THE HAEMODYNAMIC AND VASCULAR EFFECTS OF ANGIOTENSIN-CONVERTING ENZYME INHIBITION FOLLOWING ACUTE STROKE

Doctor of Medicine Thesis

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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>Alx</td>
<td>augmentation index</td>
</tr>
<tr>
<td>ACEI</td>
<td>angiotensin-converting enzyme inhibitor</td>
</tr>
<tr>
<td>ARB</td>
<td>angiotensin receptor blocker</td>
</tr>
<tr>
<td>BP</td>
<td>blood pressure</td>
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<tr>
<td>bpm</td>
<td>beats per minute</td>
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<tr>
<td>BPV</td>
<td>blood pressure variability</td>
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<tr>
<td>BRS</td>
<td>baroreceptor sensitivity</td>
</tr>
<tr>
<td>CA</td>
<td>cerebral autoregulation</td>
</tr>
<tr>
<td>CCB</td>
<td>calcium channel blocker</td>
</tr>
<tr>
<td>CBF</td>
<td>cerebral blood flow</td>
</tr>
<tr>
<td>CHIPS</td>
<td>Control of Hypertension Immediately Post-Stroke trial</td>
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<tr>
<td>CHHIPS</td>
<td>Control of Hypertension and Hypotension Immediately Post-Stroke trial</td>
</tr>
<tr>
<td>CI</td>
<td>confidence intervals</td>
</tr>
<tr>
<td>COSSACS</td>
<td>Continue Or Stop post-Stroke Antihypertensives Collaborative Study</td>
</tr>
<tr>
<td>CPP</td>
<td>cerebral perfusion pressure</td>
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<tr>
<td>DBP</td>
<td>diastolic blood pressure</td>
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<tr>
<td>ECG</td>
<td>electrocardiogram</td>
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<tr>
<td>FFT</td>
<td>fast Fourier transformation</td>
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<tr>
<td>HF</td>
<td>high frequency</td>
</tr>
<tr>
<td>HR</td>
<td>heart rate</td>
</tr>
<tr>
<td>IST</td>
<td>International Stroke Trial</td>
</tr>
<tr>
<td>LACS</td>
<td>lacunar stroke</td>
</tr>
<tr>
<td>LF</td>
<td>low frequency</td>
</tr>
<tr>
<td>LF/HF</td>
<td>low-to-high frequency ratio</td>
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<tr>
<td>MAP</td>
<td>mean arterial pressure</td>
</tr>
<tr>
<td>NIHSS</td>
<td>National Institutes of Health Stroke Scale</td>
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<tr>
<td>PACS</td>
<td>partial anterior circulation stroke</td>
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<tr>
<td>PI</td>
<td>pulse interval</td>
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<tr>
<td>POCS</td>
<td>posterior circulation stroke</td>
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<td>PP</td>
<td>pulse pressure</td>
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<tr>
<td>PSA</td>
<td>power spectral analysis</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>PWV</td>
<td>pulse wave velocity</td>
</tr>
<tr>
<td>SBP</td>
<td>systolic blood pressure</td>
</tr>
<tr>
<td>SD</td>
<td>standard deviation</td>
</tr>
<tr>
<td>SEM</td>
<td>standard error of the mean</td>
</tr>
<tr>
<td>SNSA</td>
<td>sympathetic nervous system activity</td>
</tr>
<tr>
<td>TACS</td>
<td>total anterior circulation stroke</td>
</tr>
<tr>
<td>TIA</td>
<td>transient ischaemic attack</td>
</tr>
<tr>
<td>Tr</td>
<td>time to reflected wave</td>
</tr>
<tr>
<td>VLF</td>
<td>very low frequency</td>
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<tr>
<td>WHO</td>
<td>World Health Organisation</td>
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Study declaration

In fulfilment of the requirement of an MD thesis, this study declaration outlines the extent to which the work contained in this thesis is my own work.

