual transfer functions is depicted in Figure 4-3. The greatest variability in the magnitude was in the higher harmonics, with little change observed with increasing numbers of transfer functions averaged above approximately 20. There was continued variability in the phases at the higher numbers of transfer functions averaged. However, beyond approximately 20 subjects the percentage change in the phase with increasing numbers of transfer functions averaged was very small for all harmonics except the 2^{nd} and 3^{rd}. However, the absolute values of phase for these harmonics are very small, with very small and stable standard errors of the mean. Given these findings it seemed that although the inclusion of transfer functions from additional subjects beyond the 30

assessed might still influence the ensemble average transfer function, the magnitude of the influence was likely to be small, and that the inclusion of data from further individuals was unlikely to result in significant improvement in any ensemble average transfer function. For this reason the derivation group was limited to the first 30 randomised subjects, and all subsequent subjects, whether initially randomised to the derivation or validation group, contributed to the prospective validation of the ensemble average transfer functions.

The ensemble average transfer functions derived from the 30 subjects contributing to the derivation are depicted in Figure 4-4. It can be seen that although the phases differ significantly, due to the effect of artificially synchronising the waveforms in TF_{a2}, the magnitudes of the 2 transfer functions are very similar. The demographic features of these subjects are presented in Table 4-3, drug therapy in Table 4-4 and measured central aortic and radial (calibrated to measured central aortic pressures) waveform parameters in Table 4-5.





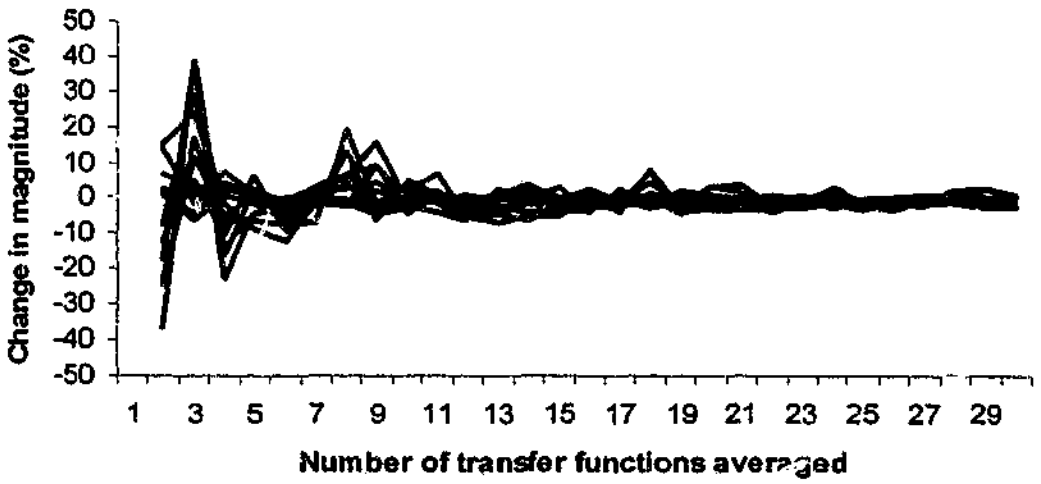
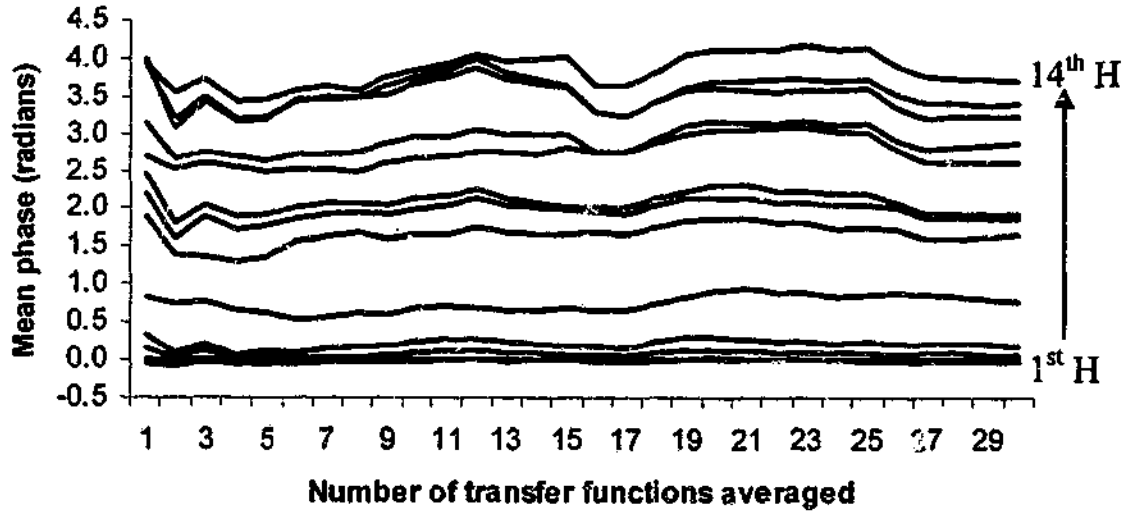
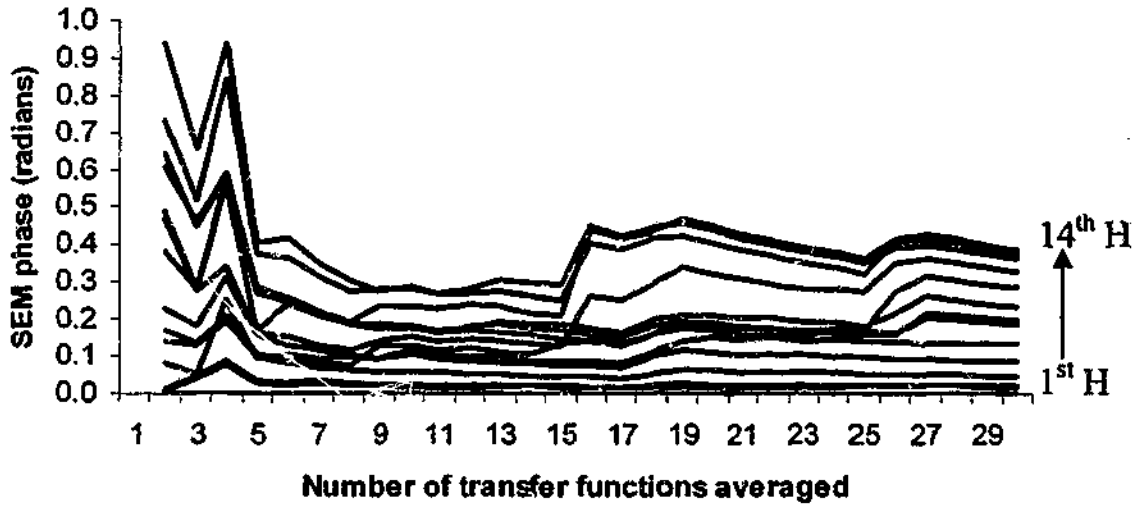


Figure 4-1. Change in mean, standard error of the mean and percentage change in magnitude with increasing numbers of transfer functions averaged (Method 1, aortic calibration of radial waveforms (TF_{a1}))

SEM is standard error of the mean. H is harmonic.





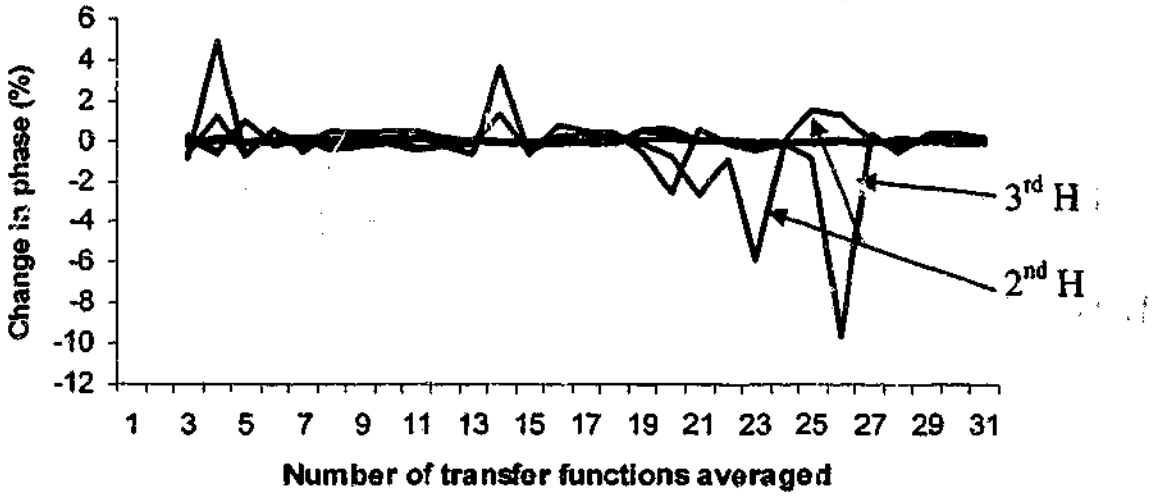


Figure 4-2. Change in mean, standard error of the mean and percentage change in phase with increasing numbers of transfer functions averaged (Method 1, aortic calibration of radial waveforms (TF_{a1}))

SEM is standard error of the mean. H is harmonic.

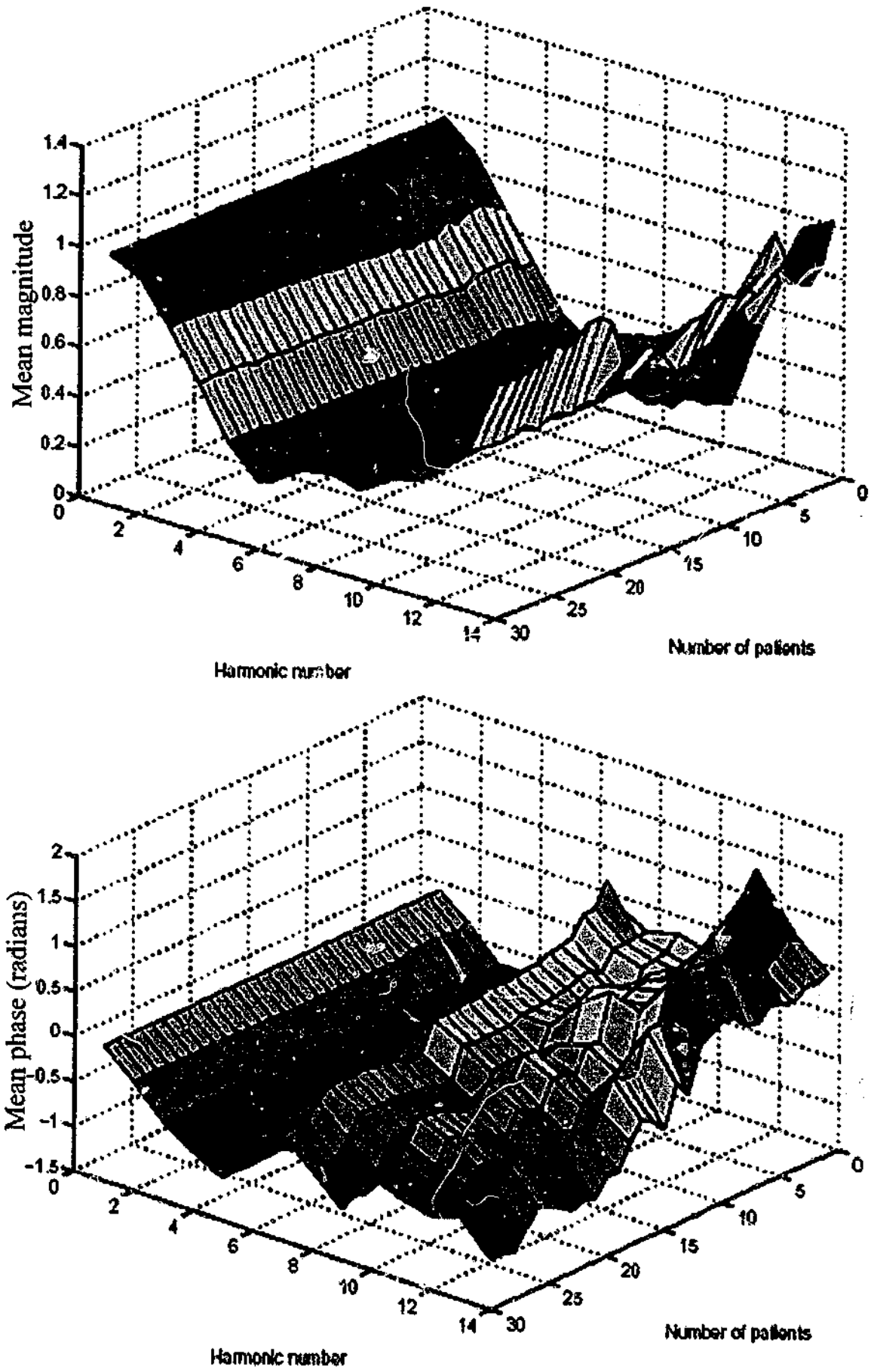


Figure 4-3. Representation of change in mean magnitude and phase of TF_{a2} with increasing numbers of transfer functions averaged.

Depicts little variability in the lower frequencies but significant variability in the higher frequencies, particularly in phase.

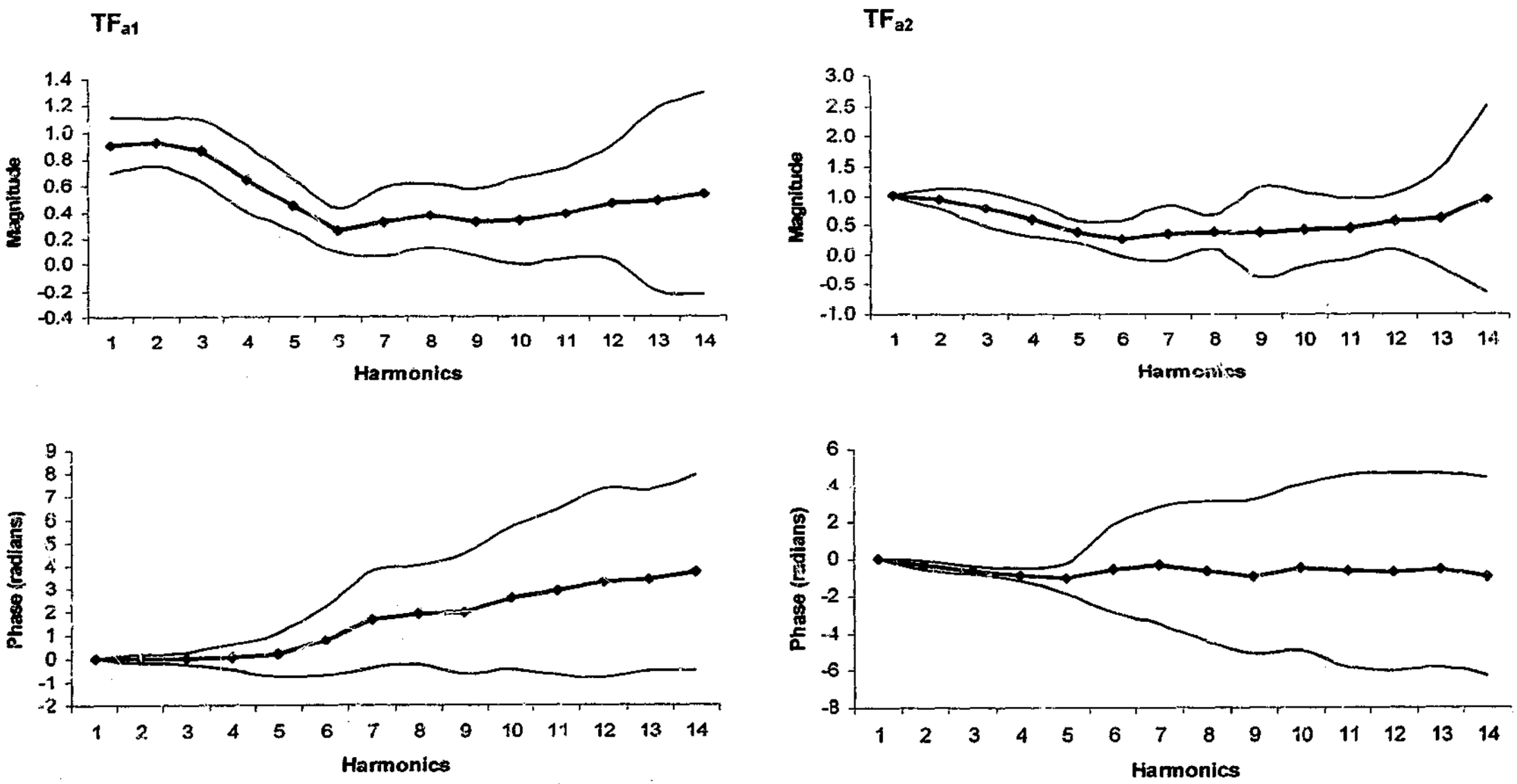


Figure 4-4. Ensemble average transfer functions TF_{a1} and TF_{a2}

Left columns are TF_{a1} and right TF_{a2}. Means and 95% confidence intervals.

Table 4-3. Characteristics of subjects contributing to transfer function derivation

Male gender	19 (63%)	**Current smoking**	4 (13%)
Age (years)	61 ± 16	**Diabetes Mellitus**	5 (17%)
Height (m)	1.70 ± 0.09	**Hypertension**	16 (53%)
Weight (kg)	77 ± 14	**Hypercholesterolaemia**	24 (80%)
Body Mass Index (kg/m^2)	27 ± 4	**Obesity (BMI>30)**	4 (13%)
Heart Rate (bpm)	63 ± 11	**Family History**	6 (20%)
SBP (mmHg)	142 ± 27	**DBP (mmHg)**	74 ± 12
MAP (mmHg)	101 ± 18	**Pulse pressure (mmHg)**	68 ± 20

BMI is body mass index, bpm beats per minute, SBP systolic blood pressure, DBP diastolic blood pressure and MAP mean arterial pressure. Blood pressures are non-invasively measured brachial artery pressures.

Table 4-4. Drug treatments of subjects contributing to transfer function derivation

β Blocker	19 (63%)	**Statin**	18 (60%)
Ca^{2+} Channel Blocker	7 (23%)	**ACE inhibitor**	12 (40%)
Aspirin	20 (67%)	**AR Blocker**	4 (13%)
Nitrate	6 (20%)	**Diuretic**	4 (13%)

ACE is angiotensin converting enzyme, AR is angiotensin receptor.

Table 4-5. Parameters of measured central aortic and radial waveforms in subjects contributing to transfer function derivation

	Aortic	Radial
SBP (mmHg)	138 ± 27	150 ± 24
DBP (mmHg)	70 ± 11	70 ± 11
PP (mmHg)	68 ± 23	80 ± 20
Ad (mmHg.s)	54.45 ± 13.42	52.25 ± 13.52
As (mmHg.s)	39.49 ± 8.86	41.78 ± 9.86
SVI	1.41 ±0.38	1.31 ± 0.50
AI (%)	36.7 ± 20.2	-10.2 ± 19.7
Ti (s)	0.122 ± 0.30	0.165 ± 0.022
Ts (s)	0.341 ± 0.33	0.332 ± 0.40
Tp (s)	0.251 ± 0.031	0.130 ± 0.054

SBP is systolic blood pressure, DBP diastolic blood pressure, PP pulse pressure, Ad diastolic pressure time integral, As systolic pressure time integral, SVI subendocardial viability index, AI augmentation index, Ti time to inflection, Ts time to end of systole and Tp time to peak pressure.

4.3.2 Impact of the method of radial waveform calibration on the derived transfer function

Comparison of transfer functions derived using radial waveforms that had been calibrated to aortic and brachial pressures revealed that although, as expected, the phase was identical at all frequencies, there were small but significant differences in the magnitude at all frequencies (13^{th} harmonic $P < 0.01$, all other harmonics $P < 0.001$). The magnitudes of both TF_{a1} and TF_{b1} are presented in Figure 4-5. The ratio of the magnitudes at all harmonics was the same, and was the same as the scaling factor between the invasively and non-invasively scaled radial waveforms. As the mean pressures did not differ, the scaling factor was entirely determined by the difference in diastolic pressures between the 2 measured blood pressures.

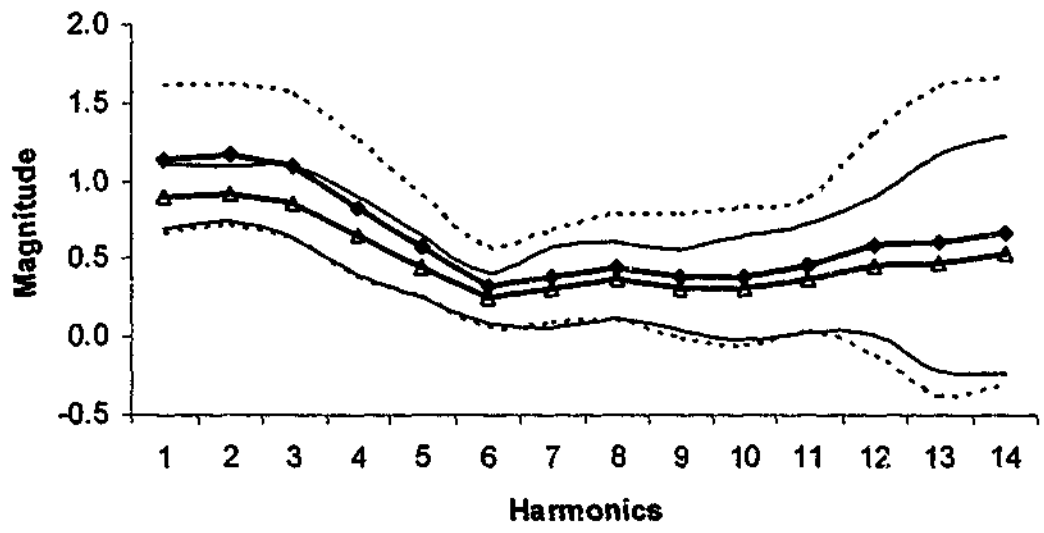


Figure 4-5. Magnitude of transfer functions TF_{a1} and TF_{b1}

△ mean and——— 95% confidence intervals for TF_{a1}, ◆mean and ------ 95% confidence intervals for TF_{b1}.

4.3.3 Prospective validation study

63 subjects, 45 male, contributed to this study. The characteristics and drug treatments of this subgroup are presented in Table 4-6 and Table 4-7. Although this group had lower brachial artery systolic, mean arterial and pulse pressures (all $P < 0.05$), it did not differ from the group that contributed to the derivation of the transfer function in any other subject characteristics or drug treatments.

Table 4-6. Subject characteristics of validation group

Male gender	45 (71%)	**Current smoking**	6 (10%)
Age (years)	61 ± 11	**Diabetes Mellitus**	12 (19%)
Height (m)	1.71 ± 0.09	**Hypertension**	30 (48%)
Weight (kg)	82 ± 14	**Hypercholesterolaemia**	51 (81%)
Body Mass Index (kg/m^2)	28 ± 5	**Obesity (BMI>30)**	15 (24%)
Heart Rate (bpm)	67 ± 11	**Family History**	18 (29%)
Systolic blood pressure	130 ± 19	**Diastolic blood pressure**	73 ± 10
Mean arterial pressure	93 ± 13	**Pulse pressure**	57 ± 17

BMI is body mass index and bpm beats per minute. Blood pressures are non-invasively measured brachial artery pressures.

Table 4-7. Drug treatments of validation group

β Blocker	32 (51%)	**Statin**	46 (73%)
Ca^{2+} Channel Blocker	14 (22%)	**ACE inhibitor**	24 (38%)
Aspirin	51 (81%)	**AR Blocker**	8 (13%)
Nitrate	16 (25%)	**Diuretic**	9 (14%)

ACE is angiotensin converting enzyme, AR is angiotensin receptor.

4.3.3.1 Reconstructed waveform characteristics

Parameters of the directly measured central aortic waveforms together with those of the waveforms reconstructed using TF_{a1} and TF_{a2} are presented in Table 4-8 and Table 4-9 respectively. There was no difference between the parameters reconstructed from invasively and non-invasively calibrated radial waveforms in any of the time parameters or augmentation index with either transfer function, TF_{a1} and TF_{a2}. Although most parameters of the reconstructed waveforms were correlated with the respective parameters of the directly measured central aortic waveforms, there were significant differences in most parameters between the measured aortic and waveforms reconstructed using both transfer functions, TF_{a1} and TF_{a2}, from radial waveforms calibrated to both invasively and non-invasively measured blood pressures. The exceptions were As reconstructed using TF_{a1}, and systolic blood pressure and the time to peak pressure reconstructed using TF_{a2} from either calibrated radial waveform, and pulse pressure reconstructed using TF_{a2} from the invasively calibrated radial waveform only. The difference between the diastolic pressures of the measured aortic and TF_{a2} reconstructed waveforms from invasively calibrated radial waveforms was small and unlikely to be of clinical significance. In this group the reconstruction of AI was poor,

with a correlation only between measured and reconstructed AI for waveforms reconstructed using TF_{a1} and invasively calibrated radial waveforms. Consistent with previously presented data, the AI of the reconstructed waveforms remained correlated with the AI of the radial waveforms ($r^2 = 0.32$ ($P < 0.001$) and $r^2 = 0.07$ ($P < 0.05$), TF_{a1} reconstructed waveforms from invasively and non-invasively calibrated radial waveforms respectively, and $r^2 = 0.17$ and $r^2 = 0.19$ (both $P < 0.001$), TF_{a2} reconstructed waveforms from invasively and non-invasively calibrated radial waveforms respectively), although less strongly than waveforms reconstructed using TF_1 (Figure A-1, Appendix A) (all $P < 0.001$).

Parameters of the directly measured central aortic waveforms together with those of the waveforms reconstructed using TF_{b1} and TF_{b2} from non-invasively calibrated radial waveforms are presented in Table 4-10. Generally there was a similar or greater difference and individual variability between parameters of directly measured aortic waveforms and waveforms reconstructed using these transfer functions than parameters of waveforms reconstructed using TF_{a1} or TF_{a2} applied to either invasively or non-invasively calibrated radial waveforms. Correlation between parameters of measured and reconstructed waveforms was no different from that between measured aortic and waveforms reconstructed by the application of TF_{a1} and TF_{a2} to non-invasively calibrated radial waveforms, with the exception that a statistically significant, although weak, correlation was apparent for AI, with both TF_{b1} and TF_{b2}.

