NON-INVASIVE CARDIOVASCULAR ULTRASOUND

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MD Thesis

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July 1997
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ABSTRACT

This thesis describes the use of non-invasive ultrasound in assessing the cardiovascular system. Ultrasound is one of the most widely used imaging techniques in clinical medicine and recent advances suggest an even greater potential. New developments in ultrasound technology include higher image resolution and faster computer processing.

Echocardiography is routinely available in clinical practice and can be used to measure both cardiac structure and function. This well validated technique is applied to an original study of hypertension where measures of left ventricular diastolic function are found to support a change in the management of white coat hypertension.

Arterial mechanical function can now be studied non-invasively allowing assessment of arterial compliance by measuring small changes in arterial diameter throughout the cardiac cycle. In addition the tensile stress applied during cardiac contraction can be estimated by measuring systolic and diastolic flow velocities within the vessel. The new technique of arterial wall tracking is described and compared to conventional Doppler examination of the arteries.

High resolution ultrasound can provide enough detail to measure the separate layers within arterial walls with a resolution of 0.01mm. This technique is used in a study of atherosclerosis and hypertension where measurements of early atherosclerosis (intima-medial thickness) are compared to plasma markers including lipoprotein (a) and fibrinogen.

Computer analysis of Doppler waveforms allows digital visual representation of blood flow. The fast Fourier transformation technique is used in transcranial Doppler ultrasound where low MHz frequency ultrasound is used to penetrate bone allowing monitoring of intracranial blood flow velocities. Continuous digital monitoring of arterial blood flow revealed signals caused by circulating microemboli in subjects with carotid artery stenosis. Transcranial Doppler ultrasound is used in this thesis to study commercial air divers and subjects with carotid atherosclerosis. These disparate groups represent sources of gaseous and solid emboli respectively.

Overall the thesis describes the original use of established and new ultrasound techniques which are applicable to clinical practice.
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ACKNOWLEDGEMENT

The studies described in this thesis would not have been possible without the much appreciated help and enthusiasm of others. The following deserve special mention: Dr Henry Elliott and Professor John Reid for many useful suggestions and helpful advice, Dr Donald Grossett for helping to shape vague notions into feasible plans and Mr Ian Sim for taming the technology used in many of the studies. Dr Kennedy Lees’ suggestions and efficient criticism of manuscripts were invaluable and his co-operation in allowing specialised (and expensive) ultrasound devices to be taken to the middle of Loch Linnhe in a cold and stormy January has to be admired.

Much of the work involved subjects participating in a longterm study of antihypertensive and potentially anti-atherosclerotic treatment. This study would have been impossible without the help of Dr Joan Curzio, Ms Ros Carter and Ms Margaret Green.

The diving research was performed with invaluable support from Mr Doug Shearer (Manager of the Underwater Centre in Fort William) and instructors Chris Tatham, Pete Berry and Alf Leadbetter. The land-based section of this study was made possible by the assistance of Dr Gavin Brown and the nursing staff of the Belford Hospital in Fort William. Dr James Douglas provided expertise in hyperbaric medicine essential to this venture in a typically enthusiastic manner.

Finally, Fiona deserves recognition for her continuing support and sense of reality which has been crucial to this project.
AUTHORS DECLARATION

The research described in this thesis is original work which I conceived, performed, analysed and described during a research fellowship in the Department of Medicine and Therapeutics in the Gardiner Institute, University of Glasgow between 1993 and 1995. It has not been submitted previously for a higher degree.

I recruited the majority of subjects from the Western Infirmary who took part in the studies involving echocardiography, carotid Duplex and B-mode ultrasound and transcranial Doppler ultrasound. I recruited all the divers who took part in the right-to-left shunt study. I performed all echocardiography and the majority of transcranial Doppler ultrasound monitoring and vascular compliance measurements.

The following were performed by other individuals:

Recruitment of remaining subjects for the European Lacidipine Study on Atherosclerosis (ELSA) by the consultants of the Western Infirmary Blood Pressure Clinics including Professor John Reid, Drs Anna Dominiczak, Kennedy Lees, Henry Elliott and Gordon McInnes. Dr Frank Dunn of Stobhill Hospital also contributed significantly. Local general practitioners were involved in primary recruitment including Drs Barry Glekin, Alan Wade, Brian Robson, Fiona Davidson, Kate Pickering and Malcolm Brown.

Carotid B-mode ultrasound was performed by Mrs Ros Carter and Ms Margaret Green. Mr Ian Sim performed a significant proportion of carotid Duplex and vascular compliance measurements. Dr Joan Curzio assisted with patient administration and the use of ambulatory blood pressure monitors. The clinical biochemistry laboratory at Gartnavel General Hospital performed all biochemical analyses.

All of the research studies were approved by the West Glasgow Hospitals Ethics Committee and written informed consent was obtained from all subjects.
CHAPTER 1  INTRODUCTION

This MD thesis describes the application of non-invasive ultrasound techniques in the assessment of cardiovascular structure and function. It is intended to demonstrate the clinical versatility of ultrasound in cardiovascular medicine by describing techniques that can be used to measure left ventricular wall thickness and contractility, arterial wall thickness and compliance, atherosclerotic severity, and to detect signals caused by circulating emboli.

In terms of end points, there are effective forms of treatment for many aspects of cardiovascular disease but the potentially reversible benefits decrease as the disease progresses. For example, young healthy arteries have adaptive mechanisms which compensate for reduced blood flow, and age or disease related gradual functional and structural deterioration may only become clinically apparent in middle or old age. In addition the eventual clinical presentation may be irreversible whereas early intervention might have retarded or prevented the progression. The key issue therefore is to identify high risk individuals at an early stage. Non-invasive techniques are required which are capable of screening large numbers of individuals with high levels of specificity and sensitivity but with low risk of potential side effects. Ultrasound is such a technique. There have been no clinically
significant side effects from ultrasound energy used in medical imaging.\textsuperscript{1,2} Although high energy ultrasound can cause small gas bubble formation in vitro this does not occur with the energy levels used in clinical practice.\textsuperscript{2} This inexpensive technique can be used safely to study asymptomatic individuals and to improve patient selection for treatment or further investigation. This thesis describes how ultrasound has evolved into specialised techniques that are capable of measuring both structure and function. The thesis is arranged in anatomical order; starting with cardiac studies (Chapter 5) before assessing the mechanical properties of large arteries (Chapters 6 and 7), measuring arterial structure (Chapter 8) and finally describing signals caused by circulating emboli (Chapters 9 and 10).

1. Echocardiography

The first study describes echocardiographic assessment of cardiac function and structure in hypertension. Echocardiographic measurement of left ventricular structure is widely available and has been validated extensively with invasive measurements and post mortem studies.\textsuperscript{3-5} The Framingham cohort follow-up study is an example of a population based screening programme where ultrasound was used to estimate left ventricular mass. This subsequently was
shown to be an important prognostic marker of cardiovascular mortality.6-8

In addition, echocardiography can be used to measure the velocity of blood travelling within the cardiac chambers by Doppler ultrasound. It is possible, for example, to measure the flow of blood through the mitral valve during left ventricular filling to determine ventricular compliance during relaxation.9 The ventricle normally fills by energy dependent active relaxation which effectively drains most of the blood contained in the atrium by suction. The left atrium then contracts to complete the small remainder of ventricular filling. However, in hypertension the ventricle is less compliant and relaxes inadequately thus requiring proportionally more active atrial filling.10 This impairment of filling can be measured objectively by the E:A ratio (see figure 1) which is determined by the ratio of Early (passive) filling related to Active (atrial) filling. This is described in detail in chapters 4 and 5. This is clinically relevant since left ventricular diastolic dysfunction can be detected early in disease processes such as hypertension and may precede symptomatic left ventricular systolic dysfunction.

The aim of the study was to measure parameters of structure and function in subjects who remained hypertensive throughout an ambulatory blood pressure monitoring period (persistent hypertensives).
Pulse wave Doppler sample volume placed between the tips of the mitral valve leaflets to analyse blood flow into the left ventricle during diastole.

Normal diastolic function with Early filling contributing most of ventricular filling and Atrial filling serving to top-up the ventricle.

Abnormal diastolic filling with a reduction in Early relaxation and an increase in Atrial contraction. This reversal of the E:A pattern is common in hypertension.

Figure 1. Echocardiographic measurement of diastolic function.
and to compare the findings with matched groups of normotensive and white coat hypertensives. White coat hypertensives by definition were normotensive after leaving the hospital but were significantly hypertensive within a clinical setting. The groups were matched for body characteristics such as weight, height, sex and age which can affect the pattern of ventricular filling. The aim was to determine if white coat hypertensives had objective evidence of cardiac dysfunction which could benefit from antihypertensive treatment.

2. Arterial compliance

The next study describes the measurement of arterial compliance in the same patient groups. This involves a relatively new ultrasound technique to detect arterial diameter changes throughout the cardiac cycle. The principles involved in describing mechanical properties of arteries are described in detail in chapter 2 and the use of wall tracking ultrasound in hypertension is reviewed. This involves very high resolution Doppler ultrasound to track the movement of the arterial walls (wall tracking technique) and gives a measure of the mechanical properties of the artery which can change in disease processes such as atherosclerosis and hypertension. The large arteries act as an elastic buffer during cardiac contraction and help to smooth the pulsatile flow of blood to the periphery.11-15 They absorb reflected pressure waves
caused by peripheral resistance during cardiac contraction.\textsuperscript{12} With increasing age this buffering capacity decreases because of changes in the mechanical properties and load bearing capacity of the vessels. Studies of the large arteries in hypertension\textsuperscript{12,16-20} have shown that these functional abnormalities may be reversible with treatment. These include abnormalities of arterial diameter, distension, elasticity and compliance which are implicated in the progression of atherosclerosis and failure of the elastin portion of the arterial wall. This is thought to be a major factor in the development of systolic hypertension in the elderly\textsuperscript{12} and is also involved in the pathogenesis of aneurysm formation. Ultrasound measurement of vascular dysfunction allows calculations of derived parameters which describe arterial function while correcting for arterial size, wall thickness or blood pressure at the time of measurement. These are discussed in detail in a review of arterial compliance measurement (chapter 2). The wall tracking technique is applied to the patients described in chapter 5 with additional comparisons between vascular mechanical properties and cardiac structure and function. Having identified functional cardiac abnormalities in the white coat hypertensive patients the next step was to look for similar vascular abnormalities. Hypertension may initially cause peripheral vascular dysfunction (eg vasoconstriction, or
mechanical damage through repetitive strain) before secondary cardiac dysfunction.

An alternative approach to the wall tracking technique of vascular mechanical stress measurement is described in a study of carotid arterial pulsatility in hypertension (chapter 7). This study explores the relation between hypertension and mechanical stress in the large arteries leading to the cerebral circulation. Using the wall tracking technique described above it is possible to measure parietal stress, a measure which describes the stretching force within an artery based on the distending pressure, radius of the vessel and wall thickness. The pulsatility index also reflects mechanical stress and is based on the speed of blood travelling within the artery. This can be measured using pulsed wave Doppler ultrasound (as described in chapters 4 and 7). These measurements are performed in groups of normotensive and hypertensive patients and are used to investigate the changing pattern of stroke incidence world-wide following the introduction of antihypertensive therapy which has resulted in a greater reduction in haemorrhagic compared to atherosclerotic stroke.

3. Vascular structure

High resolution ultrasound can be used to measure arterial wall thickness with axial resolution approaching 200μm (as described in
chapter 4). This technique is used in an extension of the study of white coat hypertensives to describe measurements of common carotid arterial intima-medial thickness (IMT) in relation to blood pressure patterns. There is increasing evidence that large vessel IMT may be an important predictor of cardiovascular disease and can reflect the severity of arterial disease elsewhere in the body including the coronary arteries which are still inaccessible to non-invasive ultrasound imaging.

High resolution B-mode ultrasound provides anatomical images of tissues allowing measurements of arterial wall thickness that have been shown to correlate well with surgical and post-mortem specimens of carotid arteries.\textsuperscript{21-23} It is important to study arterial wall structure rather than lumen diameter (eg measurement of stenosis by invasive angiography) since arteries enlarge outwards in the early stages of atherosclerosis without any decrease in luminal diameter. This is explored in chapter 8 where the effect of persistent and white coat hypertension on carotid wall thickness is compared to normotensive subjects as a measure of end organ damage. While chapters 5 and 6 show functional abnormalities in the white coat hypertensives, this study shows mild structural changes in the large arteries. The clinical implications are discussed in detail.
4. Circulating embolus detection

The final technique used in this thesis describes ultrasound measurement of the properties of the blood carried within the arteries. One of the first uses of ultrasound in medicine was as a safety alarm warning of gas emboli in bypass circuits.\textsuperscript{25} The technique of embolus detection has since developed and was used initially to refine decompression tables for sub-aqua divers\textsuperscript{26} but now is used in clinical practice as transcranial Doppler ultrasound (TCD).

TCD embolus detection has developed as a separate technique following a study which used ultrasound to monitor the cerebral circulation of patients undergoing carotid artery surgery. Abnormal intermittent high intensity, short duration embolic signals were detected during the surgical procedure particularly during cross clamp release.\textsuperscript{27-29} These signals were thought to result from small blood clots or air bubbles introduced during the procedure. Two distinct patterns of embolic signals have emerged in TCD research. Gas emboli cause intense reflectance of ultrasound energy and correspondingly show as high amplitude signals compared to a solid embolus of a similar size. This is discussed in a review of the clinical studies using TCD embolus detection (chapter 3).
Chapter 9 describes TCD ultrasound monitoring of commercial divers during decompression and was the first published use of TCD in divers, using the technique as a non-invasive screening test for right-to-left intracardiac shunting through a patent foramen ovale and then monitoring the arterial circulation during decompression. The TCD shunt detection technique is compared to contrast transthoracic echocardiography.

The second TCD study (Chapter 10) is of embolus detection in carotid atherosclerosis, a setting associated with solid circulating microemboli.\textsuperscript{30-35} Patients with stenosis of the internal carotid artery are at risk of embolic stroke. However, only a minority ever become symptomatic\textsuperscript{36,37} and there is as yet no reliable way of identifying the high risk individuals. The aim of this study was to establish if circulating signals were present in subjects with atherosclerotic plaque but without significant haemodynamic disturbance of blood flow. This is important if TCD is to become clinically useful. In addition the results help to explain the origin of the signals in atherosclerosis, and evidence is presented which supports turbulent blood flow as a cause of microembolic signals formation.
CHAPTER 2 VASCULAR COMPLIANCE

1. Introduction

Measurement of arterial compliance in vivo allows greater insight into the pathogenesis of hypertension and enables an objective approach to treatment. The measurement techniques are also applicable to other clinical settings such as cardiac failure\textsuperscript{13,38-9} and hyperlipidaemia\textsuperscript{40-42} where arterial function may be disturbed.

2. Arterial compliance

The large arteries act as an elastic buffer to help smooth the pulsatile delivery of blood from the left ventricle and thereby provide almost continuous flow through the peripheral arterioles and capillaries.\textsuperscript{43} Various models have been used to describe this flow pattern and one of the earliest was the Windkessel which first was described by Stephen Hales in 1769. The Windkessel was the air filled dome in early fire engines which acted as a cushion to absorb fluctuations in water pressure delivered to the engine reservoir, thus allowing a smooth delivery of water to the fire hose (see figure 2). The physiological analogy is obvious with the pulsatile pump representing the heart, the Windkessel the elastic arteries and the fire hose as the peripheral
Figure 2. **Windkessel model of arterial compliance.**
Adapted from O’Rourke MF, Brunner HR. J Hyperten 1992;10(S6):S3-S5
resistance. However, this model assumes that the arterial circulation is uniform but in vivo this is not the case. Larger vessels, such as the aorta and carotid arteries, differ in compliance and elasticity to smaller, more muscular arteries such as the brachial and radial vessels. In addition arterial compliance varies along the length of arteries, particularly around junctions, curves and bifurcations. The relative proportions of elastin, collagen and muscle fibres in the arterial wall determine the buffering capacity of the artery. Dynamic changes in compliance due to arterial constriction or dilation resulting from changes in sympathetic tone also need to be considered when measuring arterial function.

Interest in arterial compliance started last century before the development of manometers for measuring blood pressure. It was noted that some patients had palpable abnormalities of radial, brachial or carotid arterial pulsation. The pressure required to obliterate the pulse was estimated by hand and the notches in the pulse waveforms were also recognised. Age related changes were also described at this time with the elderly having stiffer arterial walls. Early descriptions of hypertension therefore were based on systolic pressure since this corresponded to the manual effort required to overcome an arterial pulse. However, following the development of the manometer, there was increased recognition of diastolic blood pressure which was
thought to be related to peripheral resistance and arteriolar tone, whereas systolic pressure was thought to be a measure of cardiac function. Results from large prospective studies such as the Framingham cohort follow-up, Systolic Hypertension in the Elderly Program (SHEP), and Multiple Risk Factor Intervention Trial (MRFIT) relate systolic rather than diastolic pressure to target organ damage including left ventricular hypertrophy, as well as mortality from cardiac and cerebrovascular causes.

A major determinant of systolic blood pressure is the stiffness of the large arteries. Stiffer, less compliant arteries cause an increase in systolic pressure because of the lack of elastic buffering effect during left ventricular contraction. In addition, reflected pressure waves return earlier from the periphery thereby increasing the systemic systolic pressure and left ventricular load. In normotensive subjects these reflected waves return during early diastole when the left ventricle is relaxing (see figure 3). Arterial stiffness in turn is dependent on the relative proportions of elastin and collagen within the arterial wall. The elastin fibres become disorganised with increasing age and may fragment leading to a compensatory increase in the collagen component. This degeneration may result from repeated mechanical stress during left ventricular contraction as well as a decrease in the blood supply to the vessel wall through the vasa vasorum.
Figure 3. **Effect of hypertension on aortic pressure waveform.**

This is a diagrammatic representation of ascending aortic pressure tracings taken in a hypertensive subject (top) and a normotensive subject (bottom) showing the effects of (1) increased peripheral resistance, (2) decreased aortic distensibility and (3) early return of reflected pressure waves which now coincide with peak systolic pressure rather than occurring in early diastole.
Consequently the arteries become stiffer and increase in diameter and length.\textsuperscript{43,47,55,59} Arterial wall thickness as measured by ultrasound in vivo also increases in proportion to systolic pressure.\textsuperscript{60} These changes result in an increase in systolic blood pressure which in itself will accelerate the degenerative process through increased mechanical cyclic strain.

The pressure-diameter relationship in physiological conditions is essentially curved.\textsuperscript{61} This is because at lower pressures elastin fibres alone are sufficient to restrict the arterial distension. However at higher pressures the collagen fibres are progressively recruited resulting in a decrease in distensibility per unit of pressure increase, thus the artery becomes stiffer as it is dilated. Muscular tone alters the ratio of elastin and collagen fibres which are used and this also affects arterial compliance. The smooth muscle fibres in the arterial wall are aligned in series with the collagen strands and in parallel with the elastin. When the muscle fibres contract this transfers the load bearing component to the collagen fibres and causes the artery to stiffen during vasoconstriction.\textsuperscript{61,62}

3. Ultrasound measurement techniques

There are two main approaches to the non-invasive assessment of arterial compliance in vivo. Early studies described ultrasound
measurement of pulse wave velocity whereas more recent advances in high resolution ultrasound have allowed continuous measurement of dynamic changes in arterial diameter during cardiac contraction.

The pulse wave velocity is calculated by measuring the delay in the start of the pulse pressure wave between two points in the arterial circulation. Dividing the distance between the two measuring sites by the time difference allows the pulse wave velocity to be estimated, and this is usually in the range of 500 to 2000 cm/second. This can be used to assess arterial compliance by calculating Young's modulus which is a measure of arterial elasticity described in 1807 by Thomas Young (as discussed recently in an editorial\textsuperscript{63}). It was defined at that time as “The modulus of elasticity of any substance is a column of the same substance, capable of producing a pressure on its base which is to the weight causing a certain degree of compression as the length of the substance to the diminution of its length”. This was applied to human physiology in 1826 by the French mathematician Navier by using Young's modulus as a measure of arterial stiffness which controls for vessel wall thickness and includes pulse pressure in its determination (see below for equations). The Moens Kortewig equation allows Young's elastic modulus to be calculated from pulse wave velocity (PWV):
\[ \text{PWV} = \sqrt{\frac{E \cdot h}{2r \cdot \rho}} \quad \text{Units: cm/second} \]

where \( E \) is Young's elastic modulus, \( h \) is arterial wall thickness, \( r \) is internal radius and \( \rho \) is the density of blood. Blood density is normally around 1.05 g/ml and this is often approximated to 1 to simplify the calculation.

In addition arterial distensibility can be indirectly estimated according to the Bramwell and Hill formula as \( 3.57 / \text{PWV} \).

There are limitations with this approach, in particular the assumption that arterial segments are uniform in behaviour, which certainly is not the case in vivo.\(^{44,45} \) The pulse wave velocity measures the global rigidity of an arterial segment. However, continuous measurement of arterial diameter during the cardiac cycle allows the calculation of local arterial distensibility, which is essential if the localised nature of atherosclerosis is to be considered.