The design, organisation and administration of this study was performed by the author with the help and advice of Professor John Potter, Professor of Medicine for the Elderly, University of Leicester and Dr Tom Robinson, Senior Lecturer in Medicine for the Elderly, University of Leicester.

The recruitment and study of all subjects was performed by the author except for 8 stroke patients included in the data presented in Chapter 3 studied by Dr Nainal Shah, Clinical Research Fellow, University of Leicester. For these patients, the raw data provided by Dr Shah was analysed and interpreted by the author.

The data handling and statistical analysis in this study was performed by the author.

Professor Ronney Panerai, Professor of Medical Physics, University of Leicester developed the software for the recording, calibration and editing of the digitised beat-to-beat blood pressure and heart rate recordings and the software for the beat-to-beat variability, sequence and power spectral analysis techniques.

Dr Sanjoy Paul, Lecturer in Medical Statistics assisted with the statistical analysis of the data presented in Chapters 2 and 3.
Ethical declaration

The studies presented herein were approved by the local research ethics committee, in accordance with the Declaration of Helsinki (2000) of the World Medical Association. Verbal and written information was provided for study participants and written patient consent or relative assent (where the stroke patient lacked capacity) was obtained. The patient information leaflets and consent forms for the studies are detailed in Appendix 2.
Acknowledgements

I am indebted to my supervisor, Professor John Potter, for his expert advice, support and patience throughout this study.

I gratefully acknowledge my colleagues in the Ageing and Stroke Medicine group with whom this research was made possible. I would like to particularly acknowledge the help of Dr Penny Eames, Dr Nainal Shah, Ms Anne Moore, Dr Tom Robinson, Professor Ronney Panerai, Dr Dilesh Lakhani, Dr Sanjoy Paul and Mr Bhavesh Popat.

I was fortunate to be awarded a 2 year research fellowship by the Research and Development department at University Hospitals Leicester NHS Trust allowing these studies to be undertaken.

Special thanks go to my wife, Sarah, who has followed the evolution of this thesis from its inception, and has provided unwavering support throughout.

This thesis is dedicated to my children, Thomas and Alexander.
Abstract

Stroke is the third commonest cause of adult death and the commonest cause of adult disability in the UK. Arterial stiffness is a recognised independent risk factor for cerebrovascular disease. Phase I of the thesis examines arterial stiffness in the context of stroke, evaluating its role as a risk factor and relevance to other abnormalities of cardiovascular regulation during the acute stroke phase. Central, but not peripheral, arterial stiffness was increased in acute ischaemic stroke, particularly in lacunar and atherothrombotic but not cardioembolic subtypes compared to matched controls. Prognostically-important haemodynamic parameters following stroke, for example impaired cardiac baroreceptor sensitivity and increased beat-to-beat blood pressure (BP) variability, were related to central arterial stiffness.

There is uncertainty over the treatment of elevated BP levels following acute stroke. Angiotensin-converting enzyme inhibitors (ACEI) have not been tested in the immediate post-stroke phase, but studies suggest beneficial effects in secondary stroke prevention. Phase II of the thesis presents pilot work evaluating the oral ACEI, Lisinopril, for hypertension treatment immediately following acute stroke. A single 5mg dose resulted in prompt BP reduction within the first 4 hours of administration and a once-daily regimen over the subsequent 14 days lead to sustained BP reduction. Measures of patient outcome in the short and medium-term showed a neutral effect of treatment. However, no drug-related improvement was shown in other cardiovascular variables such as arterial stiffness, BP variability and cardiac baroreceptor sensitivity despite the hypotensive effect.