The error in most parameters of the reconstructed waveforms was related to the absolute value of the measured central aortic waveform, such that the greater the measured value, the greater the error of the reconstructed waveform parameter (waveforms reconstructed using invasively calibrated radial waveforms and TF_{a1} SBP $P < 0.001$ $r^2 = 0.20$, DBP $P < 0.05$ $r^2 = 0.06$, Ad $P < 0.01$ $r^2 = 0.11$, As $P < 0.001$ $r^2 = 0.33$, SVI $P < 0.001$ $r^2 = 0.17$, AI $P < 0.001$ $r^2 = 0.47$, Ti $P < 0.001$ $r^2 = 0.30$, Ts $P < 0.001$ $r^2 = 0.46$, Tp $P < 0.001$ r^2

= 0.41, using invasively calibrated radial waveforms and TF_{a2} SBP $P < 0.01$ $r^2 = 0.15$, PP $P < 0.05$ $r^2 = 0.07$, As $P < 0.05$ $r^2 = 0.10$, SVI $P < 0.01$ $r^2 = 0.11$, AI $P < 0.001$ $r^2 = 0.57$, Ti $P < 0.001$ $r^2 = 0.30$, Ts $P < 0.001$ $r^2 = 0.45$, Tp $P < 0.01$ $r^2 = 0.15$). The result of this is that in individuals in whom a given measured waveform parameter has a high value, the parameter is underestimated, and for those with a low value it is overestimated, in the reconstructed waveforms. Examples of the relationship are illustrated for SBP and AI for TF_{a1} reconstructed waveforms in Figure 4-6. The findings were similar for waveforms reconstructed from non-invasively calibrated radial waveforms. The use of transfer functions derived from non-invasively calibrated radial waveforms resulted in no relationship between the error in SBP estimation and measured aortic SBP, however the findings were similar for other waveform parameters. The error in the reconstruction of AI was not related to the error in the reconstruction of systolic or pulse pressures. However, the error in the reconstruction of systolic pressure was strongly related to the peripheral amplification of systolic pressure between the central aorta and radial artery ($P < 0.001$ $r^2 = 0.70$ TF_{a1} and $P < 0.001$ $r^2 = 0.67$ TF_{a2}) (Figure 4-7). Findings were similar for the relationship between the error in the reconstruction of pulse pressure and the peripheral amplification of pulse pressure ($P < 0.001$ $r^2 = 0.70$ TF_{a1} and $P < 0.001$ $r^2 = 0.67$ TF_{a2}).

The error in the reconstruction of central aortic systolic pressure was also inversely related to the foot-to-foot delay in the pressure waveform between the central aorta and radial artery for all transfer functions applied to radial waveforms calibrated to both invasive aortic and non-invasive brachial artery blood pressures ($P < 0.001$ $r^2 = 0.33$ TF_{a1} and $P < 0.001$ $r^2 = 0.30$ TF_{a2} applied to invasively calibrated radial waveforms), with the regression equation suggesting an error of approximately zero for an average aortic-radial delay (Figure 4-8). The findings were similar for the pulse pressure ($P < 0.01$ $r^2 = 0.26$ TF_{a1} and $P < 0.001$ $r^2 = 0.31$ TF_{a2} applied to invasively calibrated radial

waveforms). This was also associated with a positive relationship between the error in the reconstruction of Tp and the aortic-radial delay ($P < 0.001$ $r^2 = 0.20$ TF_{a1} and $P < 0.001$ $r^2 = 0.26$ TF_{a2} applied to invasively calibrated radial waveforms) (Figure 4-9). These associations might be explained by the relationship between the foot-to-foot delay and the peripheral amplification of both systolic blood pressure and pulse pressure (both $P < 0.001$). There was no consistent association between the error in any other waveform parameter and the aortic-radial delay. It is interesting to note particularly that there was no association with the error in the reconstruction of the augmentation index, although there was an association with the error in reconstruction of Ti with TF_{a2} only ($P < 0.05$ $r^2 = 0.08$ from invasively calibrated radial waveforms and $P < 0.05$ $r^2 = 0.07$ from non-invasively calibrated radial waveforms). Other associations were limited to DBP TF_{a2} ($P < 0.01$ $r^2 = 0.12$) and SVI TF_{a1} ($P < 0.05$ $r^2 = 0.07$) both applied to invasively calibrated radial waveforms only. Although similar relationships between the error in reconstruction of SBP and arm length were apparent they reached statistical significance only for transfer functions applied to non-invasively calibrated radial waveforms ($P < 0.01$ $r^2 = 0.15$ TF_{a1} and $P < 0.01$ $r^2 = 0.16$ TF_{a2}).

Comparison of the waveforms reconstructed by the application of TF_{a1} and TF_{a2} to radial waveforms calibrated to both invasive and non-invasive pressures revealed that the errors in several parameters differed significantly (SBP, DBP, PP, Ad, As all $P < 0.001$ and Tp $P < 0.01$). For waveforms reconstructed from invasively calibrated radial waveforms, with the exception of As, the errors for all parameters were smaller with TF_{a2}, whereas with non-invasively calibrated radial waveforms errors were smaller with TF_{a2} for SBP, Ad and Tp. For diastolic blood pressure TF_{a1} was associated with an underestimation of 6 ± 6 mmHg whereas TF_{a2} was associated with an overestimation of 6 ± 6 mmHg, which resulted in a smaller error in pulse pressure with TF_{a1}.

An alternative approach to the analysis of the augmentation index is to consider the classification proposed by Murgo *et al*, in which an augmentation index of > 12% is classified as type A, of > 0 and ≤ 12% as type B and ≤ 0% as type C.(Murgo, *et al.* 1980) The proportion of subjects with measured central aortic augmentation index in these categories in the derivation and validation groups did not differ (26, 4, 0 and 56, 5 and 2, types A, B and C in the derivation and validation groups respectively). When the augmentation indices of the reconstructed waveforms were considered, the proportions classified to types A, B and C were similar to those of the measured central aortic augmentation indices in both the derivation and validation groups for all 6 reconstructed waveforms presented in this chapter (TF_{a1} and TF_{a2} applied to radial data calibrated to both invasive and non-invasive blood pressures and TF_{b1} and TF_{b2} applied to radial data calibrated to non-invasive blood pressures). However, whereas at first sight this might suggest that individuals were correctly categorised, further analysis revealed that although between 70 and 86% of subjects were correctly categorised, depending upon the particular reconstructed waveform, of those individuals that should have been classified to type C, none were correctly categorised in any reconstructed waveform, and of those individuals that should have been classified to type B, between 0 and 60% were correctly classified. Indeed, if those subjects with measured central aortic augmentation index of either type B or type C were considered together, on average 74% (range 57 – 100%) of these subjects were incorrectly classified on the basis of reconstructed waveforms as having an augmentation index of type A.

Table 4-8. Parameters of measured central aortic waveforms and waveforms reconstructed using TF_{a1} from invasively and non-invasively calibrated radial waveforms

	Measured	Invasive calibration		Non-invasive calibration	
Parameter	**Aortic**	**Mean difference**	**Pearson's *r***	**Mean difference**	**Pearson's *r***
SBP (mmHg)	125 ± 20	6 ± 8 ***	0.92 ***	9 ± 12 *** ††	0.82 ***
DBP (mmHg)	66 ± 9	11 ± 2 ***	0.97 ***	6 ± 6 *** †††	0.76 ***
PP (mmHg)	58 ± 17	-5 ± 9 ***	0.88 ***	3 ± 13 * †††	0.76 ***
As (mmHg.s)	35.33 ± 6.84	0.02 ± 3.10	0.89 ***	-0.08 ± 4.39	0.78 ***
Ad (mmHg.s)	47.53 ± 10.89	7.31 ± 2.89 ***	0.96 ***	6.05 ± 6.03 *** ††	0.94 ***
SVI	1.37 ± 0.29	0.22 ± 0.19 ***	0.77 ***	0.18 ± 0.22 *** †	0.72 ***
AI (%)	27.5 ± 15.6	4.7 ± 16.0 *	0.35 **	5.4 ± 18.7 *	0.21
Ti (s)	0.150 ± 0.025	-0.019 ± 0.030 ***	0.30 *	-0.023 ± 0.046 ***	0.12
Tp (s)	0.252 ± 0.034	-0.007 ± 0.022 *	0.76 ***	-0.009 ± 0.022 **	0.78 ***
Ts (s)	0.332 ± 0.033	-0.032 ± 0.028 ***	0.57 ***	-0.035 ± 0.030 ***	0.48 ***

Mean difference is measured aortic minus reconstructed waveform value. * denotes $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$ for difference from, or correlation with respective measured aortic parameter. † denotes $P < 0.05$, †† $P < 0.01$ and ††† $P < 0.001$ for difference from derived parameters using invasively calibrated radial waveform. SBP is systolic blood pressure, DBP diastolic blood pressure, PP pulse pressure, Ad diastolic pressure time integral, As systolic pressure time integral, SVI subendocardial viability index, AI augmentation index, Ti time to inflection, Ts time to end of systole and Tp time to peak pressure.

Table 4-9. Parameters of measured central aortic waveforms and waveforms reconstructed using TF_{a2} from invasively and non-invasively calibrated radial waveforms

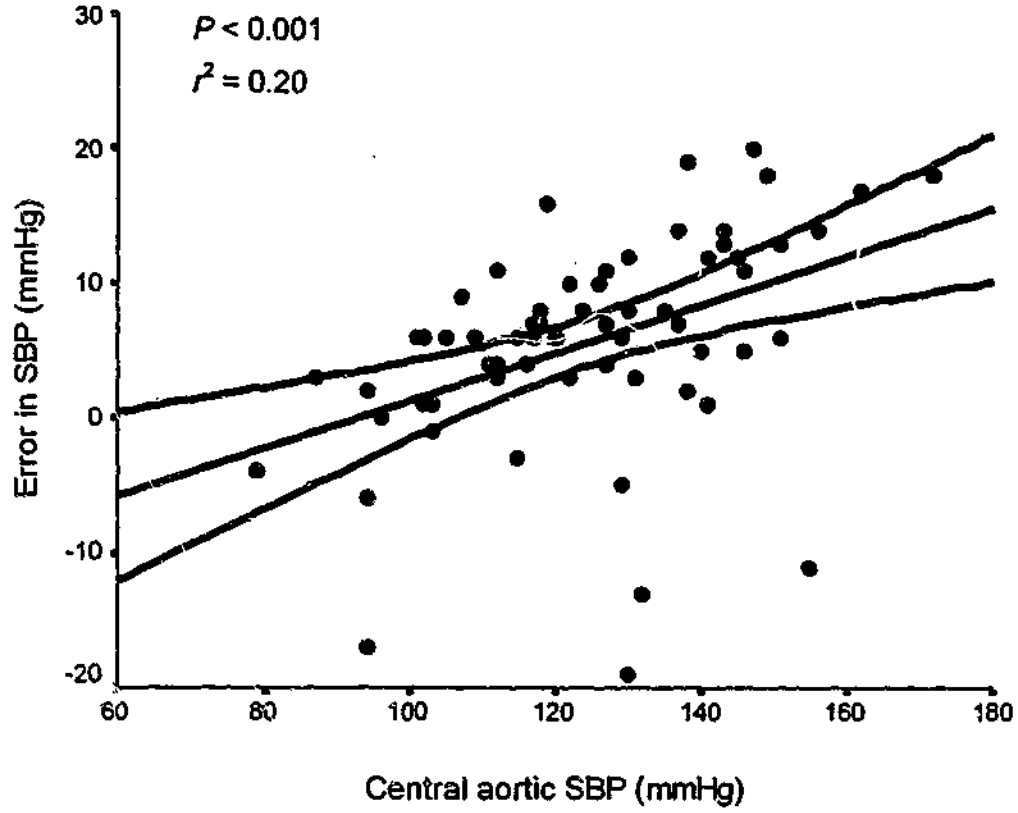
	Measured	Invasive calibration		Non-invasive calibration	
Parameter	**Aortic**	**Mean difference**	**Pearson's *r***	**Mean difference**	**Pearson's *r***
SBP (mmHg)	125 ± 20	-1 ± 7	0.93 ***	2 ± 11 †	0.83 ***
DBP (mmHg)	66 ± 9	-1 ± 1 ***	0.99 ***	-6 ± 6 *** †††	0.79 ***
PP (mmHg)	58 ± 17	0 ± 8	0.89 ***	8 ± 12 *** †††	0.77 ***
As (mmHg.s)	35.33 ± 6.84	-4.01 ± 4.43 ***	0.79 ***	-3.86 ± 5.80 ***	0.70 ***
Ad (mmHg.s)	47.53 ± 10.89	3.66 ± 4.39 ***	0.93 ***	1.90 ± 5.13 ** ††	0.90 ***
SVI	1.37 ± 0.29	0.23 ± 0.25 ***	0.66 ***	0.18 ± 0.25 *** ††	0.65 ***
AI (%)	27.5 ± 15.6	7.9 ± 18.0 ***	0.18	6.2 ± 20.1 *	0.00
Ti (s)	0.130 ± 0.025	-0.018 ± 0.035 ***	0.18	-0.014 ± 0.041 **	-0.04
Tp (s)	0.252 ± 0.034	-0.001 ± 0.030	0.64 ***	-0.003 ± 0.029	0.67 ***
Ts (s)	0.332 ± 0.033	-0.037 ± 0.043 ***	0.13	-0.037 ± 0.042 ***	0.29 *

Mean difference is measured aortic minus reconstructed waveform value. * denotes $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$ for difference from, or correlation with respective measured aortic parameter. † denotes $P < 0.05$, †† $P < 0.01$ and ††† $P < 0.001$ for difference from derived parameters using invasively calibrated radial waveform. SBP is systolic blood pressure, DBP diastolic blood pressure, PP pulse pressure, Ad diastolic pressure time integral, As systolic pressure time integral, SVI subendocardial viability index, AI augmentation index, Ti time to inflection, Ts time to end of systole and Tp time to peak pressure

Table 4-10. Parameters of measured central aortic waveforms and waveforms reconstructed using TF_{b1} and TF_{b2} from non-invasively calibrated radial waveforms

Parameter	Measured Aortic	Mean difference (TF_{b1})	Pearson's *r*	Mean difference (TF_{b2})	Pearson's *r*
SBP (mmHg)	125 ± 20	-2 ± 14 ***	0.82 ***	-7 ± 13 *** †††	0.82 ***
DBP (mmHg)	66 ± 9	-9 ± 7 ***	0.76 ***	-2 ± 6 ** †††	0.78 ***
PP (mmHg)	58 ± 17	-12 ± 16 ***	0.75 ***	-4 ± 14 * †††	0.76 ***
As (mmHg.s)	35.33 ± 6.84	-8.83 ± 4.52 ***	0.80 ***	-5.44 ± 6.10 *** †††	0.66 ***
Ad (mmHg.s)	47.53 ± 10.89	-5.49 ± 5.45 ***	0.93 ***	2.30 ± 4.72 *** †††	0.92 ***
SVI	1.37 ± 0.29	0.16 ± 0.21 ***	0.75 ***	0.23 ± 0.26 *** †††	0.62 ***
AI (%)	27.5 ± 15.6	-0.5 ± 16.9	0.33 *	5.0 ± 15.8 * †††	0.31 *
Ti (s)	0.130 ± 0.025	-0.010 ± 0.032 *	0.28 *	-0.008 ± 0.030 *	0.20
Tp (s)	0.252 ± 0.034	-0.007 ± 0.023	0.74 ***	-0.0002 ± 0.024 ††	0.73 ***
Ts (s)	0.332 ± 0.033	-0.032 ± 0.029 ***	0.52 ***	-0.035 ± 0.043 ***	0.14

Mean difference is measured aortic – reconstructed waveform value. * denotes $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$ for difference from, or correlation with respective measured aortic parameter. †† denotes $P < 0.01$ and ††† $P < 0.001$ for difference from derived parameters using TF_{b1}. SBP is systolic blood pressure, DBP diastolic blood pressure, PP pulse pressure, Ad diastolic pressure time integral, As systolic pressure time integral, SVI subendocardial viability index, AI augmentation index, Ti time to inflection, Ts time to end of systole and Tp time to peak pressure.



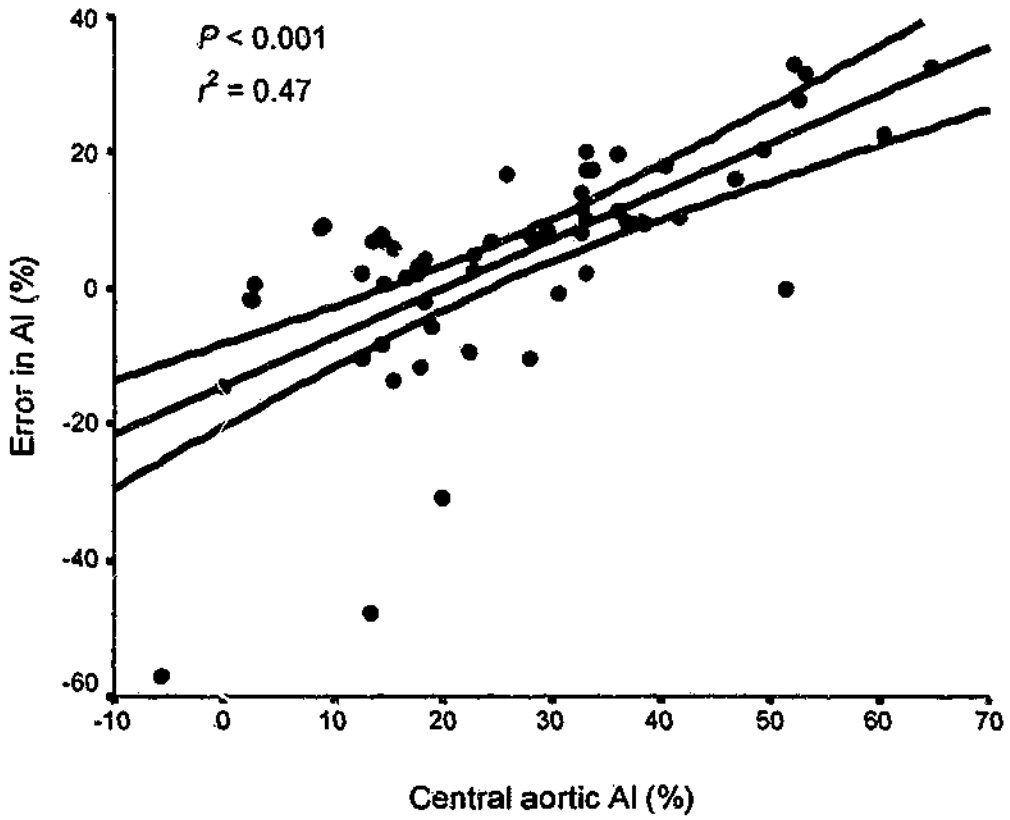


Figure 4-6. Relationships between the error in the reconstruction of systolic blood pressure and augmentation index and measured central aortic parameters

Error is measured aortic minus corresponding TF_{a1} reconstructed parameter. SBP is systolic blood pressure, AI augmentation index.

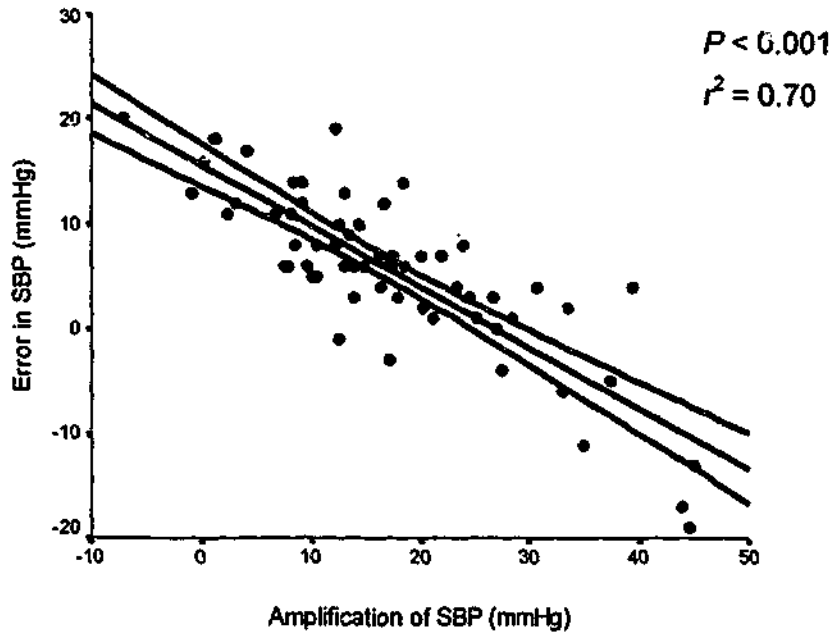


Figure 4-7. Relationship between the error in reconstruction of systolic blood pressure and peripheral amplification of systolic blood pressure

Error is measured aortic minus TF_{a1} reconstructed systolic blood pressure. Amplification is radial minus measured aortic systolic blood pressure. SBP is systolic blood pressure.

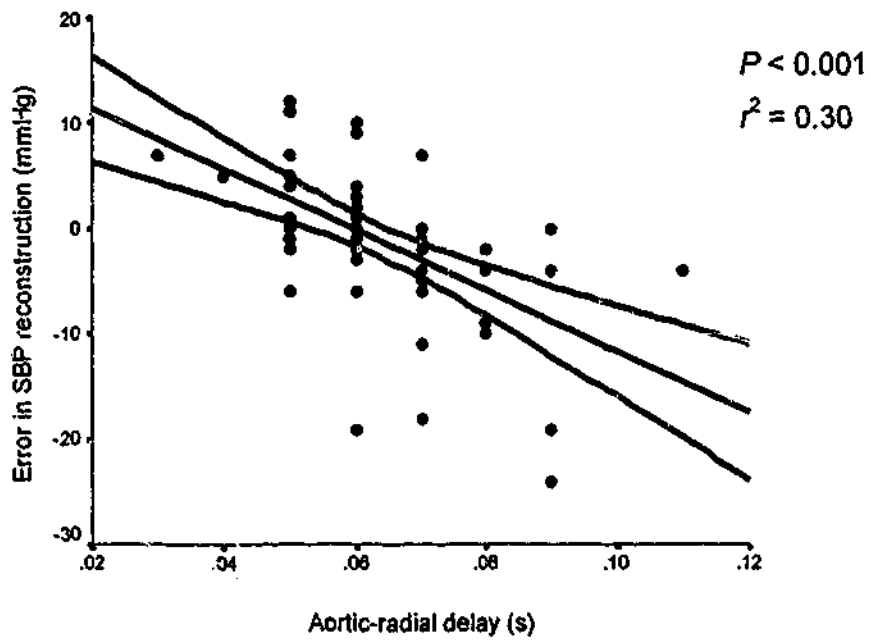


Figure 4-8. Relationship between the error in reconstruction of systolic blood pressure and aortic-radial delay (TF_{a2} from invasively calibrated radial waveform)

Error is measured aortic minus TF_{a2} reconstructed systolic blood pressure. SBP is systolic blood pressure.

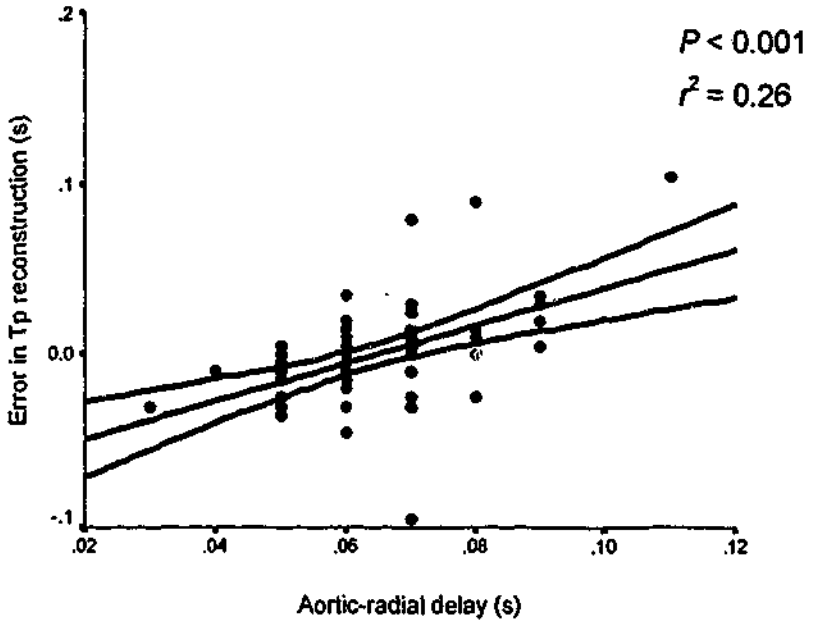


Figure 4-9. Relationship between the error in reconstruction of the time to peak pressure and aortic-radial delay (TF_{a2} from invasively calibrated radial waveforms)

Error is measured aortic minus TF_{a2} reconstructed time to peak pressure. Tp is time to peak pressure

4.3.3.2 The impact of gender and diabetes mellitus on reconstructed waveforms

There were significant differences in the error in the reconstruction of a number of waveform parameters with gender, particularly when reconstructed from radial waveforms calibrated to non-invasive brachial artery pressures (Table 4-11 and Table 4-12). Of particular note were the errors in the reconstruction of systolic blood pressure from non-invasively calibrated radial waveforms, 6 ± 12 mmHg and 17 ± 8 mmHg (P = 0.001) (male and female subjects respectively, waveforms reconstructed using TF_{a1}) (Figure 4-10) and -1 ± 11 mmHg and 10 ± 8 mmHg ($P < 0.001$) (male and female subjects respectively, waveforms reconstructed using TF_{a2}). These differences were consistent with the errors in the reconstruction of Tp in the same waveforms, -0.005 ±

0.023 s and -0.019 ± 0.012 s ($P < 0.05$) (male and female subjects respectively, waveforms reconstructed using TF_{a1}) (Figure 4-11) and 0.002 ± 0.031 s and -0.016 ± 0.016 s ($P < 0.05$) (male and female subjects respectively, waveforms reconstructed using TF_{a2}). These findings are consistent with the trend to a shorter foot-to-foot delay between central aortic and radial artery waveforms in the female subjects (0.066 ± 0.014 s and 0.059 ± 0.012 s, male and female subjects respectively ($P = 0.08$)).

Although the differences in the reconstruction of systolic blood pressure between subjects with and without diabetes mellitus were consistent with those seen in *Chapter 3*, the differences did not reach statistical significance, probably due to the small number of subjects with diabetes mellitus in this group (12) (Figure 4-12).

Table 4-11. Errors in male and female subjects in the reconstruction of central aortic waveform parameters from non-invasively calibrated radial waveforms

	Mean error	
	Female	**Male**
TF_{a1}		
SBP (mmHg) **	17 ± 8	6 ± 12
DBP (mmHg) *	9 ± 6	5 ± 6
Tp (s) *	-0.019 ± 0.012	-0.005 ± 0.023
As (mmHg.s) **	2.65 ± 3.17	-1.11 ± 4.36
SVI *	0.09 ± 0.15	0.22 ± 0.23
TF_{a2}		
SBP (mmHg) ***	10 ± 8	-1 ± 11
DBP (mmHg) **	-3 ± 6	-7 ± 6
Tp (s) *	-0.16 ± 0.016	0.002 ± 0.031

* denotes $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$ for difference in error between male and female subjects. Error is measured aortic minus corresponding reconstructed parameter.

Table 4-12. Errors in male and female subjects in the reconstruction of central aortic waveforms from invasively calibrated radial waveforms

	Mean error	
	Female	**Male**
TF_{a1}		
Tp (s) **	-0.020 ± 0.014	-0.002 ± 0.023
SVI *	0.14 ± 0.16	0.25 ± 0.20
TF_{a2}		
SBP (mmHg) *	2 ± 6	-2 ± 7
Ad (mmHg.s) *	1.74 ± 3.55	4.43 ± 4.48
As (mmHg.s) *	-2.04 ± 3.61	-4.80 ± 4.51
SVI **	0.10 ± 0.17	0.29 ± 0.26

* denotes $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$ for difference in error between male and female subjects. Error is measured aortic minus corresponding reconstructed parameter.