The first description of this technique was by Arndt\(^{64} \) in 1968 using pulsed wave ultrasound. He developed a device which detected reflected ultrasound energy from arterial walls and allowed measurement of the arterial diameter during the cardiac cycle. There have been great advances in technology since then and modern devices
have much improved reproducibility and resolution. Most link to conventional ultrasound imaging machines used in clinical practice and allow the operator to visualise the appropriate artery before analysing its function using a wall tracking device. This can track the interfaces of the anterior and posterior walls with much higher resolution than is visible on the television monitor. Theoretically it is possible to measure to a resolution of 2 μm in the latest machines, but in vivo results tend to be less precise because of biological variability, and a resolution of 75 μm has still to be exceeded. This reflects assumptions which are made of the velocity of ultrasound energy through the connective tissue and blood. Although this varies according to the tissue density most manufacturers use the velocity of sound through blood at 37°C as a compromise. This requires that measuring sessions are performed in strictly temperature controlled environments and that patient surroundings are also standardised to minimise between visit variability.

Wall tracking devices allow measurement of changes in arterial diameter throughout the cardiac cycle. From these measurements parameters can be calculated which describe arterial stiffness, distensibility, elasticity, and compliance and which can allow for confounding factors such as the blood pressure at the time of measurement or the thickness of arterial wall. These calculations are
described in detail below. This thesis includes the evaluation of patients with a wall tracking device rather than measurement of pulse wave velocity, so particular emphasis has been placed on the parameters which are available from such devices.

4. Compliance calculations from wall tracking data

Fractional distensibility can be calculated if the minimum arterial diameter and maximum distension are known:

\[
\text{Fractional distensibility} = \frac{D_s - D_d}{D_d}
\]

where \( D_s \) is the systolic (maximum) diameter and \( D_d \) is the diastolic (minimum) diameter. This measure of distensibility can be used to calculate the pressure-strain elastic modulus (Peterson modulus, \( E_p \)):

\[
E_p = \frac{\text{Pulse pressure}}{\text{Fractional distensibility}}
\]

This parameter includes blood pressure as a determinant and is dependent on the filling pressure at the time of measurement. This can be a confounding factor, for example when comparing groups of patients with differing levels of blood pressure. The stiffness index is considered to be relatively independent of blood pressure and is
calculated as the natural logarithm of the ratio of systolic to diastolic pressure divided by the fractional distensibility:

\[ \text{Stiffness index} = \ln \left( \frac{\text{Systolic}}{\text{Diastolic}} \right) \quad \text{No units} \]

Fractional distensibility

Young's elastic modulus (E) measures stiffness but controls for arterial wall thickness, an important consideration if the duration of hypertension is not known or is known to be different in the groups being compared.

\[ E = \frac{R \times \text{Pulse pressure}}{\text{IMT}} \quad \text{Units: kPa} \]

where \( R \) is the outer radius of the artery, and \( \text{IMT} \) is the intima plus medial thickness.

These parameters measure different aspects of arterial elasticity. As arteries become stiffer the compliance decreases and the stiffness index, \( E_p \) and \( E \) increase.
5. Wall tracking Doppler ultrasound technology

The first use of wall tracking technology was described in 1968 when M (motion) mode ultrasound was used to determine carotid arterial diameter. Technology has advanced considerably and the first study using Doppler ultrasound was described in 1985 by Hoeks et al. Significant limitations were present with the technology available at that time, particularly since it was necessary to sample ultrasound reflectance within a tightly controlled sample volume. In addition, measurements could not be performed on-line.

An A (amplitude) mode Doppler device was developed in 1990 which allowed the user to select the segment of artery to be studied using a cursor in a B (brightness) mode image. The various ultrasound modes are described in chapter 4. M-mode ultrasound was used to measure arterial diameter changes in that segment and radiofrequency signal analysis of the changes in arterial wall motion were transferred to computer for analysis. This technology has continued to develop but the basic principles remain unchanged. The most highly developed wall tracking device to date is the NIUS 02 high resolution Doppler angiometer (Capital Medical Services, Paris) which uses a 10 MHz probe contained within a stereotactic positioning arm. This device can be used alone or in conjunction with a B-mode ultrasound imaging.
system. The basic mechanism of the NIUS 02 is described below. The ultrasound probe contains both emitter and receiver units. The emitter units generate up to 500 very short, high amplitude, ultrasonic pulses per second with frequencies up to 10 MHz and a rise time of less than 10 ms to penetrate the tissue being studied. The receiver units detect reflected ultrasound energy and this is analysed at high frequency (over 100 MHz) by the computer. Earlier machines stored 5-10 seconds of information in the computer memory, or on disc. The latest machines allow continuous real-time analysis of reflected energy, and also storage of much longer periods for off-line analysis. Additional features can include simultaneous continuous measurement of blood pressure (using photoplethysmographic finger cuffs) and estimation of blood flow using Doppler ultrasound.

Much of the research published to date in hypertension has used the earlier versions of the NIUS. This is summarised below.

6. Abnormalities of vascular function in hypertension

Early research using wall tracking technology demonstrated potential limitations with the technique. Far from being static, compliance in both the elastic and muscular arteries varies in individuals. Diurnal variation of carotid arterial diameter and compliance has been demonstrated in a small study of 12 healthy men\textsuperscript{70} where small but
significant increases in carotid arterial diameter were found at night. The brachial artery was also studied but the differences were not found to be statistically significant. Such diurnal variation is unlikely to be troublesome in research if subjects are studied at similar times each session. However, short term spontaneous diameter oscillations have been found to be present in the radial artery with cycle frequencies of 45-70 seconds. This results in significant changes in both arterial diameter and compliance and is thought to result from intrinsic muscle cell activity rather than sympathetic stimulation. Such changes are more difficult to compensate for and research continues to try to identify a suitable technique of analysis.

That arterial compliance is altered early in disease states, and thus may potentially be used as an early marker of future cardiovascular disease, is suggested by the finding of early vascular structural changes in the offspring of hypertensive patients. This suggests a loss of elasticity and compliance in the peripheral vasculature similar to the cardiac abnormalities found in a study of diastolic left ventricular function using an analogous cohort of parents and offspring.

The common carotid artery is most often used in studies of arterial compliance because of ease of access and because its relatively large size allows more accurate measurement of diameter. Such work has shown increased vessel stiffness in both treated and untreated
Carotid wall compliance decreases both with ageing and increasing blood pressure, and is associated with the development of left ventricular hypertrophy.

Local variations of arterial compliance have been found in small sections of the carotid artery in hypertensives consistent with the focal effects of both hypertensive vascular damage and atherosclerosis. This is a strong argument for the use of wall tracking equipment to measure compliance in one section of an artery (most often the distal common carotid artery proximal to the bulb) to allow meaningful comparisons to be made between groups, rather than pulse wave velocity measurements which reflect the mechanics of an entire arterial segment.

Recently it has become possible to study smaller arteries such as the radial and brachial vessels and with the latest technology vessels as small as the digital arteries can be examined, as well as measurements of vascular compliance in small laboratory animals.

One interesting paradox apparent from research involving smaller arteries has been the finding of an increase in radial artery isobaric compliance in patients with essential hypertension. Although this at first seems surprising, it may in part explain why the radial artery usually is found to be atheroma free (and thus suitable for coronary artery bypass grafting as an alternative to the internal thoracic artery).
It also contrasts with the results from plethysmographic studies of forearm vascular resistance,\textsuperscript{80,81} although these results are influenced more by arteriolar rather than small arterial tone. In addition, many of the previous studies of conduit artery compliance were based on pulse wave velocity which includes brachial or in some cases aortic compliance rather than local measurements of the radial artery.

The effects of treatment have yet to be assessed in large studies. Preliminary work\textsuperscript{17,20,82,83} involving treatment with angiotensin converting enzyme (ACE) inhibitors, suggests a beneficial effect in terms of arterial compliance. Previous work using pulse wave velocity confirms the likely benefits of antihypertensive vasodilators in reducing arterial compliance: such studies\textsuperscript{12} included ACE inhibitors, calcium channel antagonists, nitroprusside and dihydralazine. However, beta blockers adversely affect the return of reflected pressure waves from the periphery and may paradoxically increase arterial stiffness.

In summary, accurate and reproducible measurement of arterial compliance is now possible with ultrasound wall tracking devices. The compliance parameters are influenced by arterial wall properties including wall thickness which, in turn, is affected by conditions including hypertension and atherosclerosis. The effect of treatment requires further investigation.
CHAPTER 3

Transcranial Doppler embolus detection

1. Introduction

The development of transcranial Doppler ultrasound (TCD) to detect circulating solid and gas emboli is described in this chapter. TCD has been introduced to clinical applications only very recently and the significance of emboli signals is yet to be established. It is important to understand some of the basic principles involved so that the limitations can be appreciated and these are detailed below. TCD is applied later to a study of gas emboli in divers (Chapter 9), and solid emboli in patients with carotid atherosclerosis (Chapter 10). There are important differences between the embolic particles and the resultant signals differ greatly.

2. Historical background

The principle behind embolus detection is the Doppler frequency shift which was first described by Christian Doppler in 1842.\textsuperscript{84} He noted that the measured frequency of emitted energy varied when the source of energy moved in relation to the observer. This can be observed, for example, when sirens appear to rise in pitch when approaching an
ultrasound where moving objects such as circulating blood cells reflect ultrasound energy at frequencies relative to their motion.

Doppler ultrasound first was used to detect embolic material by Austen\textsuperscript{25} in 1965 as a safety device to prevent air embolism in a cardiac bypass circuit. Air emboli were successfully detected and the technique subsequently was developed and widely used as a safety alarm. However the first study of human blood vessels \textit{in vivo} was by Spencer\textsuperscript{85} in 1968 who investigated the incidence of venous gas emboli in decompression sickness. He developed portable battery powered ultrasound monitors which allowed the observer to listen to a derived Doppler waveform of circulating blood. It was possible with training to recognise the patterns of blood flow in the veins, arteries and heart as well as detecting signals from heart valve movement. Using this technique he observed high frequency signals which were distinct from the background waveforms and which were later shown to result from gas bubbles in the venous system\textsuperscript{26,86}. He monitored the subclavian veins, right heart and inferior vena cava. It was hoped that Doppler ultrasound monitoring would provide an objective measure of decompression risk or nitrogen gas load but unfortunately little correlation was found between the bubble counts in the venous system and the incidence or severity of decompression sickness.
Gas emboli in motion are easy to detect because of the large difference in density compared to surrounding blood components. This large difference causes a greater reflectance of ultrasound from the interface of the bubble and the blood and thus a higher signal amplitude. Solid emboli composed of platelets or thrombus are more difficult to detect since there is little difference in density between the emboli and circulating blood which results in less intense signals. This basic principle is crucial to the clinical relevance of Doppler embolus detection.

3. Carotid surgery, angiography and angioplasty.

Conventional transcranial Doppler ultrasound is reviewed elsewhere but the first description of TCD embolus detection was in 1986 by Padayachee et al during carotid endarterectomy. While attempting to assess cerebral collateral circulation by Doppler ultrasound during temporary occlusion of the internal carotid artery, high amplitude signals suggestive of circulating emboli were detected in the middle cerebral arteries. They found that 17 of 19 patients had high intensity Doppler signals as shunting started but found no correlation with clinical outcome.
Further work by Spencer demonstrated high intensity signals suggestive of gas embolism in 35 of 91 patients undergoing carotid endarterectomy. Lower intensity signals consistent with formed element or solid embolism also were found in 24 of these patients. Embolic signals were defined as transient (lasting 0.001 to 0.1 seconds), random in timing, and having an amplitude at least 10 dB greater than the background Doppler blood flow signal. Gas emboli were associated with the release of arterial cross clamps and typically had amplitudes 60 dB greater than the background signal. Formed element signals were less intense (10 - 40 dB greater than background) and were less frequent compared to gas emboli signals. They occurred mainly during compression of the common carotid artery during surgery or several hours after arteriotomy closure. Some circumstantial evidence was presented which suggested that the solid signals were more likely to be clinically significant but this was not conclusive.

Microembolic signals were detected during cerebral angiography by Markus et al in 1993. Seven patients were studied during cerebral angiography which was being performed to evaluate cerebrovascular disease or to investigate the source of subarachnoid haemorrhage. Signals were found in the middle cerebral arteries during the injection of contrast into the ipsilateral internal or common carotid artery and these lasted for approximately 3 seconds after injection. In addition
signals were detected during flushing of the catheter with saline. There was a higher rate of embolism during fast injections, and when using contrast medium which had not been left to stand for several minutes. Microscopic gas bubbles in the injection medium were the most likely cause of the high intensity signals. Cerebral angiography is an invasive procedure with associated morbidity and very occasional mortality. The risk of cerebral injury during angiography is approximately 4% and the authors suggested that this may be related to air embolism. Similar signals were found during carotid angioplasty.

TCD embolus detection is now used in many centres to detect and prevent gas embolism particularly during carotid surgery, as well as during angiography and cardiac bypass surgery. Transoesophageal echocardiography recently has been used to confirm gas bubbles as the cause of TCD embolic signals in these settings. This may be clinically important since silent gas embolism has been implicated in the neurological impairment seen following bypass surgery. Some centres use the technique post-operatively to identify solid emboli forming at the arteriotomy site and will re-operate if there are frequent embolic signals during this period. The discovery of pre-operative solid emboli signals has stimulated much research into embolus detection in carotid atherosclerosis.
4. Carotid atherosclerosis

In 1992 Siebler described microembolic signals in two patients with internal carotid artery stenosis and one subject with occlusion, and compared their findings with 10 normal subjects. Signals were found in all three diseased patients with an average rate of embolism of four signals per hour. These were detected ipsilateral to the diseased carotid artery and exceeded the background arterial waveform by 12-21 dB (compared to gas embolism signals which typically exceed the background signal by up to 40 dB). This initial short report was then expanded as a study of 14 patients before and after carotid endarterectomy. All the patients were symptomatic and had signals detected ipsilateral to the diseased internal carotid artery. Four also had contralateral signals. There was a drop in the mean rate of embolism (from 11 to 0.4 per hour) following endarterectomy. The authors suggested that TCD embolus detection may represent a "new marker of disease activity of extracranial carotid artery stenosis". Additional evidence in favour of this was their discovery that symptomatic patients with carotid artery stenosis had a higher rate of embolism than asymptomatic patients. The mean rate of signals in 27 symptomatic patients was 14 signals per hour. These subjects all had high grade stenosis of the ipsilateral internal carotid artery and a recent (<121
days) history of ischaemic symptoms attributable to the diseased artery. Asymptomatic subjects were found to have a mean rate of 0.35 per hour and only 9 of 56 subjects had detectable signals. Another study of symptomatic patients found a 94% incidence of microembolism with a mean of 14 signals per hour in the ipsilateral artery and 4 per hour in the contralateral side. The signals were abolished following endarterectomy.

Markus found embolic signals in 3 of 10 symptomatic patients prior to carotid angioplasty. Only one subject had signals following the procedure. In a separate study they found signals in 6 of 25 patients with asymptomatic carotid artery stenosis.

If signals in carotid or cerebral atherosclerosis are caused by platelet or leukocyte clumps then treatment with either aspirin or anticoagulants would be expected to show an effect on the numbers of signals detected. Three case reports have now been published with conflicting results. Randomised controlled trials are obviously required and provisional results in prosthetic valve patients have shown no effects. Further studies in different clinical settings are underway.

The importance of embolic signals in carotid artery stenosis was emphasised by the publication of results from the Asymptomatic Carotid Atherosclerosis Study (ACAS). This large multi-centre
American study is a randomised trial of carotid endarterectomy for asymptomatic high grade stenosis of the internal carotid artery. It is discussed in detail later in chapter 10. All patients enrolled for the study had computed tomography brain scans performed at baseline and 126 of 848 patients studied (15%) were found to have cerebral infarcts. This incidence of silent cerebral infarction is very similar to the incidence of silent cerebral embolism detected by TCD in carotid artery stenosis. It suggests that the signals detected may represent harmful emboli which result in cerebral injury. In addition embolus detection may help to identify which asymptomatic subjects with carotid stenosis are most at risk of embolic stroke and therefore benefit from surgery. This is particularly important since the perioperative morbidity and mortality for carotid endarterectomy is 2-3% even for experienced surgeons. The absolute risk reduction offered by endarterectomy in asymptomatic individuals is only 5.8%, therefore a technique for identifying high risk individuals is needed to increase the benefit / risk ratio.

In vitro studies have been performed in sheep to determine signal characteristics of differing embolic materials. Markus\textsuperscript{105} introduced thrombi, platelet aggregates and atheroma into the proximal carotid artery of a sheep and monitored the cerebral circulation. Emboli as small as 5-20 μm were detected successfully. There was a significant
correlation between the embolus size and the duration and intensity of the signal. However it was not possible to determine the embolic constituents unless the particle size was known. For example, a small fat embolus may produce the same signal as a large solid embolus.\textsuperscript{106-8} This has been particularly relevant in determining the nature of emboli in subjects with prosthetic heart valves where many hundreds of signals may be detected per hour.

5. Cardiac valves

Rams et al\textsuperscript{109} studied 26 patients with prosthetic aortic valves and found a variable incidence and rate of cerebral embolism. Signals were detected in 14 subjects (53\%) with a mean rate of 38 per hour. The maximum rate was 138 per hour in a subject with a Bjork-Shiley valve prosthesis. Although the patients were asymptomatic the authors were concerned about previously published evidence of long-term functional psychometric abnormalities in prosthetic valve patients\textsuperscript{110} which may be related to chronic subclinical cerebral embolism. The signals detected were of high amplitude and thus suggestive of gas embolism but the cause of the emboli was unclear. Cavitation during valve leaflet closure is one possibility but this would be unlikely in bioprosthetic valves which have lower valve leaflet closing velocities and less resultant turbulence. In addition bubbles produced by cavitation were
thought to persist for only a few milliseconds\textsuperscript{111} and thus would not persist in the circulation for the time taken to travel from the heart to the cerebral circulation.

Grosset et al\textsuperscript{112} studied 50 patients with mechanical prostheses and 14 with porcine bioprosthetic implants. There was a significantly higher incidence of microembolic signals in subjects with mechanical prostheses compared to porcine valves (88\% versus 14\%, $p<0.01$) and also a higher rate of embolism in patients who had undergone double valve replacement. A further study by the same group\textsuperscript{113} found a higher rate of embolism in patients with Bjork-Shiley valves compared to Medtronic-Hall and Carpentier-Edwards (89\% versus 50\% and 53\% respectively, $p<0.001$). They studied a total of 179 patients, 85 with Bjork-Shiley, 56 Medtronic Hall, 38 Carpentier-Edwards valves and compared the results to 25 normal subjects. No correlation was found between microembolic signals and clinical parameters such as history of neurological deficit or intensity of anticoagulation. A study comparing coagulation activity and emboli counts in patients with prosthetic valves found no correlation between microembolic signals and D-dimer, antithrombin III, thrombin-antithrombin III complex or intensity of anticoagulation.\textsuperscript{114} These results suggested that the emboli did not cause activation of the coagulation cascade and as such were
unlikely to result from platelet or leukocyte activation during valve closure or caused by turbulent flow through the valve.

Comparing signal characteristics between patients with carotid artery disease, atrial fibrillation and prosthetic valves\textsuperscript{115} it was possible to develop an algorithm to help determine the underlying nature of the embolus. Using this technique an estimated 92\% of signals in prosthetic valve patients were gaseous (based on the maximal amplitude and the sum of amplitudes of the signals). The signals detected during cardiac catheterisation were used to define the characteristics of gas emboli and carotid atherosclerosis signals were assumed to be due to solid or formed matter emboli.

There is accumulating evidence to support the theory of cavitation as a cause for gaseous microembolic signals in prosthetic valve patients and a recent study using transoesophageal echocardiography\textsuperscript{116} appears to confirm this. In this study 138 patients with prosthetic cardiac valves underwent transoesophageal echocardiography. Microbubbles were directly visualised in 69 (35\%) of subjects. The bubbles were more common in mitral compared to aortic valves and were similar to those detected during injection of contrast to detect right-to-left shunting. This suggests that cavitation does occur in vivo and that bubbles persist in the circulation presumably because of plasma viscosity to be detected in the middle cerebral arteries by transcranial Doppler.
ultrasound. There is no convincing evidence to link the microemboli to cerebral injury but it is of interest that some valve types cause less signals than others, and perhaps function in a more physiological manner without the risk of red cell injury and haemolysis. Embolus detection may provide an in vivo method of determining the degree of turbulence caused by valve types and be used to refine valve design.

6. Shunt detection

The high levels of sensitivity demonstrated by TCD in detecting gas emboli are already of clinical relevance. Investigation for right-to-left shunting is required in young patients with embolic stroke but without an obvious source of embolism in the arterial circulation. Studies suggest that an appreciable proportion may have venous thrombosis which can embolise through the atrial septum, so-called paradoxical embolism. A study of 406 patients with clinically suspected embolic events found that 264 had unexplained emboli with no overt source of embolism (defined as endocarditis, mitral valve stenosis, left ventricular mural thrombus or akinesia, spontaneous echocardiographic contrast, left atrial or appendage thrombus or myxoma). Of these, 49 subjects (19%) had right-to-left shunting detected by transoesophageal echocardiography. These subjects then underwent venography and 24 (57%) were found to have venous thrombosis. Up to 30% of healthy
adults have a potential route from the right to left heart through a patent foramen ovale.\textsuperscript{121} This may also be relevant to divers where paradoxical embolism of venous gas bubbles has been implicated in the development of decompression sickness.\textsuperscript{122} This is particularly relevant to individuals who develop decompression sickness despite following recommended decompression procedures.