Reduction of arterial stiffness might be a valid therapeutic target in the primary prevention of stroke and in the acute phase of stroke. Lisinopril administered early in the acute stroke phase
appears to be an effective hypotensive agent and is well-tolerated. On the basis of these findings, larger multicentre studies are now ongoing evaluating the effects of ACEI and other drugs on outcome immediately following acute stroke.
1. INTRODUCTION
1.1 Background

1.1.1 The burden of stroke

Approximately 120,000 people in the United Kingdom experience a first-ever stroke each year with the majority (over 90%) of strokes occurring in people over the age of 55. The annual incidence rate of first-ever stroke in a UK-based population has been estimated at 14 per 1000 of the population aged between 75 and 84 years, but increases in frequency with age at 20 per 1000 in those aged 85 years and older (19). Despite recent evidence showing a decrease in age specific stroke incidence over the past 20 years, after ischaemic heart disease and cancer, stroke remains the third commonest cause of adult death in the UK, accounting for approximately 1 in 10 deaths per year (37). Early mortality from stroke is high with up to 34% of stroke patients dead at one month and it is the commonest cause of adult disability in the UK with approximately one-third of stroke survivors being carer-dependent at one year (36).

The economic burden of stroke can be defined in terms of the direct costs of providing medical and nursing care to patients and the indirect costs associated with lost productivity. On this basis, it has been estimated that the lifetime per-person cost of a first-ever stroke, in first-world societies, is around $91,000 (~£57,000) and is greater, around $124,000 (~£78,000), for primary intracerebral haemorrhage. It has been estimated that 45% of the costs of a stroke are accounted for by the acute care, with the remainder accounted for by the long-term care of the patient (299). However, additional burdens exist that are difficult to quantify, particularly the strain placed on the carers of a stroke patient, who are often unpaid and unrecognised.
With the substantial impact placed on society by stroke, even relatively small improvements in mortality and morbidity will have important and measurable effects. A reduction in stroke incidence and associated disability has been a priority of UK policymakers in recent years, via a number of different initiatives. The establishment of UK-wide stroke services is an aim of the current National Service Framework for the Elderly (Standard 5), which includes the provision of nationwide specialist acute stroke care, comprehensive rehabilitation and secondary preventative services (81), closely integrated with primary care. The new GMS (general medical services) contract provides financial incentive for primary health care physicians to develop and implement management pathways for stroke and TIA (transient ischaemic attack). Fortunately, in tandem with these initiatives, is a growing evidence-base highlighting the effectiveness of therapeutic intervention in the primary preventative, acute and secondary preventative phases of stroke.

1.1.2 The arterial wall

In recent years, there has been a greater understanding of the pathophysiological processes that increase the risk of stroke, that occur during the acute stroke phase and that drive the increased cardiovascular risk once a stroke has occurred. For example, there is novel information on how established risk factors for ischaemic stroke (for example, hypertension, diabetes and ageing) are associated with haemodynamic changes in the systemic and cerebral circulation, functional and structural changes in arteries and changes in the thrombotic tendency of the blood. Recent interest has focused on the effects of these
and other cardiovascular risk factors on the properties of the arterial wall, in particular the associated increase in the wall stiffness of central arteries, for example the aorta and the carotid artery. A number of large observational and prospective studies have found arterial wall stiffness to be an independent risk factor for fatal stroke and to be increased in acute ischaemic stroke patients independently of other cardiovascular risk factors (163;166;292). As arterial stiffness can be measured non-invasively, it has been suggested that it may be useful in identifying patients with a high risk of stroke, in whom a more aggressive primary preventative strategy may be justified (292). In the acute stroke phase, arterial stiffness might be one of the underlying mechanisms behind some of the cardiovascular abnormalities that have subsequent prognostic significance (for example impaired cardiac baroreceptor sensitivity), and, following stroke, arterial stiffness might provide useful prognostic information about the risks of a further stroke or other cardiovascular event. Phase I of this thesis further explores arterial stiffness in the context of stroke disease.

1.1.3. Blood pressure and cardiovascular instability following stroke

Elevated blood pressure (BP) levels (casual brachial, 24-hour and beat-to-beat) are common immediately following stroke and have been found to be associated with increased morbidity and mortality in the short, medium and long-term, independently of other factors (170). The cause of elevated BP levels following stroke is unclear, but may be due to a number of factors including increased activation of the sympathetic nervous system (22). Despite the association with adverse outcome, drug trials designed to lower
BP levels early in the acute stroke phase have reported inconclusive findings, with most showing neutral outcomes, while others demonstrate possible adverse effects of treatment. The reasons for this discrepancy are likely to be multiple, and include study design and the mode of drug administration. Increasing evidence suggests the class of antihypertensive drug used in the acute stroke phase might be important.