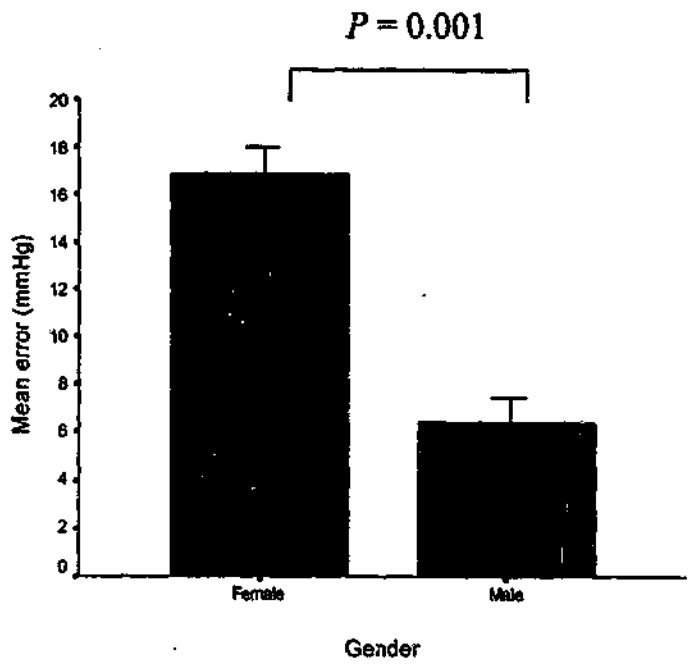


Figure 4-10. Mean error in male and female subjects in the reconstruction of central aortic systolic blood pressure using TF_{a1} and non-invasively calibrated radial waveforms

Bars represent the standard error of the mean. Error is measured aortic minus TF_{a1} reconstructed systolic blood pressure.

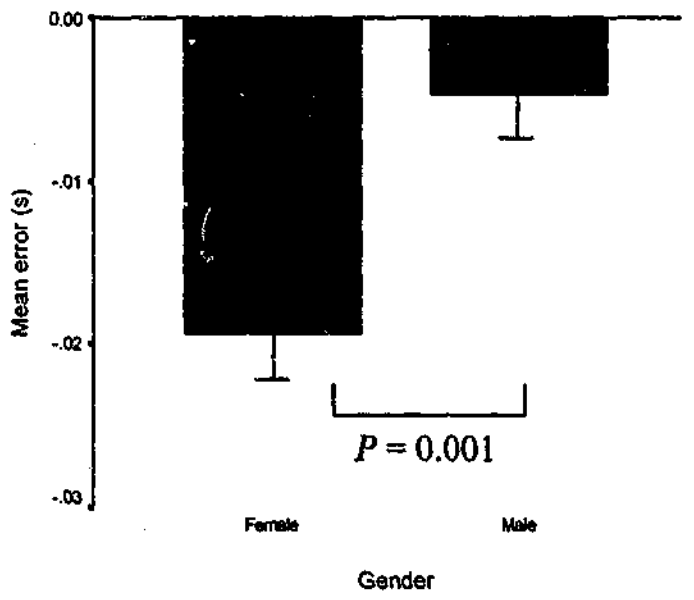


Figure 4-11. Mean error in male and female subjects in the reconstruction of central aortic time to peak pressure using TF_{a1} and non-invasively calibrated radial waveforms

Bars represent the standard error of the mean. Error is measured aortic minus TF_{a1} reconstructed time to peak pressure.

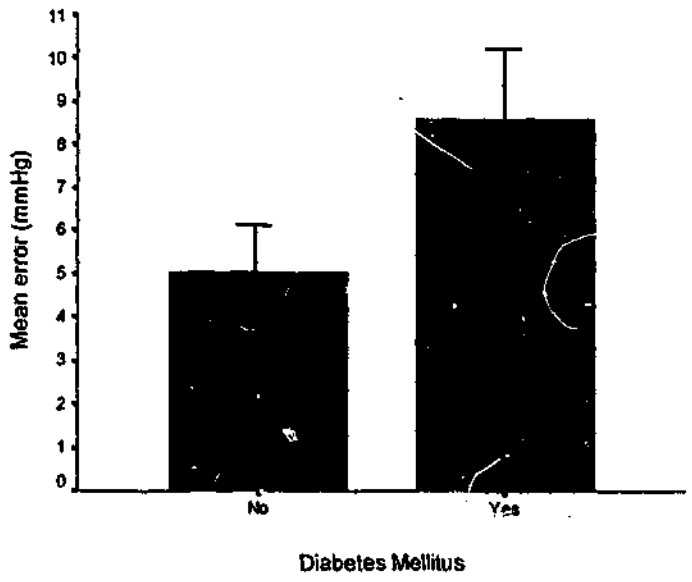


Figure 4-12. Mean error in subjects with and without diabetes mellitus in the reconstruction of central aortic systolic blood pressure using TF_{a1} and invasively calibrated radial waveforms

Bars represent the standard error of the mean. Error is measured aortic minus TF_{a1} reconstructed systolic blood pressure.

4.4 DISCUSSION

4.4.1 Number of subjects contributing to a generalised arterial transfer function

Although there is significant variability in individual arterial transfer functions in both magnitude and phase, particularly at the higher frequencies, it appears from the data presented in this chapter that there is likely to be little improvement in a generalised arterial transfer function by the inclusion of data from more than approximately 20 subjects when transfer functions are derived by this FFT-based method. This is of relevance for the interpretation of data in the literature since, although generalised

arterial transfer functions have been previously published, all with wide confidence intervals, there has been no exploration of the minimum number of subjects that might be required to yield a representative generalised arterial transfer function. It is of note that the previously published generalised arterial transfer functions in the studies of both Chen *et al* and Fetics *et al* have been derived from 20 subjects, although using an autoregressive exogenous method.(Chen, *et al.* 1997, Fetics, *et al.* 1999) It might be expected therefore, provided the characteristics of transfer functions derived by the 2 methods were similar, that the transfer functions derived by these authors might be representative of the population from which the sample was drawn. In addition to this, the arterial transfer functions derived Fetics *et al* were prospectively evaluated, and therefore the findings of these investigators might be generalisable to other subject groups.(Fetics, *et al.* 1999) Karamanoglu *et al*, however, derived their transfer function from data from only 14 subjects, and Sugimachi *et al* from just 8 patients in atrial fibrillation.(Karamanoglu, *et al.* 1993, Chen, *et al.* 1997, Sugimachi, *et al.* 1997, Fetics, *et al.* 1999) This might be of relevance if these generalised arterial transfer functions were to be applied to other subjects groups, and may in part explain the error that was seen in the reconstruction of systolic blood pressure when the transfer function of Karamanoglu *et al* was prospectively evaluated.(Karamanoglu, *et al.* 1993, Takazawa, *et al.* 1996)

4.4.2 Calibration of the radial waveform

Although the subject of expressed concern, there has been no previously published evaluation of the effects of the method of calibration of the radial waveform on the parameters of the central aortic waveform reconstructed using a generalised arterial transfer function. Given that the fundamental data of the waveform are not altered by

the calibration process, but the absolute values in mV are simply scaled by a different factor depending on the measured central aortic or brachial artery mean and diastolic pressures to yield values in mmHg, it should not be surprising that the calibration process was associated with no difference in the time parameters of the reconstructed waveforms, nor in the AI of the reconstructed waveforms which represent pressure ratios and are therefore dimensionless. The minor variations observed in individuals are attributable to the errors introduced by the limited resolution of the blood pressures used in the calculation of AI. As demonstrated, however, there were significant differences in the pressure and pressure-time integral parameters of the reconstructed waveforms dependent upon the method of calibration of the radial waveform. This is of significance in the interpretation of the limited data in the literature validating arterial transfer function techniques for the reconstruction of central aortic pressures. It clearly demonstrates that a transfer function which reconstructs central aortic pressures with accuracy and precision from radial waveforms that have been calibrated to invasively measured blood pressures (Fetics, *et al.* 1999), or indeed from invasively measured radial artery waveforms (Pauca, *et al.* 2001), will be associated with different errors and individual variability when radial waveforms are calibrated to non-invasively measured blood pressures, such that the error and individual variability might exceed that which is acceptable in clinical practice. It is also apparent that the error and variability in the reconstructed waveform pressures will be dependent at least in part upon the characteristics and inaccuracies of the particular device used to measure blood pressure non-invasively. Therefore, although it is appropriate to conclude that the individual variability of the reconstructed central aortic pressures increases significantly with the non-invasive calibration of the radial waveforms, the absolute errors and variability might differ significantly with the use of an alternative blood pressure measurement device.

4.4.3 General consistency of arterial transfer functions

Despite being derived from different populations of patients and considering the potential frequency response limitations of the fluid-filled catheter system compared with the Millar pressure transducer-tipped catheters, both the magnitudes and phases of TF_1, presented in *Chapter 3*, and TF_{a1}, presented in this chapter, are remarkably similar (Figure 4-13 and Figure 4-14), which provides further support for the contention that the frequency response characteristics of the system used in *Chapter 3* were indeed sufficient for the purposes of the study. These findings are consistent with the similarities described between previously published generalised arterial transfer functions. For example the aortic-radial generalised arterial transfer functions of Karamanoglu *et al*, derived by a non-parametric FFT-based method, and those of Chen *et al* and Fetics *et al*, derived using parametric autoregressive exogenous methods, are similar,(Karamanoglu, *et al.* 1993, Chen, *et al.* 1997, Fetics, *et al.* 1999) and the similarities between the radial-aortic generalised arterial transfer function of Fetics *et al* and TF_1, have been demonstrated in *Chapter 3* (Figure 3-8).(Fetics, *et al.* 1999)

That generalised arterial transfer functions derived by different methods from different populations of subjects are very similar might be regarded as encouraging for their potential to reconstruct central aortic waveform parameters from radial data. It should be remembered, however, that the confidence intervals for all generalised arterial transfer functions are wide, particularly at the higher frequencies, and this marked individual variability might be predicted to result in significant errors in the reconstruction of central aortic waveform parameters in individuals, even if mean waveform parameters were reconstructed to a satisfactory standard for a group of

subjects. Additionally, it should also be remembered that these arterial transfer functions have all been derived from subjects with a clinical indication for cardiac catheterisation, and it is possible, if not probable, that the relationship between the central aortic and radial artery pressure waveforms may differ significantly in other groups, for example in young subjects without arterial degeneration. Therefore, although the studies presented here have prospectively evaluated arterial transfer functions in patients who have not contributed to their derivation, nevertheless the subjects have also all had a clinical indication for cardiac catheterisation, and these studies cannot adequately validate the technique for use in subjects without such an indication.

The findings for the waveforms reconstructed from radial data are generally consistent for the different generalised arterial transfer functions that have been evaluated in this chapter. Specifically, the reconstruction of central aortic waveforms from radial waveforms which were calibrated to invasively measured blood pressures resulted in reconstruction of systolic pressure with relatively little error and limited individual variability, that might be considered to be of no clinical significance.(White, *et al.* 1993) This is consistent with the findings of Karamanoglu *et al* and Chen *et al* when transfer functions were applied to the radial data which contributed to the derivation of the transfer functions, and also with the findings for the prospective evaluation of the transfer function of Fetics *et al*.(Karamanoglu, *et al.* 1993, Chen, *et al.* 1997, Fetics, *et al.* 1999) The latter authors found the calibration of radial waveforms to non-invasively measured blood pressures to be associated with an unacceptable level of error that was not further delineated.(Fetics, *et al.* 1999) However, their comments are consistent with the findings presented in this chapter for the reconstruction of central aortic systolic pressure from radial waveforms calibrated to non-invasive blood pressures, of an increase in both the mean error and individual variability to levels which might be

considered to be of clinical significance. These findings are consistent with those of the 3 published prospective validation studies which have calibrated radial waveforms to non-invasive blood pressures and demonstrated a significant underestimation of central aortic systolic pressure.(Takazawa, *et al.* 1996, Davies, *et al.* 2003, Smulyan, *et al.* 2003) As might be predicted, the reconstruction of central aortic waveforms using an arterial transfer function derived from radial data which was been calibrated to non-invasively measured blood pressures offers no advantage, simply introducing additional error to the transfer function, resulting in similar or greater errors and individual variability in the reconstructed waveform parameters.

The data presented in this chapter for the reconstruction of central aortic augmentation index are also consistent with previously published findings. Regardless of the transfer function used or the method of calibration of radial waveform data, there was little or no relationship between the augmentation index of the reconstructed waveforms and that of the directly measured central aortic waveform. Indeed there was a significant relationship only when there was a significant relationship between the AI of the measured aortic and radial artery waveforms. These findings are consistent with those of both Chen *et al* and Fetics *et al* who found the reconstruction of central aortic AI to be poor with a percentage error of 30 ± 45 % in the former and -54 ± 232 % in the latter study.(Chen, *et al.* 1997, Fetics, *et al.* 1999) Those who have reported a significant relationship between the reconstructed and directly measured central aortic AI have done so using combined data sets including measurements in the same subjects before and after an intervention.(Takazawa, *et al.* 1996, Segers, *et al.* 2001) If the repeated values are correlated within the individual, such a practice will falsely strengthen any underlying relationship, or indeed create an apparent statistical relationship where no such relationship exists in the baseline data. Additionally, regardless of the transfer function used or the method of calibration of radial waveform data, the AI of the

reconstructed waveforms retained a stronger relationship with the AI of the radial waveforms than with that of the directly measured central aortic waveforms.

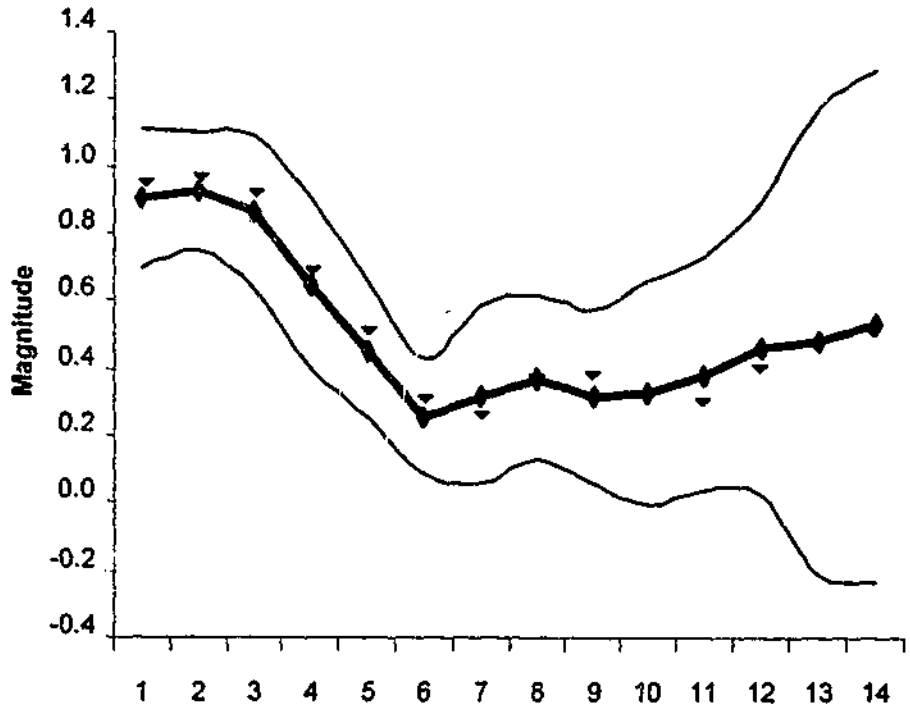


Figure 4-13. Magnitude of transfer functions TF_1 and TF_{a1}

♦ denotes the mean and —— 95% confidence intervals of TF_{a1}, and ▲ the mean of TF_1.

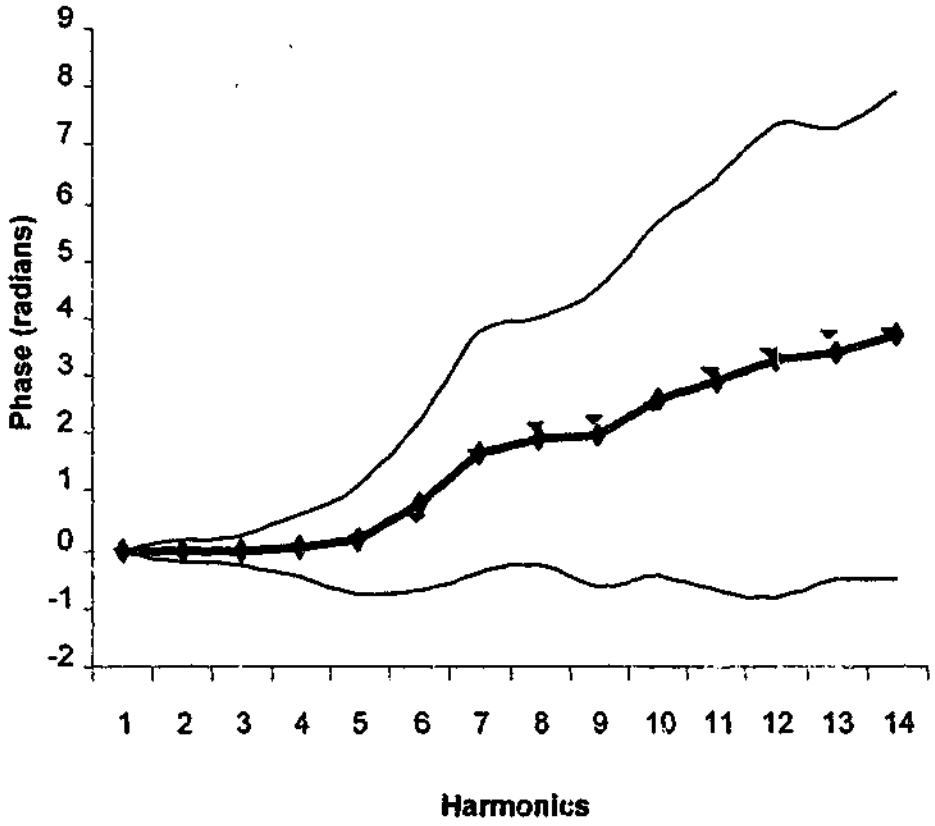


Figure 4-14. Phase of transfer function TF_1 and TF_{a1}

♦ denotes the mean and —— 95% confidence intervals of TF_{a1}, and ▲ the mean of TF_1.

4.4.4 Factors influencing the error in reconstructed central aortic waveform parameters

Although yielding generally similar results, the method of derivation of the transfer function used for the reconstruction of central aortic waveforms clearly influences the observed error in parameters of the reconstructed waveform. In general the error in the reconstructed parameters was smaller with TF_{a2} than TF_{a1}, although when applied to radial waveforms calibrated to non-invasively measured blood pressures the error in the reconstruction of central aortic pulse pressure was smaller with TF_{a1}, due to the differences in the errors in the reconstruction of the diastolic blood pressure. The

generally greater errors with TF_{a1} may be contributed to by the probably greater errors in the calibration of the radial waveforms used in the derivation of the transfer function as described in *Section 2.3*, and also by the reconstruction of waveforms from representative radial waveforms, as were used in the initial derivation of TF_{a2}, but not TF_{a1}, as discussed in *Chapter 3*.

Of considerable concern is the systematic nature of the errors in the reconstructed central aortic waveform parameters, with for example increasing underestimation of central aortic systolic pressure with increasing values of measured central aortic systolic pressure. It has been suggested that the blood pressure related cardiovascular risk of an individual is likely to be more closely related to the individual's central aortic blood pressures than to brachial artery pressures. However, if this technique were to be used in clinical practice this type of systematic error would potentially result in some subjects with elevated central aortic pressures, and presumed increased cardiovascular risk, not being identified, and therefore potentially being denied appropriate treatment. The findings were similar for most parameters including AI, although given the limited relationship with the measured central aortic AI the potential clinical significance of this latter systematic error is likely to be small.

Of perhaps greater interest in illuminating a potential source of the error in the reconstructed waveforms is the association of the error in the derivation of systolic and pulse pressures with the peripheral amplification of systolic and pulse pressures, and particularly the association of the error in the derivation of systolic and pulse pressures and the time to peak pressure with the foot-to-foot delay in the pressure waveform between the central aorta and radial artery. These associations are inter-related and are potentially dependent upon differences in the phases of the individual arterial transfer functions. The potential influence of differences in the phases of individual transfer functions has not been explored. However, as illustrated in Figure 4-15 for the

simplistic condition of the summation of 2 sine waves with a given phase shift, one of the fundamental and the second of twice the fundamental frequency, if the phase difference of φ between the 2 waves is reduced then the peak pressure is increased, and the time to peak pressure reduced, whereas if the phase difference between the 2 waves is increased then the peak pressure is reduced, and the time to peak pressure increased. Since increasing underestimation of systolic pressure is associated with increasing overestimation of the time to peak pressure and *vice versa* this illustration simulates the errors observed in the reconstructed central aortic waveforms, such that if the central aortic waveform is reconstructed with a transfer function with a phase shift of greater than the individual transfer function then the reconstructed waveform might be expected to underestimate the systolic pressure and overestimate the time to peak pressure. If all else were equal, a decrease in phase shift would be expected to be associated with a higher pulse wave velocity, indicative of a less compliant arterial system, and therefore also with a reduction in peripheral pressure amplification. Thus differences in the phase shift between the generalised and individual transfer functions might explain the association not only between the errors in the reconstruction of systolic pressure and the time to peak pressure with the foot-to-foot delay in the arterial pressure waveform between the central aorta and the radial artery, but also the association in the error in systolic pressure and the measured central aortic systolic pressure, since pulse wave velocity, and thus the phase shift of the individual transfer function will also be associated with central aortic blood pressure. This may in part explain the reduction in the error in the reconstruction of central aortic systolic blood pressure after the fall in systolic blood pressure induced by the administration of glyceryl trinitrate in the study of Takazawa *et al.*(Takazawa, *et al.* 1996)

Since the waveform parameters are intimately inter-related it is difficult to estimate the relative importance of the contribution of different factors to the error in the

reconstruction of central waveform parameters. However, although differences in the magnitude of the arterial transfer function undoubtedly influence the observed errors in reconstructed waveform parameters, as illustrated by the differences in waveforms reconstructed from radial waveforms calibrated to invasive and non-invasive blood pressures, it appears that errors in the phase of the transfer function, relative to the individual transfer function, may contribute largely to a relationship between the error in the reconstructed waveform parameters and fundamental arterial mechanical properties, reflected by changes in pulse wave velocity and the observed association with the foot-to-foot pressure waveform delay.

A similar argument might also explain the difference in the errors in the reconstruction of central aortic systolic blood pressure that was observed between men and women, and also between those subjects with and without diabetes mellitus. Since, if all other factors were equal, women will on average have shorter arms and therefore a shorter foot-to-foot delay between the central aorta and radial pressure waveform. Consequently, on average the generalised arterial transfer function would be expected to have a greater phase shift than the individual transfer functions in women, and therefore to result in an underestimation of central systolic blood pressure, and overestimation of the time to peak pressure, as was observed. Similarly, if all other factors were equal, since subjects with diabetes mellitus would be expected to have stiffer arteries, and a faster pulse wave velocity than average, the generalised arterial transfer function would again be expected to have a greater phase shift than the individual transfer functions, and therefore to result in an underestimation of central systolic blood pressure, consistent with the observed trend.

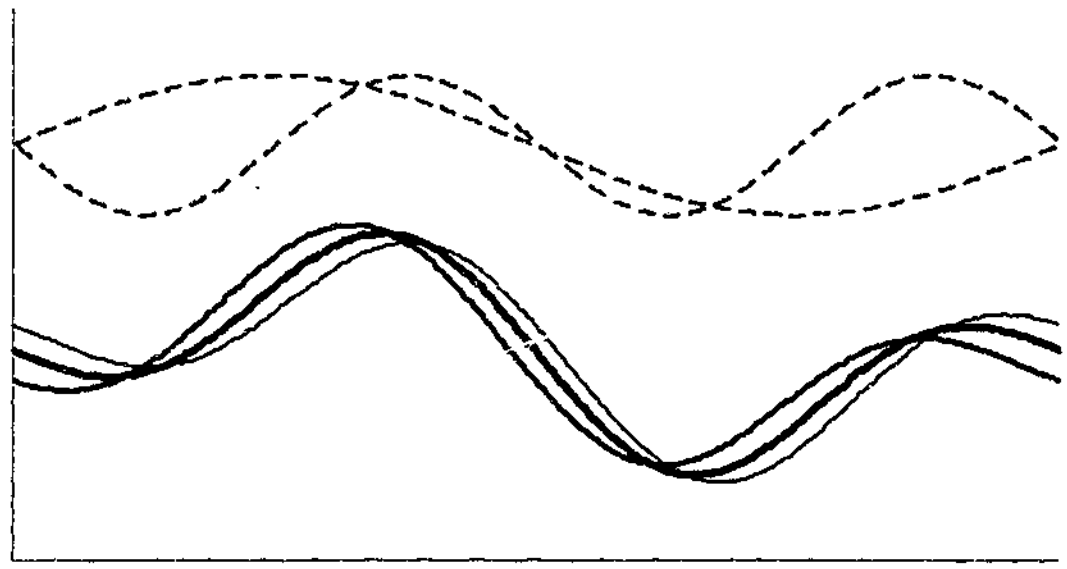


Figure 4-15. Example of the effects of differing phase between harmonics on the resultant overall waveform

Waveforms are the result of adding 2 waveforms of equal magnitude of frequency *f* and frequency 2*f* with differing phase difference. ▬▬ results from phase difference of φ, ——— from phase difference of $\varphi - \Delta\varphi$ and —— from phase difference of $\varphi + \Delta\varphi$. - - - - represent waveforms of frequency *f* and 2*f* with phase shift φ.

4.5 CONCLUSIONS

The findings for transfer functions derived by different methods from different populations using either fluid-filled or transducer-tipped catheters for the acquisition of central aortic waveform data are consistent. However, the method of calibration of the radial waveform has a significant impact on the accuracy and precision with which central aortic waveform parameters are reconstructed, such that the error in the reconstruction of systolic blood pressure might be unacceptable for use in clinical practice. The reconstruction of central aortic augmentation index is poor regardless of the transfer function or method of radial waveform calibration employed, and the accuracy is insufficient even to allocate subjects appropriately to broad categories of aortic augmentation index. The contribution of the phase of the transfer functions to the

errors in the reconstruction of waveform parameters, and particularly the systematic association with factors reflecting fundamental arterial mechanical properties, is important and merits further exploration.

Chapter 5

The impact of physiological interventions on the relationships between central aortic and radial artery pressure waveforms

TABLE OF CONTENTS

5.1 INTRODUCTION

In *Chapters 3* and *4* the relationship between central aortic and radial pressure waveforms has been explored in subjects under resting baseline conditions. Significant variability in individual transfer functions has been demonstrated and in the capacity for a generalised arterial transfer function to reproduce central aortic waveform parameters.

In this chapter the relationships between central aortic and radial pressure waveforms under different physiological conditions, namely during a period of isometric handgrip exercise or a Valsalva manoeuvre, are explored. It has previously been suggested that although central waveform parameters may change with changes in physiological conditions, the relationship between the central aortic and radial waveforms does not change, and therefore that a single generalised transfer function is equally applicable under differing physiological conditions. (Karamanoglu, *et al.* 1993, O'Rourke 1994) However on the basis of first principles this appears unlikely since, as previously discussed, if all other factors are equal, the phase of the transfer function reflects the phase velocities of the individual frequency components. Since pulse wave velocity is influenced by blood pressure,(Bramwell and Hill 1923) with higher blood pressure associated with higher pulse wave velocity, any change in physiological conditions which alters arterial pressure would be predicted to alter the transfer function relationship between central aortic and radial pressure waveforms, unless balanced by changes in arterial dimensions or vessel wall properties. However, Chen *et al* have demonstrated that a single generalised transfer function may track the changes in systolic, diastolic and pulse pressures during transient haemodynamic changes.(Chen, *et al.* 1997) These authors did not assess the reconstruction of other waveform parameters. The capacity of a single generalised transfer function to reconstruct central aortic pressures and other parameters of the central aortic waveform under different

physiological conditions is tested in this study by the application of TF_{n2} to the radial waveforms of subjects obtained under both baseline conditions and during the physiological interventions.