Until recently the most commonly used technique for the detection of shunting was transthoracic echocardiography during the injection of intravenous contrast into a peripheral vein. However, performing echocardiography during the provocation necessary to increase right atrial pressure (coughing and Valsalva manoeuvres) is difficult. The most sensitive and specific technique for shunt detection is transoesophageal echocardiography, but this is an invasive technique which is unsuitable for screening healthy individuals, such as divers. TCD during peripheral contrast injection was compared directly with transthoracic echocardiography in a study of 46 patients.\textsuperscript{123} Shunting was detected in 41\% of subjects by TCD, but only 26\% by echocardiography. A further study\textsuperscript{124} compared TCD with transoesophageal and transthoracic echocardiography. Transoesophageal echocardiography detected shunting in 19 of 49 subjects, TCD detected paradoxical signals in 13 of these subjects whereas the transthoracic technique only detected 9 subjects. TCD had
68% sensitivity and 100% specificity relative to transoesophageal echocardiography, and was superior to transthoracic echocardiography (only 47% and 100% respectively). A further direct comparison was made between TCD and transoesophageal echocardiography and TCD was found to have 93% sensitivity, detecting 14 of 15 patients with PFO.

It is possible to increase the detection of shunting by increasing right atrial pressure, usually by coughing or performing a Valsalva manoeuvre. This is possible during TCD without losing the ultrasound signal, unlike transthoracic echocardiography.

7. Summary

TCD ultrasound is a reliable and convenient method of monitoring the arterial circulation for circulating emboli. The clinical relevance of gas emboli is uncertain in prosthetic valve patients but evidence suggests that solid emboli are more likely to cause cerebral injury. It is possible to estimate the constituents of an embolus if assumptions are made regarding the particle size. Artificial gas emboli can be introduced into the venous system and used as a non-invasive technique for detecting right-to-left shunts.
Ultrasound techniques

All of the techniques described below require high frequency energy to be emitted, reflected from body tissues or moving material and then detected, analysed and displayed. The basic mechanism is the same in all types of ultrasound imaging which simply involves the use of reflected ultrasonic energy waves. The most commonly used frequencies in clinical medicine are between 2 and 10 MHz (audible sound extends to 20kHz, or 20,000 cycles per second). The higher frequencies allow greater resolution of detail when imaging but at the cost of poor penetration such that, for example, frequencies greater than 5MHz are rarely useful in adult echocardiography because of poor penetration through the chest wall. However, more superficial structures such as the carotid or brachial arteries can be studied with frequencies exceeding 10MHz and thus with much higher resolution.

Various methods of ultrasound analysis are available:

A-mode refers to amplitude and provides radiofrequency displays which are used in wall tracking devices to measure small changes in arterial diameter during the cardiac cycle. The display does not provide any structural information other than distance within a single line of
ultrasonic energy. Strong reflectance signals are presented as high amplitude peaks.

B-mode refers to Brightness and is used in clinical practice to provide anatomical images, for example of the carotid artery. A B-mode image is normally constructed from multiple lines of ultrasound energy to provide a 2 dimensional image. Strong reflectance signals are shown as bright dots or pixels. High resolution B-mode uses high frequency ultrasound (typically 8-10MHz) and can be used to measure distances approaching 0.01mm.

M-mode displays Motion analysis of a single B-mode scanning line. By imaging one line of analysis continuously and scrolling the display horizontally it is possible to analyse movement of structures against time. This is used during echocardiography, for example to measure left ventricular dimensions during systole and diastole. The ECG is usually superimposed on the M-mode image to allow accurate timing.

Doppler ultrasound is used to measure the speed of blood flow based on the shift in frequency between transmitted and reflected energy waves. Colour flow Doppler allows colour mapping of flow jets and is used in clinical practice, for example in valvular heart disease or carotid artery stenosis.
Echocardiography

Echocardiography was performed in these studies to measure left ventricular structure and function. It was also used to exclude patients with significant cardiac structural abnormalities such as valvular disease. Left ventricular structural assessment involved measuring wall thickness and internal dimensions during systole and diastole. From this it was possible to estimate left ventricular mass. Diastolic function was also assessed by measuring the speed of blood flowing through the tips of the mitral valve leaflets using pulsed wave Doppler as described below.

The examinations were performed in a standardised manner with the subject lying in the left lateral position. An Acuson 128 (Acuson, Mountain View, California) with a 3.5MHz probe was used. Three representative M-mode images from the left parasternal view of the left ventricle were displayed as full screen images and recorded on videotape. Each image allowed measurement of dimensions during up to 5 cardiac cycles depending on heart rate. Subsequent analysis was performed off-line on five cardiac cycles to allow estimation of interventricular septal thickness in systole and diastole (IVSs, IVSd), left ventricular end systolic and diastolic diameters (LVESD, LVEDD) and left ventricular posterior wall thickness (LVPWs, LVPWd). Measurements were performed according to the recommendations of the American Society of Echocardiography.129
Figure 4. Example of M-mode echocardiography.

M-mode image of left ventricle (LV) at the level of the mitral valve leaflets (AMVL = anterior, PMVL posterior mitral valve leaflets). IVS (interventricular septum) and PW (posterior wall) move together in systole. M-mode cursor placed according to the miniature 2-D image seen at the top of the screen.
2-D parasternal long axis view showing left atrium (LA), left ventricle (LV), interventricular septum (IVS), posterior wall (PW) and aortic root at the level of the valve cusps (AO).
Diastolic function was assessed using pulsed wave Doppler with the sample volume positioned between the tips of the mitral valve leaflets. The E:A ratio was calculated as the ratio of the peak E or early phase of left ventricular filling to the A velocity which represents active atrial contraction. The isovolumetric relaxation time (IVRT) was defined as the interval between the aortic valve closing and the start of the E wave and was measured using continuous wave sampling across the aortic root and mitral valve. The E:A ratio and IVRT reflect left ventricular compliance during diastolic filling. All diastolic measurements were performed off-line using the ACUSON analysis software on five cardiac cycles recorded during end expiration. Each video recording was a full screen image frozen prior to recording to allow accurate calibration. All video recordings were on broadcast quality super VHS video tape.

High resolution B-mode carotid ultrasound

High resolution B-mode ultrasound was used to examine the common carotid artery and to measure intima-medial thickness (IMT) as well as detection of atherosclerotic plaque. The technique has been reviewed in detail elsewhere and has been well validated against post mortem and surgical specimens.
Figure 6. **Example of high resolution B-mode ultrasound scan**

This image has been digitised from a video recording of a high resolution B-mode carotid ultrasound scan. The scan is identified by a randomised examination number (top left). The calibration marker is placed on screen by the Biosound device and allows accurate calibration for measurement of intima-medial thickness. The size of the calibration marker is displayed in the top right corner.

This scan is of the right common carotid artery with the skin on the left of the image and layers of subcutaneous fat and the jugular vein between the surface and the carotid artery.
The first published use of high resolution B-mode ultrasound was by Pignoli et al in 1986\textsuperscript{131} who demonstrated the two parallel lines resulting from the intima-medial layer and found that it was not possible to discriminate between the intimal and medial layers. Axial resolution was found to be 400\textmu m and subsequent work with the B-mode technique has shown variable axial resolution between 200 to 600 \textmu m depending on the frequency of ultrasound. The Biosound 2000 II SA (Bio Dynamics inc., Indianapolis) used in this thesis has a maximum resolution of 385\textmu m when used with a 8 MHz probe. The image is composed of 256 levels of grey (30 are distinguishable by eye) and stored on super VHS tape which gives 450,000 pixel images.

The ultrasound examination was performed according to the protocol for the ELSA study (European Lacidipine Study on Atherosclerosis, Glaxo S.p.A. and Boehringer Ingelheim) which is a large multicentre study of carotid IMT progression in hypertension and which involves serial measurements of IMT in patients randomised to either an atenolol or a lacidipine based antihypertensive drug regimen. The Biosound 2000 was chosen as the instrument to perform high resolution B-mode scans because it has been well validated in previous large scale epidemiological studies including the Atherosclerosis Risk in Communities study, ARIC.\textsuperscript{189,205}
The examination was performed with the subject lying in a supine position which allowed head rotation to either side. Instrument settings on the Biosound 2000 II SA were standardised at the beginning of the examination. The examination started on the right side by placing the transducer on the skin longitudinal to the common carotid artery. The image of the relevant arterial segment was placed in the middle third of the screen to minimise axial distortion. The transducer then was moved slowly cranially keeping the common carotid artery in focus until the start of the carotid bulb immediately proximal to the bifurcation. The probe then was gradually rotated first anteriorly then posteriorly to allow measurement of the maximum IMT in this arterial segment thus accounting for both concentric and eccentric thickening.

A similar procedure was adopted for the left side but the transducer design causes the image to be inverted with the cranial end of the artery at the bottom of the screen. A bilateral examination took between 25 and 30 minutes. Sonographers were specially trained to perform research quality B-mode scans with a tightly controlled examination protocol. Regular quality control and annual recertification ensured continuing high standards. Examinations were recorded on super VHS video tape and identified on screen by a random number without identifiable patient details allowing subsequent analysis independent from any clinical data.
**Measurement of IMT**

The measurements of carotid artery IMT are from my own blinded analysis of the ultrasound recordings rather than central analysis by the ELSA measurement centre in the Bowman Gray School of Medicine (Winston-Salem, North Carolina). The problem of calibration was overcome by using the Biosound to display a marker of known length on screen throughout the ultrasound examination. This line varied in length and position throughout the recording period. A problem with studies involving video tape analysis of arterial disease is that calibration is usually based on an intra-arterial catheter of known diameter. This causes difficulty since the video image is a two dimensional representation of a three dimensional structure which causes distortion of both catheter and arterial size. B-mode ultrasound provides images of a two dimensional slice of tissue, a significant advantage.

Analysis of video tapes was then performed blinded to the clinical data. The tape was played through a frame stabilising device interfaced with an image digitiser and a 486DX microprocessor based computer (Digital time base corrector FA-310 P, FOR-A Company Ltd, Tokyo). The image was frozen when a suitable view of the common carotid artery immediately proximal to the bifurcation was available.
The image was magnified by a factor of eight before measuring the length of the calibration marker and calculating IMT using the quantitative computerised analysis system (Cardiotrace version 3.03, Cinegraphic Inc, Grand Prairie, Texas). The final IMT value was based on the mean of three separate measurements. When a discrete arterial plaque was present, IMT was measured in the segment immediately proximal to that plaque. Plaque thickness was also measured where present and the echogenic characteristics of the lesion were noted including the presence of calcification, ulceration and intraplaque haemorrhage. Plaque was defined as a focal area of intima-medial thickening exceeding that of the adjacent segment by over 30% and being at least 1.3mm in thickness as defined in the ELSA study protocol (Glaxo S.p.A., Italy and Boehringer Ingelheim, GmbH, Germany).

The IMT values were entered into a database file containing the random identification number only. This was unblinded automatically by computer by a specially written computer program which combined separate database files independently of operator control. Subjects had individual clinical information database files and separate files with tape identification numbers to record the IMT values. Thus all measurement was completely independent of clinical data.
Carotid Doppler ultrasound and arterial pulsatility

Carotid Doppler ultrasound is used clinically to measure blood flow velocity and to estimate lumen stenosis based on an increase in velocity. It involves duplex ultrasound which combines B-mode images of the arterial segment and pulse wave Doppler sampling of blood flow velocity within a small sample volume which can be moved to each of the carotid artery branches.

Carotid Doppler ultrasound was performed using an Acuson 128 with a 7.5 MHz probe. The subject lay supine and the probe was placed over the common carotid artery above the clavicle and moved gradually towards the bifurcation and origin of the internal and external carotid arteries. Duplex scanning was used to obtain B-mode images of the carotid arteries before colour flow mapping to confirm the high blood flow velocities of arterial rather than venous blood flow. A cursor was then placed in the centre of the common, internal and external carotid arteries and three separate measurements of systolic and diastolic velocity were made, each consisting of the average of five cardiac cycles. When measuring blood flow velocity, the sampling volume was angled along the line of blood flow but kept to less than 30° from the cursor to minimise distortion which can exaggerate blood flow velocity.
Representative waveforms were stored on super VHS videotape and identified by number without patient details. Post examination analysis was possible since the Acuson recorded electronic calibration information which allowed estimation of blood flow velocities using the Acuson analysis software. This was performed in a blinded manner and unblinded by computer as above.

A-mode arterial compliance measurement

Carotid arterial compliance was measured using a wall tracking device (AMA, Holland) linked to the Acuson 128. The device allows accurate and reproducible measurement of dynamic changes in arterial diameter during the cardiac cycle. A 7.5 MHz probe was used to provide a B-mode image of the carotid bifurcation. The common carotid bifurcation was identified and the segment 2cm proximal to the bulb was aligned in the centre of the screen. An M-mode cursor was then placed through the centre of the section and the subsequent M-mode output was enlarged to occupy the entire screen. Using a foot switch the wall tracker was triggered to analyse five cardiac cycles of carotid dimensions. The wall tracker provided an audible tone once this information had been stored and the ultrasound probe was removed from the subject’s neck. This procedure was repeated 3 times.
The radiofrequency profiles (A-mode output) were analysed and sample volume cursors placed around the anterior and posterior wall signals as identified by the distance measured from the M-mode image. The computer was then used to analyse movement within the sample volumes and calculate a high resolution graph of arterial dimensions throughout five cardiac cycles. Three measurement recordings were stored (five cardiac cycles each) if they were of adequate quality. The recordings were stored on computer hard disc and identified by a numerical examination number.

All measurements were performed off-line on five cardiac cycles to allow mean distensibility, minimum diameter (end diastole) and rise time to be calculated. The rise time is the time taken to move from 10% to 90% on the distensibility curve. In addition Duplex ultrasound was used to exclude haemodynamically significant atherosclerosis (not present in any subject in the compliance study). Measurement results were entered into a database file containing subject identification numbers only. These were then transferred automatically to the clinical database files to avoid observer unblinding.

**Transcranial Doppler ultrasound embolus detection**

TCD monitoring was performed using a Nicolet TC4040 or TC2000 (Nicolet, Warwick, UK) with a 2 MHz probe. This low frequency
enables detection of reflected ultrasound energy waves through bone. The probe was held in position over the temporal window using an elasticated head piece. In the case of the TC4040, bilateral monitoring was performed simultaneously. Patients rested supine with the head supported on two pillows and were asked to remain as still as possible. Talking was discouraged to eliminate any artefact caused by jaw movement, although such artefact is easy to distinguish from embolic signals as described below.

The middle cerebral arteries were monitored for 30 minutes on each side focusing on the signal at 48-52 mm from the skin. All recordings were stored on videotape for independent analysis by two observers. In addition digital data from the fast Fourier transformation of the Doppler waveform data were stored on computer hard disc for subsequent analysis. In the study described in Chapter 10 (carotid atherosclerosis) embolus counting was performed prior to the carotid Doppler ultrasound to reduce any potential bias. Microembolic signals were defined as characteristic high intensity transient signals which were easily distinguished from the background arterial waveform. They had to be unidirectional, unlike artefact which typically produces bi-directional signals, and associated with an audible chirp or blip.
Shunt detection

Divers were screened for right-to-left shunting by simultaneous transthoracic echocardiography and transcranial Doppler ultrasound during injection of contrast. An 18 gauge indwelling cannula was inserted into a left brachial fossa vein. Microcavitation contrast was generated by agitating 5mls of 0.9% saline, 0.2mls air and 0.5mls of the subject's blood between two 10ml syringes using the three way tap method. The mixture contained microscopic air bubbles which cause very intense reflection of ultrasound energy and which can be detected in the heart or in the peripheral arteries if there is a connection between the venous and arterial systems. The mixture was injected with the subject supine and breathing quietly. The injection was repeated following the sudden release of a Valsalva manoeuvre, and if necessary after coughing. Each stage was repeated twice if embolic signals were not detected. These techniques have been shown to maximise the chance of detecting right-to-left shunting by increasing right atrial pressure and provoking shunting.

A positive test was defined during echocardiography as the appearance of bubbles in the left heart within five cardiac cycles of the right heart opacifying. Shunting during transcranial ultrasound was defined as the appearance of characteristic audible blips and the presence of embolic signals superimposed on the middle cerebral artery Doppler
waveform within the same period. The signals detected were of high amplitude, short duration and were irregular in relation to the cardiac cycle. In addition signals had to be detected bilaterally to confirm a cardiac source of embolism.
CHAPTER 5  ECHOCARDIOGRAPHY

Cardiac abnormalities in white coat hypertension

Background

Echocardiography is widely used in clinical practice to assess cardiac function and structure. It includes techniques which allow estimation of left ventricular mass as well as measurement of ventricular filling velocities. This is relevant to hypertension where early abnormalities of ventricular filling can be found before the more serious development of muscle hypertrophy which is a prognostic marker for cardiovascular morbidity and mortality. It is clinically important to identify individuals at risk of developing left ventricular hypertrophy and to direct antihypertensive treatment accordingly.

Left ventricular hypertrophy

Much of the data concerning left ventricular hypertrophy comes from the cohort follow-up studies performed in Framingham, Massachusetts. This long-term population based follow-up study first started in 1948 and involved repeated medical assessments in addition to echocardiography. Measurements of left ventricular dimensions were made with M-mode echocardiography and were used to estimate left ventricular mass. Devereux et al developed a formula to estimate left
ventricular mass from ultrasound measurement of ventricular diameter and wall thickness following post-mortem comparisons with cardiac weight.\textsuperscript{5,139} This approach has been validated in other centres\textsuperscript{3,4} and echocardiographic estimation of left ventricular mass is now widely accepted.

One of the Framingham follow-up studies\textsuperscript{6} involved monitoring 3220 subjects over four years in terms of cardiovascular mortality following estimation of left ventricular mass by echocardiography. During the study period 208 cardiovascular events were recorded. Left ventricular mass was found to be an independent predictor of cardiovascular events even after correction for confounding factors including age, diastolic blood pressure, pulse pressure, treatment for hypertension, cigarette smoking, diabetes, obesity and cholesterol. There was a continuous relationship between left ventricular mass and cardiovascular risk such that increments in left ventricular mass were associated with correspondingly higher rates of cardiovascular events. The relative risk of all cause mortality if left ventricular hypertrophy was present was 1.49 (95\% CI 1.14 to 1.94) for men, and 2.01 (95\% CI 1.44 to 2.81) for women, compared to subjects without ventricular hypertrophy. Left ventricular mass was corrected for subject height in this study whereas more recent studies use body weight to derive the left ventricular mass index.
The Framingham study authors hypothesised that left ventricular hypertrophy demands an increase in myocardial oxygen requirement while reducing the coronary blood flow reserve and this imbalance may be responsible for the increased risk of angina, myocardial infarction and sudden death.

Further research from the Framingham studies confirmed the prognostic value of estimating left ventricular mass in elderly subjects with hypertension. A separate smaller study of 140 men confirmed that echocardiographic measurement of left ventricular mass had greater prognostic value than electrocardiographic grading of left ventricular hypertrophy. They also identified abnormalities of left ventricular filling using Doppler ultrasound in hypertensive subjects. This has stimulated further research into ventricular diastolic function which is discussed below.

**Left ventricular diastolic function**

Left ventricular filling normally consists of an early passive phase when the ventricle actively relaxes and draws blood from the atrium by suction. This active phase is energy dependent and results from myocardial cell lengthening as calcium ions are removed from the cytoplasm and contractile proteins by an adenosine triphosphate dependent enzyme in the sarcoplasmic reticulum. Removing calcium
causes the actin and myosin bonds to dissociate and causes muscle fibres to lengthen. The later stage of ventricular filling is determined by the mechanical properties of the ventricle in terms of elasticity and compliance. As the ventricle becomes stiffer more active atrial contraction is required to overcome the reduction in ventricular compliance.

Using pulsed wave Doppler it is possible to identify two discrete phases of ventricular filling. The early (E) phase is the active relaxation phase where the ventricle fills by suction and the second is caused by active (A) atrial contraction. If ventricular compliance is reduced there is a fall in the E:A ratio and this provides an objective measure of ventricular elasticity. In addition, changes in the E deceleration and A deceleration time are also observed (see table 5.1).

The isovolumetric relaxation time (IVRT) is the interval between the aortic valve closing and the mitral valve opening. This indicates the time required for ventricular pressure to fall below atrial pressure and this is prolonged in hypertension.