As cerebral autoregulation (the ability of the cerebral circulation to maintain a constant cerebral blood flow [CBF] despite changes in cerebral perfusion pressure [CPP]) is impaired following acute stroke (75), a fall in arterial BP levels and hence CPP is likely to be associated with a parallel fall in CBF, thereby putting ischaemic brain tissue at further risk of infarction. However, some drugs, notably the angiotensin-converting enzyme inhibitors (ACEI) and the angiotensin receptor blockers (ARB) appear to promote maintenance of CBF in the face of a systemic BP reduction following stroke, by altering cerebral autoregulatory function (86;318). ACEI’s may have other benefits on systemic and cerebral circulatory function in the acute stroke phase (for example, on cardiac baroreceptor sensitivity) and have not yet been explored as acute treatment for hypertension following stroke (within the first 24 hours of stroke). Phase II of this thesis presents the results of a randomised, controlled, double-blind study of oral Lisinopril administered within the first 24 hours following stroke-symptom onset including primary intracerebral haemorrhage.
1.2 Arterial wall properties and stroke

1.2.1 History

The study of arterial wall properties in relation to cardiovascular disease is not new, but has recently undergone resurgence. In fact, the importance of the structure of the arterial wall has long been recognised, highlighted by this quote attributed to John Wesley (1703-1791):

'In extreme old age, the arteries themselves, the grand instrument of the circulation, by the continual apposition of the earth, become hard, and as it were bony, till, having lost the power of contracting themselves they can no longer propel the blood, even through the largest channels, in consequence of which death naturally ensues.'

In the 1870s, prior to the advent of non-invasive BP measurement, Frederick Akbar Mahomed (1849-1884), as a medical student at Guy’s Hospital in London, developed a quantitative sphygmogram whereby the peripheral pulse contour could be recorded and measured. A probe was rested over the radial artery, deflected by arterial pulsations and the pulse waveform was recorded on a moving paper trace (188). Mohamed was the first to describe the characteristic features of the peripheral arterial pulse in association with ageing commenting on the accentuated and prompt systolic component of the waveform and the depressed diastolic component. He also observed this in association with hypertension and concluded:
'The pulse ranks the first among our guides; no surgeon can despise its counsel, no physician shut his ears to its appeal.'

The pressure wave changes detailed by Mohamed are largely explained through increased arterial wall stiffening, particularly of the central arteries. In 1920, Bramwell and Hill published work showing the stiffness of the arterial wall in man was the principal determinant of the velocity of the pulse wave (46). However, as the sphygmomanometer was introduced at the turn of the 20th century, the study of arterial wall properties waned for almost a century, as this device dominated the assessment of arterial BP due to its simplicity and portability. Little information on arterial wall properties or the arterial pulse wave was inferred from the results of brachial BP (although we now recognise pulse pressure as being representative of central arterial wall function), and systolic and diastolic BP variables became the principal method of measuring the interaction between the heart and arterial vessels, subsequently being found to be powerful predictors of future cardiovascular morbidity and mortality.

Over the last decade, attention has returned to methods of assessing circulatory status in terms other than BP measurement in the search for additional useful indices of circulatory function. In particular, new non-invasive methods have evolved, based on the work of Mohamed and Bramwell and Hill, assessing the function of the arterial wall through changes in the arterial pulse wave contour and its speed of conduction at various sites of the arterial tree, thereby giving rise to alternative indices of circulatory function and
arterial dysfunction and damage. Despite the advantages of global cerebrovascular disease risk assessment it has been estimated that only half of cerebrovascular disease risk is explained by conventional risk factors alone (110). Although in their infancy and not yet utilised in routine clinical practice, researchers have suggested that these measures offering greater insight into the interaction between the heart and arteries might provide additional, and perhaps more powerful, cardiovascular prognostic information.
1.2.2 Arterial wall mechanics