5.2 METHODS

5.2.1 Subjects

The subjects that contributed to the studies presented in this chapter represent a subgroup of those that participated in the studies presented in *Chapter 4*. 40 subjects performed one of 2 physiological interventions; 20 performed a period of isometric handgrip exercise and 20 a Valsalva manoeuvre.

Of the 20 subjects who participated in the study of the effects of isometric handgrip exercise 15 were male. In addition to meeting the inclusion and exclusion criteria described in *Section 2.1.1*, subjects were excluded in the presence of critical disease of the left main coronary artery. Subject characteristics are presented in Table 5-1. Half of the subjects, 9 male, were taking regular β blocker therapy. There were no significant differences between those taking and not taking β blockers in any demographic characteristics, the presence of conventional cardiovascular risk factors or their other cardiac medications. All patients took their regular cardiac medication as usual on the morning of the study.

Of the 20 subjects who participated in the study of the effects of a Valsalva manoeuvre 15 were male. The inclusion and exclusion criteria were as described in *Section 2.1.1*, and subject characteristics are presented in Table 5-2. Fourteen of the subjects, 10 male, were taking regular β blocker therapy. All patients took their regular cardiac medication as usual on the morning of the study.

The 2 groups differed only in a higher resting heart rate ($P < 0.05$) in the group that performed isometric handgrip exercise and a higher prevalence of current smoking ($P < 0.05$) in the group that performed a Valsalva manoeuvre.

Table 5-1. Baseline characteristics of subjects performing isometric handgrip exercise

Male gender	15 (75%)	**Smoking (current)**	0 (0%)
Age (years)	58 ± 14	**Hypertension**	9 (45%)
Height (m)	1.69 ± 0.09	**Diabetes mellitus**	2 (10%)
Weight (kg)	80 ± 12	**Hypercholesterolaemia**	14 (70%)
BMI (kg/m^2)	28 ± 5	**Family history**	7 (35%)
Heart rate (bpm)	67 ± 9	**Obesity (BMI > 30)**	5 (25%)
SBP (mmHg)	129 ± 17	**DBP (mmHg)**	72 ± 11
MAP (mmHg)	92 ± 14	**Pulse pressure (mmHg)**	57 ± 14

BMI is body mass index, bpm beats per minute, SBP systolic blood pressure, DBP diastolic blood pressure and MAP mean arterial pressure. Blood pressures are non-invasively measured brachial artery pressures.

Table 5-2. Baseline characteristics of subjects performing Valsalva manoeuvre

Male gender	15 (75%)	**Smoking (current)**	5 (25%)
Age (years)	61 ± 13	**Hypertension**	10 (50%)
Height (m)	1.73 ± 0.07	**Diabetes mellitus**	3 (15%)
Weight (kg)	81 ± 14	**Hypercholesterolaemia**	17 (85%)
BMI (kg/m^2)	27 ± 5	**Family history**	5 (25%)
Heart rate (bpm)	60 ± 9	**Obesity (BMI > 30)**	3 (15%)
SBP (mmHg)	127 ± 22	**DBP (mmHg)**	72 ± 9
MAP (mmHg)	93 ± 13	**Pulse pressure (mmHg)**	55 ± 15

BMI is body mass index, bpm beats per minute, SBP systolic blood pressure, DBP diastolic blood pressure and MAP mean arterial pressure. Blood pressures are non-invasively measured brachial artery pressures.

5.2.2 Data acquisition and waveform analysis

Data acquisition and waveform analysis were performed as described in *Chapter 4*, with central aortic waveform data acquired with the use of Millar Mikro-tip® catheters. Radial waveforms were calibrated to measured aortic mean and diastolic pressures, and individual transfer functions derived by Method 2 described in *Section 2.5.2*.

5.2.3 Isometric handgrip exercise

Subjects performed isometric exercise with the right hand using a handgrip dynamometer (BASELINE® hydraulic hand dynamometer, Fabrication Enterprises Incorporated, Irvington, New York, USA). Prior to the study maximum handgrip was established. Following acquisition of baseline data, subjects performed continuous

handgrip isometric exercise at 30% of maximum effort for between 3 and 4 minutes. Although the increase in plasma norepinephrine with this protocol is variable, it usually rises by between 50% to 300%.(Taylor and Marcus 1990) Further waveform data were acquired after 3 minutes, with continuing exercise until data acquisition was complete. Individual transfer functions were derived for each subject under both baseline and isometric handgrip exercise conditions. Time domain waveform parameters and transfer functions were compared. Central aortic waveforms were also reconstructed using TF_{a2} applied to both the baseline and handgrip exercise radial waveforms to assess the validity of this generalised transfer function under different physiological conditions.

5.2.4 Valsalva manoeuvre

Subjects were requested to inspire maximally and to perform a Valsalva manoeuvre with maximum effort for as long a period as they could sustain. This was explained and demonstrated prior to the commencement of the cardiac catheterisation procedure to enable the subjects to practice the manoeuvre before the acquisition of waveform data. A satisfactory response was accepted on the basis of observed changes in measured central aortic pressure consistent with at least phases 1, 2 and 4 of a normal haemodynamic response to a Valsalva manoeuvre.(Taylor and Marcus 1990) These were defined as 1) an anticipatory increase in pressure, 2) a progressive decrease in blood pressure and narrowing of pulse pressure, 3) a transient further decrease in pressure as raised intrathoracic pressure was abruptly halted, and 4) an increase in pressure to higher than baseline, with or without a reflex slowing of the heart rate. An example of the changes observed in central aortic blood pressure is depicted in Figure 5-1. Following the acquisition of baseline data, pressure waveforms were acquired continuously throughout the period of the Valsalva manoeuvre. Data were selected from

the plateau of phase 2, at the peak of the haemodynamic changes, for waveform analysis and the derivation of a transfer function. Time domain waveform parameters and transfer functions were compared. Central aortic waveforms were also reconstructed using TF_{a2} applied to both the baseline and Valsalva radial waveforms further to assess the validity of this generalised transfer function under different physiological conditions.

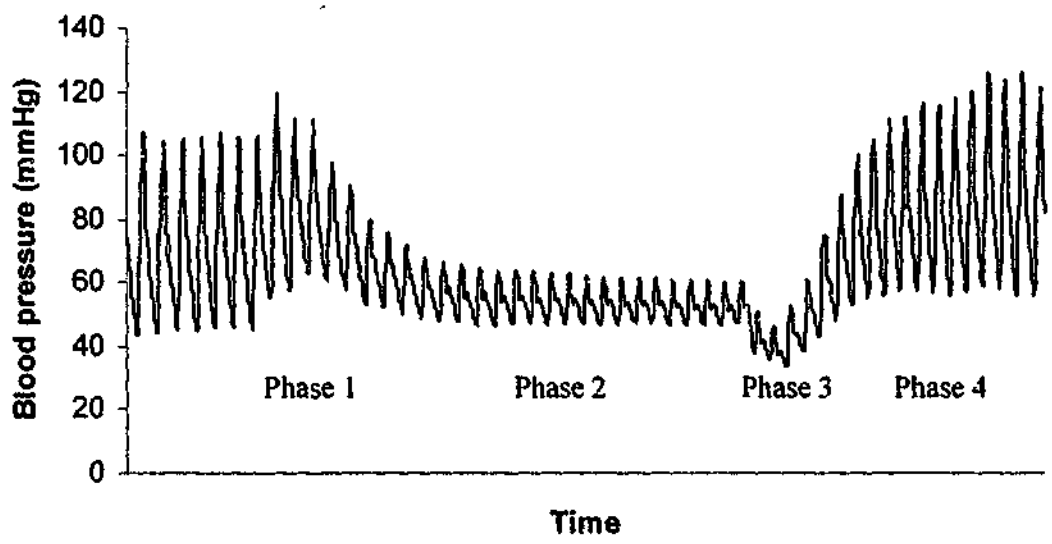


Figure 5-1. Example of measured central aortic pressure during 4 phases of a Valsalva manoeuvre

Phase 1 is the anticipatory increase in blood pressure during deep inspiration, Phase 2 is the progressive decrease in systolic pressure and pulse pressure, Phase 3 is the transient further fall in blood pressure with the abrupt reduction of intrathoracic pressure and Phase 4 is the increase in blood pressure to above baseline levels.

5.2.5 Statistical analysis

Categorical variables are presented as number and percentage, and continuous variables as mean ± standard deviation. Differences in subject features between groups were assessed using unpaired t tests, χ^2 tests or Fisher's Exact test as appropriate.(Zar 1984)

Differences between parameters of radial and measured central aortic waveforms, between measured central aortic and reconstructed waveforms, and between transfer function parameters at baseline and during a physiological intervention were assessed using paired t tests. The relationships between parameters of the radial and measured central aortic and between the measured central aortic and reconstructed waveforms were explored using regression techniques and Pearson's correlation. Differences in regression relationships were assessed as described in *Biostatistical Analysis* (Zar 1984) and Pearson's correlation coefficients compared using Fisher's *Z* transformation.

5.3 RESULTS

5.3.1 Isometric handgrip exercise

5.3.1.1 Time domain analysis

Baseline directly measured central aortic and radial waveform parameters are presented in Table 5-3. Aortic and corresponding radial waveforms were correlated for all parameters except Ti and Tp in this group (AI $P < 0.01$, all others $P < 0.001$). The groups taking and not taking β blockers differed in their baseline waveform characteristics only in the central aortic Tp, Tp being longer in those taking β blockers (0.245 ± 0.019 and 0.225 ± 0.016 ($P < 0.05$)).

Following isometric handgrip exercise heart rate and blood pressure increased, together with changes in all other waveform parameters except Ts, both aortic and radial, and Tp, radial only (Table 5-4). Despite these changes the overall waveform morphology was generally similar during handgrip exercise (Figure 5-2). The change in waveform parameters with handgrip exercise did not differ between those taking and not taking β

blockers except in aortic Tp ($P < 0.05$). Tp increased significantly only in those not taking β blockers, such that post exercise Tp did not differ between the groups.

Following exercise all waveform parameters, both central aortic and radial, were correlated with the corresponding baseline parameters (radial Ti $P < 0.05$, radial AI $P < 0.01$, all others $P < 0.001$), and the correlation between central aortic and corresponding radial waveform parameters did not differ from baseline. However, the regression relationship between the systolic blood pressure of the central aortic and radial artery waveforms differed significantly during isometric handgrip exercise from that at baseline ($P < 0.05$) (Figure 5-3). This change in relationship might be of significance for the capacity of a single generalised arterial transfer function to reconstruct the central aortic waveform under differing physiological conditions. There was no change with isometric handgrip exercise in the regression relationship between the central aortic and radial artery waveforms in any other waveform parameter for which a relationship existed at baseline.

Table 5-3. Baseline aortic and radial waveform parameters in isometric handgrip exercise group

Parameter	Central aortic	Radial
Delay (s)		0.068 ± 0.013
Heart rate (bpm)	67 ± 9	67 ± 9
SBP (mmHg) ***	121 ± 16	137 ± 12
DBP (mmHg)	66 ± 10	66 ± 10
PP (mmHg) ***	55 ± 17	71 ± 14
Ad (mmHg.s) ***	45.14 ± 7.79	42.52 ± 7.24
As (mmHg.s) ***	34.34 ± 4.85	37.05 ± 4.91
SVI ***	1.33 ± 0.27	1.16 ± 0.20
AI (%) ***	26.6 ± 10.9	-19.7 ± 9.4
Ti (s) ***	0.128 ± 0.022	0.182 ± 0.021
Ts (s)	0.326 ± 0.029	0.326 ± 0.026
Tp (s) ***	0.235 ± 0.020	0.105 ± 0.014

*** denotes $P < 0.001$ for difference between aortic and radial parameters. SBP is systolic blood pressure, DBP diastolic blood pressure, PP is pulse pressure, Ad diastolic pressure time integral, As systolic pressure time integral, SVI subendocardial viability index, AI augmentation index, Ti time to inflection point, Ts time to end of systole, Tp time to peak pressure, bpm beats per minute.

Table 5-4. Change in waveform parameters following isometric handgrip exercise

Parameter	Central aortic	Radial
Delay (s)		- 0.010 ± 0.008 ***
Heart rate (bpm)	4 ± 7 **	4 ± 7 **
SBP (mmHg)	29 ± 14 ***	24 ± 12 ***
DBP (mmHg)	15 ± 7 ***	15 ± 7 ***
PP (mmHg)	13 ± 8 ***	9 ± 10 ***
Ad (mmHg.s)	4.11 ± 6.24 **	4.82 ± 6.40 **
As (mmHg.s)	8.21 ± 4.30 ***	8.34 ± 3.89 ***
SVI	-0.17 ± 0.18 ***	-0.11 ± 0.14 **
AI (%)	7.7 ± 6.7 ***	5.3 ± 7.9 *
Ti (s)	-0.011 ± 0.015 **	-0.011 ± 0.017 *
Ts (s)	0.005 ± 0.013	0.006 ± 0.012
Tp (s)	0.007 ± 0.013 *	-0.03 ± 0.007

Change is presented as post-exercise – baseline parameters. * denotes $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$ for change from baseline. SBP is systolic blood pressure, DBP diastolic blood pressure, PP is pulse pressure, Ad diastolic pressure time integral, As systolic pressure time integral, SVI subendocardial viability index, AI augmentation index, Ti time to inflection point, Ts time to end of systole, Tp time to peak pressure, bpm beats per minute.

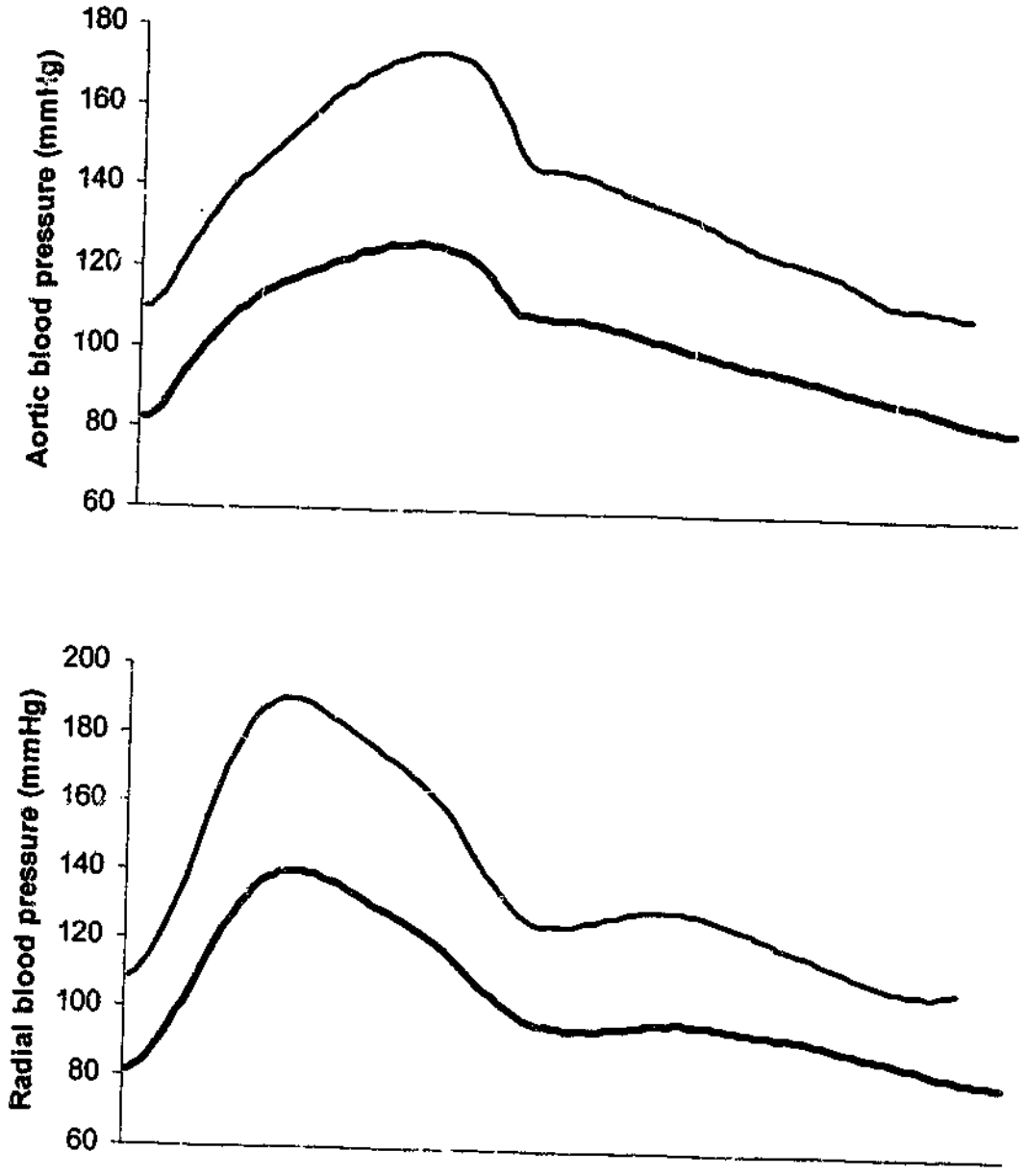


Figure 5-2. Example of representative central aortic and radial waveforms in an individual before and during isometric handgrip exercise

——— represents baseline waveforms and ——— waveforms during isometric handgrip exercise.

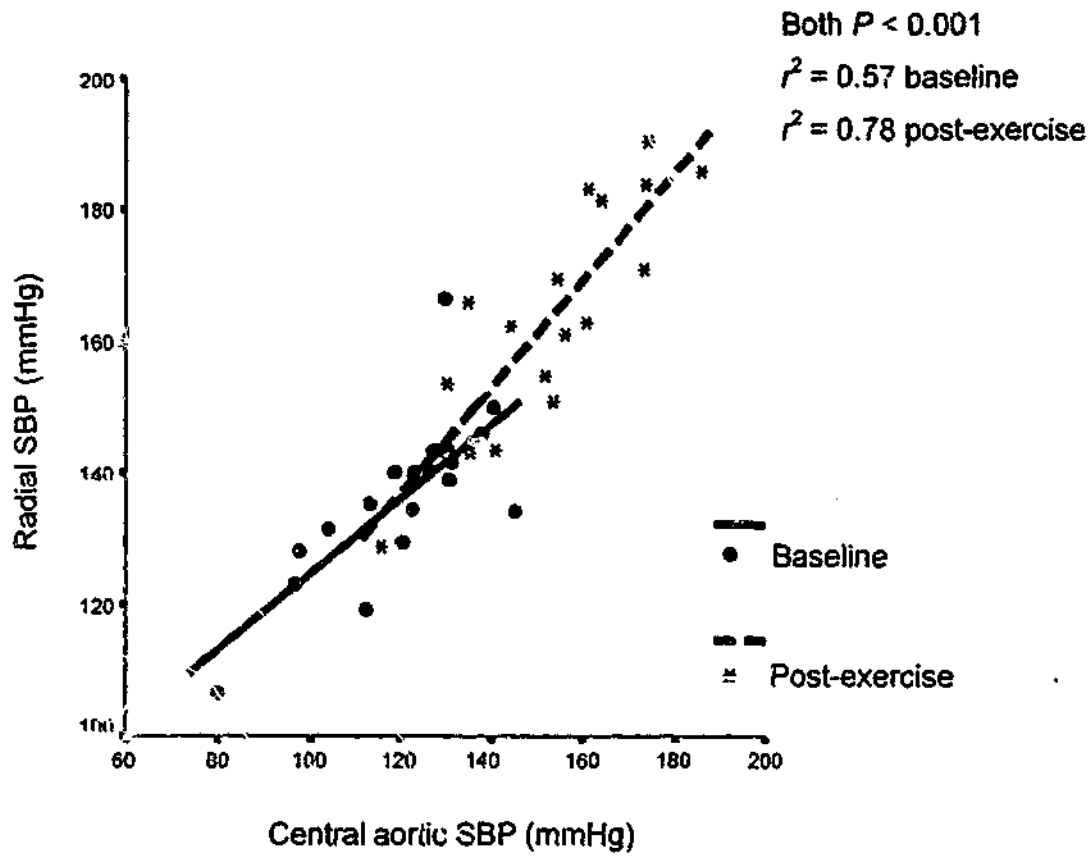


Figure 5-3. Relationship between central aortic and radial SBP before and after isometric handgrip exercise.

The slope of the regression lines differs significantly ($P < 0.05$). SBP is systolic blood pressure.

5.3.1.2 Frequency domain analysis

The magnitudes and phases of both the baseline and isometric handgrip ensemble average transfer functions of this group are presented in Figure 5-4, together with the mean and 95% confidence intervals for TF_{a2} (described in *Chapter 4*). Paired t tests suggest that the baseline and isometric handgrip exercise transfer functions differ in magnitude at the 5th ($P < 0.05$), 6th ($P < 0.05$) and 9th ($P < 0.001$) harmonics, and phase at the 4th ($P < 0.001$), 5th ($P < 0.05$), 8th ($P < 0.05$) and 9th ($P < 0.05$). Although not reaching statistical significance at all frequencies, the direction of the apparent change in the phase of the higher frequencies with isometric handgrip exercise is as would be expected to be associated with an increase in measured pulse wave velocity, and are

therefore consistent with the decrease in the delay between the central aortic and radial pressure waveforms seen in the time domain analysis above. However, it can be seen that, despite the statistical differences demonstrated, both the baseline and isometric handgrip exercise transfer functions are very similar to, and fall entirely within the confidence intervals of, TF_{a2}.

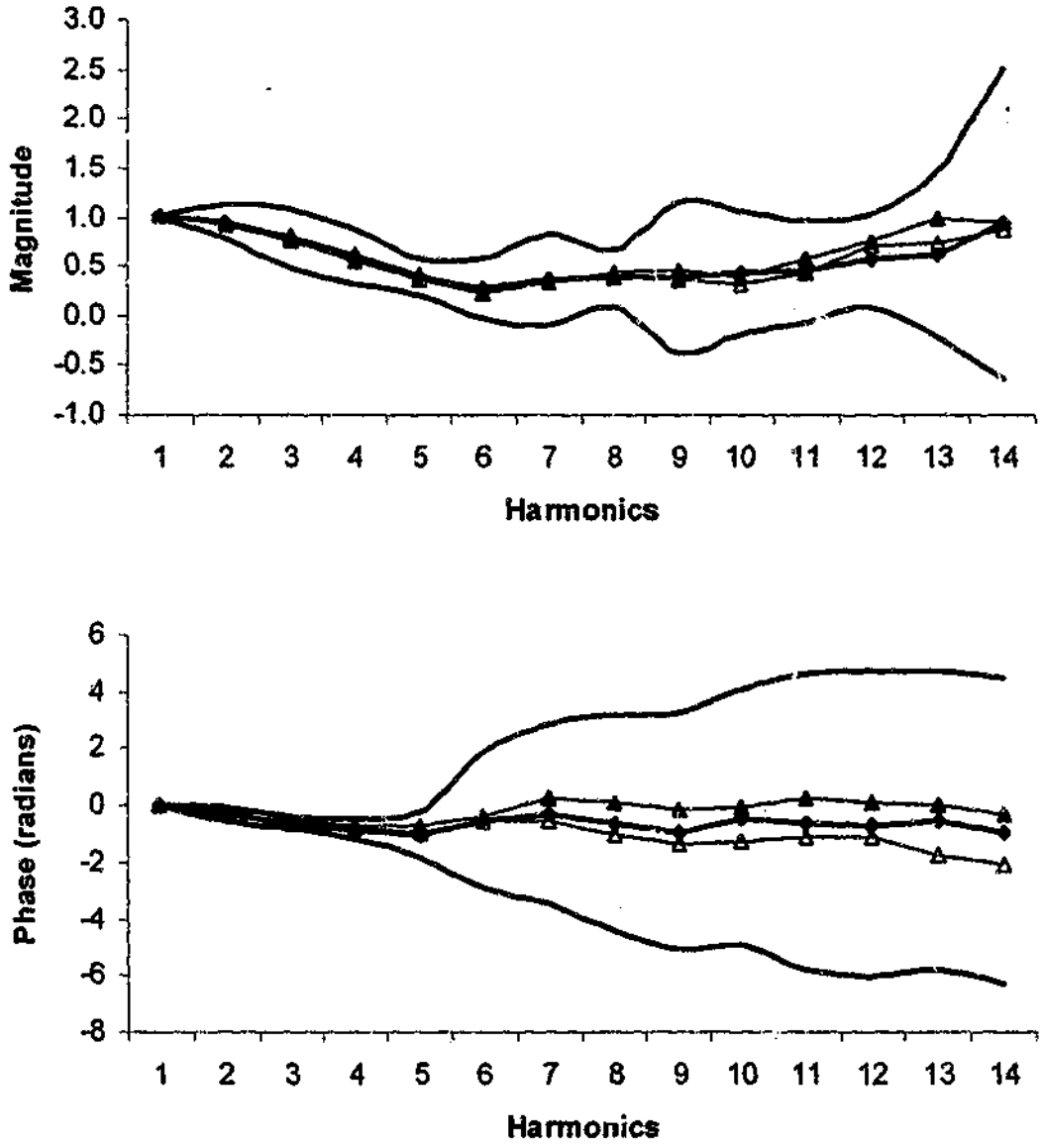


Figure 5-4. Magnitude and phase of baseline and isometric handgrip exercise radial aortic transfer functions together with TF_{a2}.

▲ mean baseline and △ isometric handgrip exercise magnitude and phase. ◆ mean and — 95% confidence intervals for TF_{a2}.

5.3.1.3 Reconstructed waveforms

The parameters of measured central aortic and reconstructed waveforms both at baseline and during the isometric handgrip exercise for 16 subjects are presented in Table 5-5. Four subjects were excluded from this comparison since they contributed to the derivation of TF_{a2}. Small differences are apparent between the parameters of the measured central aortic waveform presented here and in Table 5-3 for this reason, and also because those presented here are the parameters of the time domain average representative central aortic waveform whereas those in Table 5-3 represent the average of the parameters of 10 typical waveforms. Most parameters of the reconstructed waveforms were correlated with the respective measured central aortic parameters, but AI and Ti were not correlated either at baseline or during isometric handgrip exercise. The errors in the parameters of the reconstructed waveforms at baseline and during exercise were similar for all parameters.