There has been considerable research examining left ventricular diastolic function in hypertension and this has been shown to be influenced by age, sex, body weight, height, family history of hypertension, antihypertensive treatment, presence of left ventricular hypertrophy and coronary artery disease.7,9,73,132-3,135,137,142-147

61
<table>
<thead>
<tr>
<th>Diastolic parameter</th>
<th>Normal range</th>
<th>Effect of hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>E velocity</td>
<td>0.85 ± 0.16 m/sec</td>
<td>↓</td>
</tr>
<tr>
<td>A velocity</td>
<td>0.56 ± 0.13 m/sec</td>
<td>↑</td>
</tr>
<tr>
<td>E deceleration time</td>
<td>199 ± 32 msec</td>
<td>↑</td>
</tr>
<tr>
<td>Isovolumetric relaxation</td>
<td>69 ± 12 msec (&lt;40 years)</td>
<td>↑</td>
</tr>
<tr>
<td>relaxation time</td>
<td>76 ± 13 msec (&gt;40 years)</td>
<td></td>
</tr>
</tbody>
</table>

*Table 5.1 Effect of hypertension on diastolic function*
Changes in diastolic function have been described in the offspring of hypertensive parents which may develop prior to left ventricular hypertrophy. However, diastolic dysfunction may also be associated with the future development of systolic dysfunction and the clinical consequences of left ventricular failure.

Antihypertensive treatment can result in favourable changes in diastolic function as well as reducing the incidence and slowing the progression of left ventricular hypertrophy. Calcium channel antagonists have been shown to improve diastolic function in hypertension and myocardial disease. However, no study yet has shown significant benefit in terms of mortality after improvement of diastolic dysfunction. This is discussed in detail in a recent review and is summarised below. Diuretics decrease venous return and therefore reduce left ventricular filling volume in a similar manner as nitrates. Beta blockers have also been shown to be effective (metoprolol and nadolol) but only if blood pressure is reduced. They act by prolonging the period available for ventricular filling during diastole, partly by reducing the resting heart rate. This counterbalances their adverse effect on ventricular relaxation which is slowed.

**White coat hypertension**

The benefits of treating established hypertension are well recognised
with significant reductions in cerebrovascular, cardiac and even vascular disease. There may also be additional benefits in that drug treatment may interfere with the development and progression of atherosclerotic vascular disease with potential long-term reductions in cardiovascular morbidity. However, the major trials of antihypertensive treatment relied upon conventional clinic measurement of blood pressure to identify hypertensive patients and this has led to the inclusion of individuals with white coat hypertension. Blood pressure measurements are usually higher when first attending a doctor and even after repeated visits this startle reaction can persist. Using ambulatory blood pressure monitoring it has been shown that 20-40% of individuals classified as persistent or borderline hypertensives by conventional clinical measurement can be reclassified as normotensive during daytime monitoring. Unfortunately the criteria for defining white coat hypertension varied in these studies and there is not yet a universally agreed definition. For example, one group used an elevated clinic diastolic pressure (between 90-104mmHg) but with normal daytime ambulatory blood pressures (below the 90th percentile of a normotensive control group). Another study defined the syndrome as a mean office blood pressure at least 6 mmHg higher than the ambulatory mean blood pressure. While the influence of medical personnel on blood pressure
measurement has also been well studied, leading to recommendations for repeated clinic measurements before initiating treatment; it now is established that even those clinical studies which included white coat hypertensives showed reductions in cardiovascular disease. In general it has been assumed that the inclusion of such patients diluted the magnitude of benefit but an alternative possibility is that the white coat hypertensives may also have benefited from treatment. There is no definitive answer to this question from end-point studies. However, since the effects of hypertension on the cardiovascular system also manifest as functional abnormalities, or surrogate end-points, including abnormalities of arterial compliance and of diastolic left ventricular function, there is the additional possibility that these may also be reversible with treatment.

The principal aim of our study was to determine whether or not white coat hypertensives differ from persistent hypertensives or normotensives in terms of known markers of hypertensive cardiovascular disease. Thus a range of indices of cardiovascular function were assessed in patients referred for evaluation of their hypertension.

**Methods**

65 patients referred for assessment of hypertension were invited to give
written informed consent to this study which had prior approval from the local Ethics Committee. Eligible patients were aged 45-75 years and had no evidence of clinically significant disease, including previous myocardial infarction, stroke, cardiac failure, insulin dependent diabetes, renal impairment, liver disease, atrial fibrillation or significant heart valve disease. They were not taking antihypertensive treatment, or any other treatment liable to alter arterial compliance or left ventricular function at the time of the study, and had not received any such treatment within 28 days of the study. Patients had attended for blood pressure measurements on at least two previous occasions.

**Blood pressure measurements**

Clinic blood pressure was measured using a semi-automatic oscillometric device (Sentron, Bard Inc, UK) which was programmed to record blood pressure automatically without a member of staff present. This was performed to diminish any elevation of blood pressure related to the presence of medical staff. Measurements were taken in a standard setting after the patient had rested supine for a minimum of 15 minutes following a 10 hour fast. Three measurements were taken with intervals of 5 minutes, and the mean was calculated.

Ambulatory blood pressure monitoring was performed over a 28 hour period using SpaceLabs 90207 monitors (SpaceLabs, Inc. Redmond,
WA) which were programmed to record blood pressure every 15 minutes during daytime, and every 20 minutes overnight.

A minimum of 3 readings per hour during daytime and 2 readings per hour overnight were required for a record to be deemed satisfactory.

Cardiac indices

Echocardiography was performed using an Acuson 128 as described in chapter 4. All echocardiographic measurements were analysed by one observer. The coefficient of variation for E:A ratio measurement in a random sample of 20 subjects from the study population was 2.8%.

Classification of patients

According to the study protocol, three groups of patients were defined on the basis of ambulatory blood pressure monitoring profiles and clinic recordings: persistent hypertensives who had a diastolic pressure \( \geq 95 \) mmHg both at the clinic and on daytime ambulatory monitoring; white-coat hypertensives who had a diastolic pressure of 95 mmHg (or more) at the clinic but not on ambulatory monitoring; and normotensives who had diastolic pressures below 95 mmHg at all times. These arbitrary definitions were based on the thresholds for initiating treatment recommended by the World Health Organisation and the International Society of Hypertension, and the criteria
defined in a large study of white coat hypertension.\textsuperscript{158}

All ultrasound analysis was done independently of the blood pressure recordings. The E:A ratio and IVRT were corrected for clinic blood pressure by division using the appropriate blood pressure variable, recorded at the time of the ultrasound measurement, and normalising for an arbitrary pressure of 120/80 mmHg. Dimensions of the left ventricle were measured according to the recommendations of the American Society of Echocardiography.\textsuperscript{129} Relative wall thickness (a measure of the degree of concentric hypertrophy) was calculated as the sum of the septal wall thickness and posterior wall thickness at end diastole divided by the left ventricular internal dimension. Measurements of the left ventricle were calculated by standard methods described below:

Left ventricular mass (LVM) was calculated as:

\[
LVM = 1.04 \left[ (LVEDD + LVPWd + IVSd)^3 - LVEDD^3 \right] - 13.6 \text{ g}
\]

where LVEDD is left ventricular end diastolic diameter, LVPWd is posterior wall thickness and IVSd is intraventricular septum thickness. This was divided by the body surface area to give the left ventricular mass index.\textsuperscript{139}

Left ventricular fractional shortening was defined as:

\[
\text{Fractional shortening} = \frac{[LVEDD - LVESD]}{LVEDD}
\]
where LVESD is left ventricular end systolic diameter.

**Statistical analysis**

Statistical interpretation of the results was by analysis of variance with Fisher’s pairwise comparisons for between-group differences. A chi squared ($\chi^2$) test was used to compare the sex distribution of the groups. A p value of 0.05 was considered significant.

**Results**

**Demographic summary**

The characteristics of the 65 study patients are presented in table 5.2. There were no significant differences in sex distribution, age, weight or height between groups. By definition, clinic blood pressures were higher in persistent and white coat hypertensives compared to normotensives and ambulatory pressures were higher in persistent hypertensives compared to both white coat and normotensives (figure 7). There were no significant differences in heart rate or pulse pressure between groups. Serum creatinine, cholesterol and triglyceride levels tended to be higher in the persistent hypertensives but the differences did not reach statistical significance (table 5.2).
<table>
<thead>
<tr>
<th></th>
<th>Persistent</th>
<th>White coat</th>
<th>Normal</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male / female</td>
<td>11 / 9</td>
<td>14 / 8</td>
<td>8 / 15</td>
<td>NS (χ²)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>55 ± 6</td>
<td>58 ± 8</td>
<td>61 ± 9</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>80.1 ± 18.3</td>
<td>78.9 ± 16.8</td>
<td>70.0 ± 12.4</td>
<td>NS</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>166 ± 6</td>
<td>168 ± 11</td>
<td>168 ± 11</td>
<td>NS</td>
</tr>
<tr>
<td>Body surface area m²</td>
<td>1.86 ± 0.22</td>
<td>1.89 ± 0.23</td>
<td>1.88 ± 0.21</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate / minute</td>
<td>68 ± 8</td>
<td>63 ± 8</td>
<td>64 ± 10</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine (µmol/l)</td>
<td>87 ± 16</td>
<td>75 ± 30</td>
<td>78 ± 26</td>
<td>NS</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>6.29 ± 0.88</td>
<td>5.39 ± 1.98</td>
<td>5.79 ± 1.07</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>2.08 ± 0.95</td>
<td>1.43 ± 0.97</td>
<td>1.47 ± 1.17</td>
<td>NS</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>5.5 ± 1.8</td>
<td>4.8 ± 1.8</td>
<td>5.3 ± 0.5</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table 5.2 Patient characteristics (mean ± standard deviation)

NS, not significant
Figure 7. Comparison of blood pressure characteristics
*p<0.001 compared with normotensive patients.
ABPM, ambulatory blood pressure monitoring
Cardiac indices

Analysis of the whole study population confirmed no significant sex differences in echocardiographic measurements.

Left ventricular function: these measurements are presented in figures 8 and 9. The E:A ratio was reduced in both persistent and white coat hypertensives (0.94 ± 0.23 and 1.06 ± 0.21 compared to 1.24 ± 0.31 respectively, p<0.005 ANOVA). This remained statistically significant after correction for systolic and diastolic pressures at the time of the ultrasound measurement. The isovolumetric relaxation time (IVRT) was prolonged in both persistent and white coat hypertensives compared to normal (85.7 ± 14.1 ms and 88.8 ± 19.0 ms compared to 70.8 ± 14.7 ms, p<0.001 ANOVA) but this was not significant after correcting for blood pressure.

Left ventricular mass: LV mass, LV mass index and relative wall thickness were significantly higher in the persistent hypertensives but not in the white coat hypertensives or normotensives; for example LV mass index was 118 ± 36 g/m² compared to 86±15 g/m² and 99±19 g/m² (p<0.01) respectively. Fractional shortening was similar in all groups.
Figure 8. **Comparison of E:A ratios (mean ± SD)**

*p<0.005, **p<0.001 compared to normotensives.*

SBP, systolic blood pressure

DBP, diastolic blood pressure
Figure 9. Isovolumetric relaxation times (mean ± SD).

**p<0.001 compared to normotensives.

SBP, systolic blood pressure
DBP, diastolic blood pressure
<table>
<thead>
<tr>
<th></th>
<th>Persistent</th>
<th>White coat</th>
<th>Normal</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV mass (g)</td>
<td>209 ± 47*</td>
<td>163 ± 32</td>
<td>169 ± 53</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LV mass index (g/m²)</td>
<td>118 ± 36*</td>
<td>86 ± 15</td>
<td>99 ± 19</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Relative wall thickness (%)</td>
<td>46 ± 5*</td>
<td>39 ± 5</td>
<td>43 ± 5</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Fractional shortening (%)</td>
<td>22 ± 5</td>
<td>23 ± 12</td>
<td>23 ± 11</td>
<td>0.970</td>
</tr>
</tbody>
</table>

Table 5.3 Left ventricular systolic function and mass (mean ± SD)  
* significant difference compared to normotensives.
DISCUSSION

Persistent and white coat hypertensives had similar abnormalities of left ventricular diastolic function. These changes are consistent with the known effects of hypertension and are caused by impaired diastolic filling with a relative increase in atrial activity to complete the filling process. Overall there was a reduction in ventricular compliance which has been described previously in hypertension. However, the abnormalities were also present in the white coat hypertensives and the two groups had a similar degree of dysfunction.

These results correspond with the findings of a study in elderly hypertensives which reported similar disturbances of diastolic function in 17 subjects (mean age 74 yrs) with white coat hypertension. These early changes may precede systolic dysfunction and the development of cardiac failure. However, we found no significant increase in left ventricular mass or mass index in the white coat hypertensives compared to normal but our patients were younger on average by 15 years and this may simply reflect an earlier stage of disease. In contrast the persistent hypertensives in our study, presumably at a later stage in the disease process, had increased left ventricular mass and mass index, as well as increased relative wall thickness consistent with ventricular hypertrophy.
While the particular level of diastolic blood pressure will certainly influence the categorisation of the patient groups, 95 mmHg was based on the thresholds for initiation of treatment recommended by the World Health Organisation and the International Society of Hypertension. This was intended to allow the results to be interpreted clinically in the context of initiating antihypertensive treatment in a patient found to be hypertensive in the clinic but not according to the daytime ambulatory blood pressure average. The threshold chosen led to the inclusion, in the white coat hypertensive group, of individuals who might be classified as persistent hypertensives according to alternative criteria. However, this also led to the inclusion in the normotensive group of patients who otherwise might be classified as hypertensive. Irrespective of the definition, there is a close comparability between the daytime and night time values in the white coat and normotensive groups, and these are significantly different from the corresponding values in the persistent hypertensives.

Other than by statistical means it is difficult to control for differences in blood pressure at the time of measurement in the white coat hypertensives since pharmacological manipulation of blood pressure would itself change arterial compliance and diastolic function. Therefore all diastolic measurements were adjusted relative to an arbitrary blood pressure of 120/80 and, after correction, it could be
seen that prolongation of the IVRT was attributable to hypertension during measurement. However, even after this correction for blood pressure, highly significant differences in the E:A ratio remained. These differences would persist if any other arbitrary blood pressure was chosen, since the statistical correction involves dividing by the subjects individual blood pressure at the time of ultrasound and then multiplying by a numerical constant, in this case either 120 or 80. The discriminating feature is the blood pressure, not the constant. There are limitations in the standardisation procedures for the functional cardiovascular measurements but in the absence of a previously accepted procedure, the measurements were standardised by allowing for the slope of the relation between blood pressure and the dependent variable (eg E:A ratio or IVRT).

There is recent evidence that white coat hypertension is associated with the development of cardiovascular disease with increased rates of target organ damage and functional abnormalities such as microalbuminuria.162,163 Thus white coat hypertension probably represents an intermediate or latent group for morbidity and mortality and may have corresponding benefits from antihypertensive treatment.

The clinic blood pressure should be used as a guide to the requirement for antihypertensive therapy since it was this measurement that was used to include patients in the mortality studies of antihypertensive
treatment. However, ambulatory blood pressure monitoring is becoming more widely available and is frequently used to avoid starting or increasing medication. Until prognostic studies have been performed there is no clear evidence to support this approach. Previous small studies have shown low cardiovascular morbidity in subjects with white coat hypertension\textsuperscript{24} followed for up to 7.5 years but 29\% of these received drug treatment. Other studies have shown that persistent hypertension develops in the majority of white coat hypertensives (75\%) and that this progression could not be predicted by clinic blood pressure.\textsuperscript{153} Therefore it is important to avoid classifying white coat hypertensives as normotensive and the possibility of transition to persistent hypertension should be considered.

The results of this study suggest that white coat hypertension is associated with abnormalities of cardiac function. These abnormalities have been shown in previous studies of persistent hypertension to be reversible with treatment and this suggests that white coat hypertensives also may benefit from antihypertensive treatment.
Carotid arterial compliance in hypertension

Background

This section describes the use of a Doppler ultrasound wall tracking device to study the persistent, white coat and normotensive patients detailed in chapter 5. The abnormalities of carotid arterial compliance in hypertensives have been reviewed earlier but to date there have been no studies of white coat hypertensives using wall tracking technology. In addition, left ventricular diastolic function has yet to be related to vascular compliance measurements even though they essentially measure complementary aspects of the arterial circulation. These techniques have been described earlier. The principal aim of this sub-study was to investigate functional aspects of the large arteries in relation to the functional abnormalities in the left ventricle.

Methods

The inclusion and exclusion criteria are described in chapter 5. This study used the same population with blood pressure profiles as defined previously.
Carotid arterial compliance was measured using a wall tracking device connected to the Acuson 128 as described in chapter 4.

**Wall tracking analysis**

All ultrasound measurements and calculations were performed independently of any blood pressure data. The pressure-strain elastic modulus (Peterson's modulus; $E_p$) and stiffness index were calculated as defined earlier in chapter 2.

The distensibility coefficient (DC) was calculated as:

\[
DC = \frac{[2 \times \text{distension}]}{[\text{minimum diameter} \times \text{pulse pressure}]}
\]

**Statistical analysis**

Statistical interpretation was by analysis of variance with Fisher's pairwise comparisons for between group differences. A p value of 0.05 was considered significant.

**RESULTS**

The clinical characteristics of the 65 study patients are described in chapter 5 (table 5.2).
Arterial compliance

Table 6.1 demonstrates the correlation between right and left common carotid arterial compliance measurements. There was excellent correlation between sides thus the results are presented as the mean of the two arteries. The coefficient of variation for mean arterial diameter measurement in a random sample of 20 patients from the study was 4.2%.

Carotid arterial compliance results are shown in table 6.2. Arterial diameter was significantly greater in both hypertensive groups compared to the normotensives and was associated with a reduction in distensibility and rise time. The distensibility coefficient was significantly lower in both hypertensive groups compared to normal reflecting an increase in arterial stiffness (and a decrease in compliance).

Adjusting for the blood pressure at the time of ultrasound allows the pressure-strain elastic modulus \( E_p \) to be calculated and this was also significantly higher in subjects with either form of hypertension. There was no significant correlation between compliance data and age in each patient group, however the age range in each group was deliberately restricted to allow between group comparisons.
<table>
<thead>
<tr>
<th>Compliance parameter</th>
<th>Mean right (pm)</th>
<th>Mean left (pm)</th>
<th>R</th>
<th>p</th>
<th>CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distensibility (µm)</td>
<td>730 ± 239</td>
<td>720 ± 256</td>
<td>0.931</td>
<td>&lt;0.001</td>
<td>12.8</td>
</tr>
<tr>
<td>Diameter (mm)</td>
<td>6.05 ± 0.85</td>
<td>6.04 ± 0.84</td>
<td>0.933</td>
<td>&lt;0.001</td>
<td>5.1</td>
</tr>
<tr>
<td>Rise time (ms)</td>
<td>134 ± 30</td>
<td>129 ± 32</td>
<td>0.839</td>
<td>&lt;0.001</td>
<td>13.4</td>
</tr>
</tbody>
</table>

Table 6.1

Correlation between right and left carotid compliance parameters
(mean ± SD)
<table>
<thead>
<tr>
<th></th>
<th>Persistent</th>
<th>White coat</th>
<th>Normal</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum diameter (mm)</td>
<td>6.31 ± 0.70*</td>
<td>6.30 ± 0.88*</td>
<td>5.56 ± 0.79</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Absolute distension (mm)</td>
<td>0.67 ± 0.25*</td>
<td>0.67 ± 0.26*</td>
<td>0.84 ± 0.23</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>% Distensibility</td>
<td>11.4 ± 3.8*</td>
<td>11.3 ± 4.0*</td>
<td>15.0 ± 4.5</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Rise time (ms)</td>
<td>122 ± 18*</td>
<td>122 ± 27*</td>
<td>149 ± 27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>$E_p$ (kPa)</td>
<td>4.64 ± 1.47*</td>
<td>4.36 ± 2.12*</td>
<td>2.89 ± 1.07</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Distensibility $10^{-3}$kPa-1</td>
<td>2.84 ± 0.09*</td>
<td>3.39 ± 0.16*</td>
<td>4.37 ± 0.14</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Stiffness index</td>
<td>4.53 ± 1.38*</td>
<td>4.32 ± 1.90*</td>
<td>3.27 ± 0.95</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Table 6.2. Carotid arterial compliance (mean ± SD)

* significant difference compared to normotensives.
**Correlations with echocardiographic parameters**

Table 6.3 lists Pearson’s correlation coefficients for echocardiographic predictors of distensibility parameters. Univariate analysis suggested significant associations between arterial distensibility and left ventricular end systolic and diastolic diameters (LVEDD, LVESD), posterior wall and septal thickness in diastole (LVPWd, IVSd), E velocity and isovolumetric relaxation time (IVRT). Multiple regression analysis confirmed that the only significant relations were in fact with LVEDD (p=0.025) and IVRT (p=0.005). No echocardiographic measurement was significantly related to arterial diameter.

**Correlations with blood pressure measurements**

Table 6.4 lists Pearson’s correlation coefficients for blood pressure predictors of arterial compliance measures. The most statistically significant associations were between arterial diameter and blood pressure measurements obtained during the ultrasound examination and calculated from the daytime ambulatory monitoring. Overall arterial diameter was directly related to the level of blood pressure. Conversely, there were generally negative associations between blood pressure and carotid arterial rise time.