The mechanical properties of the arterial wall have an important influence over cardiac function and arterial BP levels. There are different ways of describing arterial wall properties, using different indices according to the technique used. An overview of the principles behind them follows:

The capacity of the elastic aorta to buffer the systolic ejection of blood from the left ventricle, absorb the increasing volume and smooth the ejection of blood to the periphery during diastole is dependent upon its compliance. This property differs according to the arterial segment studied and can be calculated according to:

\[
C = \frac{(\Delta D)}{D} / \Delta P
\]

where C is compliance, D initial diameter at end-diastole, \(\Delta D\) change in diameter with pulse and \(\Delta P\) pulse pressure. This property is also often described as vessel distensibility. The inverse of this figure is known as Peterson's elastic modulus (Ep):

\[
Ep = \frac{\Delta P}{(\Delta D/D)}
\]

Utilising a similar principle, recent investigators have quoted an arterial stiffness index (SI) or \(\beta\) index defined by:
(4) \[ \beta = \log \left( \frac{P(s)/P(d)}{AD/D} \right) \]

where \( P(s) \) is systolic BP and \( P(d) \) is diastolic BP.

The forward-going velocity of the pressure pulse along an arterial segment (pulse wave velocity [PWV]) is dependent upon the elastic modulus of the arterial segment. In 1926, Otto Frank described an equation to calculate the wave velocity along an infinitely-long tube, containing an incompressible fluid, with the walls of the tube having the same elastic modulus throughout:

(5) \[ PWV = \sqrt{\frac{E_p}{\rho}} \]

where \( \rho \) is fluid density. However, intra-arterial pressure is itself influenced by the tension of the vessel wall, which in turn is a function of vessel wall thickness. Young's incremental elastic modulus (\( E_{inc} \)) took this into account, describing the elastic properties of the arterial wall material and the stress/strain relationship, with the equation:

(6) \[ E_{inc} = \Delta P D^2/2h\Delta D \]

where \( h \) is vessel thickness. Elements of this equation are described by \( E_p \) in Otto Frank's equation 5 and, incorporating this, Moens and Korteweg's equation derived in 1820 (154;204) calculates PWV for an artery taking all parameters into account:
Thus the velocity of the pulse pressure wave is a function of the following properties of the vessel wall: the blood density, the Young's elastic modulus of the arterial wall, the wall thickness and the vessel radius at end-diastole. Many researchers now use the term "stiffness" to describe arterial wall properties, which may be considered as dependent upon these latter three variables.

However, the elastic modulus is not static and changes according to the luminal distension pressure of the vessel, as the load is shifted with increasing pressure from the elastic laminae to the less-distensible collagen fibres and smooth muscle cells. Thus vessel stiffness increases in a non-linear fashion with increasing BP as different components of the arterial wall become loaded, each with their own distensibility characteristics.

1.2.3 Relationship of arterial wall mechanics and pulse wave reflection to arterial BP

Aortic pulse pressure (PP) is determined by the mechanical properties of the elastic arteries via two principal mechanisms: a 'Windkessel' effect and due to the effects of pulse wave transmission.

\[ PWV = \sqrt{\frac{E_{\text{inch}}}{2R_p}} \]
1.2.3.1 The Windkessel model

The ‘Windkessel’ model describes that the volume of blood ejected from the left ventricle during systole is accommodated through expansion of proximal vessels which subsequently release the stored blood during diastole, thereby smoothing the ejection of blood to the periphery. A decrease in proximal elastic aortic compliance will serve to buffer less efficiently the pressure oscillations generated by left ventricular ejection leading to a surge in systolic BP (SBP) and, as there is reduced potential energy in the proximal aorta to release back in diastole, a reduction in diastolic BP (DBP). Therefore decreased aortic compliance serves to widen PP.