Table 5-5. Parameters of measured central aortic and reconstructed waveforms at baseline and during isometric handgrip exercise

	Baseline		Handgrip	
Parameter	**Measured**	**Reconstructed**	**Measured**	**Reconstructed**
SBP (mmHg)	120 ± 16	121 ± 14 ‡	149 ± 19	146 ± 18 ‡
DBP (mmHg)	65 ± 10	66 ± 10 *** ‡	81 ± 14	82 ± 14 *** ‡
PP (mmHg)	54 ± 14	55 ± 14 ‡	68 ± 18	64 ± 16 ‡
Ad (mmHg.s)	43.08 ± 6.83	40.00 ± 7.25 *** ‡	47.13 ± 8.91	45.19 ± 7.82 *** ‡
As (mmHg.s)	33.86 ± 4.58	37.24 ± 4.78 *** ‡	42.00 ± 5.85	44.28 ± 5.77 *** ‡
SVI	1.29 ± 0.26	1.09 ± 0.23 *** ‡	1.14 ± 0.26	1.03 ± 0.20 *** ‡
AI (%)	24.0 ± 12.2	19.2 ± 14.5	31.7 ± 11.9	22.2 ± 10.3 *
Ti (s)	0.132 ± 0.028	0.146 ± 0.033	0.124 ± 0.018	0.146 ± 0.028 **
Ts (s)	0.328 ± 0.026	0.359 ± 0.028 ***	0.332 ± 0.028	0.355 ± 0.033 *** ‡
Tp (s)	0.249 ± 0.023	0.248 ± 0.024	0.253 ± 0.019	0.262 ± 0.024 *** †

SBP is systolic blood pressure, DBP diastolic blood pressure, PP is pulse pressure, Ad diastolic pressure time integral, As systolic pressure time integral, SVI subendocardial viability index, AI augmentation index, Ti time to inflection point, Ts time to end of systole, Tp time to peak pressure. * is $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$ for significant difference from respective measured central aortic parameter. † is $P < 0.01$ and ‡ $P < 0.001$ for significant correlation with respective measured central aortic parameter.

5.3.2 Valsalva manoeuvre

5.3.2.1 Time domain analysis

Baseline directly measured central aortic and radial waveform parameters are presented in Table 5-6. Aortic and corresponding radial waveforms were correlated for all parameters except Ti and Tp in this group (all $P < 0.001$).

Whereas with isometric handgrip exercise, although the waveform parameters differed significantly from baseline, the general morphology of both central aortic and radial waveforms was very similar to baseline, during the Valsalva manoeuvre the waveform morphology changed substantially for both the central aortic and radial waveforms (Figure 5-5), with muscle artifact apparent in some central aortic waveforms. Mean heart rate and diastolic blood pressure increased, whilst there was a substantial fall in systolic blood pressure and pulse pressure (Table 5-7) and trend towards a small fall in mean arterial pressure ($P < 0.07$). There were also changes in all other parameters except Ad, both radial and aortic, and the delay between aortic and radial waveforms. Although the change in radial augmentation index and time to the inflection point in those subjects in whom an inflection point was identified during the Valsalva manoeuvre did not reach statistical significance, having been present on all radial waveforms at baseline, an inflection point was present on only 6 radial waveforms during the Valsalva manoeuvre ($P < 0.001$).

Although most aortic waveform parameters during the Valsalva manoeuvre were correlated with the respective parameters at baseline (Ad and AI $P < 0.001$, DBP $P < 0.01$, SBP, As and Ti $P < 0.05$), in the radial waveforms only Ad ($P < 0.001$), DBP ($P < 0.01$) and Ti ($P < 0.05$ in the few subjects with an inflection point during the Valsalva manoeuvre) were related. As with exercise, the correlation between central aortic and radial waveform pressures was unchanged during the Valsalva manoeuvre, as was the correlation between Tp, however the correlation between the other parameters differed significantly ($P < 0.001$ Ts, $P < 0.01$ Ad, As and SVI (AI and Ti not analysed due to presence on small number of radial waveforms during the Valsalva manoeuvre)). For those parameters for which a relationship existed between central aortic and corresponding radial parameters at baseline and between which the correlation did not

differ during the Valsalva manoeuvre, that is SBP and PP only, the regression relationship did not differ during the Valsalva manoeuvre.

Table 5-6. Baseline aortic and radial waveform parameters in Valsalva group

Parameter	Central aortic	Radial
Delay (s)		0.064 ± 0.015
Heart rate (bpm)	60 ± 9	60 ± 9
SBP (mmHg) ***	124 ± 21	141 ± 19
DBP (mmHg)	66 ± 9	66 ± 9
PP (mmHg) ***	58 ± 15	75 ± 16
Ad (mmHg.s) ***	54.97 ± 13.80	52.32 ± 14.08
As (mmHg.s) ***	35.31 ± 7.01	38.02 ± 7.31
SVI ***	1.56 ± 0.30	1.38 ± 0.31
AI (%) ***	34.3 ± 16.6	-16.4 ± 13.7
Ti (s) ***	0.124 ± 0.025	0.175 ± 0.028
Ts (s) **	0.336 ± 0.034	0.326 ± 0.034
Tp (s) ***	0.243 ± 0.026	0.118 ± 0.034

** denotes $P < 0.01$ and *** $P < 0.001$ for difference between aortic and radial parameters. SBP is systolic blood pressure, DBP diastolic blood pressure, PP is pulse pressure, Ad diastolic pressure time integral, As systolic pressure time integral, SVI subendocardial viability index, AI augmentation index, Ti time to inflection point, Ts time to end of systole, Tp time to peak pressure, bpm beats per minute.

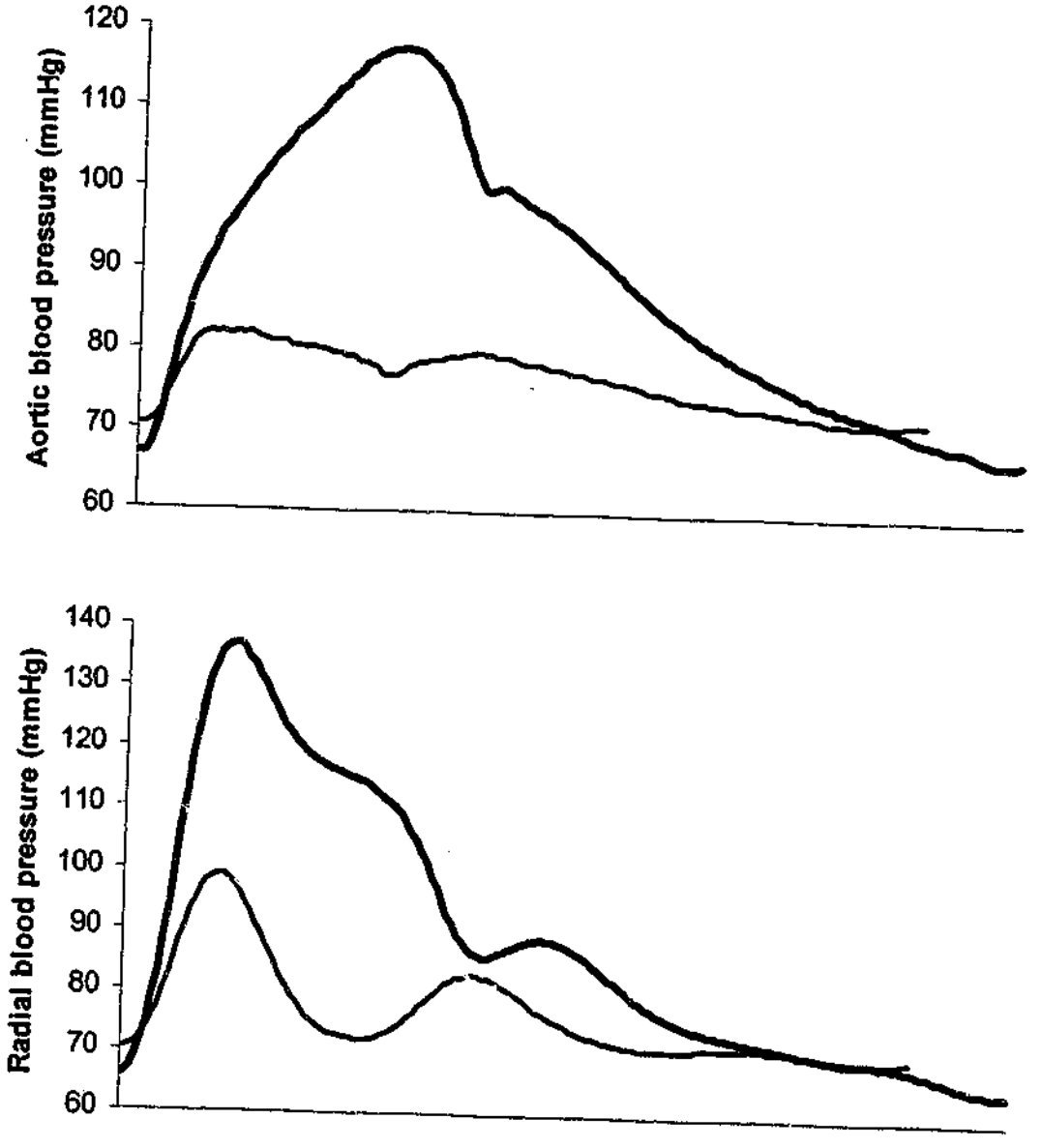


Figure 5-5. Example of representative central aortic and radial waveforms in an individual before and during a Valsalva manoeuvre

——— represents baseline waveforms and ——— waveforms during Valsalva manoeuvre Central aortic and radial waveforms during the Valsalva manoeuvre are shorter than at baseline due to the concomitant increase in heart rate.

Table 5-7. Change in waveform parameters during Valsalva manoeuvre

Parameter	Central aortic	Radial
Delay (s)		0.003 ± 0.012
Heart rate (bpm)	7 ± 7 ***	7 ± 7 ***
SBP (mmHg)	-26 ± 20 ***	-25 ± 21 ***
DBP (mmHg)	7 ± 10 **	7 ± 10 **
PP (mmHg)	-33 ± 17 ***	-32 ± 19 ***
Ad (mmHg.s)	-3.01 ± 9.48	2.35 ± 7.71
As (mmHg.s)	-11.26 ± 6.81 ***	-16.83 ± 8.78 ***
SVI	0.72 ± 0.80 ***	1.45 ± 1.03 ***
AI (%)	-29.5 ± 16.4 ***	-26.7 ± 37.2
Ti (s)	0.018 ± 0.031 *	0.003 ± 0.018
Ts (s)	-0.067 ± 0.064 ***	-0.113 ± 0.060 ***
Tp (s)	-0.101 ± 0.062 ***	-0.021 ± 0.033 *

Change is presented as Valsalva – baseline parameters. * denotes $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$ for change from baseline. SBP is systolic blood pressure, DBP diastolic blood pressure, PP is pulse pressure, Ad diastolic pressure time integral, As systolic pressure time integral, SVI subendocardial viability index, AI augmentation index, Ti time to inflection point, Ts time to end of systole, Tp time to peak pressure, bpm beats per minute.

5.3.2.2 Frequency domain analysis

The magnitudes and phases of the ensemble average transfer functions of this group both at baseline and during the Valsalva manoeuvre are presented in Figure 5-6, together with the mean and 95% confidence intervals for TF_{a2}. Paired t tests suggest that the baseline and Valsalva transfer functions differ in magnitude at the 2nd, 3rd, 6th and 8th harmonics (all $P < 0.05$), and phase at the 4th ($P < 0.01$), 5th ($P < 0.001$), 8th ($P < 0.05$) and 9th – 13th (all $P < 0.001$) and 14th ($P < 0.05$) harmonics. The direction of

change in the phase of the higher frequencies is consistent with a fall in the phase velocities of these frequencies, and might be expected to be associated with a fall in pulse wave velocity, and increase in the delay between the central aortic and radial waveforms. This was not however apparent in the time domain analysis of these waveforms (Table 5-7). Again, despite the differences between the transfer functions, both fall entirely within the confidence intervals of TF_{a2}.

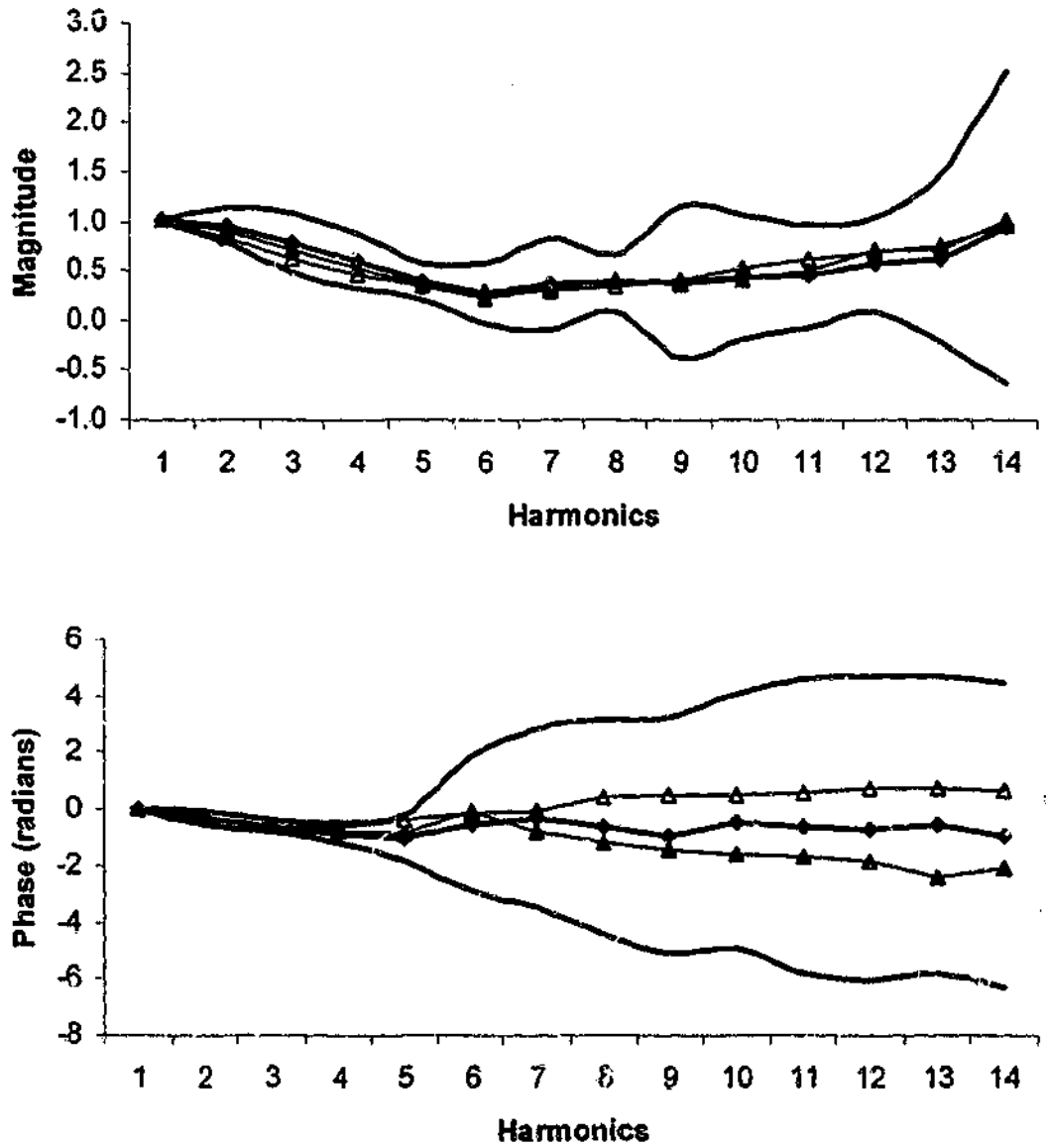


Figure 5-6. Magnitude and phase of radial aortic transfer functions at baseline and during a Valsalva manoeuvre together with TF_{a2}

▲ mean baseline and △ Valsalva magnitude and phase. ◆ mean and — 95% confidence intervals for TF_{a2}.

5.3.2.3 Reconstructed waveforms

The parameters of measured central aortic and reconstructed waveforms both at baseline and during the Valsalva manoeuvre are presented in Table 5-8. Small differences are apparent between some parameters of the measured central aortic waveform presented here and in Table 5-6 since those presented here are the parameters of the time domain average representative central aortic waveform whereas those in Table 5-6 represent the average of the parameters of 10 typical waveforms. Most parameters of the reconstructed waveforms were correlated with the respective measured central aortic parameters at baseline, but only systolic, diastolic and pulse pressures during the Valsalva manoeuvre. As can be seen, the error in the reconstructed waveforms was similar for most parameters, but was significantly greater for AI ($P < 0.001$) and Ti ($P < 0.01$) during the Valsalva manoeuvre.

Table 5-8. Parameters of measured central aortic and reconstructed waveforms at baseline and during a Valsalva manoeuvre

	Baseline		Valsalva	
Parameter	**Measured**	**Reconstructed**	**Measured**	**Reconstructed**
SBP (mmHg)	124 ± 21	126 ± 19 ‡	98 ± 19	100 ± 17 *‡
DBP (mmHg)	66 ± 9	67 ± 10 **‡	73 ± 13	74 ± 13 ‡
PP (mmHg)	58 ± 15	59 ± 16 ‡	24 ± 13	27 ± 13 *‡
Ad (mmHg.s)	51.50 ± 12.20	46.45 ± 13.80 ***‡	48.27 ± 12.85	42.49 ± 14.47
As (mmHg.s)	35.56 ± 7.92	40.96 ± 8.39 ***‡	24.61 ± 7.25	30.90 ± 17.28
SVI	1.47 ± 0.29	1.16 ± 0.38 ***†	2.10 ± 0.77	1.97 ± 1.51
AI (%)	32.4 ± 15.0	19.6 ± 10.7 **	2.8 ± 27.2	23.9 ± 18.9 *
Ti (s)	0.127 ± 0.025	0.151 ± 0.033 **	0.138 ± 0.032	0.104 ± 0.050
Ts (s)	0.337 ± 0.034	0.386 ± 0.035 ***	0.277 ± 0.081	0.336 ± 0.159
Tp (s)	0.258 ± 0.030	0.257 ± 0.035 ‡	0.165 ± 0.066	0.160 ± 0.042

SBP is systolic blood pressure, DBP diastolic blood pressure, PP is pulse pressure, Ad diastolic pressure time integral, As systolic pressure time integral, SVI subendocardial viability index, AI augmentation index, Ti time to inflection point, Ts time to end of systole, Tp time to peak pressure. * is $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$ for significant difference from respective measured central aortic parameter. † is $P < 0.01$ and ‡ $P < 0.001$ for significant correlation with respective measured central aortic parameter.

5.4 DISCUSSION

5.4.1 Isometric handgrip exercise and β blockade

The haemodynamic changes observed with isometric handgrip exercise are believed to result from activation of the sympathetic nervous system, with a demonstrable increase in plasma catecholamine levels, particularly noradrenaline. It might therefore be

expected that parameters of the central aortic or radial waveforms may differ between those individuals taking and not taking β blocker therapy, and particularly that any change in the parameters resulting from the exercise protocol might differ between the groups. It is interesting to note therefore that there were no differences between the 2 groups except that at baseline those taking β blocker therapy had a longer time to peak pressure, and that Tp increased with isometric handgrip exercise only in the group not taking β blocker therapy, such that there was no difference between the groups in Tp following exercise. Although the difference between the groups may be thought to implicate the β blocker therapy as the cause for the prolonged Tp, it must be remembered that all that has been demonstrated is association. The association could simply result from chance, or indeed it might be that the baseline sympathetic nervous system activation differs between the groups, and that it is the clinical indication for β blocker therapy that is causally related to the longer Tp in this group. This hypothesis is supported by the finding that the exercise protocol abolishes all differences between the 2 groups. The findings do, however, imply that the observed haemodynamic effects are either due to mechanisms that do not involve β_2 adrenoceptors, probably involving α adrenoceptor effects of noradrenaline, or, if the mechanisms do involve β_2 adrenoceptors, that the individuals taking β blocker therapy were not adequately β blocked to prevent the changes in waveform parameters. It is not possible to elucidate this further from the available data.

changes might be clarified by the inclusion of data from a greater number of subjects, particularly for isometric handgrip exercise. The change with isometric handgrip exercise is consistent with higher phase velocities, and during the Valsalva manoeuvre with lower phase velocities, of the higher frequencies. Under baseline conditions it has previously been demonstrated that measured aortic foot-to-foot pulse wave velocity is related to the average of the phase velocities of frequencies above 3Hz.(McDonald 1968, Nichols and McDonald 1972, Latham, *et al.* 1985) This is consistent with the decrease in the delay between the foot of the aortic and foot of the radial waveforms in the handgrip group. The change in delay with the Valsalva manoeuvre did not reach statistical significance, but is consistent with the fall in pulse wave velocity which has previously been demonstrated in the aorta.(Latham, *et al.* 1985) Whether these changes in pulse wave velocity are simply related to the changes in blood pressure, or perhaps to changes in arterial wall properties, or a combination of both is a matter for speculation.

If central aortic waveforms are to be reconstructed from radial waveform data, then of greater interest is the question as to whether the differences demonstrated here in the relationships between central aortic and radial waveforms under different physiological conditions are of sufficient magnitude to influence the general applicability and accuracy with which a generalised arterial transfer function may reconstruct central waveform parameters. This question is addressed in the following section.

5.4.3 The applicability of a generalised arterial transfer function for the reconstruction of central aortic waveforms

Although the higher frequencies contribute little energy to the arterial waveforms, they are thought to contribute to specific waveform parameters, and particularly to the augmentation index.(Chen, *et al.* 1997) If the higher frequencies make a significant contribution to the arterial waveform, then the differences in phase that have been demonstrated above may adversely influence the capacity for a single generalised arterial transfer function to reconstruct central aortic waveforms under the different physiological conditions resulting from isometric handgrip exercise or a Valsalva manoeuvre. Consistent with the findings of Chen *et al*, on a group basis there was good reconstruction of central aortic systolic, diastolic and pulse pressures both at baseline and during the physiological interventions.(Chen, *et al.* 1997) There were however significant differences between the parameters of the reconstructed waveforms and of the directly measured central aortic waveforms during the physiological interventions, but only for AI and Ti during the Valsalva manoeuvre did the errors differ from the equivalent errors under baseline conditions. This may reflect the lower phase velocities of the higher frequencies during the Valsalva manoeuvre compared with the generalised transfer function, although it should be remembered that the reconstruction of AI and Ti is also unsatisfactory at baseline, with no significant correlation between reconstructed and directly measured values in either group either under baseline conditions or during the physiological intervention. It appears therefore that the demonstrated differences in the relationships between the central aortic and radial waveforms are not sufficient to influence the accuracy of reconstruction of any waveform parameter which is adequately reconstructed under baseline conditions.

5.5 CONCLUSIONS

Although the morphology of the central aortic waveforms differs considerably under different physiological conditions, the relationship between the waveforms remains very similar to that under baseline conditions, with apparent differences mainly confined to the higher frequencies. These differences were associated with an increased error in the reconstruction of central aortic augmentation index and the time to the inflection point during the Valsalva manoeuvre only, but in no other waveforms parameters. However, since the augmentation index and time to the inflection point are not adequately reconstructed under baseline conditions, it appears that a single generalised transfer function may be equally applicable, with the same limitations, for the reconstruction of central aortic waveform parameters under different physiological conditions.

Chapter 6

The non-invasive estimation of central aortic pressure waveform parameters: Is an arterial transfer function necessary?

TABLE OF CONTENTS

6.1 INTRODUCTION

It has been demonstrated in previous chapters that, although the application of a transfer function to non-invasively acquired radial artery pressure waveform data yields reconstructed waveforms which more closely approximate the central aortic waveform than the radial, many parameters of the reconstructed waveform nevertheless differ significantly from those of the measured central aortic waveform. In particular the central aortic augmentation index is very poorly reconstructed, and remains closely related to the radial. This raises the question as to whether, in an individual subject, the non-invasive estimation of central aortic waveform parameters by the application of an arterial transfer function to the radial artery waveform data improves upon an estimate based directly upon the untransformed radial data itself. In approaching this question it is necessary to consider not only the relationships between parameters of the radial artery waveform and the measured central aortic, but particularly to consider and compare those waveforms that are accessible non-invasively, that is the non-invasively acquired radial artery pressure waveform calibrated to non-invasively measured brachial artery blood pressures and the waveform reconstructed by the application of an arterial transfer function to this waveform. The accuracy with which the central aortic waveform parameters might be predicted in any individual will be determined not only by the mean difference between the measured central aortic and the surrogate waveform, which might be corrected by a simple arithmetical adjustment, but more particularly by the individual variability of the estimate, as described by the degree of correlation and the limits of agreement. These issues will be addressed in this chapter.

6.2 METHODS

The 63 subjects (45 male) who contributed to the prospective validation of the transfer functions described in *Chapter 4* contributed to the analysis presented in this chapter. Their characteristics and drug treatments are presented in Table 4-6 and Table 4-7 respectively. Non-invasively measured blood pressures were unavailable for technical reasons for 2 female subjects who were therefore excluded from this analysis.

6.2.1 Relationships between central aortic and both radial and reconstructed central aortic waveform parameters

Parameters of the measured central aortic waveforms and those reconstructed from radial waveforms by the application of a generalised arterial transfer function were presented in *Chapter 4*. The reconstructed waveforms analysed in this chapter are limited to those reconstructed by the application of TF_{a2} to radial waveforms calibrated to non-invasively measured brachial artery pressures. The untransformed, but calibrated, radial waveforms from which these reconstructed waveforms were derived were also analysed for the same waveform parameters as previously described.

6.2.2 Statistical analysis

Parameters of the directly measured central aortic waveforms were compared with the corresponding parameters of the reconstructed or untransformed radial waveforms by paired t tests, and their relationships explored by regression and correlation techniques. Differences in correlation coefficients were explored using Fisher's Z transformation,

and 95% limits of agreement between parameters of the measured central aortic and corresponding parameters of the reconstructed or untransformed radial waveforms according to the method of Bland and Altman.(Bland and Altman 1986)

6.3 RESULTS

The parameters of the measured aortic and those of the reconstructed waveforms together with their correlation coefficients, mean differences and 95% limits of agreement are presented in Table 6-1. Similar data are presented for the measured aortic and untransformed radial waveforms in Table 6-2, and for measured aortic and brachial artery pressures in Table 6-3. Comparison of the correlation coefficients for the relationships between parameters of the measured central aortic and both the reconstructed and untransformed radial waveforms revealed significant differences for As, AI, Tp (all $P < 0.01$) and Ts ($P < 0.001$) only. Measured central aortic Tp was more closely related to that of the reconstructed waveforms, but AI, As and Ts were all significantly more closely related to the untransformed radial waveforms. The relationships for AI are illustrated in Figure 6-1. As previously demonstrated, the reconstructed AI remained significantly more closely related to the radial ($r = 0.43$) than to the measured central aortic AI ($r = -0.01$) ($P < 0.05$). Although the difference in the correlation coefficients for SBP and PP did not reach significance there was a trend for the relationship to be closer to the reconstructed waveforms ($P < 0.1$). However, when the correlation coefficients for the relationships between the measured central aortic and brachial artery pressures were compared, although they did not differ from those for the reconstructed waveforms, the coefficients for SBP and PP were significantly greater than for those of the untransformed radial waveforms. The relationships between the SBP of the measured aortic and that of both the reconstructed waveforms and brachial

5.4.2 The impact of changing physiological conditions on the radial aortic arterial transfer function

As was demonstrated in *Chapter 4*, the confidence intervals of the generalised arterial transfer functions are wide, and it is therefore not surprising that the transfer functions derived both before and during isometric handgrip exercise, and before and during a Valsalva manoeuvre should fall entirely within these confidence intervals. It should be acknowledged that the similarity between the baseline transfer function in the handgrip group and TF_{a2} will be enhanced by subjects common to both groups, although the numbers involved are small, with only 4 subjects contributing to both the isometric handgrip exercise and TF_{a2} derivation groups, and there are no subjects in the Valsalva group that contributed to TF_{a2}.