Multiple regression analysis confirmed persisting correlations between arterial diameter and clinic systolic blood pressure (p=0.010) but not
for diastolic pressure (p=0.359). There was a similar pattern for daytime ambulatory blood pressure averages (p=0.019 for systolic and p=0.880 for diastolic daytime averages). Rise time was correlated with the diastolic blood pressure measurements obtained during the ultrasound examination (p=0.530, 0.280 for systolic and diastolic pressures respectively) and during daytime monitoring (p=0.986, 0.046 for systolic and diastolic daytime averages respectively).
<table>
<thead>
<tr>
<th>Echocardiographic parameter</th>
<th>Mean distensibility</th>
<th>Mean diameter</th>
<th>Mean rise time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p</td>
<td>r</td>
</tr>
<tr>
<td>IVSs</td>
<td>0.085</td>
<td>0.536</td>
<td>0.163</td>
</tr>
<tr>
<td>IVSd</td>
<td>0.197</td>
<td>0.150</td>
<td>0.068</td>
</tr>
<tr>
<td>LVPWs</td>
<td>0.035</td>
<td>0.798</td>
<td>0.223</td>
</tr>
<tr>
<td>LVPWd</td>
<td>0.210</td>
<td>0.123</td>
<td>0.161</td>
</tr>
<tr>
<td>LVEDD</td>
<td>0.279</td>
<td>0.038</td>
<td>0.044</td>
</tr>
<tr>
<td>LVESD</td>
<td>0.341</td>
<td>0.010</td>
<td>0.083</td>
</tr>
<tr>
<td>E</td>
<td>0.346</td>
<td>0.007</td>
<td>0.034</td>
</tr>
<tr>
<td>A</td>
<td>0.130</td>
<td>0.323</td>
<td>0.156</td>
</tr>
<tr>
<td>E dec</td>
<td>0.087</td>
<td>0.508</td>
<td>0.194</td>
</tr>
<tr>
<td>A dec</td>
<td>-0.054</td>
<td>0.682</td>
<td>-0.015</td>
</tr>
<tr>
<td>IVRT</td>
<td>0.352</td>
<td>0.006</td>
<td>0.087</td>
</tr>
<tr>
<td>E:A ratio</td>
<td>-0.008</td>
<td>0.952</td>
<td>0.038</td>
</tr>
</tbody>
</table>

Table 6.3 Pearson's correlation coefficients for echocardiographic predictors of distensibility parameters.

Key to abbreviations:

**IVSs, IVSd** interventricular septum in systole or diastole

**LVPWs, LVPWd** left ventricular posterior wall in systole or diastole

**LVEDD, LVESD** left ventricular end diastolic or systolic diameter

**E** early velocity of ventricular filling

**A** active or atrial velocity of ventricular filling

**E dec** E velocity deceleration time;

**A dec** A velocity deceleration time

**IVRT** isovolumetric relaxation time

**E:A ratio** ratio of E and A velocities
<table>
<thead>
<tr>
<th>Blood pressure parameter</th>
<th>Distensibility</th>
<th>Diameter</th>
<th>Rise time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p</td>
<td>r</td>
</tr>
<tr>
<td>Clinic Systolic</td>
<td>-0.165</td>
<td>0.219</td>
<td>0.511</td>
</tr>
<tr>
<td>Pressure Diastolic</td>
<td>-0.302</td>
<td>0.022</td>
<td>0.419</td>
</tr>
<tr>
<td>Daytime Systolic</td>
<td>-0.094</td>
<td>0.475</td>
<td>0.463</td>
</tr>
<tr>
<td>Average Diastolic</td>
<td>-0.252</td>
<td>0.052</td>
<td>0.366</td>
</tr>
<tr>
<td>Daytime Systolic</td>
<td>-0.126</td>
<td>0.367</td>
<td>0.277</td>
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<tr>
<td>Load Diastolic</td>
<td>-0.245</td>
<td>0.062</td>
<td>0.274</td>
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<tr>
<td>Night time Systolic</td>
<td>-0.038</td>
<td>0.771</td>
<td>0.308</td>
</tr>
<tr>
<td>average Diastolic</td>
<td>-0.183</td>
<td>0.162</td>
<td>0.290</td>
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<tr>
<td>Night time Systolic</td>
<td>-0.005</td>
<td>0.977</td>
<td>0.386</td>
</tr>
<tr>
<td>load Diastolic</td>
<td>0.061</td>
<td>0.737</td>
<td>-0.010</td>
</tr>
</tbody>
</table>

*Table 6.4 Pearson's correlation coefficients for blood pressure predictors of mean compliance parameters*
DISCUSSION

This sub-study has demonstrated similar abnormalities of arterial elasticity in both persistent and white coat hypertensives. The persistent hypertensives had larger arteries than the normotensives as has been previously described, however the white coat hypertensives also had larger arteries. Although these abnormalities might simply reflect higher blood pressures at the time of the ultrasound examination the differences persisted after calculating the pressure strain elastic modulus, stiffness index and the distensibility coefficient which, mathematically at least, take account of blood pressure. Overall these vascular abnormalities represent a reduction in arterial compliance which normally provides elastic recoil during left ventricular contraction. This is thought to increase pulse pressure as a consequence and accelerate both the development of cardiac hypertrophy and the progression of atherosclerosis.

As previously outlined it is not possible, other than by statistical means, to control for differences in blood pressure at the time of measurement in the white coat hypertensives since manipulation of blood pressure would itself change arterial compliance. This explains the need to represent arterial function by calculating multiple parameters since no single expression can adequately describe the
mechanical properties of an artery throughout the cardiac cycle. The stiffness index has been described in previous studies of both muscular (eg, brachial) and elastic arteries (eg, carotid, femoral and the abdominal aorta) and, although wide variations were found in the brachial artery in response to changes in sympathetic tone, the index remained relatively constant in the carotid artery.44

The results also demonstrate links between abnormal arterial function and abnormal left ventricular diastolic function. In particular, the relations between LVEDD, IVRT and arterial distensibility persisted despite correction for other echocardiographic measures. It is interesting, however, that an increase in LVEDD was associated with an increase in distensibility, rather than an inverse relationship. Cardiac failure attributable to systolic left ventricular dysfunction is associated with a decrease in arterial compliance14,39 but in this condition there is significant peripheral vasoconstriction.13 It is possible, therefore, that the left ventricle in hypertension dilates as a secondary response to increased vascular stiffness, hence the positive association. The association between IVRT and arterial stiffness similarly suggests that left ventricular dysfunction could develop as a secondary phenomenon in hypertension. This obviously requires further research in longitudinal studies.
In conclusion, there are two important aspects to these results. The first is the demonstration of vascular abnormalities in white coat hypertensives, similar to those found in persistent hypertensives. The second is the close association between diastolic left ventricular dysfunction and vascular compliance abnormalities.
CHAPTER 7  DOPPLER ULTRASOUND

Carotid arterial pulsatility in hypertension

Background

The clinical consequences of untreated hypertension have long been recognised with an increased risk of vascular complications particularly in the cerebral and coronary circulation. Systolic hypertension is thought to cause arterial damage through repeated mechanical cyclic strain which leads to fibrotic or hyaline degeneration in the media of large arteries. Such degeneration decreases arterial elasticity and increases the stiffness of the arterial bed. This has significant consequences for left ventricular strain and is associated with an increase in left ventricular mass and an increase in systolic blood pressure partly because of the rapid return of reflected pressure waves from the periphery during systole (rather than diastole) as reviewed in Chapter 2. Previous work by other research workers confirmed an increase in intima-medial thickness (IMT) in both large and medium sized arteries (carotid and radial). In addition to these structural abnormalities, it has also been shown that carotid artery compliance is reduced, as demonstrated earlier in chapter 6 and in work by others. However, the consequences and possible predictive factors for decreased arterial compliance in the carotid
arteries require to be evaluated further to identify the nature of the mechanical strain.

Measurement of carotid arterial blood flow velocity using pulsed wave Doppler ultrasound is a convenient non-invasive method of determining intravascular blood flow properties. While it is only possible to determine actual blood flow (in ml/min) if the arterial diameter is known throughout the cardiac cycle, blood flow velocity gives an indication of the mechanical stress placed on the arterial wall. It is possible to calculate a pulsatility index\(^{170}\) which provides an indication of the tensile stress sustained by the artery during systole. In addition it is possible to calculate a measure of parietal stress (as defined in chapter 4) in the area of brain supplied by the artery.\(^{171}\)

It is interesting to note that systolic rather than diastolic hypertension correlates more closely with the cerebrovascular consequences of hypertension\(^{49}\) although many of the large hypertension trials used diastolic blood pressure as an inclusion criterion.\(^{152}\) The SHEP study confirmed significant benefit from treating isolated systolic hypertension in the elderly\(^{53}\) and work on vascular compliance, particularly by O'Rourke,\(^{12,57}\) suggests that systolic blood pressure control should be the primary target of antihypertensive treatment.

The aim of this study was to determine the carotid arterial blood flow velocities in the persistent, white coat and normotensives described in
chapter 5. From these velocities we intended calculating measures of mechanical arterial strain in an attempt to determine the correlations with blood pressure measurements and the possible future development of clinically significant atherosclerosis.

Methods

The subjects in this section are described in chapter 5. The same inclusion and exclusion criteria apply. In addition to the clinical details presented, haematocrit also was measured in these subjects since previous studies suggested an increase in haematocrit in hypertensive subjects which influences cerebral blood flow. Carotid Doppler ultrasound was performed as described in chapter 4.

Calculations

Pulsatility index was calculated as:

\[
\frac{\text{Systolic - diastolic velocities}}{\text{Mean velocity}}
\]

Parietal stress was calculated according to Lame’s approximation for the cylindrical structures of Laplace’s law:

\[
\frac{\text{Mean Blood pressure} \times \text{Carotid artery radius}}{\text{Arterial wall thickness}}
\]
Blood pressure was converted to kPa for this calculation.

**Statistical analysis**

Analysis of variance with Fisher's pairwise comparisons was performed to compare the patient groups. Pearson’s correlation coefficients were calculated for right and left velocity comparisons and to assess predictors of pulsatility index before multiple regression analysis. A p value <0.05 was considered significant

**Results**

Patient characteristics are described in chapter 5. Mean haematocrit in the persistent, white coat and normotensives was 0.43±0.03, 0.42±0.03, 0.41±0.03 respectively (p=0.068 ANOVA).

**Ultrasound measurement**

**Reproducibility**

Reproducibility was assessed on a random sample of 20 subjects. The coefficient of variation was 6.3% for common carotid velocity measurements (r=0.958, r²=0.918). There was no significant difference between the right and left sides for any of the blood flow velocity measurements (see table 7.1) although the correlation between right
<table>
<thead>
<tr>
<th></th>
<th>Right</th>
<th>Left</th>
<th>r</th>
<th>r²</th>
</tr>
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<tbody>
<tr>
<td><strong>Systolic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common carotid</td>
<td>47.5 ± 14.8</td>
<td>46.7 ± 10.5</td>
<td>0.628</td>
<td>0.394</td>
</tr>
<tr>
<td>Internal carotid</td>
<td>43.6 ± 26.3</td>
<td>38.1 ± 21.6</td>
<td>0.719</td>
<td>0.517</td>
</tr>
<tr>
<td>External carotid</td>
<td>49.7 ± 20.8</td>
<td>48.6 ± 15.0</td>
<td>0.446</td>
<td>0.199</td>
</tr>
<tr>
<td><strong>Diastolic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common carotid</td>
<td>10.2 ± 4.2</td>
<td>10.9 ± 3.8</td>
<td>0.668</td>
<td>0.446</td>
</tr>
<tr>
<td>Internal carotid</td>
<td>15.0 ± 8.3</td>
<td>13.3 ± 6.9</td>
<td>0.621</td>
<td>0.386</td>
</tr>
<tr>
<td>External carotid</td>
<td>8.0 ± 5.3</td>
<td>7.5 ± 3.0</td>
<td>0.171</td>
<td>0.029</td>
</tr>
</tbody>
</table>

Table 7.1

Comparison of right and left carotid blood flow velocities in cm/sec

(mean ± SD)
and left external carotid velocities was poor. Correlations were good for the internal and common carotid segments. Analysis was performed with the mean of the right and left measurements.

**Patient groups**

A comparison of the blood flow velocities in the three patient groups is shown in table 7.2 and illustrated in figures 10 and 11. There were no significant differences between groups for the common carotid artery measurements. However, systolic velocities in the internal carotid artery were significantly higher in the persistent hypertensives (42.7 ± 14.2 cm/sec) compared to both white coat (35.5 ± 9.7 cm/sec) and normotensives (33.4 ± 8.3 cm/sec). In addition, pulsatility indices were significant greater in both the persistent (1.24 ± 0.19) and white coat hypertensives (1.20 ± 0.25) compared to normal (0.96 ± 0.22).

Multiple regression analysis (table 7.4) confirmed a significant association with systolic blood pressure measurement obtained during the ultrasound but not for the others.
Figure 10. **Comparison of internal carotid artery velocities**

*significant difference compared to white coat and normotensive groups, p=0.019
Figure 11. Comparison of pulsatility indices
* significant difference compared to normal, p=0.001
Figure 12. Comparison of parietal stress
*significant difference compared to normal, p<0.001
<table>
<thead>
<tr>
<th></th>
<th>Persistent</th>
<th>White coat</th>
<th>Normal</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>49.5 ± 12.4</td>
<td>47.0 ± 12.0</td>
<td>48.0 ± 10.5</td>
<td>0.775</td>
</tr>
<tr>
<td>Diastolic</td>
<td>11.4 ± 2.8</td>
<td>10.2 ± 3.7</td>
<td>11.3 ± 3.7</td>
<td>0.398</td>
</tr>
<tr>
<td>Mean</td>
<td>24.1 ± 5.3</td>
<td>22.5 ± 5.7</td>
<td>23.5 ± 5.3</td>
<td>0.587</td>
</tr>
<tr>
<td>PI</td>
<td>1.57 ± 0.24</td>
<td>1.65 ± 0.28</td>
<td>1.56 ± 0.24</td>
<td>0.392</td>
</tr>
<tr>
<td><strong>Internal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>42.7* ± 14.2</td>
<td>35.5 ± 9.7</td>
<td>33.4 ± 8.3</td>
<td>0.019</td>
</tr>
<tr>
<td>Diastolic</td>
<td>13.8 ± 5.4</td>
<td>12.0 ± 4.0</td>
<td>13.9 ± 3.8</td>
<td>0.190</td>
</tr>
<tr>
<td>Mean</td>
<td>23.4 ± 8.1</td>
<td>19.8 ± 5.4</td>
<td>20.4 ± 4.8</td>
<td>0.121</td>
</tr>
<tr>
<td>PI</td>
<td>1.24 ± 0.19</td>
<td>1.20 ± 0.25</td>
<td>0.96 ± 0.22</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>External</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>53.4° ± 14.1</td>
<td>44.2 ± 11.4</td>
<td>47.1 ± 13.2</td>
<td>0.063</td>
</tr>
<tr>
<td>Diastolic</td>
<td>7.9 ± 2.2</td>
<td>7.0 ± 1.8</td>
<td>8.2 ± 3.4</td>
<td>0.208</td>
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<tr>
<td>Mean</td>
<td>23.0° ± 5.7</td>
<td>19.4 ± 4.5</td>
<td>21.1 ± 5.7</td>
<td>0.073</td>
</tr>
<tr>
<td>PI</td>
<td>1.97 ± 0.19</td>
<td>1.91 ± 0.22</td>
<td>1.85 ± 0.35</td>
<td>0.347</td>
</tr>
</tbody>
</table>

Table 7.2 Comparison of blood flow velocities in the patient groups (mean ± SD)

*significant difference compared to normal

*significant difference compared to white coat hypertensives
Table 7.3 Pearson’s correlation coefficients for predictors of pulsatility index in the common, internal and external carotid arteries.

Blood pressure indices presented as systolic/diastolic. $p$ refers to significance of association with internal carotid pulsatility.
Table 7.4 Multiple regression of internal carotid pulsatility predictors

<table>
<thead>
<tr>
<th></th>
<th>r</th>
<th>SD</th>
<th>t Ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP during ultrasound</td>
<td>0.0058</td>
<td>0.0029</td>
<td>2.02</td>
<td>0.048</td>
</tr>
<tr>
<td>Diastolic BP during ultrasound</td>
<td>0.0034</td>
<td>0.0040</td>
<td>0.86</td>
<td>0.392</td>
</tr>
<tr>
<td>Daytime systolic</td>
<td>0.0024</td>
<td>0.0068</td>
<td>0.35</td>
<td>0.725</td>
</tr>
<tr>
<td>Daytime diastolic</td>
<td>-0.0015</td>
<td>0.0090</td>
<td>-0.16</td>
<td>0.871</td>
</tr>
<tr>
<td>Night time systolic</td>
<td>-0.0013</td>
<td>0.0060</td>
<td>-0.21</td>
<td>0.834</td>
</tr>
<tr>
<td>Night time diastolic</td>
<td>-0.0006</td>
<td>0.0085</td>
<td>-0.07</td>
<td>0.946</td>
</tr>
</tbody>
</table>
Discussion

This sub-study has demonstrated significant abnormalities in internal carotid blood flow velocities in persistent and white coat hypertensive patients.

Systolic hypertension is associated with an increased risk of both haemorrhagic and ischaemic stroke.\textsuperscript{4,174,175} Treatment of hypertension has been shown to markedly reduce the incidence of haemorrhagic stroke which is thought to be due to arteriolar disease\textsuperscript{176-9} but has a smaller effect on the incidence of ischaemic stroke due to atherosclerosis.

Internal carotid artery atherosclerosis is associated with cerebrovascular injury both through embolism from ruptured plaque and through ischaemia due to diminished blood flow. These results show an increased mechanical strain in the wall of the internal carotid artery but also indicate an increased level of parietal stress in the distribution territory of the artery. Parietal stress refers to the mechanical strain placed on the arterioles and smaller blood vessels. Reduction of blood pressure with antihypertensive drugs is known to alter blood flow velocities in the carotid arteries\textsuperscript{180-182} but studies have yet to be performed examining for the effects of treatment on parietal stress.
Our results suggest two important possible clinical consequences. The first is that the abnormalities of blood flow velocities within the internal carotid artery may respond to treatment. The second is that white coat hypertensives were found to have significant flow velocity abnormalities, albeit to a lesser degree than the persistent hypertensives, which might also be amenable to treatment.

Our results are consistent with a previous study which compared blood flow velocities in hypertensives and matched normals. Although an increase in parietal strain was found in their hypertensive group there was no increase in either pulsatility index or arterial diameter. This is surprising since other studies of large arteries in hypertensives, including that described in chapter 6, have found significantly higher diameters than in normotensives but mean arterial velocities rather than systolic or diastolic velocities were presented. In this published paper the mean internal carotid artery velocity in hypertensives was found to be higher compared to normotensives (mean 37.5 ± 9.1 versus 32.7 ± 3.9 cm/s, p<0.02). Our results do not show any difference in mean velocities. However our patients were older (mean 59 years compared to 49 years) and had higher blood pressures during the ultrasound examination (mean 165/107 compared to 161/99 in their hypertensive group). Arterial stiffness and blood pressure increase with age and this may partly explain the difference in results.
In addition, only a subgroup of the study population were studied using Doppler ultrasound (30 hypertensive and 20 normotensive subjects) and the criteria for diagnosing hypertension were not stated.

In conclusion, abnormalities of internal carotid artery pulsatility were found in hypertensive patients, whether persistent or white coat, which correspond to an increase in mechanical strain in the arterial wall and an increase in parietal stress within the brain. These abnormalities are likely to be related to the pathogenesis of both atherosclerotic and haemorrhagic cerebrovascular disease. The specific effects of antihypertensive treatment on parietal stress require further evaluation, as do the differential effects of the various classes of antihypertensive drugs.
Carotid intima-medial thickness in hypertension

**Background**

This section describes the use of high resolution B-mode ultrasound to measure carotid wall thickness in an extension of the study of white coat hypertensives described in chapters 5. Having already demonstrated functional abnormalities of cardiac and large vessel function, the next step was to attempt to identify structural abnormalities in these subjects. This further study includes additional patients recruited during the 12 months following the original study.

Carotid intima-medial thickness (IMT) has been identified as a marker of cardiovascular disease corresponding to the presence of coronary artery disease (table 8.1), peripheral arterial disease (table 8.2) and there is increasing evidence that IMT can be used to predict the future development of myocardial infarction and stroke.\textsuperscript{130,183}

Arterial wall thickening is known to develop in untreated hypertensives\textsuperscript{60} and several large multicentre studies are underway to examine the potential benefit of antihypertensive treatment in preventing the progression of intima-medial thickening. This includes the European Lacidipine Study on Atherosclerosis, the source of our
patients, which is due to report its four year follow-up results in 1999. Intima-medial thickening can be detected early in disease processes and may function as an early or surrogate marker for long-term cardiovascular morbidity and mortality. Increased IMT has been described in hypertension in the common carotid, femoral and radial arteries. The microscopic changes associated with increased IMT are unclear but are thought to represent diffuse atherosclerosis and this is consistent with the increased risk of myocardial infarction seen in a recent prospective study. The other possibility is that intima-medial thickening is caused by smooth muscle hyperplasia rather than atherosclerosis and there are close associations between IMT and systolic blood pressure which causes vessel wall hypertrophy. IMT is also strongly correlated with age and was found to increase by 0.01 mm/year in both male and female populations. This is important in the design of cross sectional studies which should be matched for age. Other factors which have been shown to influence IMT include hypercholesterolaemia, smoking, LDL cholesterol, systolic blood pressure, diabetes, triglycerides, fibrinogen, pulse pressure, uric acid, type A personality score, copper, platelet aggregability, low selenium levels, waist-hip ratio, body mass index, insulin, ACE genotype, ACE activity and saturated fat intake.
<table>
<thead>
<tr>
<th>Study</th>
<th>Reference</th>
<th>Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crouse et al 1986</td>
<td>197</td>
<td>Obstructive CAD associated with increased carotid IMT</td>
</tr>
<tr>
<td>Chambers &amp; Norris 1986</td>
<td>198</td>
<td>Carotid atherosclerosis associated with increased risk of clinical CAD</td>
</tr>
<tr>
<td>Rubens et al 1988</td>
<td>199</td>
<td>Obstructive CAD associated with increased carotid IMT</td>
</tr>
<tr>
<td>Howard et al 1990</td>
<td>200</td>
<td>Carotid atherosclerosis present in majority of patients with symptomatic CAD</td>
</tr>
<tr>
<td>Craven et al 1990</td>
<td>201</td>
<td>Obstructive CAD associated with increased carotid IMT especially &gt;50 years</td>
</tr>
<tr>
<td>Wofford et al 1991</td>
<td>202</td>
<td>B-mode changes predicted coronary angiography findings</td>
</tr>
<tr>
<td>Scudlova et al 1991</td>
<td>203</td>
<td>85% of patients with myocardial infarction have carotid atherosclerosis</td>
</tr>
<tr>
<td>Salonen et al 1991</td>
<td>183</td>
<td>Carotid wall morphology predicts future risk of angina and myocardial infarction</td>
</tr>
<tr>
<td>Salonen et al 1994</td>
<td>204</td>
<td>Carotid IMT and plaque associated with clinical CAD and CAD risk factors</td>
</tr>
<tr>
<td>Geroulakos et al 1994</td>
<td>194</td>
<td>Relation between IMT and number of coronary arteries involved</td>
</tr>
<tr>
<td>Burke et al (ARIC) 1995</td>
<td>205</td>
<td>Carotid IMT and prevalence of symptomatic CAD in middle aged adults</td>
</tr>
<tr>
<td>Crouse et al 1995</td>
<td>193</td>
<td>Quantitative associations between B-mode IMT and angiographic CAD severity</td>
</tr>
</tbody>
</table>

*Table 8.1*

*Association between carotid IMT and coronary artery disease (CAD).*
<table>
<thead>
<tr>
<th>Study</th>
<th>Reference</th>
<th>Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spurk et al 1989</td>
<td>206</td>
<td>Association between carotid wall thickening and peripheral vascular disease (pressure index)</td>
</tr>
<tr>
<td>Pujia et al 1989</td>
<td>207</td>
<td>Direct correlation between peripheral and carotid atherosclerosis ( r=0.3, p&lt;0.001 )</td>
</tr>
<tr>
<td>Wendelhag 1993</td>
<td>208</td>
<td>Correlation between carotid IMT and presence of femoral plaque</td>
</tr>
<tr>
<td>Wilt et al 1993</td>
<td>209</td>
<td>Carotid plaque thickness related to presence of peripheral vascular disease</td>
</tr>
<tr>
<td>The MIDAS Study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bots et al 1993</td>
<td>195</td>
<td>Common carotid IMT in elderly women associated with abdominal aortic calcification on X-ray (although ultrasound performed up to 5 years after X-ray)</td>
</tr>
<tr>
<td>Bots, Hofman &amp; Grobbee 1994</td>
<td>210</td>
<td>Common carotid IMT correlates with ankle/arm pressure index</td>
</tr>
<tr>
<td>Joensuu et al 1994</td>
<td>196</td>
<td>Correlations and determinants of femoral and carotid IMT</td>
</tr>
<tr>
<td>Bots et al 1996</td>
<td>211</td>
<td>Common carotid IMT associated with indicators of peripheral vascular disease including ankle/arm index and femoral IMT</td>
</tr>
</tbody>
</table>

Table 8.2

*Association between carotid IMT and peripheral vascular disease*
Such thickening also occurs in dyslipidaemic states and hypercholesterolaemic children have been shown to have increased IMT.\textsuperscript{185} Furthermore, intima-medial thickening has been shown to be treatable with lipid lowering therapy.\textsuperscript{186}

The fact that serial measurements can detect the progression of IMT in clinical studies gives an indication of the levels of accuracy and reproducibility possible with high resolution B-mode ultrasound. Guidelines have been formulated to maximise reproducibility when measuring IMT\textsuperscript{187-8,190,197} and these have been adopted in the multicentre studies via the development of rigorous measurement protocols.

High resolution B-mode ultrasound measurement of IMT has been validated against histological specimens\textsuperscript{22,131} with a correlation coefficient of 0.76 to 0.82 (p<0.001) in these early studies. In addition it was confirmed that the echogenic lines in the B-mode scan did indeed correspond to the intimal and medial layers.

Our aim was to use high resolution B-mode ultrasound to examine the common carotid arterial segment for IMT in an extension of the study of persistent, white coat and non-hypertensive patients described in chapters 5. We chose to concentrate on the common carotid artery rather than examining the internal carotid artery and bifurcation since pilot work suggested that over 35\% of our subjects would present
technical difficulty when aligning the ultrasound probe to give an adequate view of these segments. This was consistent with previous work from the large multicentre Atherosclerosis Risk in Communities (ARIC) study\(^{189}\) where 41% of carotid bifurcations and 59% of internal carotid arteries could not be measured reliably. The problem of missing data in such a large study can be overcome (over 14,106 baseline ultrasound examinations) but would be seriously damaging to a smaller study. Unless the ultrasound probe can be aligned perpendicularly to the arterial segment to be studied it is impossible to demonstrate the intima-medial segment reliably.

**Methods**

Subjects were recruited using the inclusion and exclusion criteria described in chapter 5. Recruitment to the study continued in a consecutive referral manner and blood pressure measurement was performed in a standard fashion as previously described (page 5.9).

Ultrasound examination was performed as described in chapter 4.

**Statistical analysis**

Blood pressure load was defined as the percentage of ambulatory systolic measurements of 160 mmHg or more, or diastolic of 90 mmHg or more. A \( \chi^2 \) test was used to test for sex distribution between groups.
Analysis of variance with Fisher’s pairwise comparisons was used to determine between group differences. Pearson’s correlation coefficients were used to summarise carotid IMT predictors before multiple regression analysis of predictors with significant correlations. A p value of <0.05 was considered significant.

Results

A total of 95 subjects were studied. Their clinical details are summarised in table 8.3 (below). There were no significant differences between groups in terms of sex distribution, age, weight, height, or heart rate. However, the persistent hypertensives had significantly higher creatinine levels (92 ±17 compared to 80 ± 16 and 79 ± 17 μmol/l, p=0.004) and triglycerides (1.98 ± 1.09 compared to 1.56 ± 0.74 and 1.31 ± 0.72 respectively, p=0.013) compared to both white coat and normotensives. Plasma markers including cholesterol, glucose, fibrinogen and lipoprotein (a) were similar in the three groups.

Blood pressures

The blood pressure profiles are shown in figures 13 and 14. By definition the persistent and white coat hypertensives had higher blood pressures at the clinic compared to normotensives (p<0.001). There was no significant difference between white coat and normotensives in terms of ambulatory daytime and night time averages.
<table>
<thead>
<tr>
<th></th>
<th>Persistent</th>
<th>White coat</th>
<th>Normal</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>21/12</td>
<td>17/19</td>
<td>10/16</td>
<td>NS*</td>
</tr>
<tr>
<td>Age (years)</td>
<td>58 ±7</td>
<td>60 ± 8</td>
<td>60 ± 8</td>
<td>0.493</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>67 ± 9</td>
<td>64 ± 7</td>
<td>64 ± 8</td>
<td>0.529</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>79 ± 17</td>
<td>75 ± 16</td>
<td>76 ± 17</td>
<td>0.795</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>167 ± 7</td>
<td>165 ± 9</td>
<td>172 ± 11</td>
<td>0.217</td>
</tr>
<tr>
<td>Creatinine (µmol/l)</td>
<td>92 ± 17°</td>
<td>80 ± 16</td>
<td>79 ± 17</td>
<td>0.004</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>6.1 ± 1.0</td>
<td>5.8 ± 0.9</td>
<td>5.7 ± 1.1</td>
<td>0.297</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.98 ± 1.09°</td>
<td>1.56 ± 0.74</td>
<td>1.31 ± 0.72</td>
<td>0.013</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>5.71 ± 1.42</td>
<td>5.49 ± 1.01</td>
<td>5.32 ± 0.63</td>
<td>0.388</td>
</tr>
<tr>
<td>Fibrinogen (u/l)</td>
<td>297 ± 80</td>
<td>304 ± 84</td>
<td>322 ± 77</td>
<td>0.480</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>20.0 ± 16.3</td>
<td>23.4 ± 17.8</td>
<td>22.0 ± 15.6</td>
<td>0.719</td>
</tr>
</tbody>
</table>

*Table 8.1*
*Comparison between persistent, white coat and non hypertensives (mean ± SD)*

*p > 0.10 (χ² test), °significant difference compared to normal.*
Figure 13. **Daytime blood pressure measurements.**

*p<0.001 compared to normotensive patients.*
Figure 14. Night time blood pressure measurements.
*p<0.001 compared to normotensives.
Sex differences

While there were no significant differences between groups in terms of sex distribution it was important to exclude small differences which might potentially explain patterns of IMT described below. The entire study population therefore was analysed in terms of sex (table 8.4).

This confirmed that males had higher weight, height, creatinine and average diastolic blood pressures. Females had significantly higher cholesterol levels. However there was no significant sex-related difference in carotid IMT (p=0.101).

Carotid IMT

Reproducibility was assessed by comparing results of IMT values from the two ultrasound examinations available for each subject in 50 randomly selected cases. The mean IMT measurement for exam 1 was 0.632mm ± 0.175 and for exam 2 was 0.617 ± 0.177 giving a correlation coefficient r=0.869 and r²=0.755.

There was no significant difference between right and left IMT measurements. The overall mean right IMT was 0.683 ± 0.193mm and that for the left was 0.6991 ± 0.236.
<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>86.9 ± 11</td>
<td>65.7 ± 13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>174 ± 7</td>
<td>161 ± 5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>5.56 ± 1.02</td>
<td>5.42 ± 1.10</td>
<td>0.515</td>
</tr>
<tr>
<td>Creatinine (μmol/l)</td>
<td>96 ± 18</td>
<td>73 ± 13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>5.41 ± 0.98</td>
<td>5.94 ± 1.02</td>
<td>0.046</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.60 ± 0.94</td>
<td>1.53 ± 0.81</td>
<td>0.726</td>
</tr>
<tr>
<td>Mean IMT (mm)</td>
<td>0.705 ± 0.215</td>
<td>0.645 ± 0.151</td>
<td>0.101</td>
</tr>
<tr>
<td>Fibrinogen (u/l)</td>
<td>306 ± 79</td>
<td>311 ± 80</td>
<td>0.796</td>
</tr>
<tr>
<td>Lp(a) (u/l)</td>
<td>20.5 ± 15.1</td>
<td>28.2 ± 27.5</td>
<td>0.111</td>
</tr>
<tr>
<td>Day load (systolic) %</td>
<td>63 ±30</td>
<td>54 ± 32</td>
<td>0.175</td>
</tr>
<tr>
<td>Day load (diastolic) %</td>
<td>56 ± 29</td>
<td>50 ± 28</td>
<td>0.003</td>
</tr>
<tr>
<td>Night load (systolic) %</td>
<td>48 ±33</td>
<td>40 ± 32</td>
<td>0.306</td>
</tr>
<tr>
<td>Night load (diastolic) %</td>
<td>36 ± 28</td>
<td>23 ± 19</td>
<td>0.054</td>
</tr>
</tbody>
</table>

Table 8.4 Comparison of male and female characteristics
The correlation coefficient for right and left sided measurements was 0.832 ($r^2=0.692$) therefore the data are presented as the mean of the right and left IMT values.

Persistent hypertensives had the highest IMT of $0.760 \pm 0.247\text{mm}$, white coat hypertensives had an intermediate value of $0.695 \pm 0.200\text{mm}$, and normotensives $0.583 \pm 0.100\text{mm}$ (see figure 15). Both persistent and white coat hypertensives IMT values were significantly higher than normotensives ($p=0.004$ ANOVA with Fishers pairwise comparisons).

Further analysis of IMT predictors was performed and is shown in table 8.5.

The correlation coefficients suggest significant links with age, day and night systolic mean pressure, daytime systolic load, and day and night pulse pressure. However, multiple regression analysis (table 8.6, below) confirms that these weak associations were no longer significant after controlling for age.
<table>
<thead>
<tr>
<th></th>
<th>R</th>
<th>R^2</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.231</td>
<td>0.053</td>
<td>0.019</td>
</tr>
<tr>
<td>Height</td>
<td>0.211</td>
<td>0.045</td>
<td>0.204</td>
</tr>
<tr>
<td>Weight</td>
<td>0.118</td>
<td>0.014</td>
<td>0.456</td>
</tr>
<tr>
<td>Day systolic</td>
<td>0.259</td>
<td>0.067</td>
<td>0.009</td>
</tr>
<tr>
<td>Day diastolic</td>
<td>0.124</td>
<td>0.015</td>
<td>0.213</td>
</tr>
<tr>
<td>Night systolic</td>
<td>0.303</td>
<td>0.092</td>
<td>0.002</td>
</tr>
<tr>
<td>Night diastolic</td>
<td>0.179</td>
<td>0.032</td>
<td>0.074</td>
</tr>
<tr>
<td>Day load (systolic)</td>
<td>0.213</td>
<td>0.045</td>
<td>0.034</td>
</tr>
<tr>
<td>Day load (diastolic)</td>
<td>0.126</td>
<td>0.016</td>
<td>0.209</td>
</tr>
<tr>
<td>Night load (systolic)</td>
<td>0.324</td>
<td>0.105</td>
<td>0.008</td>
</tr>
<tr>
<td>Night load (diastolic)</td>
<td>0.031</td>
<td>0.001</td>
<td>0.819</td>
</tr>
<tr>
<td>Day pulse pressure</td>
<td>0.265</td>
<td>0.070</td>
<td>0.007</td>
</tr>
<tr>
<td>Night pulse pressure</td>
<td>0.319</td>
<td>0.102</td>
<td>0.001</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>0.091</td>
<td>0.008</td>
<td>0.380</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>-0.117</td>
<td>0.014</td>
<td>0.248</td>
</tr>
</tbody>
</table>

*Table 8.5*

*Pearson's correlation coefficients for common carotid IMT predictors*
Figure 15. Comparison of carotid intima-medial thickness. *significant difference compared to normotensives (see text)
<table>
<thead>
<tr>
<th>Partial correlation coefficient</th>
<th>SD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.0052</td>
<td>0.0026</td>
</tr>
<tr>
<td>Day systolic</td>
<td>0.0001</td>
<td>0.0035</td>
</tr>
<tr>
<td>Night systolic</td>
<td>0.0016</td>
<td>0.0032</td>
</tr>
<tr>
<td>Day pulse pressure</td>
<td>-0.0016</td>
<td>0.0061</td>
</tr>
<tr>
<td>Night pulse pressure</td>
<td>0.0026</td>
<td>0.0062</td>
</tr>
</tbody>
</table>

*Table 8.6*

*Multiple regression analysis of common carotid IMT predictors*
Discussion

The most significant finding of this study is the demonstration of arterial wall thickening in white coat hypertensives.

The persistent hypertensives had evidence of target organ damage with significantly higher serum creatinine levels compared to both white coat and normotensives. It is interesting to note that carotid wall thickening occurred without any other sign of target organ damage in the white coat hypertensives. Echocardiographic results from chapter 5 confirm that there was no increase in left ventricular mass in the earlier cohort of white coat hypertensives. Previous work has shown close correlations between increasing IMT in hypertensives and LV mass and significant associations with left ventricular posterior wall thickness, end diastolic diameter and relative wall thickness. This study suggests that early arterial wall thickening may develop before left ventricular structural changes and that IMT measurements could be used as an early predictor of end organ damage and thus be used to direct the most effective use of antihypertensive therapy. However, further research is required to substantiate the association of intimal-medial thickening and cardiovascular morbidity or mortality.

There is convincing evidence that untreated hypertension causes an increase in vascular mass because of arterial wall thickening. This has
been shown in medium sized muscular arteries such as the radial
ttery as well as larger more elastic carotid arteries. Such wall
thickening is likely to represent an adaptive response to hypertension
to reduce media tensile stress. However, wall thickening also
decreases arterial compliance by increasing vessel stiffness and this is
implicated in the development of left ventricular hypertrophy,
atherosclerosis and systolic hypertension. Thus intima-medial
thickening exacerbates the underlying driving force of systolic
hypertension which was found to be one of the strongest predictors of
IMT in our study (in univariate analysis) and in work by other
groups.

Treatment with lipid lowering drugs halts the progression of IMT seen
in untreated hypercholesterolaemic individuals (mean 0.018 mm/year)
and after one year of treatment reduces IMT from baseline to reach a
plateau. It is probable that wall thickening increases in response to
hypertension or hypercholesterolaemia to reach a threshold before the
development of atherosclerotic plaque. IMT is unlikely to increase in a
linear manner indefinitely. This is consistent with the widely accepted
concept of the pathogenesis of atherosclerosis from foam cells to fatty
streaks, discrete plaque development and finally plaque rupture and
subsequent thrombus formation.
Carotid IMT corresponds with disease in other arterial beds and it is reasonable to assume that the adaptive changes seen in the carotid arteries in our study are also present in other vessels such as the aorta, femoral and coronary arteries.

While convincing long-term follow up studies are required to determine the predictive value of carotid IMT in cardiovascular disease there is accumulating evidence to support the hypothesis that it is a surrogate marker of early end organ damage in hypertension and hypercholesterolaemia. Surrogate markers such as IMT may be valuable in future studies assessing treatment benefits because they reduce sample size and follow-up requirements in studies of cardiovascular disease.

Thus we have identified early structural abnormalities in patients with white coat hypertension: these abnormalities have been shown in some other studies to be correlated with cardiovascular morbidity and mortality, and this suggests that white coat hypertension may not be wholly innocent. Two unresolved issues remain; first, to demonstrate that IMT does consistently correspond with, and is predictive of, cardiovascular morbidity and mortality; and second, to show that treatment with antihypertensive therapy indeed causes a reduction in IMT. Large multicentre prospective studies are underway and are due to report in several years.
CHAPTER 9  
TRANSCRANIAL DOPPLER

Embolus detection in divers during decompression

Introduction

This chapter describes the use of transcranial Doppler ultrasound (TCD) in commercial air breathing divers to detect right-to-left shunting, and to determine the incidence of bubbles in the cerebral circulation during decompression. It is the first published application of TCD monitoring in divers.

Background

Divers rely on decompression tables to maximise the dive duration at depth without resulting in decompression illness. These tables were first developed for the Royal Navy by Haldane in 1906 using animal models, such as the goat. The United States Navy proceeded to human experimentation in 1932 subjecting recruits to dives of increasing depth and duration and monitoring for complications by clinical examination and questioning. Many of the resulting tables were dangerous because there was a significant level of under-reporting of symptoms by the divers and a lack of objective measurement of decompression risk. This led to considerable interest in developing objective techniques capable of determining which
individuals were at risk of decompression illness, and which could be used to monitor the response to recompression.

Spencer was the first to use Doppler ultrasound in divers over 20 years ago and his studies confirmed the presence of venous bubble signals in asymptomatic divers using decompression tables available at that time.\textsuperscript{85} Many other groups, including the United States Navy and the Royal Navy, conducted further research with ultrasound detectors aiming to develop decompression tables based on Doppler bubble counts which were thought to be directly related to the pathogenesis of decompression illness.\textsuperscript{214} However, studies failed to confirm a significant correlation between venous bubbles and the incidence or severity of decompression illness.\textsuperscript{215} This was disappointing and confirmed that decompression illness is a multifactorial condition which is more complicated than the development of nitrogen bubbles in venous blood. Circulating nitrogen bubbles have many harmful effects including mechanical disruption of tissue, obstruction of blood vessels, activation of leukocytes, endothelial cells and platelets, as well as activation of coagulation and complement pathways.\textsuperscript{216} Models have shown that inert gas supersaturation and subsequent bubbling first occurs in the peripheral tissues and then in the veins. These venous bubbles are usually trapped by the lungs and resolve by diffusion into the alveoli without adverse effect\textsuperscript{217} unless there is an overwhelming
quantity of gas or there is conduit for right-to-left shunting of blood and bubbles, such as a patent foramen ovale.

**Patent foramen ovale**

With widespread use of decompression tables it became clear that some individuals were more susceptible to decompression illness than others, despite identical dive characteristics for depth, duration, temperature and physical exertion. A case report by Wimshurst in 1986 described the development of serious neurological decompression illness in a diver who had operated within the recommended decompression limits. Investigation revealed the presence of an atrial septal defect which was thought to be related to this individual’s symptoms. Although asymptomatic divers have detectable venous gas bubbles, the lungs usually dissipate such gas loads without harm. However, if a potential route is present between the venous and arterial systems then the lungs would be bypassed and arterial gas embolism would result. Shunting is more likely to occur when diving since immersion in cold water increases right heart pressures relative to the left thus causing blood to cross from the right to left heart.