It has previously been demonstrated that there may be substantial changes in the magnitudes of the individual transfer function of some subjects during a Valsalva manoeuvre, whereas in other subjects there is very little change.(Chen, *et al.* 1997) No data has been previously published on the phase of a transfer function during any transient change in physiological conditions, although this could have a substantial influence on the capacity of a single generalised transfer function to reconstruct central aortic waveform parameters under different conditions. On paired analysis of the data presented in this chapter it appears that there may be significant changes in the ensemble average radial aortic transfer functions with changes in physiological conditions. Although the phases of the lower frequencies and the magnitudes appear generally very similar, there appear to be significant changes in the phases of the transfer functions at the higher frequencies with both the isometric handgrip exercise and the Valsalva manoeuvre, but in opposite directions. The significance of these

artery pressures is illustrated in Figure 6-2. It can be seen that, although there is a difference in the SBP of the reconstructed waveforms and brachial artery, which might be corrected by a simple arithmetical adjustment, their relationships with the measured aortic SBP are otherwise virtually indistinguishable.

As demonstrated in *Chapter 4*, the error in most parameters of the reconstructed waveforms was related to the absolute value of the corresponding measured central aortic waveform parameter. There was a similar relationship between the differences between the measured aortic and both radial waveform and brachial artery blood pressures (systolic $r = 0.30, 0.27, 0.29$, diastolic $r = 0.28, 0.32, 0.25$ and pulse pressures $r = 0.32, 0.30, 0.35$, reconstructed waveforms, radial waveforms and brachial blood pressures respectively). Of the other parameters for which a relationship existed between the absolute value of the measured aortic waveform and the error in the reconstructed waveform, there were similar relationships for the difference between the radial and measured aortic parameters for AI, and Ti, but no relationship for As or SVI (AI $r = 0.78, 0.64$, Ti $r = 0.64, 0.73$, As $r = 0.25, 0.04$, SVI $r = 0.34, -0.09$, reconstructed and radial waveforms respectively). For Tp only was the relationship stronger for the difference between the radial and measured aortic waveforms ($r = 0.34$, 0.71 ($P < 0.01$) reconstructed and radial waveforms respectively).

As was demonstrated in *Chapter 4*, the error in the reconstruction of the central aortic systolic pressure was related to the foot-to-foot delay in the transmission of the pulse wave from the central aorta to the radial artery. Similarly, the difference in the systolic pressure between the central aorta and radial artery is also related to the delay (Figure 6-3).

Table 6-1. Relationships between parameters of the measured central aortic and reconstructed waveforms

Parameter	Measured aortic	Reconstructed	Pearson's *r*	Mean difference	95% limits of agreement
SBP (mmHg)	125 ± 20	123 ± 20	0.83 ***	2	± 23
DBP (mmHg)	67 ± 9	73 ± 9	0.78 ***	-6 ***	± 12
PP (mmHg)	58 ± 17	51 ± 17	0.77 ***	8 ***	± 23
Ad (mmHg.s)	47.58 ± 10.84	45.70 ± 11.91	0.90 ***	1.87 **	± 10.33
As (mmHg.s)	35.42 ± 6.93	39.36 ± 7.87	0.70 ***	-3.94 ***	± 11.61
SVI	1.37 ± 0.29	1.19 ± 0.31	0.65 ***	0.18 ***	± 0.51
AI (%)	27.6 ± 15.8	21.4 ± 12.6	-0.01	6.2 *	± 40.5
Ti (s)	0.130 ± 0.025	0.144 ± 0.031	-0.04	-0.014 *	± 0.082
Ts (s)	0.331 ± 0.033	0.368 ± 0.037	0.29 *	-0.037 ***	± 0.084
Tp (s)	0.253 ± 0.035	0.255 ± 0.037	0.67 ***	-0.003	± 0.058

Mean difference is measured aortic – reconstructed waveform value. * denotes $P < 0.05$ and *** $P < 0.001$ for difference from, or correlation with respective measured aortic parameter. SBP is systolic blood pressure, DBP diastolic blood pressure, PP pulse pressure, Ad diastolic pressure time integral, As systolic pressure time integral, SVI subendocardial viability index, AI augmentation index, Ti time to inflection, Ts time to end of systole and Tp time to peak pressure.

Table 6-2. Relationships between parameters of the measured central aortic and radial artery waveforms

Parameter	Measured aortic	Radial	Pearson's *r*	Mean difference	95% limits of agreement
SBP (mmHg)	125 ± 20	137 ± 22	0.68 ***	-12 ***	34
DBP (mmHg)	67 ± 9	72 ± 9	0.78 ***	-6 ***	12
PP (mmHg)	58 ± 17	65 ± 20	0.59 ***	-7 **	35
Ad (mmHg.s)	47.58 ± 10.84	50.78 ± 12.99	0.93 ***	-3.21 ***	10.05
As (mmHg.s)	35.42 ± 6.93	37.05 ± 7.69	0.88 ***	-1.63 ***	7.31
SVI	1.37 ± 0.29	1.42 ± 0.46	0.69 ***	-0.05	0.66
AI (%)	27.6 ± 15.8	-15.7 ± 12.8	0.52 ***	43.3 ***	28.5
Ti (s)	0.130 ± 0.025	0.177 ± 0.023	0.04	-0.047 ***	0.066
Ts (s)	0.331 ± 0.033	0.321 ± 0.042	0.74 ***	0.011 **	0.059
Tp (s)	0.253 ± 0.035	0.114 ± 0.027	0.29 *	0.139 ***	0.075

Mean difference is measured aortic – radial waveform value. * denotes $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$ for difference from, or correlation with respective measured aortic parameter. SBP is systolic blood pressure, DBP diastolic blood pressure, PP pulse pressure, Ad diastolic pressure time integral, As systolic pressure time integral, SVI subendocardial viability index, AI augmentation index, Ti time to inflection, Ts time to end of systole and Tp time to peak pressure.

Table 6-3. Relationships between measured central aortic and brachial artery blood pressures

Parameter	Measured aortic	Brachial	Pearson's *r*	Mean difference	95% limits of agreement
SBP (mmHg)	125 ± 20	130 ± 19	0.86 ***	-5 ***	21
DBP (mmHg)	67 ± 9	73 ± 10	0.76 ***	-6 ***	13
PP (mmHg)	58 ± 17	57 ± 17	0.82 ***	1	20

Mean difference is measured aortic – brachial waveform value. *** denotes $P < 0.001$ for difference from, or correlation with respective measured aortic parameter. SBP is systolic blood pressure, DBP diastolic blood pressure, PP pulse pressure.

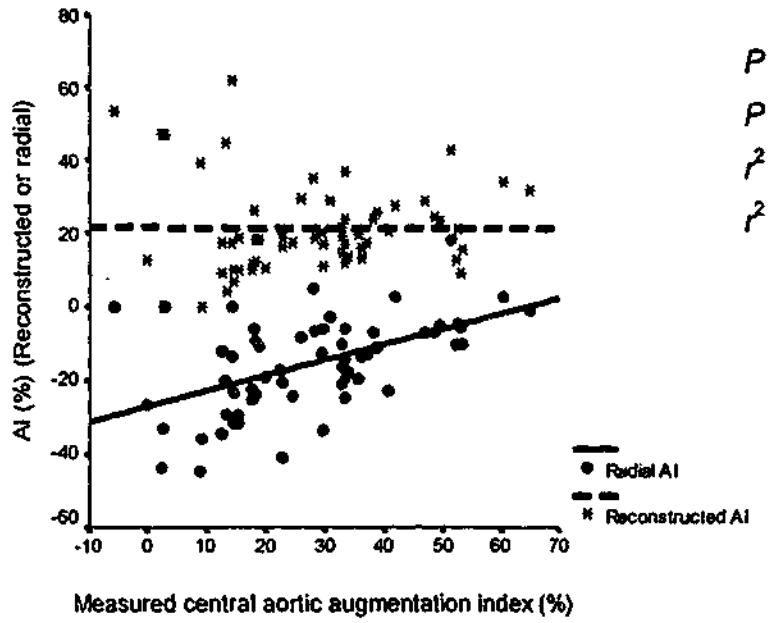


Figure 6-1. Relationships between measured central aortic and both reconstructed and radial waveform augmentation index

AI is augmentation index.

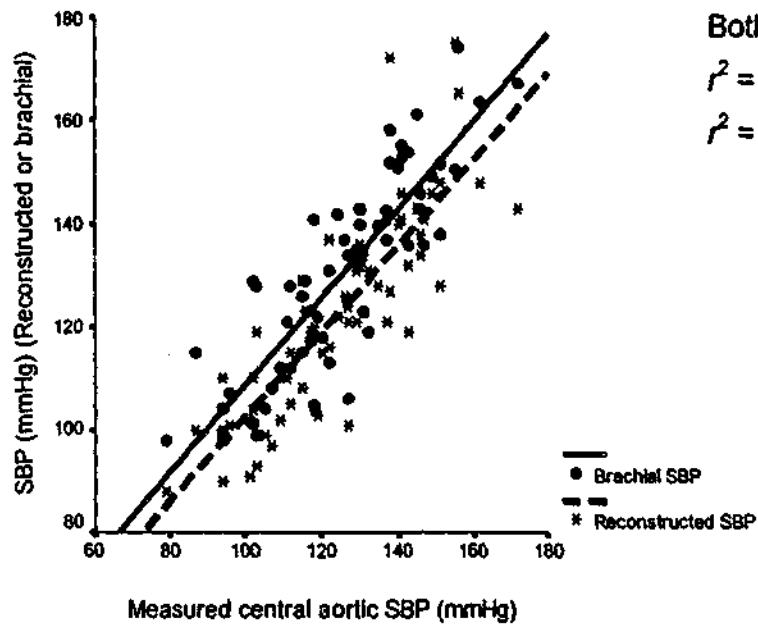


Figure 6-2. Relationships between measured central aortic and both reconstructed and brachial artery systolic blood pressure

SBP is systolic blood pressure.

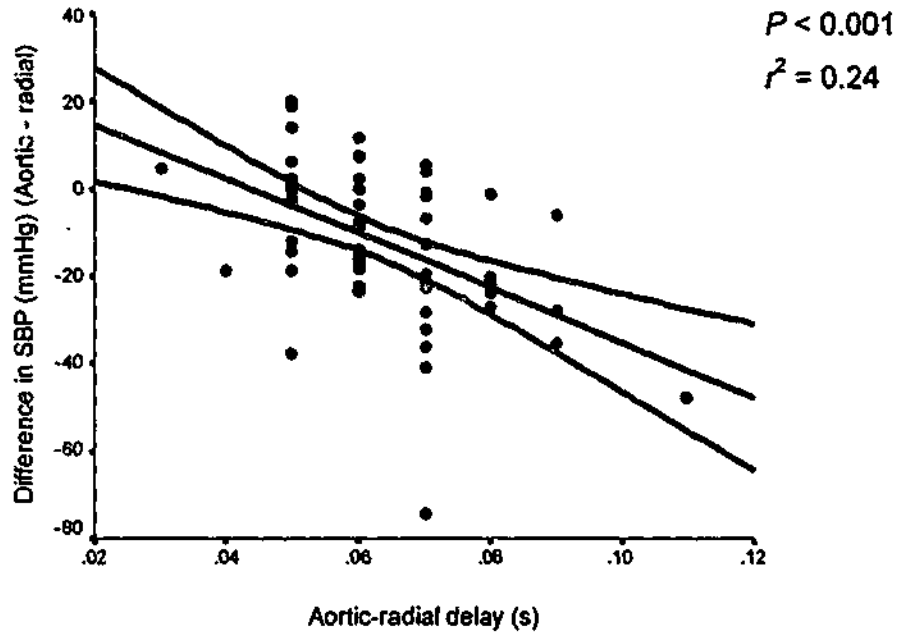


Figure 6-3. Relationship between the difference in the systolic blood pressure in the central aorta and radial artery and the aortic-radial delay

SBP is systolic blood pressure.

6.4 DISCUSSION

6.4.1 Prediction of central aortic waveform parameters

The non-invasive prediction of central aortic waveform parameters is widely believed to have potential clinical value. However, non-invasive estimation of waveform parameters by the application of a generalised arterial transfer function to non-invasively acquired radial artery waveforms requires that the radial waveforms be calibrated to non-invasively measured brachial artery pressures. As was demonstrated in *Chapter 4*, this approach is associated with significant errors in the estimation of most central aortic waveform parameters, with the error in most parameters influenced by the measured central aortic value, and also considerable individual scatter. It has long been

known that the morphology of the arterial pressure waveform at the radial artery differs substantially from that in the central aorta, and it has generally been accepted that central aortic waveform parameters can be estimated only from a waveform which is morphologically similar, however this assumption has not been adequately tested. The merits of the use of a generalised arterial transfer function for the estimation of central aortic waveform parameters can only be fully evaluated by comparison with data that is accessible by other non-invasive approaches, namely the simple non-invasive measurements of brachial artery blood pressure, and the untransformed radial artery waveforms which might be subject to the application of the arterial transfer function.

The accuracy of estimation of central aortic waveform parameters in an individual is dependent firstly upon there being a relationship between the measured and estimated parameters. Given that a relationship exists, the individual accuracy may be evaluated by the strength of the relationship expressed both as the correlation coefficient, and in terms of the 95% limits of agreement calculated according to the method of Bland and Altman.(Bland and Altman 1986) Technically this method demands that the mean difference between the 2 measurements to be compared should not differ from zero. However, when this is not the case the limits of agreement still provide an appropriate description of the individual variability about the mean difference. A significant difference in mean values between the 2 measurements does not preclude the successful prediction of one from the other since, as previously alluded to, a simple arithmetical correction might be all that is required to compensate for this.

The mean difference in systolic pressure between the radial and measured central aortic waveforms demonstrated in this study is within the range previously quoted. (Karamanoglu, *et al.* 1993, Chen, *et al.* 1997) The 2 measurements are closely related, although the limits of agreement are greater than those between the measured aortic and reconstructed waveforms. Those between the measured aortic and the brachial artery are

either similar or smaller than for the reconstructed waveforms. For the other waveform parameters, as demonstrated, the relationship is similar or closer between the radial and aortic than between the reconstructed and aortic waveforms for all parameters except the time to peak pressure, and the limits of agreement similar for all parameters except the augmentation index for which they are substantially smaller for the radial waveform. In summary therefore, the best non-invasive estimate of central aortic pressures may be obtained from the brachial artery, and the best estimate of other waveform parameters, excluding the time to peak pressure, obtained from the untransformed radial waveform. It seems that the reconstruction of central aortic waveforms by the application of a generalised arterial transfer function has little to offer, unless there is a clinical requirement for an estimation of the time to peak pressure, and with respect to the estimation of central aortic augmentation index it is positively inferior. As a point of interest, the data presented in *Chapter 4* demonstrated the reconstruction of central aortic augmentation index to be better with TF_{a1} than TF_{a2}. However, comparison of the results of the reconstruction of the augmentation index with this transfer function and the untransformed radial waveform demonstrates the radial waveform to remain superior in terms of both correlation and limits of agreement.

6.4.2 Non-invasive measurement of brachial artery blood pressure

If central aortic waveform parameters are to be predicted entirely non-invasively, whichever method is adopted is dependent upon the non-invasive measurement of brachial artery blood pressure, which may be measured by one of a number of different methods. Each potential method will be associated with some error, compared with invasive intravascular pressure measurements, and the error may differ between

methods. As discussed in *Section 1.2.3* the conventional sphygmomanometer is considered to be the gold standard, despite the tendency towards a small underestimate of systolic pressure and an overestimate of diastolic pressure.(Breit and O'Rourke 1974) Although oscillometric methods of blood pressure measurement are generally considered to overestimate systolic and underestimate diastolic pressures compared with a conventional sphygmomanometer, the method adopted in this study has been documented to yield systolic pressures very similar to those obtained with the conventional sphygmomanometer, but lower diastolic pressures which may therefore more closely approximate the true diastolic pressure.(van Popele, *et al.* 2000) The errors associated with this device are therefore likely to be, at worst, no greater than those associated with any potential method of non-invasive blood pressure measurement.

A potential source of additional error is related to the measurement of brachial artery blood pressure in the contralateral arm to that from which radial waveforms were acquired, in all patients who had undergone no prior radial artery surgery, since there may be some difference in the pressure in the 2 arms. This source of error was minimised by the exclusion of any subject with either symptomatic or clinical evidence of any significant difference in blood pressure between the arms. The method is consistent with that used by several investigators (Cohn, *et al.* 1995, McVeigh, *et al.* 1999, Wong, *et al.* 2003, Van Doornum, *et al.* 2003), and offers the advantage that pressures can be measured simultaneously with the acquisition of the radial waveforms, rather than sequentially. The sequential approach has been adopted by other investigators (Wilkinson, *et al.* 2001a, Mahmud and Feely 2002b, Obuobie, *et al.* 2002), but is potentially complicated by temporal changes in blood pressure in the individual. Both approaches probably have sufficient merits and deficiencies as to be considered equally valid.

6.5 CONCLUSIONS

For the non-invasive prediction of parameters of the central aortic waveform in individual subjects the use of a generalised arterial transfer function offers no advantage over the simple non-invasive measurement of brachial artery blood pressures together with the analysis of other parameters of the untransformed radial waveform, with the exception of the prediction of the time to peak pressure. Specifically, if it is required to predict the central aortic augmentation index, whereas the relationship between the augmentation index of the radial and measured aortic waveforms may be weak, estimation from this waveform is significantly superior to that obtained by the application of a generalised arterial transfer function.

Chapter 7

The relationship between pressure waveform characteristics with distal progression along the aorta

TABLE OF CONTENTS

7.1 INTRODUCTION

As discussed in *Chapter 1* the augmentation of central systolic pressure, associated with increasing age and cardiovascular mortality, is often presented as the augmentation index. Although the existence of reflected waves within the vascular system has not been universally accepted, the augmentation of central pressure is widely believed to result from pressure wave reflection from the distal aorta or its branches.(Karamanoglu and Feneley 1999, Nichols and O'Rourke 1990) Consistent with this hypothesis are the findings that increased central augmentation index is associated with increased pulse wave velocity, when the reflected wave would be expected to return earlier in systole due to the decreased transit time, and the association with small height, when the reflected wave would be expected to return earlier in systole due to the shorter distance to the putative reflection point.(London, *et al.* 2001, London, *et al.* 1992, Smulyan, *et al.* 1998) The site of the putative reflection point has been debated, with some authors suggesting the predominant reflection point to be either at the renal arteries, or at the aortic bifurcation, with others suggesting that the reflection point has no physical reality, but represents the combined effects of reflection from many peripheral sites.(Hamilton and Dow 1939, Hamilton 1944, Latham, *et al.* 1985)

According to the hypothesis that central pressure augmentation is caused by reflection of pressure waves from the periphery, the time to the augmentation point would be expected to decrease, and the augmentation index to increase with distal progression from the aortic root towards the putative reflection point. This hypothesis has been previously tested, and supported, in only 2 small groups of subjects.(Latham, *et al.* 1985, Murgo, *et al.* 1980) This study was designed to explore the changes in all waveform parameters with distal progression along the aorta and to elucidate further the

role of pressure wave reflection in the phenomenon of central aortic pressure augmentation.

7.2 METHODS

7.2.1 Subjects

40 subjects, 26 male and 14 female, were recruited from those referred for elective coronary angiography or percutaneous coronary procedures to the Cardiac Catheterisation Laboratory of Monash Medical Centre. Inclusion and exclusion criteria were as described in *Section 2.1.1*. Subject characteristics are displayed in Table 7-1. All patients were in sinus rhythm at the time of the study, although some patients experienced occasional ventricular ectopic beats. The study was approved by the Southern Health Human Research Ethics Committee and subjects gave written consent to participate in the study.

Table 7-1 Subject characteristics

Number	40	**PCI**	8 (20%)
Male gender	26 (65%)	**Smoking (current)**	4 (10%)
Age (years)	65 ± 12	**Hypertension**	22 (55%)
Height (m)	1.70 ± 0.08	**Diabetes mellitus**	9 (23%)
Weight (kg)	79 ± 14	**Hypercholesterolaemia**	34 (85%)
BMI (kg/m^2)	28 ± 5	**Family history**	9 (23%)

BMI is body mass index, PCI is percutaneous coronary intervention. Continuous variables are mean ± standard deviation, categorical variables are numbers (percentage) of subjects.

7.2.2 Data acquisition

Data were acquired under baseline conditions following completion of the clinically indicated procedure. Aortic waveforms were acquired using a 2 French Millar Mikro-tip® catheter transducer introduced via a 6 French multipurpose or right coronary guiding catheter positioned at the aortic root under fluoroscopic control. The Millar transducer was positioned just distal to the tip of the guiding catheter. Waveforms from the Millar transducer were acquired to a personal computer using Chart for PowerLab® (ADInstruments) at 200Hz in 23 and 2000Hz in 17 subjects as described in *Section 2.2.1.2*. The electrocardiogram was also recorded simultaneously from the Mennen Cathlab System using Chart for PowerLab®. Following the acquisition of 30 seconds of data from the aortic root, the guiding catheter and Millar transducer were pulled back together and similar data were recorded from the transverse aortic arch, the level of the diaphragm, the level of the renal arteries and at the aortic bifurcation. All positions were confirmed by fluoroscopy, and the levels of the renal arteries and aortic bifurcation also by angiography. The relative positions of the data-acquisition points were recorded by

the use of a marker catheter to record the length of catheter external to the patient at each point.

In 10 subjects the catheter and transducer were re-positioned at the same point at the aortic root guided by fluoroscopy and the marker catheter. Repeat data were then acquired from the same 5 aortic points, with positions guided by the marker catheter.

The data recorded at 2000Hz were resampled at 200Hz for waveform analysis.

7.2.3 Time domain analysis

Ten representative waveforms identified by the onset of the systolic pressure upstroke were analysed for each subject for each of the 5 aortic sites. In those subjects experiencing ectopic beats, pre-ectopic, ectopic and post-ectopic beats were excluded from analysis. Waveforms were analysed for parameters of interest as previously described.

The time delay between a constant point on the electrocardiogram and the initial upstroke of the systolic waveform was also recorded. For most patients the peak of the R wave was chosen, but for those with very poor R waves the nadir of the S wave was used instead, since this point could be identified more reliably. The difference in the delay between 2 recording points was taken as the transit time between those points, and was used in calculating the pulse wave velocity between those points (distance/transit time). Pulse wave velocity was calculated using data both recorded or resampled at 200Hz and also recorded at 2000Hz.

7.2.4 Frequency domain analysis

Ten representative waveforms defined by the RR interval of the electrocardiogram were identified for each aortic site for each subject. These were averaged and subjected to FFT spectral analysis and transfer functions derived according to Method 2 described in *Section 2.5.2*. In contrast to the radial-aortic transfer functions derived in previous chapters, transfer functions were derived in the physiological direction with the waveform at the proximal site being defined as the input and at the distal site as the output of the system. Although there was a short time interval between the acquisition of data from the different sites, the average waveforms were assumed to be acquired simultaneously for the purposes of the derivation of transfer functions between the aortic sites using the R wave as the constant reference point. Apparent phase velocities were calculated from the phases of the transfer function between the aortic root and bifurcation and the measured distance between these 2 sites for each subject.

7.2.5 Statistical analysis

The change in waveform parameters with distal progression along the aorta was assessed by repeated measures analysis of variance. When a significant difference was defined, this was explored by examining within subjects simple contrasts to identify where differences lay. Statistical significance was taken as $P < 0.05$.

7.3 RESULTS

7.3.1 Time domain analysis

Waveform characteristics at the 5 aortic sites, together with non-invasively measured brachial pressures are detailed in Table 7-2. An example of waveforms from the 5 sites in an individual subject is presented in Figure 7-1. Despite individual variability at some aortic sites (Figure 7-2), mean augmentation index was found to decrease progressively between the aortic root and bifurcation ($P < 0.001$) (Figure 7-3), and Ti to increase ($P < 0.01$) (Figure 7-4) by repeated measures analysis of variance. Despite this, as expected there was progressive peripheral amplification of systolic and pulse pressures and fall in the time to peak pressure (all $P < 0.001$) (Figure 7-5 and Figure 7-6). The time to the end of systole also decreased progressively (Figure 7-6). AI was associated with both Ti and heart rate ($r^2 = 0.90$ root, $r^2 = 0.86$ arch, $r^2 = 0.70$ diaphragm, $r^2 = 0.78$ renal arteries, $r^2 = 0.79$ bifurcation, all $P < 0.001$), but was not associated with pulse wave velocity over any aortic segment. On multiple regression analysis aortic pulse wave velocity was associated with proximal pulse pressure and As only ($r^2 = 0.37$ $P < 0.001$). Heart rate did not differ by more than 2 beats per minute between individual recordings, and the difference cannot explain the progressive differences observed in the waveform parameters between aortic sites. There was no difference with gender, or between those who had undergone percutaneous coronary intervention rather than simple angiography. There was also no difference between the first and second pullback in the 10 patients who had this procedure repeated.

Mean arterial blood pressure differed significantly between the 5 aortic sites ($P < 0.05$) (Figure 7-7), with MAP significantly higher at the diaphragm than all other sites ($P < 0.05$). However, the difference between the MAP at the aortic root and the diaphragm was small (3.6 ± 4.6 mmHg (mean ± standard deviation). The pattern of diastolic

pressure was similar to that of MAP (Figure 7-8), with a significant difference between sites ($P < 0.001$), with DBP being higher at the diaphragm than all other sites ($P < 0.001$). Again mean differences between the aortic root and diaphragm were small (3.7 ± 3.4 mmHg). The differences between non-invasively measured brachial and aortic root MAP and DBP were also small (3.5 ± 6 mmHg and 5 ± 6 mmHg respectively).

Measured foot-to-foot pulse wave velocities for the 4 aortic segments were 13.3 ± 7.0, 8.0 ± 2.6, 11.0 ± 8.3 and 4.1 ± 31.5 m/s for all 40 subjects (200Hz data) and 18.4 ± 14.7, 8.8 ± 4.0, 23.7 ± 59.1 and 15.0 ± 12.5 m/s (2000Hz data). When three subjects with apparently negative measured pulse wave velocity (200Hz data) in the renal artery-bifurcation segment were excluded from the entire group, and one with apparent measured pulse wave velocity 252 m/s (2000Hz data) in the renal artery-bifurcation segment was excluded from the group with data recorded at 2000Hz, the results were as depicted in Figure 7-9 and Figure 7-10 respectively.

Table 7-2. Aortic waveform characteristics at 5 sites and non-invasive brachial pressures

Aortic Site	Root	Arch	Diaphragm	Renal	Bifurcation	Brachial
Delay ***	0.059 ± 0.015	0.066 ± 0.017	0.089 ± 0.020	0.103 ± 0.023	0.111 ± 0.024	
SBP (mmHg) ***	135 ± 22	136 ± 23	142 ± 23	141 ± 23	143 ± 24	140 ± 22
DBP (mmHg) ***	68 ± 10	68 ± 10	72 ± 10	69 ± 10	69 ± 10	73 ± 10
MAP (mmHg) *	92 ± 13	90 ± 18	96 ±12	93 ± 13	93 ± 14	95 ± 12
PP (mmHg) ***	67 ± 21	68 ± 20	70 ± 20	72 ± 19	75 ± 19	67 ± 18
Ad (mmHg.s) ***	53.26 ± 12.50	54.16 ± 12.88	57.30 ± 13.83	54.33 ± 13.04	53.48 ± 12.99	
As (mmHg.s)	38.27 ± 8.80	38.18 ± 8.25	38.43 ± 9.68	38.40 ± 8.25	38.73 ± 9.09	
SVI	1.43 ± 0.35	1.45 ± 0.34	1.64 ± 0.99	1.44 ± 0.33	1.41 ± 0.35	
AI (%) ***	31.3 ± 19.6	20.3 ± 14.9	16.4 ± 9.9	11.2 ± 11.1	7.9 ± 9.1	
Ti (s) **	0.127 ± 0.028	0.140 ± 0.029	0.138 ± 0.026	0.146 ± 0.035	0.156 ± 0.044	
Tes (s) ***	0.336 ± 0.037	0.329± 0.035	0.321 ± 0.033	0.316 ± 0.032	0.316 ± 0.035	
Tp (s) ***	0.242 ± 0.037	0.230 ± 0.033	0.215 ± 0.028	0.199 ± 0.029	0.193 ± 0.030	
Pi (mmHg) ***	112 ± 17	120 ± 20	130 ± 18	134 ± 20	138 ±24	
AP (mmHg) ***	23 ± 17	15 ± 12	12 ± 8	9.3 ± 9	7 ± 7	

Variables are presented as mean ± standard deviation. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ for difference between aortic sites. Delay is time between electrocardiogram and foot of pressure wave.