There are three main mechanisms implicated in the pathogenesis of decompression illness. These are arterial embolism, venous infarction and autochthonous bubble formation (the formation of bubbles within
tissues). These are described in detail elsewhere\textsuperscript{222} and are summarised below. Historically it was noted by Boycott et al (1908) and Bert (1878) that goats undergoing decompression developed both venous and arterial gas bubbles. Venous bubbles correlated poorly with the clinical manifestations of decompression illness, however animals with arterial bubbles almost invariably died. The histological appearances of spinal cord damage caused by experimental arterial embolism are different from those found in humans with clinical decompression illness.\textsuperscript{223,224} The venous infarction hypothesis suggests that gas bubbles become trapped in the epidural vertebral venous plexus which is a large valveless low pressure system, thus increasing the chance of gas bubble formation, subsequent aggregation of bubbles before coalescence, and finally foaming. This results in coagulation and complement activation which causes a rise in venous pressure leading to spinal cord congestion and eventually infarction.

The venous infarction hypothesis helps to explain why the spinal cord is affected much more commonly than the brain in decompression sickness despite receiving a much lower proportion of the cardiac output. However, it is unlikely that bubbles would obstruct the entire venous plexus since it is a large system. One might expect a segmental pattern of obstruction with resultant clinical signs if parts of the system are affected but this does not always occur in practice.
This difference may result from gas bubble formation in the peripheral tissues, the autochthonous bubble hypothesis. Animal experiments have shown that bubbles develop first in the peripheral tissues, then in the venous circulation before arterial bubbles finally appear. Autochthonous bubbles have been shown to develop preferentially in the white matter of the spinal cord and brain but these do not correspond histologically to all of the lesions seen in genuine cases of decompression sickness.

The fact that no theory alone can adequately explain the manifestations of decompression illness seen in humans suggests that it results from a combination of all three mechanisms with individual cases varying in the relative proportions of each. However, right-to-left shunting could increase the quantity of arterial nitrogen bubbles and this might be expected to increase the peripheral tissue nitrogen load. If this occurs in practice then a high proportion of individuals with decompression sickness would be expected to have a means of shunting from the right to left heart.

A recent review of decompression illness in amateur divers suggested that the majority of cases occurred in divers using recommended decompression limits. Recent studies suggest a possible link between the presence of a patent foramen ovale (PFO) and subsequent decompression illness with a higher incidence of PFO being
found in divers who had developed serious neurological decompression sickness. However, studies performed to date have been retrospective and cross-sectional in design and therefore are limited in their predictive value. The role of a PFO in decompression illness is far from clear and this led to the design of the study described below.

*Techniques for detecting shunting*

Until recently the only non-invasive technique available for screening for right-to-left shunting was transthoracic echocardiography with peripheral contrast injection. As discussed earlier (chapter 3) this method has been shown to be less sensitive when compared with transoesophageal and transcranial ultrasound.\textsuperscript{123,124,228} Although transoesophageal echocardiography is the most sensitive method of detecting intracardiac shunting it is an invasive procedure unsuitable for screening otherwise healthy divers. TCD can be performed in almost any setting and offers higher levels of sensitivity with considerable convenience.

*Diving practice*

Commercial diving requires different equipment and techniques to the free swimming amateur SCUBA (Self Contained Underwater
Breathing Apparatus) diver. Commercial pressures require that underwater time be maximised to allow divers to perform as much work as possible. While amateur divers monitor their own depth and dive duration, commercial divers monitor decompression procedures from the surface. The diver has a continuous air supply from a hose attached to a full face mask, compared to the goggles and mouth piece used by amateurs. Commercial divers commonly use two different decompression techniques. One technique (underwater decompression) involves halting the ascent near the surface (a decompression stop) and waiting for a recommended period, usually 10-20 minutes depending on the depth and duration underwater, allowing nitrogen to be released from the tissues and to be eliminated by the lungs. This technique is also used by amateur divers but is difficult to perform particularly if the water is cold, if there are underwater currents, or if there is a large swell which can make it impossible to remain at a constant depth. Surface decompression allows divers to ascend to the surface despite a decompression penalty, provided they then transfer immediately to a decompression chamber. They have less than 5 minutes to enter the chamber, a period known as the surface interval. They are then recompressed in the chamber and may breath 100% oxygen or mixtures of helium and oxygen before being decompressed to surface pressure at a controlled rate. The surface interval in decompression is
potentially the most hazardous time for divers since they have incurred a decompression penalty and have considerable quantities of nitrogen in the blood and tissues. A further highly specialised technique is saturation diving where divers are compressed for periods of days or weeks before very slowly being decompressed at the end of the work period. This last technique has known hazards but is commonly used in deep diving practice.

This study involved monitoring the arterial circulation of divers who had been investigated for shunting. The aim was to determine whether gas bubbles were present in the cerebral circulation of those divers with shunting (through a PFO) during surface and underwater decompression.

**Methods**

20 divers taking part in a commercial diving training course at the Underwater Centre in Fort William were invited to give written informed consent to participate in this study which had ethics committee approval from the Western Infirmary (Glasgow) and the local committee in Lochaber. Three divers declined and were excluded. The remaining 17 were healthy males (age 21-34 years) with no significant past medical history and with normal cardiac and respiratory function as determined by clinical examination,
transthoracic echocardiography and spirometry (see table 9.1). None of the subjects had a history of decompression sickness.

The divers continued the course which involved diving from two surface barges which supplied compressed air from the surface to their face masks. They performed training exercises at depth including rescue simulations, underwater searches and industrial engineering tasks. The dives generally were in cold water (6°C) and were physically demanding which, combined with the depths achieved, increases the risk of decompression illness. All dives were conducted according to the United States Navy diving tables.

The TCD machines were stationed on the barges and were powered by portable generators which developed 240V alternating current and incorporated surge suppression circuitry. TCD monitoring was performed on the divers after surfacing using an EME TC-2000 (Nicolet, Warwick, UK) with a 2 MHz probe placed over the right temporal bone. The right middle cerebral artery was identified at a depth of 46-54 mm and Doppler waveforms were stored digitally on hard disc for subsequent analysis as described in chapter 4.

Monitoring was performed during the surface interval for as long as possible in dives requiring surface decompression. For safety reasons this usually allowed 1-2 minutes of monitoring to keep the total interval to less than 3½ minutes to minimise the risk of decompression
illness. The remaining 1½ minutes allowed the diver to remove equipment and to enter the chamber. In all other cases monitoring was performed for a minimum of 5 minutes, and maximum of 20 minutes. Shunt detection was performed in the Belford Hospital in Fort William (courtesy of Dr Gavin Brown, Consultant Physician) as described in Chapter 4.

Results

1. Shunt detection.

Four divers (4/17) had evidence of right-to-left shunting as detected by TCD. Only one diver had shunting at rest, two required the Valsalva manoeuvre, and one had shunting only after coughing. Transthoracic contrast echocardiography was positive in only one subject following a Valsalva manoeuvre and transcranial Doppler ultrasound was positive in this subject at rest. In the four subjects with shunting, bubbles were detected within five cardiac cycles of the right heart opacifying suggesting intracardiac rather than transpulmonary passage of contrast.

2. Dive monitoring.

A total of 73 TCD recordings were made during the study. These are described in table 9.2. Sixty-three recordings were made after surfacing from dives varying between 16 and 51 metres of sea water (msw). The
interval between surfacing and monitoring varied between 1.5 and 23 minutes.

Ten recordings were made in the surface interval before entering the decompression chamber. All divers with right-to-left shunting had monitoring performed during this interval as it was felt that this was the best opportunity of detecting arterial bubbles since the divers had still to undergo controlled decompression stops to allow nitrogen to leave the peripheral tissues.

Twenty-three (23/73) recordings were undertaken in divers with detectable shunting. Monitoring was also performed following a dry chamber dive to 50 msw when all subjects had evidence of nitrogen narcosis with associated disinhibition and impaired mental function similar to that induced by alcohol intoxication. This chamber dive was performed as part of the training course to acclimatise the trainees to greater depths. The fact that they developed nitrogen narcosis implies that a significant amount of nitrogen had been dissolved in the peripheral tissues and might be expected to be detected following decompression. Monitoring was performed in two of the subjects with a PFO following the chamber dive.

Finally monitoring was also performed following an emergency ascent. Two divers were taking part in a rescue simulation at depth (45 m) when it became clear that the victim was in genuine distress. He did
not respond to questioning from the surface via an intercom and the rescuer in the simulation reported that he had become unconscious. The victim was dragged into the diving bell and this was pulled to the surface at the maximum rate allowed by the winch mechanical safety guard (15 metres/min). Faster ascents cause catastrophic gas bubbling and can result in fatal or disabling decompression illness or cerebral arterial gas embolism. No breathing was heard over the intercom from the diver during the ascent but on surfacing he was able to maintain his airway and was able to localise to pain, opened his eyes spontaneously, but was disorientated in time, space and person. Emergency recompression was started using hyperbaric oxygen, the treatment for both carbon dioxide narcosis and also cerebral arterial gas embolism, both diagnoses to be considered in this subject. After decompression diagnostic TCD monitoring was performed and this revealed bilateral increased velocities in the basal cerebral arteries with no evidence of gas embolism. These findings supported the clinical diagnosis of carbon dioxide narcosis and the diver recovered completely with no clinical sequelae. He had developed carbon dioxide narcosis because of breathholding to conserve air, a common mistake among inexperienced divers. The rescuer in the simulation did well to extend his partner’s neck during the ascent thus maintaining a patent airway and avoiding
the possibility of pulmonary barotrauma with subsequent arterial gas embolism.

Despite monitoring a wide variety of dive profiles and subjects, arterial ultrasound bubbles were not detected after surfacing in any diver. Subjects performed the Valsalva manoeuvre and were asked to cough repeatedly to provoke shunting during the monitoring period. Technically satisfactory recordings were obtained in all subjects and later analysis of stored information failed to reveal any abnormalities.

**Discussion**

Transcranial Doppler ultrasound has been used successfully to detect cerebral emboli in various clinical settings, including carotid artery disease, prosthetic valves, and during angiography. These different clinical settings are described in detail earlier in Chapter 3. As previously discussed, circulating gas bubbles are easy to detect because of the large difference in density between the bubble and the surrounding blood. It is possible to detect microemboli as small as 30-90 μm in diameter.\(^{105}\) The fact that no embolic signals were detected strongly suggests that no arterial gas bubbles were present after diving. In addition, since artificially introduced gas bubbles were detected during the shunt detection investigations, the embolus detection technique appeared to work satisfactorily.
The depths achieved were much greater than most amateur divers would attempt since 40 msw is rarely exceeded by air breathing amateurs. In addition the dives were longer since the option of surface decompression was available. For example, an amateur diver only has 6 minutes available at 40 msw before incurring decompression penalties. Many of the deep dives were for more than 20 minutes and included multiple underwater decompression stops. Venous bubbles are present in asymptomatic divers after surfacing from depths as little as six metres. Spencer detected venous bubbles in 4 of 11 divers following a chamber dive to 18 msw for 60 minutes. Dunford et al detected venous bubbles in 17% of amateur SCUBA divers after surfacing from 6-39 metres. The dives undertaken by the trainees in this study were deeper and thus were likely to result in bubble formation. We did not monitor for venous bubbles because of technical limitations but assumed that they were present in subjects because of the depth and duration of the dives.

The incidence of PFO from autopsy is 20-35% depending on age, however the transthoracic echocardiographic incidence in normal populations is lower at 5-20%, consistent with only moderate sensitivity. Our study had an incidence of 6% (1/17) by transthoracic contrast echocardiography and 24% (4/17) by transcranial ultrasound. This confirms that TCD shunt detection is a more sensitive technique.
than echocardiography, and our experience was that the TCD technique was highly suitable for screening healthy individuals in a diving setting with no need for hospital equipment or facilities. Contrast echocardiography added no additional information and was much more difficult to perform, particularly during coughing and Valsalva manoeuvres where inflation of the lungs obscured the left atrium and septum.

Experimental decompression in pigs with PFO resulted in arterial bubbles which were detected immediately prior to surfacing and which persisted for over one hour. The peak bubble incidence was between 10 and 30 minutes. The majority of our transcranial monitoring was performed at this time (see figure 9.1). The greatest pressure change occurs between 10 metres and the surface where pressure doubles on diving and halves on ascending (according to Boyle's law). Many cases of arterial gas embolism and decompression sickness become apparent during this period.

Bubbles develop preferentially in the venous system because of the low ambient pressure. If they cross to the arterial circulation the increased pressure may force resolution of the bubbles, hence limiting any possible damage. This would help to explain the failure of venous bubble counts to correlate with clinical decompression illness. This explanation has also been used to explain why the injection of small
gas bubbles into the venous system during shunt detection has no harmful sequelae when detected in the arterial system.

Concerns regarding the long term health of divers have been expressed with particular reference to silent bubbles causing subtle neurological damage with repeated dives.\textsuperscript{236,237} Commercial pressures led to very intensive and occasionally dangerous diving practices during the 1970's when a form of chronic brain injury was recognised in some commercial divers. This involved changes in personality as well as objective intellectual impairment. The cause of this chronic damage is uncertain but paradoxical gas embolism, high pressure gas toxicity, and autochthonous bubble formation all have been implicated. Our initial results suggest that arterial bubbles may not be involved since one would expect subjects with shunting to have detectable arterial gas embolism during dives to the depths achieved during this study. However this will have to be confirmed in larger, prospective studies.

This study involved commercial rather than amateur divers. Surface decompression has been raised as a potentially risky technique available to commercial divers and screening divers for PFO at the commercial diving medicals has been suggested. Our results have found no evidence of paradoxical embolism during routine diving using the United States Naval Decompression Tables, and no evidence
of gas embolism during the surface interval. This is the first study looking for arterial embolism during this period.

We have shown transcranial Doppler ultrasound to be a useful technique for screening divers for shunting outwith a hospital setting. Portable battery powered machines with liquid crystal displays are now available and are suitable for use inside a decompression chamber. This would be particularly valuable when treating cerebral arterial gas embolism and monitoring the response to recompression. Although venous emboli counts have little correlation with the incidence of decompression sickness it is possible that arterial counts are more specific. Further research is obviously required and TCD monitoring will be a suitable technique for this.

Very recent research using MRI scanning has shown an increased prevalence of hyperintense subcortical white matter lesions in the brains of divers with PFO compared to divers without detectable shunting. Divers with multiple brain lesions were found to have large PFO. This is concerning since there are over four million certified sport divers in the United States and Europe and the consequences of chronic paradoxical arterial gas embolism causing brain injury must be assessed further. It may be necessary to develop separate decompression tables for divers with PFO to minimise the development of venous gas bubbles. This would involve routinely
screening divers for shunting and, if this is to be performed, transcranial Doppler ultrasound is the most suitable technique available.

Conclusion

Bubbles were not detected in cerebral circulation of commercial air divers operating within the recommended decompression limits. The presence of right-to-left shunting did not affect these findings.
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Table 9.1

Subject characteristics including spirometry with predicted values in parentheses.

Key to abbreviations: VC = vital capacity, FVC = forced vital capacity, FEV1 = forced expiratory volume in 1 second, FEF 75-85 = forced expiration fraction from 75 to 85% of FVC, PEF = peak expiratory flow.
Table 9.2.

**Dive characteristics in 17 subjects undergoing transcranial Doppler monitoring.**

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Table 9.2

**Depth** is the maximum achieved during the dive in msw. **Time** is the bottom time in minutes, **Gap** is the interval between surfacing and transcranial monitoring, and **Total** is the dive duration including bottom time, the decompression stops and the time required for surfacing. **TCD** is the duration of transcranial Doppler monitoring in minutes.

* Monitoring performed during the surface interval as well as after leaving the chamber.

** Emergency ascent with monitoring performed after leaving chamber.
This graph shows that most of the TCD recordings were performed 10-20 minutes after surfacing when the peak incidence of arterial bubbling might be expected according to animal models (see text). The graph plots the number of subjects being monitored at the time specified. For example, a monitoring session starting 5 minutes after surfacing and lasting for 10 minutes will be included in each of the bars from 5 to 15 minutes.
CHAPTER 10  TRANSCRANIAL DOPPLER

Embolus detection in carotid atherosclerosis

Introduction

The increasing awareness of hypertension and its effective treatment has been associated with a decline in the incidence of stroke, particularly in North America. The major benefit of treatment has been a reduction in the incidence of haemorrhagic and lacunar strokes rather than those due to atherosclerosis. With this relative change in stroke causation there has been a relative increase in stroke due to large vessel atherosclerosis and cerebral embolism. There are several potential sources of cerebral embolism in the genesis of acute stroke, including valvular heart disease, high grade (>70%) internal carotid artery stenosis, acute myocardial infarction, intracardiac thrombus and atrial fibrillation. In addition, recent work suggests a link between plaques in the thoracic aorta, particularly if there is evidence of plaque ulceration or haemorrhage, and mitral annular calcification in the elderly is associated with an increased risk of stroke.

Carotid atherosclerosis is common. Intimal-medial thickening is present in over 50% of the general population over the age of 50 years, and non-stenotic plaque can be found in between 20-50% of those over
the age of 60 years. Up to 10% of those over the age of 65 years, and up to 30% of those attending hospital with peripheral or coronary artery disease, have greater than 50% stenosis of one carotid artery.

The indications for carotid endarterectomy remain controversial. While symptomatic patients with severe (>70%) stenosis of the internal carotid artery benefit from surgery with a 75% reduction in rate of stroke in the subsequent two to three years, selection criteria for asymptomatic patients are less certain. There was little evidence in favour of surgery in asymptomatic patients until the interim results from the Asymptomatic Carotid Atherosclerosis Study (ACAS) were published in 1994. The National Institute of Neurological Disorders and Stroke halted this study because asymptomatic patients with carotid stenosis (>60%) were found to benefit from endarterectomy. They found a 5.8% absolute risk reduction in the risk of stroke (relative risk reduction 55%) but were careful to remind physicians that endarterectomy should be recommended only after careful patient selection and performed by surgeons with a documented perioperative mortality and morbidity of less than 3%.

With these developments in surgical selection and the change in pattern of cerebrovascular disease there is a growing need to identify patients who could benefit most from carotid endarterectomy.
Transcranial Doppler (TCD) ultrasound has been used to identify microembolic signals in patients with carotid artery disease (as reviewed earlier in Chapter 3) but the specificity of the technique has yet to be assessed. One concern is the underlying nature of the signals. If they were found to be present in patients with atherosclerotic plaque but without haemodynamically significant stenosis then their clinical use would be severely limited.

**ACAS Study**

TCD embolus counting has been described in patients with carotid atherosclerosis but studies so far have concentrated on patients with high grade stenosis (>70%) of the internal carotid artery. This is logical since such patients are at risk of embolic stroke. Microembolic signals are present in 20% of patients with high grade stenosis and are more common in individuals with a recent neurological event affecting the ipsilateral hemisphere. The incidence in asymptomatic patients is similar to that of silent cerebral infarction detected by computed tomography in various small studies (6% to 29%) and matches the incidence found in the much larger baseline assessment of the ACAS patients. This was a study of 848 asymptomatic patients who were assessed and examined by neurologists to exclude any history or clinical evidence of a neurological deficit. Patients were aged 40-79
years and had unilateral or bilateral surgically accessible stenosis of the common or internal carotid artery as measured by carotid ultrasound and confirmed by invasive angiography in cases randomised to surgery. All patients had computed tomography (CT) scans of the brain at baseline which were examined for evidence of silent cerebral infarction. Of the 848 eligible patients, 126 (15%) had evidence of silent cerebral infarction with the majority (95) having a single infarct. However 24 patients had 2 silent infarcts and 7 patients had 3 or more. The majority (117) were small and deep but 45 were up to one half lobe in size. There was no relation between the severity of carotid stenosis and the prevalence of infarction. The link between subclinical infarction and subsequent clinical events is still tenuous, although there was evidence suggesting impairment of mental function associated with infarction. These results confirm that subclinical embolism does occur in carotid artery stenosis and suggest that TCD embolus counting may help to identify the individuals most at risk.

If TCD embolus counting is to be clinically useful then it is necessary to study patients across the full range of carotid disease. It is not yet known if signals are present in patients without severely stenosed arteries, or even in normal individuals. The cause of the signals in carotid artery disease is still unclear and several possible mechanisms have been suggested. Turbulent blood flow through a stenosed artery
may cause aggregation of platelets or leukocytes and these clumps could cause signals. There may be eddies or areas of stasis distal to the stenosis which result in activation and adhesion. Another possibility is that atherosclerotic plaque directly activates platelets or leukocytes. If this occurs then it would reduce the specificity of TCD embolus counting when identifying patients at risk of embolic stroke.

The aim of this study therefore was to compare patients with normal carotid arteries to those with atherosclerotic plaque. In addition a small number of patients with high grade stenosis of the internal carotid artery were studied to confirm the sensitivity of the technique.