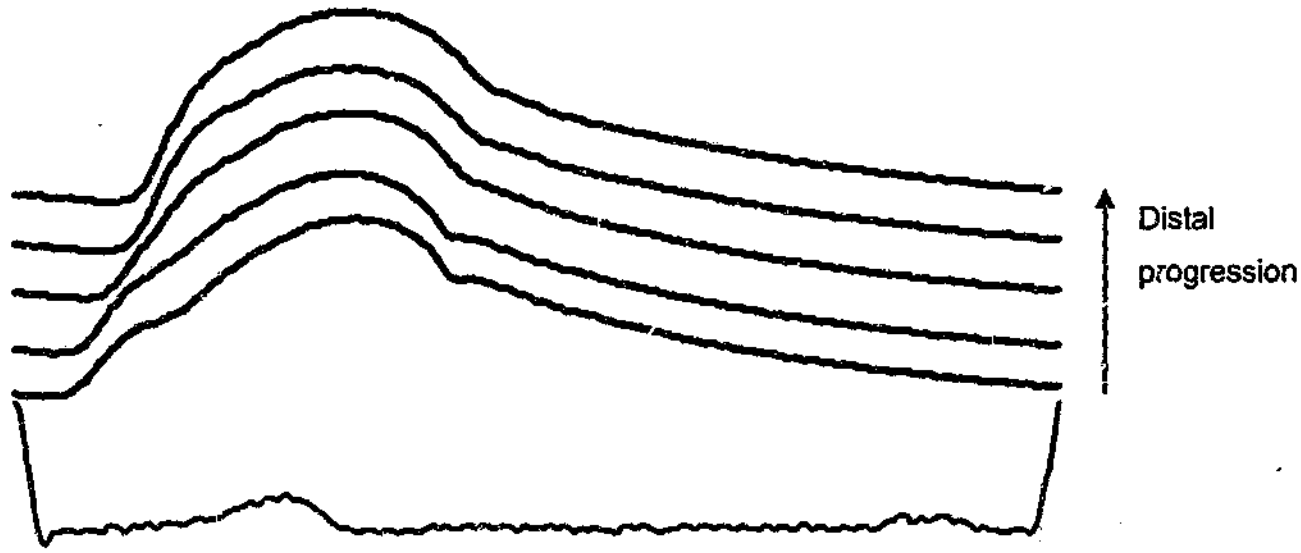


Figure 7-1. Example of decreasing augmentation index with distal progression along the aorta.

From inferior to superior the traces represent the electrocardiogram and pressure waveforms at the aortic root (augmentation index 52.3%), transverse arch (augmentation index 45.0%), level of the diaphragm (augmentation index 20.8%), level of the renal arteries (augmentation index 14.7%) and aortic bifurcation (augmentation index 14.6%) in a single subject, synchronised to the peak of the R wave of the electrocardiogram.

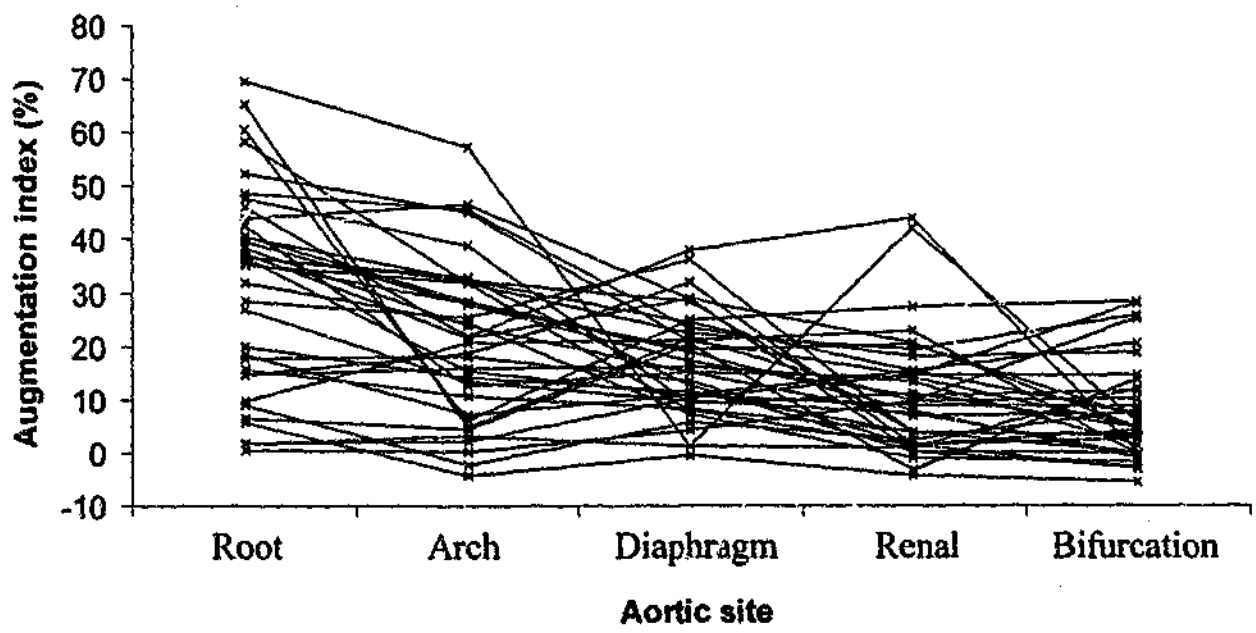


Figure 7-2. Individual augmentation indices at 5 aortic sites

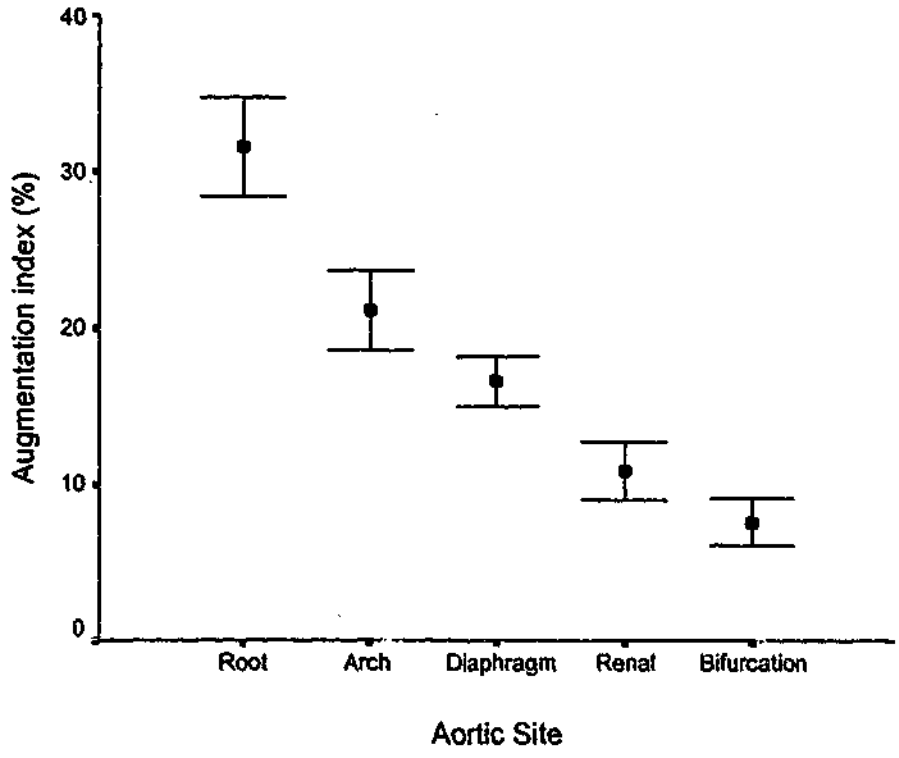


Figure 7-3. Mean augmentation index at 5 aortic sites.

Bars are standard error of the mean. $P < 0.001$ for difference between sites

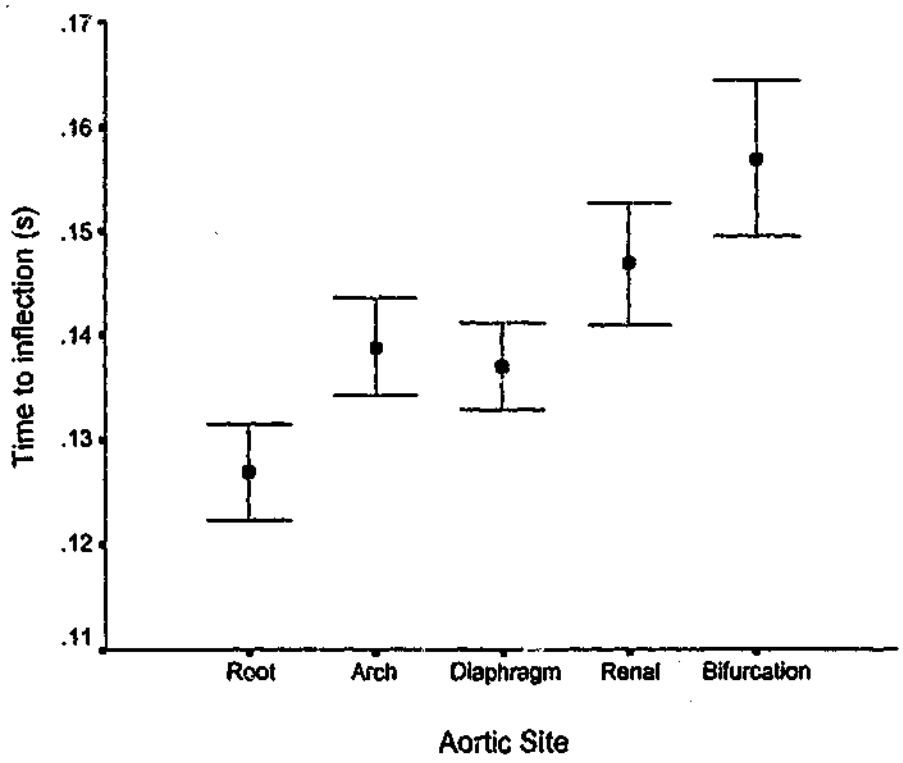


Figure 7-4. Mean time to inflection at 5 aortic sites.

Bars are standard error of the mean. $P < 0.01$ for difference between sites.

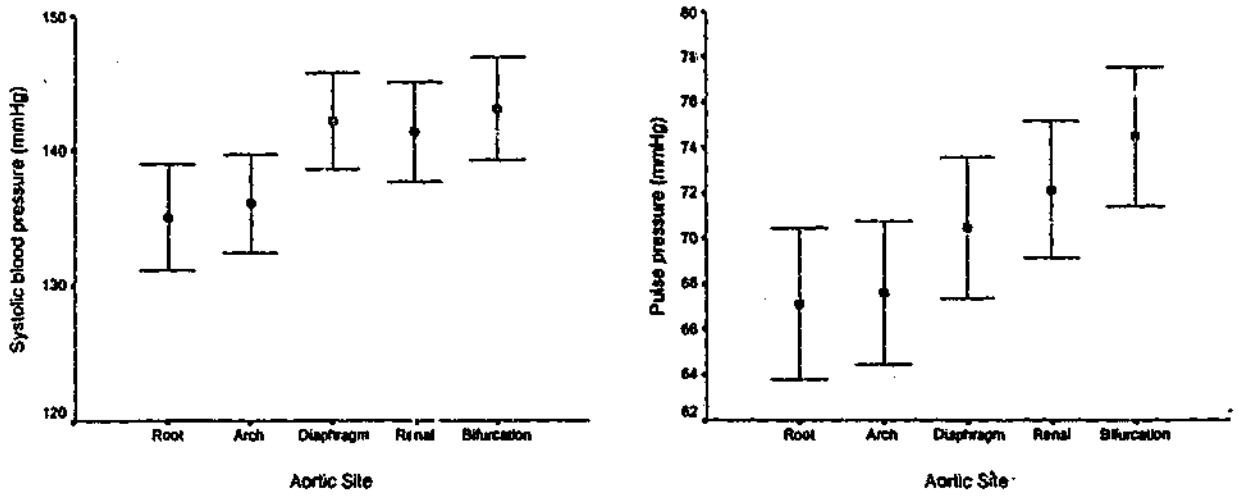


Figure 7-5. Peripheral amplification of mean systolic and pulse pressures with distal progression in the aorta.

Bars are standard error of the mean. Both $P < 0.001$ for difference between sites.

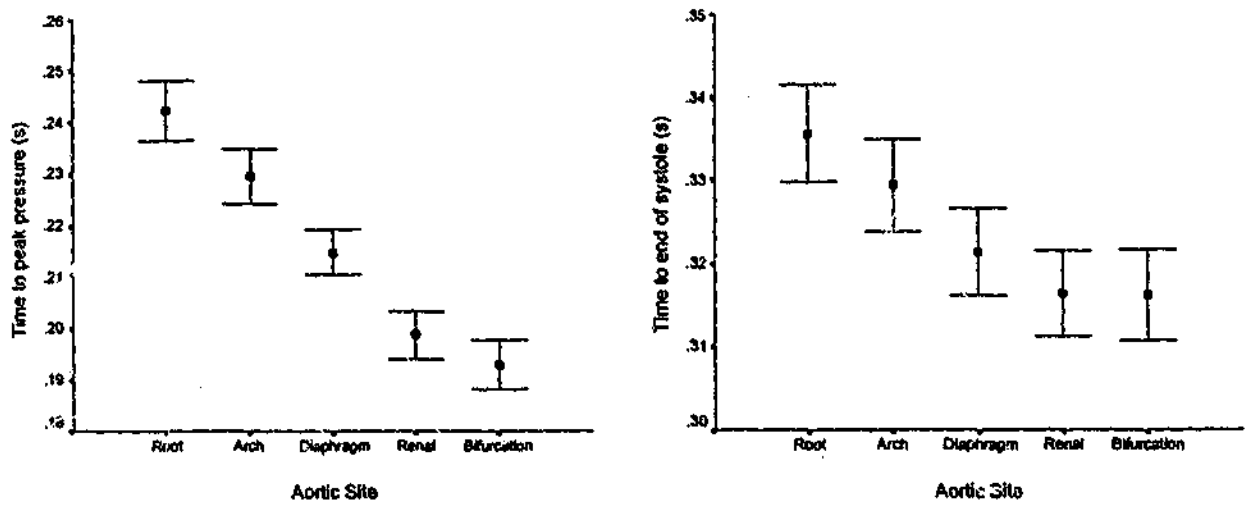


Figure 7-6. Progressive decrease in mean time to peak pressure and end of systole with distal progression in the aorta.

Bars are standard error of the mean. Both $P < 0.001$ for difference between sites.

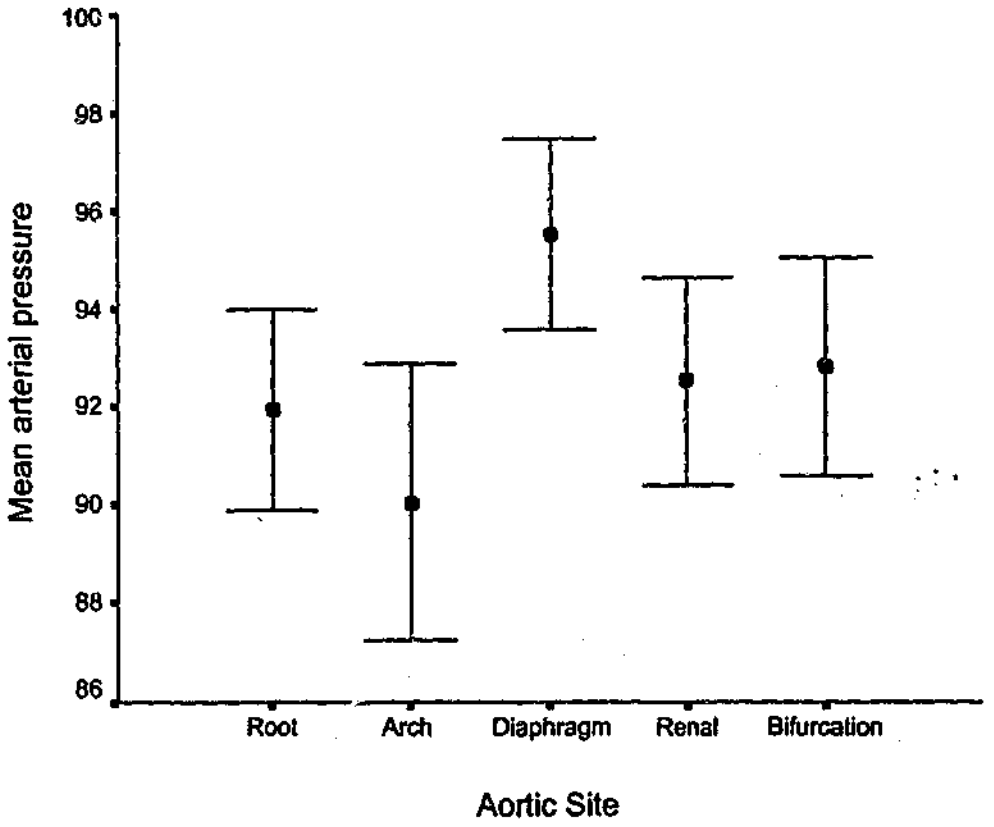


Figure 7-7. Mean arterial pressure at 5 aortic sites.

Bars are standard error of the mean. $P < 0.05$ for difference between sites.

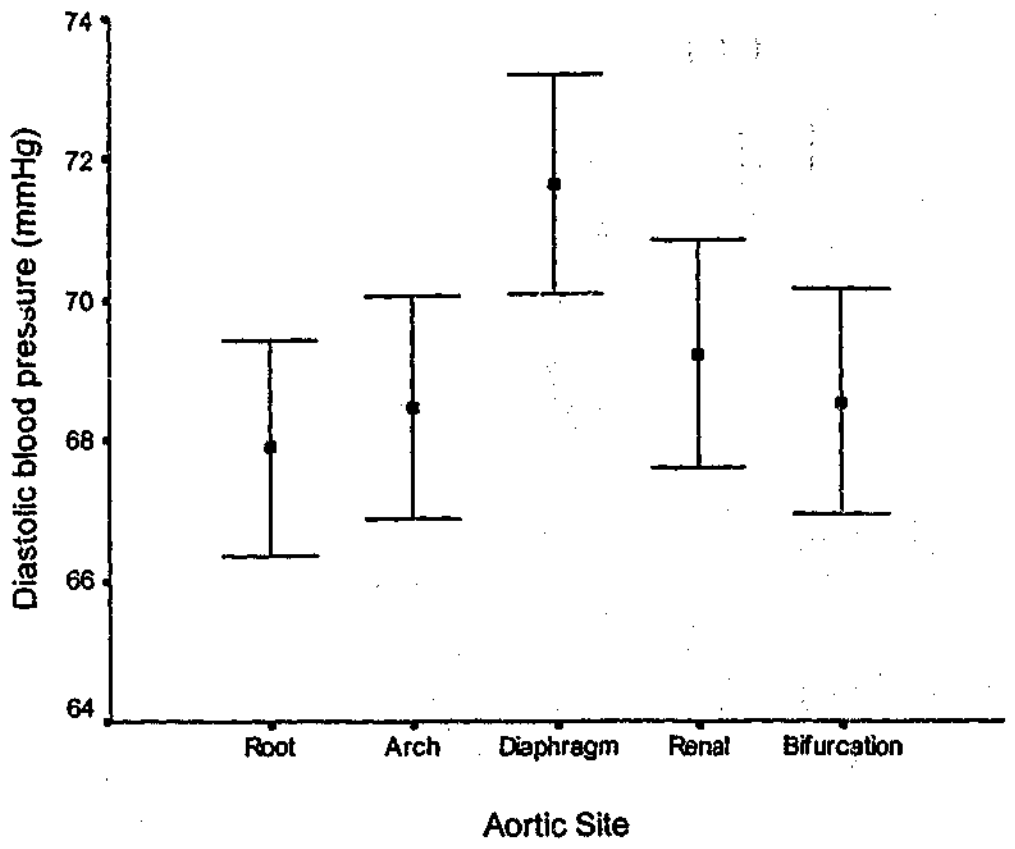


Figure 7-8.Diastolic blood pressure at 5 aortic sites.

Bars are standard error of the mean. $P < 0.001$ for difference between sites.

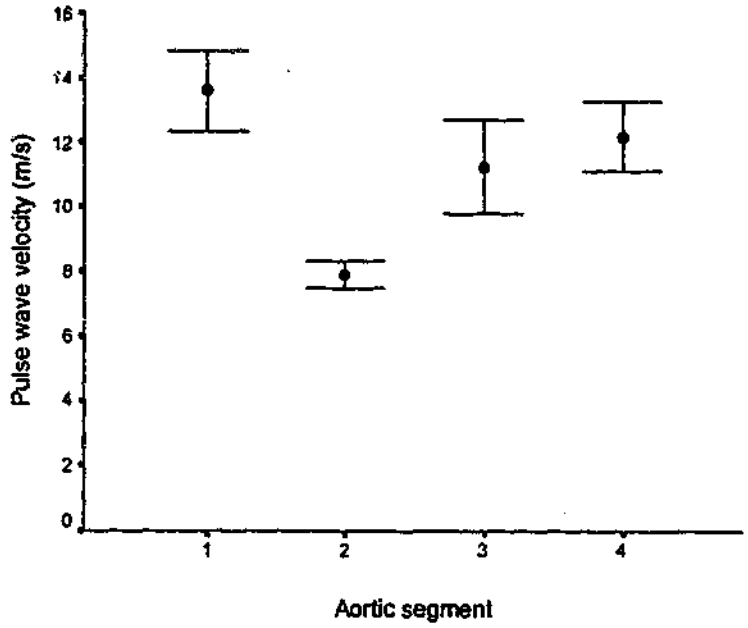


Figure 7-9. Mean pulse wave velocity across different aortic segments (200Hz data)

Depicted are mean pulse wave velocities ± standard error. 1 is aortic root to arch, 2 arch to diaphragm, 3 diaphragm to renal artery and 4 renal artery to bifurcation aortic segments. 3 subjects with apparently negative pulse wave velocity in segment 4 have been excluded.

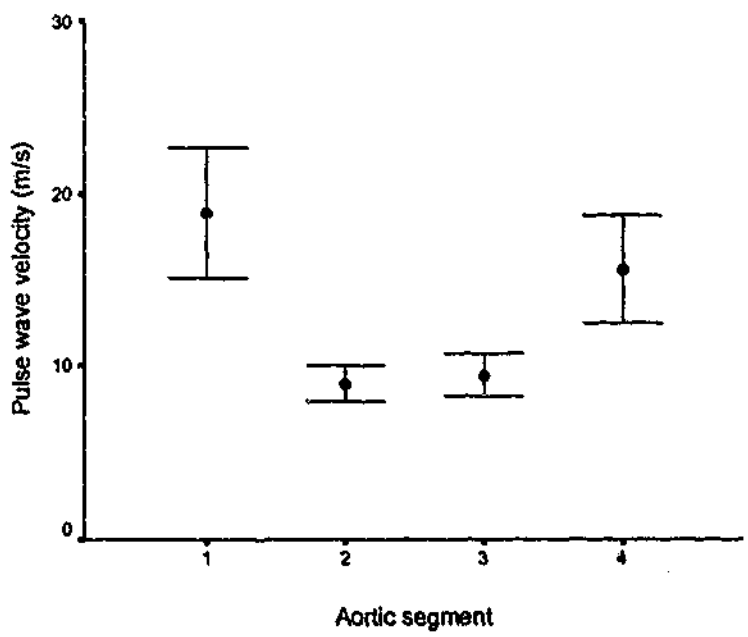


Figure 7-10. Mean pulse wave velocity across different aortic segments (2000Hz data)

Depicted are mean pulse wave velocities ± standard error. 1 is aortic root to arch, 2 arch to diaphragm, 3 diaphragm to renal artery and 4 renal artery to bifurcation aortic segments. 1 subject with pulse wave velocity of 252 m/s in segment 4 has been excluded.

7.3.2 Frequency domain analysis

The magnitude and phase diagrams for the average transfer functions between the aortic root and the 4 distal sites are depicted in Figure 7-11. There is variability in the slope of the phase of the transfer functions, and looking particularly at the transfer function between the aortic root and diaphragm and more distal sites, the slope appears flatter at the lower than the higher harmonics, in keeping with higher apparent phase velocities for the lower frequencies. The pattern of the calculated aortic root to bifurcation apparent phase velocities for most subjects was consistent with this. The measured foot-to-foot pulse wave velocity of the arterial pressure waveform was similar to the average apparent phase velocity, or group velocity, of the higher frequencies (above 3 Hz) (9.6 ± 2.7 and 7.4 ± 7.2 m/s measured and group velocity of higher frequencies respectively (*P* NS)) (Figure 7-12). However, in some individuals there were peaks of apparent phase velocity at differing specific harmonics, suggestive of significant wave reflection at these particular frequencies (Figure 7-12), and 5 subjects had negative apparent group velocities for the frequencies above 3 Hz. When the latter 5 subjects were excluded the measured foot-to-foot and group velocities above 3 Hz were much more similar (9.5 ± 2.6 and 9.8 ± 3.7 m/s respectively), and closely related ($r^2 = 0.59$) (Figure 7-13).

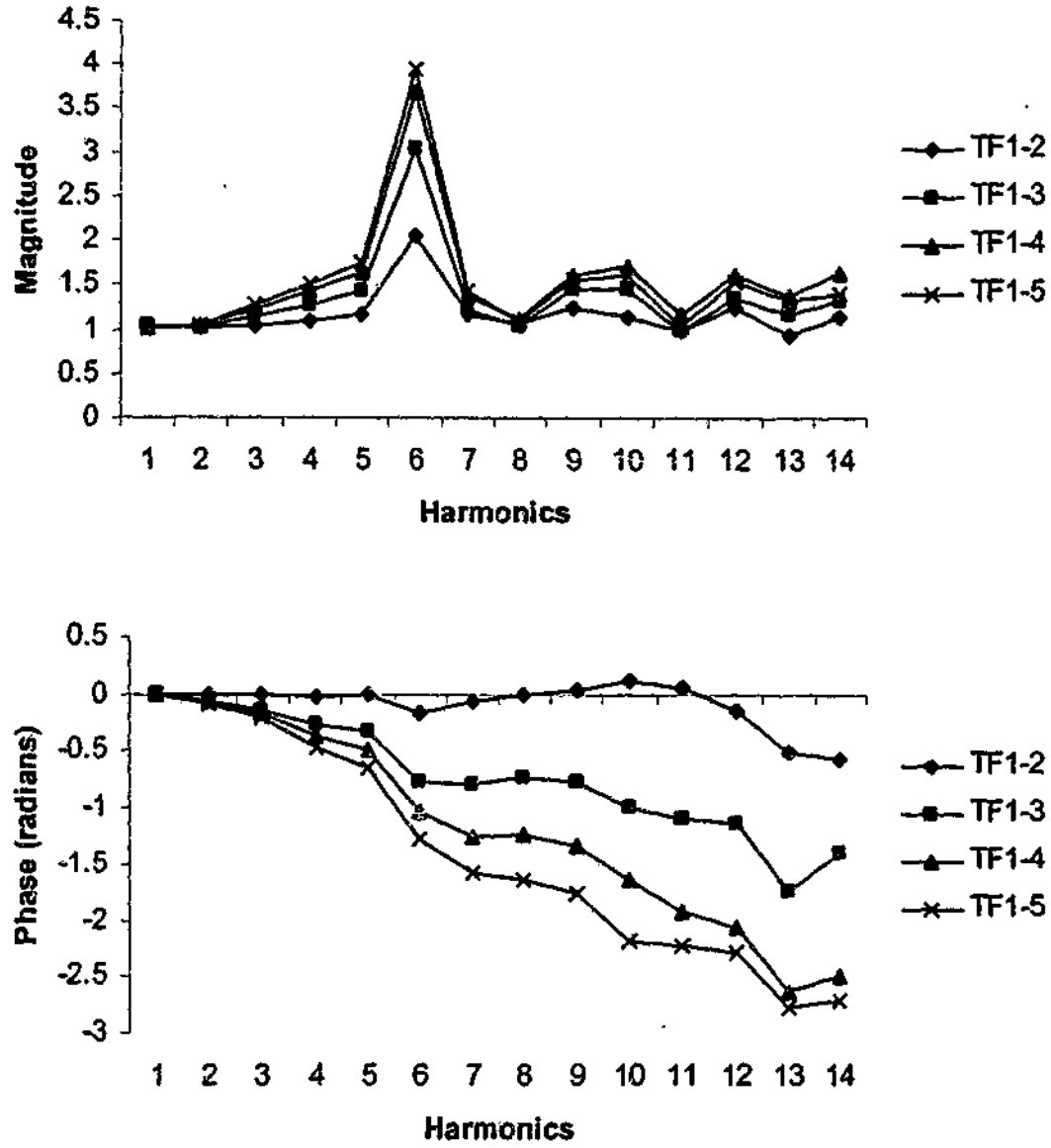


Figure 7-11. Magnitude and phase diagrams for transfer functions between pressure waveforms at the 5 aortic sites.

TF1-2 between aortic root and arch, TF1-3 between aortic root and diaphragm, TF1-4 between aortic root and renal arteries, TF1-5 between aortic root and bifurcation. Harmonic 1 represents the mean (or 0Hz frequency) of the waveform.

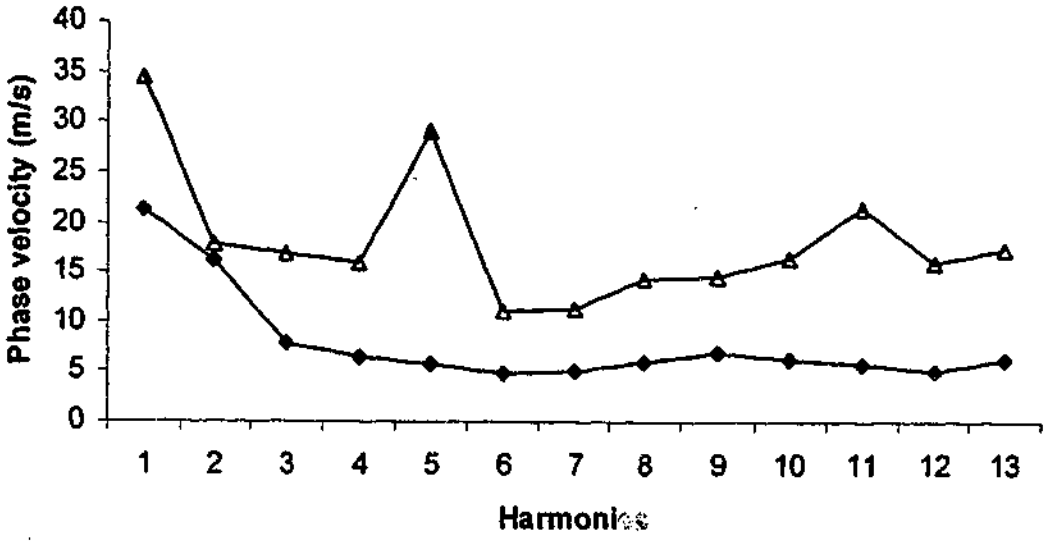


Figure 7-12. Apparent phase velocities for wave travel between the aortic root and bifurcation.

♦ depicts typical example of pattern of apparent phase velocities, Δ depicts example with peak of apparent phase velocity suggestive of reflection at this frequency.

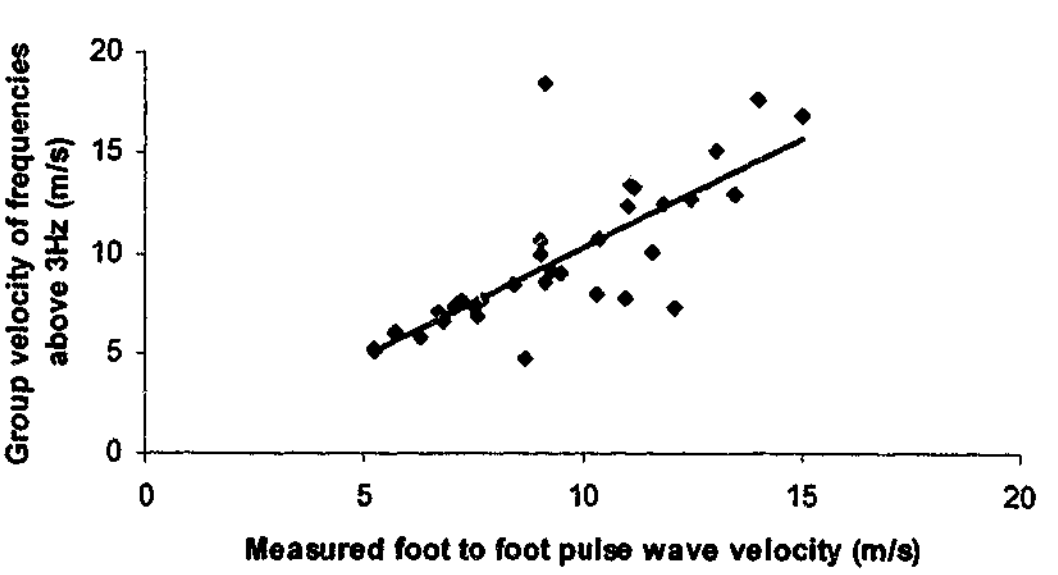


Figure 7-13. Relationship between measured pulse wave velocity and group velocity of frequencies above 3 Hz between the aortic root and bifurcation.

Subjects with negative apparent phase velocity excluded. $P < 0.001$ $r^2 = 0.59$.

7.4 DISCUSSION

7.4.1 The potential role of frequency dispersion in the phenomenon of aortic systolic pressure augmentation

The progressive decrease in the augmentation index and corresponding increase in the time to the inflection point was contrary to the expected findings according to the hypothesis that the inflection point marks the onset of influence of a reflected pressure wave. Although the findings presented here for the time to inflection differ from those of two previous small studies, there are previously published waveforms which appear consistent with these observations.(Latham, *et al.* 1985, Murgo, *et al.* 1980, O'Rourke, *et al.* 1968) The findings for other waveform characteristics are however in accordance with previously published data, with the expected peripheral amplification of systolic pressure and pulse pressure, and increase in delay in the foot of the pressure wave and decrease in time to peak pressure.(Hamilton and Dow 1939, Kelly, *et al.* 1989, O'Rourke, *et al.* 1968) It might be argued, since the pressure recordings were not acquired simultaneously from the different aortic sites, that there may have been some systematic change in the physiological condition of the subjects between recordings which might account for the findings for the time to the inflection point. However, the finding that there was no difference when the measurements were repeated in a group of 10 subjects suggests that this was not the case, raising the question as to what other factors may be contributing to the phenomenon.

Since it has long been known that the apparent phase velocities of different frequencies within the arterial pressure waveform differ, with higher velocities for the lower frequencies (Latham, *et al.* 1985, McDonald 1968, Taylor 1957, Nichols and McDonald

1972, Gabe 1964), consistent with these data, it is conceivable that the phenomenon of central pressure augmentation may arise due to frequency dispersion. The foot of the arterial waveform and the augmentation point are dependent upon high frequency components of the waveform,(McDonald 1968, Chen, *et al.* 1997) and would therefore be predicted to become relatively delayed compared to the lower frequency components with distal waveform progression. This concept was first described by Bramwell and Hill in 1923, in relation to relative delay in wavefront progression,(Bramwell and Hill 1923) and would be expected to result in the types of progressive changes along the aorta that have been demonstrated in this study, with relative delay of both the foot of the pulse wave and inflection point relative to the peak. The concept is not inconsistent with the previously described association between a short time to inflection and small stature, although this association was not evident in this study, since height might simply represent a surrogate measure of aortic diameter, and pulse wave and phase velocities are determined not only by properties of the arterial wall, but also by the physical dimensions of the vessel, with pulse wave velocity being inversely proportional to the square root of the radius (Moens-Korteweg equation) (*Section 1.2.2.1*).(Cameron 1999) The previously described association between a short time to the inflection and increased measured pulse wave velocity might also be explained, since the latter is largely equivalent to the phase velocity of the higher frequencies in the pulse pressure waveform, as confirmed by this study.(McDonald 1968, Gabe 1964, Latham, *et al.* 1985) Changes in the phase velocities of the higher frequencies, with or without changes in the lower frequencies, would be expected to result in a change in the degree of frequency dispersion, which would be reflected by changes in the time to the inflection point and the augmentation index. This phenomenon also provides a possible explanation for the previously described apparent dissociation between pulse wave velocity and augmentation index observed following caffeine ingestion, when pulse

wave velocity has been described to remain elevated after the augmentation index has returned to baseline levels, and with oral vasoactive drugs.(Vlachopoulos, *et al.* 2003, Deary, *et al.* 2002, Kelly, *et al.* 2001) It may be that differential effects on the phase velocities of high and low frequencies are responsible for observations that appear inconsistent with wave reflection phenomena. It should however be acknowledged that these findings might also be explained by inherent limitations of the single generalised arterial transfer function to reproduce accurately the central aortic augmentation index under different conditions as discussed in *Chapters 3* and *4*.

It would be unjustified to suggest that the influence of wave reflection should be completely dismissed. In any wave guiding system reflection, dispersion and attenuation will all be operative and will be dependent on both guide dimensions and wave frequency. The findings for the increasing amplitude, particularly of the 6^{th} harmonic, of the average transfer functions between the aortic root and progressively more distal sites presented in Figure 7-11 suggest that significant reflection of this harmonic may be occurring either at, or distal to, the aortic bifurcation, but that there is substantial attenuation of the reflected wave at more proximal sites with much reduced contribution of the reflected wave at the aortic root. The interpretation of apparent phase velocities is also complicated by any wave reflection, since wave reflection will influence the phase of the affected frequency in such a way that the apparent phase velocity may be either increased or decreased, depending on whether the reflected waves contribute to both the proximal and distal waveforms, or only the distal, if completely attenuated before reaching the proximal site. The variation in the transfer function phases seen in this study, which were significantly more marked in the individual than average transfer functions, has previously been accepted to indicate the presence of wave reflection.(Taylor 1957) In addition to this, the peaks in apparent phase velocity seen at individual frequencies in some subjects is highly suggestive of

significant wave reflection at these frequencies. This may explain the finding that, although there was progressive reduction in augmentation index with distal progression along the aorta as analysed by repeated measures analysis of variance, there was variation at different sites in individuals with a locally increased augmentation index, depicted in Figure 7-2, consistent with only a very localised impact of reflected waves.

7.4.2 Differences at the level of the diaphragm

It is interesting to speculate that the differences in mean and diastolic pressures at the diaphragm, and apparent non-linear changes in systolic pressure and Ti, may be due to external constraints upon the aorta as it traverses the diaphragmatic hiatus leading to apparent increase in local aortic stiffness. If the apparent differences at the level of the diaphragm are indeed due to such external constraints, this highlights the potential limitation raised previously in the capacity for studies using open chest aortic pressure measurements to validate an arterial transfer function for the non-invasive reconstruction of aortic from radial pressure waveforms in subjects with a closed chest.(Pauca, *et al.* 2001)

However, the differences between mean arterial pressure and diastolic pressure at the different aortic sites were small, as were the differences between non-invasively measured brachial and aortic root measurements of both mean and diastolic pressures. Indeed the latter lie within the criteria set by the AAMI for equivalence for blood pressure measuring devices.(White, *et al.* 1993) Although not designed for this purpose, these criteria provide a guide to differences in measurements which might be considered acceptable in clinical practice. Thus the assumption that mean and diastolic pressures are equivalent throughout the arterial system,(Hamilton and Dow 1939) which has been

adopted in the calibration of non-invasively acquired arterial pressure waveforms, remains tenable on the basis of this data.

7.4.3 Pulse wave velocity across different aortic segments

Although the values of pulse wave velocity in this study are higher than those demonstrated in 4 previous studies, 2 in humans and 2 in dogs, the subjects in these studies had no coronary artery disease, whereas those in the study presented in this chapter had a significant burden of coronary artery disease and would therefore be expected to have higher pulse wave velocities.(Luchsinger, *et al.* 1964, McDonald 1968, Nichols and McDonald 1972, Latham, *et al.* 1985). The pattern of increasing pulse wave velocity with distal progression along the descending aorta is consistent with previously published findings, however, the higher pulse wave velocity demonstrated in the ascending aorta in this study differs from the findings of 2 of the 3 previous studies which have presented comparable data.(Luchsinger, *et al.* 1964, Nichols and McDonald 1972, Latham, *et al.* 1985) This too might be explained by the presence of coronary artery disease in the particular cohort of subjects. Indeed, it is conceivable that it is causally related, since a stiffer ascending aorta, implied by the increased pulse wave velocity, would be expected to be associated with a greater pulse pressure, with a lower diastolic pressure, resulting in a reduced coronary artery perfusion pressure and possibly reduced coronary artery blood flow.

7.5 CONCLUSIONS

Although pressure wave reflection may play a role in the manifestation of the augmentation of central systolic pressure, it does not appear to be solely, or perhaps even primarily, responsible for the phenomenon, and indeed the term itself may be a misnomer. The possible contribution of frequency dispersion to this phenomenon merits further investigation.

Chapter 8

Conclusions

Dii laboribus omnia vendunt

(Hard work is the price of every achievement)

William Harvey 1578-1657

The work presented in this thesis has explored the relationships between pressure waveforms at different sites within the arterial system in subjects with suspected or proven coronary artery disease. Although the waveform morphology changes significantly with distal progression along the aorta and between the central aorta and radial artery, most of the waveform parameters explored remain closely related. Features of the arterial mechanical properties and wave mechanics that contribute to the change in waveform morphology with distal progression remain incompletely understood, but the findings presented from the different aortic sites challenge the generally accepted view that the augmentation index is a manifestation of the superimposition of a reflected pressure wave on the pressure wave resulting from myocardial contraction, and suggest that propagative phenomena, perhaps related to frequency dispersion may be of greater importance.

Arterial transfer functions describing the relationship between the arterial pressure waveforms in the central aorta and radial artery are very similar whether derived from data acquired using a fluid-filled catheter system or Millar Mikro-tip® pressure transducer-tipped catheters, and also under very different physiological conditions. However, the individual variability is substantial resulting in wide confidence intervals for all average arterial transfer functions. Probably related to this is the finding that, although waveforms can be reconstructed by the application of a generalised arterial transfer function to radial waveform data which resemble those measured in the ascending aorta, there are significant errors in the reconstruction of most waveform parameters. Of perhaps greater significance for the potential for the technique to be of value in individuals is the finding that errors are related not only to the underlying absolute value of the parameters as measured in the central aorta, but also to the pulse wave velocity, a marker of the mechanical properties of the intervening vessels. Thus, whereas the use of arterial transfer function techniques has been heralded as a method

with the potential to circumvent the limitations of conventional non-invasive blood pressure measurements in the brachial artery associated with differing arterial mechanical properties, the errors associated with arterial transfer function techniques appear to be determined by similar factors. It is perhaps not surprising therefore that for the non-invasive estimation of central aortic waveform parameters, the application of arterial transfer function techniques offers no advantage over the estimation of central aortic blood pressures directly from the non-invasive brachial artery measurements, and other waveform parameters from the untransformed radial artery waveform. Indeed, for the augmentation index, the reconstructed waveform augmentation index remained closely related to that of the untransformed radial waveform, and the latter was significantly superior in its capacity to predict the measured central aortic. These findings strongly suggest that the data in the literature purporting to represent data on central aortic waveform parameters, and particularly the augmentation index, reconstructed by the application of a generalised arterial transfer function to non-invasively acquired radial waveform data should be interpreted with some caution. In reality the data presented are likely to be no more related to the measured central aortic parameters than are the parameters of the radial waveforms from which it was derived, and for augmentation index significantly less so. Whilst these limitations do not necessarily negate the capacity for the reconstructed waveform parameters potentially to contribute to the prediction of risk of future cardiovascular disease or complications, the analysis of untransformed radial waveform parameters is more likely to be of value.

Directions for future research arising from the work presented in this thesis might include exploring whether better predictions of central aortic waveform parameters can be obtained by the direct analysis of the carotid artery waveform rather than the radial, since this waveform will have been less distorted by distance from the site of interest. Alternatively, an assessment of whether a more individualised approach to the transfer

function reconstruction of central aortic waveforms as advocated by some investigators might be of value. This might be approached by exploring the potential for a generalised arterial transfer function to be adjusted to account for subject demographic features such as gender, the presence of diabetes mellitus and arm length, all of which have the potential to influence the individual transfer function, and also physiological features such as pulse wave velocity which might be of value in compensating for the error in the reconstructed waveform parameters which appears to be associated with arterial mechanical properties. Additionally, further exploration of the propagation of the waveform in the aorta, particularly of the effects of physiological or drug interventions on the propagation of waveform features, and particularly the augmentation index, may contribute towards a greater understanding of the manifestation of this phenomenon.

A greater understanding of pulse wave propagation may contribute both to more effective identification of persons at increased risk of cardiovascular disease or complications, and also potentially to more effective individualisation of therapeutic interventions. However, whether the direction of treatment on the basis of any pressure waveform parameter, either peripheral, central aortic or reconstructed, can provide such benefits remains to be tested.

Appendix A – Prospective validation of TF_1 and the impact of non-invasive calibration of radial waveforms

METHODS

The subjects contributing this study were drawn from those contributing to the studies presented in *Chapter 4*. The first 42 consecutive subjects contributed to this study. The characteristics of this subgroup of subjects are presented in Table A-1. Reconstructed central aortic pressure waveforms were derived by the application of TF_1, the transfer function derived in *Chapter 3* by Method 1, to representative radial waveforms calibrated separately to both measured aortic and brachial artery blood pressures, as described in *Section 2.6*. This yielded 2 reconstructed central aortic waveforms for each subject. All waveforms, both measured and reconstructed, were analysed as described in *Section 2.4*. Measured aortic waveform parameters were compared with parameters of both transfer function-derived waveforms.

Table A-1. Subject characteristics for calibration subgroup.

Male gender	28 (67%)	**Current smoking**	3 (7%)
Age (years)	64 ± 12	**Diabetes Mellitus**	9 (21%)
Height (m)	1.70 ± 0.08	**Hypertension**	19 (45%)
Weight (kg)	79 ± 15	**Hypercholesterolaemia**	33 (79%)
Body Mass Index (kg/m^2)	27 ± 4	**Obesity (BMI>30)**	10 24%)
Heart Rate (bpm)	66 ± 11	**Family History**	8 (19%)
SBP (mmHg)	134 ± 21	**DBP (mmHg)**	72 ± 9
MAP (mmHg)	94 ± 13	**Pulse pressure (mmHg)**	62 ± 18

BMI is body mass index, bpm beats per minute, SBP systolic blood pressure, DBP diastolic blood pressure and MAP mean arterial pressure. Blood pressures are non-invasively measured brachial artery pressures.

RESULTS

The characteristics of the central aortic waveforms reconstructed using TF_1 and both the invasively and non-invasively calibrated radial waveforms are presented in Table A-2, together with the parameters of the directly measured central aortic waveforms. There were significant differences in most parameters between the measured aortic and both reconstructed waveforms. With the exception of Ti, which remained correlated with the radial Ti (r = 0.58. $P < 0.001$), all parameters of the reconstructed waveforms were correlated with the respective measured parameters. However, despite the significant relationship between the reconstructed and measured AI in this group, the reconstructed AI remained significantly more closely correlated with the radial (r = 0.89) than the measured aortic (r = 0.65) ($P < 0.01$) (Figure A-1).

There were significant differences between the two reconstructed waveforms in all the pressure parameters, pressure time integrals, and SVI. There was no difference between the two reconstructed waveforms in any of the time parameters or augmentation index.

There was no difference between the waveforms reconstructed from invasively calibrated radial data and the directly measured central aortic in systolic blood pressure, but significant underestimation of central systolic pressure by the application of TF_1 to the non-invasively calibrated radial waveform ($P < 0.001$). However, despite remaining different from the measured, there was a significantly smaller underestimation of diastolic pressure in the waveforms reconstructed from the non-invasively calibrated waveform ($P < 0.001$).

Table A-2. Measured aortic waveform parameters and relationships with transfer function-derived parameters from invasively and non-invasively calibrated radial waveforms

	Aortic	Invasive calibration		Non-invasive calibration	
	Mean	Mean difference	Pearson's *r*	Mean difference	Pearson's *r*
SBP (mmHg)	130 ± 23	-1 ± 8	0.94 ***	7 ± 12 *** ‡	0.86 ***
DBP (mmHg)	67 ± 9	9 ± 3 ***	0.96 ***	3 ± 6 ** ‡	0.76 ***
PP (mmHg)	63 ± 20	-10 ± 9 ***	0.92 ***	4 ± 12 * ‡	0.82 ***
Ad (mmHg.s)	48.88 ± 11.68	4.27 ± 1.93 ***	0.99 ***	2.99 ± 4.05 *** †	0.95 ***
As (mmHg.s)	37.03 ± 7.96	-0.48 ± 2.22	0.97 ***	1.29 ± 4.38 ‡	0.84 ***
SVI	1.35 ± 0.31	0.15 ± 0.15 ***	0.88***	0.05 ± 0.21 ‡	0.79 ***
AI (%)	29.3 ± 17.1	8.2 ± 12.7 ***	0.65 ***	7.7 ± 12.4 ***	0.65 ***
Ti (s)	0.125 ± 0.022	-0.023 ± 0.023 ***	0.02	-0.022 ± 0.023 ***	0.02
Ts (s)	0.337 ± 0.036	-0.018 ± 0.025 ***	0.83 ***	-0.014 ± 0.024 ***	0.77 ***
Tp (s)	0.255 ± 0.039	-0.004 ± 0.027 ***	0.46 **	0.002 ± 0.025	0.80 **

Mean difference is measured aortic minus reconstructed waveform value. * denotes $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$ for difference from, or correlation with measured aortic parameter. † denotes $P < 0.01$ and ‡ $P < 0.001$ for difference from derived parameters using invasively calibrated radial waveform. SBP is systolic blood pressure, DBP diastolic blood pressure, PP pulse pressure, Ad diastolic pressure time integral, As systolic pressure time integral, SVI subendocardial viability index, AI augmentation index, Ti time to inflection, Ts time to end of systole and Tp time to peak pressure.

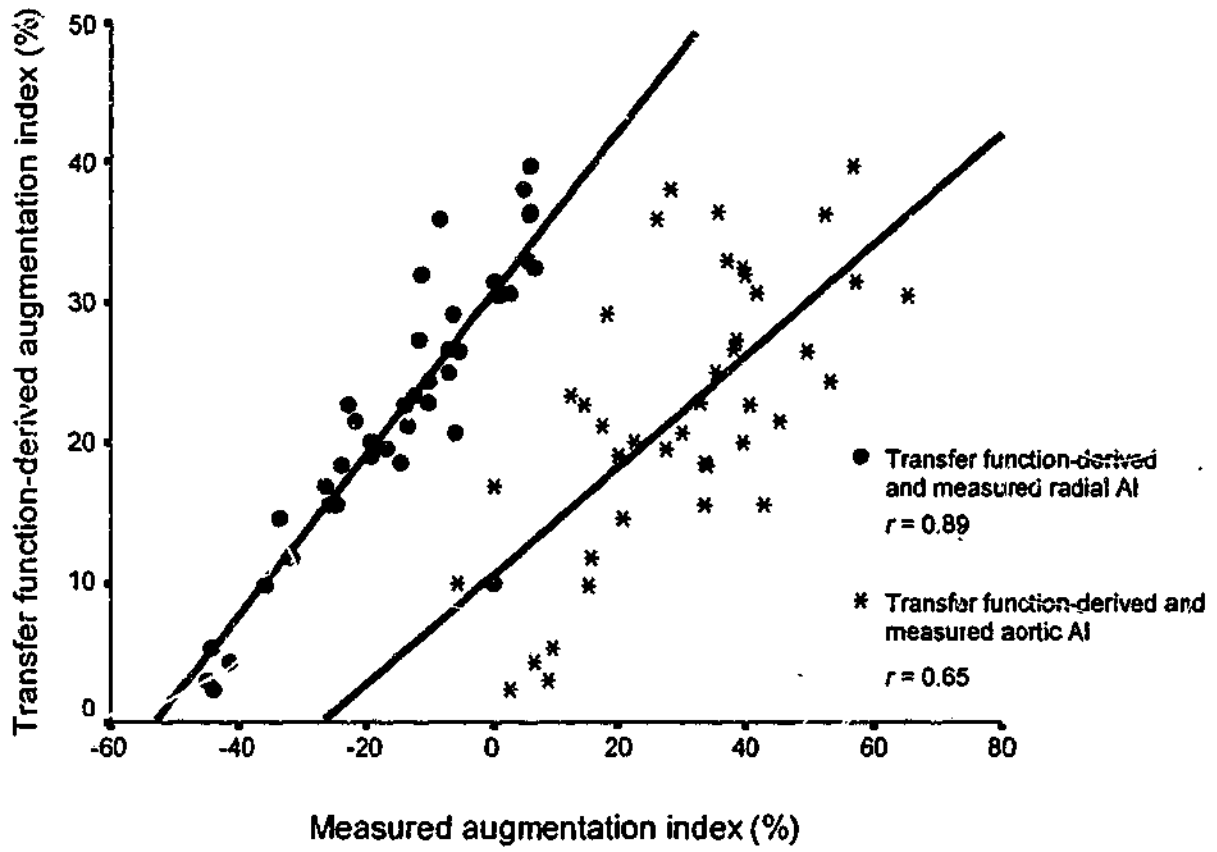


Figure A-1. Relationship between transfer function-derived and both measured aortic and radial augmentation indices.

AI is augmentation index.

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