**Methods**

All subjects gave informed consent for their participation in this study which had local Ethics Committee approval. Subjects were recruited from the cardiovascular risk factor outpatient clinics and were aged 45-75 years, not anticoagulated and had no history of cardiac or carotid surgery, or angioplasty. They had not experienced a neurological event within 12 months of the study. Other possible sources of embolism were excluded by clinical examination and transthoracic echocardiography. These included atrial fibrillation, significant aortic or mitral valve disease, mitral annular calcification or left ventricular dysfunction.
TCD monitoring was performed as described in chapter 4. The carotid arteries were examined by conventional Duplex scanning using an Acuson 128 (Acuson, Mountain View, California) with a 7.5 MHz probe as described in chapter 4. The severity of carotid stenosis was calculated according to the ratio of the internal to the common carotid artery velocities, and the presence of spectral broadening, according to recognised criteria. In addition high resolution B-mode scanning was performed using a Biosound 2000 II SA system as described in chapter 4. This allowed more detailed imaging of the arterial wall and accurate detection of atherosclerotic plaque. Plaque was defined as a focal area of intima-medial thickening (see chapter 4). All examinations were recorded on video tape and analysed independently of the TCD data by two observers. Carotid atherosclerosis therefore was staged as: (1) normal, (2) intima-medial thickening (IMT group), (3) plaque but stenosis less than 70% and (4) stenosis >70%.

The split between normal and intimal-medial thickening was made statistically once all video tapes had been analysed (see below)

Results

The clinical characteristics of the 161 study subjects are presented in table 10.1 (below). The most significant differences between groups were of age (higher in the plaque group), blood pressure and weight
(higher in the normal group), creatinine (highest in the stenosis group but no significant difference between the remaining groups) and haematocrit (lowest in the IMT group). In addition, fibrinogen levels correlated well with carotid atherosclerosis severity (see figure 17).

Ultrasound analysis

The two observers agreed on the classification of carotid disease in all cases. The majority of subjects (94%) had normal arteries or evidence only of plaque without stenosis. The mean intima-medial thickness for the entire study population without plaque or stenosis was 0.643 and this level was used to statistically divide classify subjects into normal wall thickness (≤0.643 mm) and or increased wall thickness (>0.643 mm) groups.
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<th>Stenosis</th>
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<td>Age (years)</td>
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<td>59 ± 8</td>
<td>62*± 8</td>
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<td>Blood pressure (mmHg)</td>
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<td>(mmHg)</td>
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<td>Weight (kg)</td>
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<td>γ GT (u/l)</td>
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<td>Creatinine (μmol/l)</td>
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<td>Glucose (mmol/l)</td>
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<td>Cholesterol (mmol/l)</td>
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<td>Triglycerides(mmol/l)</td>
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<td>Fibrinogen (u/l)</td>
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<td>Lipoprotein (a)</td>
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Table 10.1 Patient characteristics (mean ± SD)

Note: statistical comparison is between normal, intimal-medial thickening (IMT) and plaque groups. The stenosis group is excluded from comparison because of the smaller population size.

*χ² test, *significant difference between plaque and IMT group, *significant difference compared to normal
Figure 17. Fibrinogen and carotid atherosclerosis severity.
*significant difference compared to normal. Stenosis group highlighted to exclude from statistical comparison because of smaller sample size (see text).
Seventeen subjects had a history of stroke or transient ischaemic attack and the highest prevalence was in the stenosis group (5 of 10 subjects compared to 2, 0 and 10 for the normal, IMT and plaque groups respectively). All of these events occurred more than one year prior to the study with the majority occurring between 2 and 10 years before recruitment.

Four of the ten patients with >70% stenosis of the internal carotid artery had microembolic signals (see figure 18). The mean rate of embolism was 14 per hour (range 2-18) and all signals were detected in the middle cerebral artery ipsilateral to the stenosed carotid artery. The two observers agreed in the classification of all but one microembolic signal which was excluded from analysis. This did not alter the number of subjects with detectable signals. All four patients with detectable microembolic signals were taking regular aspirin (75 to 300 mg per day).

No signals were detected in the other patient groups. It was not possible to monitor the middle cerebral artery in two patients with normal carotid arteries because of temporal hyperostosis, a recognised limitation of the TCD technique. All other subjects had adequate temporal windows. No subject had evidence of plaque ulceration or intraplaque haemorrhage.
Figure 18. **Example of microembolic signal**
The embolus signal (arrowed) appears red on the background of the arterial waveform (blue) because of the high intensity. It is of short duration and appears above the baseline only whereas artefact causes bidirectional signals. The signal is associated with a characteristic audible chirp.
Discussion

The principal finding of this study is the absence of microembolic signals in patients with internal carotid artery atherosclerotic plaque. The sensitivity of transcranial Doppler ultrasound monitoring was confirmed by the detection of microembolic signals in the high grade stenosis patients.

Plasma fibrinogen levels correlated well with the severity of carotid artery disease and are known to reflect cardiovascular morbidity and mortality.\textsuperscript{253-255} The increase in fibrinogen suggests that the atherosclerotic changes in vascular endothelium influence plasma thrombotic potential and the highest levels of fibrinogen were seen in the high grade stenosis group. Turbulent blood flow appears to be relevant in the development of microembolic signals since none were detected in the patients with atherosclerotic plaque and no turbulence.

The ACAS study results pose a significant clinical problem.\textsuperscript{250} Only 10.6% of the medically treated patients in this study had an embolic stroke related to their carotid disease compared with 4.8% of those randomised to surgery. Carotid endarterectomy itself has a small but significant risk. Although the accepted perioperative morbidity and mortality rate is less than 3%, the absolute risk reduction regarding embolic stroke is only 5.8%. In addition invasive angiography also had
an appreciable risk with 1.2% of the ACAS patients having a stroke precipitated by this investigation. In addition, a study of ten year cerebrovascular morbidity and mortality of men with asymptomatic carotid artery stenosis found no significant increase in the incidence of stroke. This was thought to be due to a high incidence of death from myocardial infarction.

Thus there are difficulties for the clinician in deciding whether to treat asymptomatic individuals medically or whether they should be referred for surgery. If individuals could be stratified in terms of risk then the overall risk reduction would be much greater and the corresponding benefit to risk ratio would be higher. The severity of carotid stenosis did not add any prognostic information. There are no convincing means of doing this at present although TCD embolus counting theoretically may be suitable. The argument for this is detailed below.

This study confirms that microembolic signals detected by TCD are specific to patients with high grade stenosis of the internal carotid artery. TCD embolus counting was largely discounted as a clinical tool partly because of the concept of silent embolism. Original studies of patients with prosthetic cardiac valves demonstrated many hundreds of signals per hour with no objective neurological impairment as described earlier. However recent work suggests that they may be
caused by gaseous cavitation during valve leaflet closure.\textsuperscript{98,116} Carotid signals are different entirely; they tend to be less frequent and have different characteristics suggesting that they may be caused by particulate matter. Circumstantial evidence for a clinical correlation was provided by the rate of silent cerebral infarction detected by computed tomography in the ACAS patients. This was almost identical to that of microembolic signals detected by TCD.

TCD microembolic signals are specific to individuals with high grade internal carotid artery stenosis. They do not occur in patient with atherosclerotic plaque alone. The next step must be to study the relation of signals to clinical endpoints including stroke in a large prospective study. Background work has been performed which confirms high levels of reproducibility and inter-centre agreement in the classification of microembolic signals in carotid artery disease,\textsuperscript{252} thus it is technically possible to perform a multicentre study which will be essential to provide the high numbers of patients required.
CHAPTER 11 CONCLUSIONS

The studies described in this thesis have used different ultrasound approaches to examine various aspects of the cardiovascular system, but all depend on the common principle of detection of reflected ultrasound energy which first was used in divers during the 1960’s. Ultrasound is now used frequently in clinical practice to image almost every organ within the body and to study both structure and function. It has become the imaging modality of choice in many areas despite the advent of new radiological methods including high resolution and spiral computed tomography scanning. Magnetic resonance imaging may well supersede ultrasound in the future in some areas but is unlikely to become a rival in terms of convenience, portability, expense or availability. One of the main attractions of ultrasound is the opportunity to repeat scans without concern of radiation hazard which is significant with most other imaging techniques (apart from magnetic resonance imaging). Emphasis is now shifting from measurement of structural abnormalities to the early detection of more subtle dysfunction in an effort to prevent potentially harmful structural responses, for example left ventricular hypertrophy. This has led to the
involvement of ultrasound in morbidity and mortality studies although only recently have some of the functional abnormalities been linked to clinically significant events. Examples include the detection of left ventricular diastolic dysfunction which may be related to the future development of clinically significant systolic dysfunction. There is increasing pressure to use ultrasound as a way of detecting clinically silent abnormalities in an effort to increase the effectiveness of treatment and to select individuals who are at high risk of clinical events and thus could benefit most from intervention. The investigation of disease prevention or progression requires large studies involving hundreds or thousands of patients and demands long follow-up periods if mortality benefits are to be detected. Surrogate endpoints of clinical events, such as the measurement of arterial wall thickness or atherosclerosis severity, may give an earlier indication of effectiveness of treatment and thus reduce patient numbers and follow-up requirements.

This approach is the basis of the studies described in this thesis which concentrates on the ultrasound techniques applicable to cardiovascular medicine, in particular echocardiography, vascular compliance measurement by high resolution A-mode ultrasound and pulsed wave Doppler sampling, structural measurement by high resolution B-mode
ultrasound and embolus detection using fast Fourier transformation of continuous wave low frequency Doppler ultrasound (as transcranial Doppler). These are the main approaches available at present. The study involving divers was particularly attractive since it involved using the most modern ultrasound technology in the group of subjects first studied by ultrasound in medicine.

**White coat hypertension**

The study of white coat hypertension included the assessment of cardiac structure by M-mode echocardiography and diastolic function using pulsed wave Doppler ultrasound before linking these measurements to carotid arterial compliance parameters obtained by A-mode ultrasound. White coat hypertension is a well recognised clinical problem which, for the majority of physicians, continues to be regarded as a reason not to start treatment or undertake investigation. One reassuring aspect of the results was the absence of left ventricular hypertrophy in the white coat hypertensive group and this indicates that their longterm cardiovascular mortality should not be as high as the persistent hypertensive group. The main conclusion is that such patients should not be ignored and that further large scale studies of the white coat response were required to measure the benefits of treatment.
The study was designed to include the possibility that the white coat response might interfere with the functional measurements being assessed hence the multiple calculated parameters of vascular mechanics which were detailed in chapter 2. Many white coat hypertensives develop sustained hypertension (75% in a recent study\textsuperscript{[153]} and this progression could not be predicted on the office blood pressure. Such progression is more common in elderly women and might be related to the loss of cardiovascular protection following the menopause. It is interesting that the white coat response is resistant to treatment and it may become necessary to use alternative measures of cardiovascular risk in these patients such as the presence of microalbuminuria, left ventricular hypertrophy or, more controversially, diastolic dysfunction and abnormal arterial compliance. These issues all need to be addressed in future research which is likely to require very long term morbidity and mortality studies to assess the effects of treatment and the effectiveness of surrogate endpoints in predicting clinical events.
Carotid arterial pulsatility

The study of carotid arterial pulsatility by Duplex ultrasound illustrated an alternative approach to the measurement of vascular function. Duplex ultrasound is used frequently in clinical practice to measure stenosis by the increase in blood flow velocity which results when blood is forced through a vessel of reduced lumen. Further analysis of the blood flow velocity waveform is possible and this allows the mechanical stretching forces to be estimated within the artery and its distribution territory. Clinically it is unclear why the treatment of hypertension has had a much greater impact on the incidence and complications of cerebrovascular disease compared to ischaemic heart disease. One possibility suggested by Spence\textsuperscript{176} is explored in detail in chapter 7 where the beneficial effect of antihypertensive therapy on the incidence of haemorrhagic stroke has been well described and contrasted with a more disappointing effect on atherosclerotic cerebrovascular disease. This has resulted in a change in the pattern of cerebrovascular disease now presenting to clinicians. The study described in chapter 7 offers some supporting scientific evidence to show that hypertension is associated with significantly increased mechanical strain within the internal carotid artery and its distribution

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area. The effects of treatment now require further study although preliminary work by other researchers using Doppler ultrasound has shown favourable changes in carotid flow patterns dependent on the level of blood pressure reduction. Such ultrasound abnormalities reflect subclinical cerebrovascular strain and should be assessed in longterm clinical studies of antihypertensive therapy and cerebrovascular disease. The mechanical strain suggested by this technique may simply occur during periods of hypertension but also may be exacerbated by structural changes within the cerebrovascular system similar to the adverse effects of early wave reflection on diastolic left ventricular function as described earlier. Further research using blood flow velocity will soon be possible using instruments which allow simultaneous continuous measurement of arterial diameter and blood flow velocity. This also allows direct estimation of blood flow in mls/min. The differential effects of the various classes of antihypertensive medication will require to be studied and it will be necessary to link the ultrasound abnormalities to clinical endpoints so that future studies can use the ultrasound surrogate markers to save time, money and, most importantly, reduce patient morbidity and mortality.
**Carotid arterial structure**

The various functional assessments discussed above are affected by ambient physical conditions, such as blood pressure, and can be influenced by medication, diurnal variation, temperature or stress. This emphasises the need for rigorous control of the clinical environment and standardisation of patient examination to eliminate such variability. The satisfactory coefficient of variations for echocardiographic and compliance measurements indicates that this can be and was achieved. Measurement of the structural abnormalities does not suffer from such restrictions provided care is taken to standardise the methodology, for example when measuring left ventricular structure, or arterial wall thickness. High levels of training were required for the sonographers to perform scientifically reproducible carotid B-mode examinations and then detailed quality control was employed to allow accurate off-line measurement of carotid wall thickness. The finding of increased arterial wall thickness in white coat hypertensives is of clinical concern since such wall thickening is now regarded as an early sign of target organ damage reflecting a systemic structural response to the stress of hypertension. A recent conference on arterial wall thickening set out to define IMT
as a putative risk factor in cardiovascular disease and this confirmed the great potential for non-invasive monitoring of arterial wall thickening in hypertension, hyperlipidaemia, and cardiac failure. Arterial wall thickness is a risk factor which is known to be linked with arterial disease elsewhere and the association with clinical events is becoming firmer. However, while treatment of the various conditions that cause arterial wall thickening (e.g., antihypertensive therapy, lipid lowering therapy, or vasodilators in cardiac failure) reduces morbidity and mortality, the association with changes in arterial wall thickness remains to be proven. This is the underlying hypothesis behind several large scale trials of antihypertensive therapy, and has already been proven in hyperlipidaemia. Therefore, the finding of increased arterial wall thickness in white coat hypertensives is significant and the intermediate value between normotensives and persistent hypertensives is consistent with the estimated clinical risk of white coat hypertension. Arterial wall thickening was shown to be a very early sign of end organ damage since there was no evidence of left ventricular hypertrophy or of renal impairment in the white coat hypertensives. Once again large scale studies are required to validate this approach and there is a need to examine cohorts of white coat hypertensives defined in terms of detectable structural and functional abnormalities as described above.
over a long term clinical follow up to determine the links and predictive value for clinical events.

**Embolus detection**

This approach was adopted in the 1960's for Doppler embolus detection after initial studies used the new technique to detect bubble signals in decompressing divers. The significance of the signals was unclear so the researchers moved on to larger studies to examine subjects after dives of varying severity in terms of depth, duration, temperature and workload. Unfortunately there was a poor correlation between the bubble signals and the clinical events associated with decompression sickness although there were significant technical limitations at the time (ultrasound signals were only analysed as audible tones). Technology has advanced considerably since then and it is now possible to view the Doppler waveform by fast Fourier transformation as shown in figure 18. It is now possible to detect more subtle embolic signals and work continues to determine their link with the incidence and severity of decompression sickness. Using the relatively new technique of transcranial Doppler ultrasound the study described in chapter 9 was the first published study to examine the cerebral circulation of divers during decompression and to specifically
screen for right-to-left shunting. This has become increasingly topical since the number of recreational divers is increasing rapidly worldwide and interest has again focused on the possibility of silent paradoxical embolism as a cause of cerebral damage and increased susceptibility to decompression sickness. Notably a very recent study found evidence of lesions within the brains of divers with patent foramen ovale. This issue was raised by the Health and Safety Executive in the UK and the possibility of screening divers for PFO before allowing commercial training was considered. A previous problem was the lack of a suitable non-invasive screening test which is now possible with transcranial Doppler ultrasound as described earlier. While the results of the study in Chapter 9 are reassuring there remain several unanswered questions which could be addressed in a prospective study involving a large cohort of divers with shunting, comparing the incidence and severity of decompression sickness to matched controls, examining for more subtle forms of neurological damage by psychometric testing, and screening for CNS lesions by magnetic resonance imaging. A further potential study could lead to the development of a decompression table determined by venous and arterial bubble counts, including limits specifically for subjects with PFO. It may be possible to develop no-bubble tables that minimise the
risk of paradoxical embolism and transcranial Doppler ultrasound may be useful for this. These studies are already being considered by the regulatory authorities in the UK and abroad including the Divers Alert Network based in Duke University, North Carolina. Preliminary discussions with the Scottish Sub-Aqua Club are underway to initiate the research with the support of the UK Sport Diving Medical Committee.

The final study described the search for more elusive microembolic signals in carotid atherosclerosis which potentially could be used to identify high risk individuals with asymptomatic internal carotid artery stenosis. This preliminary work is essential to determine the specificity of microembolic signals in carotid atherosclerosis since larger studies are soon to be carried out evaluating the predictive value of microembolic signal counts in high grade stenosis.

Overall the research described in this thesis has confirmed the value of the various ultrasound techniques in each of the different clinical settings. The common theme was the detection of pre-clinical markers of potentially harmful disease processes. Large longterm follow-up studies are already evaluating the predictive value of such surrogate markers, and determining the effects of treatment or behaviour modification. The versatility of ultrasound in medicine is obvious and
already has been of great value. This thesis has identified further roles which require additional research. No doubt there will be further technical advances that will continue to expand future clinical applications.


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Appendix A

List of abbreviations

\( \rho \)  Density of blood
\( \gamma \text{-GT} \)  Gamma glutaryl transferase
A dec  Deceleration time for active / atrial ventricular filling
ABPM  Ambulatory blood pressure monitoring
ACAS  Asymptomatic carotid atherosclerosis study
ACE  Angiotensin converting enzyme
ANOVA  Analysis of variance
ARIC  Atherosclerosis risk in communities study
BMI  Body mass index
BP  Blood pressure
CI  Confidence interval
CT Computed tomography
dB  Decibels
DC  Distensibility coefficient
Dd  Diastolic (minimum) diameter
Ds  Systolic (maximum) diameter
E  Young's elastic modulus
E dec  Deceleration time for early left ventricular filling
E:A  Ratio of early and late ventricular filling velocities
ELSA  European lacidipine study on atherosclerosis
\( E_p \)  Peterson's pressure-strain elastic modulus
FEF 75-85  Forced expiratory fraction (from 75 to 85%)
FEV1  Forced expiratory volume in one second
FVC  Forced vital capacity
h  Arterial wall thickness
IMT  Intima-medial thickness
IVRT  Isovolumetric relaxation time
IVSd  Interventricular septal thickness in diastole
IVSs  Interventricular septal thickness in systole
IVST  Interventricular septal thickness
Ln  Natural logarithm
Lp(a)  Lipoprotein (a)
LV  Left ventricle
LVEDD  Left ventricular end diastolic diameter
LVESD  Left ventricular end systolic diameter
LVM  Left ventricular mass
LVPWd  Left ventricular posterior wall thickness in diastole
Appendix A

List of abbreviations (continued)

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>LVPWs</td>
<td>Left ventricular posterior wall thickness in systole</td>
</tr>
<tr>
<td>MHz</td>
<td>Megahertz</td>
</tr>
<tr>
<td>msw</td>
<td>Metres sea water</td>
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<tr>
<td>NS</td>
<td>Not significant</td>
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<tr>
<td>PEF</td>
<td>Peak expiratory flow rate</td>
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<tr>
<td>PFO</td>
<td>Patent foramen ovale</td>
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<tr>
<td>PI</td>
<td>Pulsatility index</td>
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<tr>
<td>PWT</td>
<td>Posterior wall thickness</td>
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<td>PWV</td>
<td>Pulse wave velocity</td>
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<tr>
<td>R</td>
<td>Outer radius</td>
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<tr>
<td>SCUBA</td>
<td>Self contained underwater breathing apparatus</td>
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<tr>
<td>SD</td>
<td>Standard deviation</td>
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<tr>
<td>SHEP</td>
<td>Systolic hypertension in the elderly programme</td>
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<tr>
<td>TCD</td>
<td>Transcranial Doppler</td>
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<tr>
<td>VC</td>
<td>Vital capacity</td>
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Appendix B

List of abstracts and publications


5. Transcranial Doppler ultrasound in commercial air divers: a field study including cases with right-to-left shunting. Glen SK, Georgiadis D, Grosset DG, Douglas JDM, Lees KR. Abstract presentation was short listed for the Cerebrovascular Research Award at the International Symposium on Cerebral Haemodynamics in Charleston, Carolina, USA (February 1995) Stroke 1995; 731 (abstract)


Appendix B

List of abstracts and publications (continued)