1.2.3.2 Incident and reflected pulse waves

Pulse wave transmission characteristics along the length of the arterial tree are also important in determining PP. The pressure wave originating from the left ventricle is transmitted along the aorta and branching vessels much faster than the blood and subsequently reflected back from sites in the distal peripheral arterial vasculature. It returns to the aorta within the cardiac cycle during which it is generated, its amplitude and timing resulting in central aortic pressure augmentation. These characteristics are determined by the mechanical properties of the arterial wall along the wave transmission path, determining PWV, and the site and efficiency of wave reflection sites in the peripheral vasculature. Late return of the reflected wave during the cardiac cycle so that it arrives during diastole, leads to augmentation of diastolic pressure and a reduction in
central PP. Early return of the wave such that it arrives in systole leads to a widening of the PP as systolic pressure is augmented and the previous augmentation of diastolic pressure is lost. Increased arterial stiffness, by causing an increase in PWV, appears to directly lead to an increase in central PP by this mechanism.

PP is also influenced by the nature of wave-reflecting sites in the peripheral vasculature. Sites of reflection occur where there is a change in vascular impedance, as influenced by the properties of smaller muscular arteries and arterioles. For example, a shift of reflecting sites proximally therefore results in an earlier return of the reflected wave. Structural and functional modifications, including arterial hypertrophy, arterial remodelling, changes in the number and branching angle of arterioles, vascular endothelial properties and arteriolar vasomotor activity influence the site and efficiency of wave reflection and thus the contribution of the pulse wave to central SBP augmentation. Therefore it can be seen that the peripheral vasculature has a role in determining PP as well as its more commonly perceived role of determining peripheral vascular resistance and thus mean arterial pressure.

Heart rate is also linked to PP as vascular impedance has been shown to be frequency dependent (216) and PWV to be positively related to the heart rate (172;267). Furthermore, at slower heart rates the peak of ventricular ejection is relatively delayed, and arrival of the reflected wave may synchronise with left ventricular ejection thereby augmenting systolic pressure. In pulse wave analysis, the degree to which central SBP levels are augmented by the reflected wave is expressed as the augmentation index (AIx)
and the time from the onset of left ventricular ejection to the time of the return of the reflected wave described as Tr (Figure 1.1).

Augmentation of systolic pressure may have adverse consequences for the heart as left ventricular afterload is increased, promoting left ventricular hypertrophy and there is a reduction in diastolic coronary perfusion. There appear also to be deleterious consequences elsewhere in the circulation, especially for the brain and this is discussed subsequently in section 1.2.6.

The PP contour at any point along the arterial tree is dependent upon the timing of the forward and backward waves, being a summation of them. The phasing of incident and reflected waves will dictate both systolic and diastolic pressure at a particular location. Where PWV is relatively slow, for example in young adults, the PP at the brachial or femoral artery may be much greater than that at the ascending aorta. With increasing age and in the presence of cardiovascular risk factors, the normal amplification of PP that occurs towards the periphery is lost (Figure 1.2), as the point at which the systolic portions of the incident and reflected wave coincide moves proximally due to increased PWV and due to proximal migration of the reflecting sites.
Summary Box

- Arterial pulse wave velocity is a function of arterial wall stiffness.
- Increased arterial wall stiffness results in an increase in pulse pressure via two principal mechanisms i) a Windkessel effect and ii) due to changes in pulse wave transmission.
- Accelerated pulse wave transmission and early return of the reflected wave from the periphery augments SBP.
- A number of factors may influence SBP augmentation including arterial stiffness, heart rate, the location and geometry of reflecting sites all of which may undergo dynamic changes.
- Novel information on cardiovascular function may be provided by measurement of central (aortic) BP, pulse wave reflection, pulse wave velocity and the degree to which pulse pressure is amplified towards the periphery.
Figure 1.1. Derived aortic pressure waveform displaying time to reflected wave (Tr) and augmentation index (AIx). PH (pulse height) is equivalent to pulse pressure, AG (augmentation) is the portion of pulse pressure resulting from the return of the pulse wave from distal reflecting sites. Aortic augmentation index = AG/PH (%).
Figure 1.2. Propagation of the pulse pressure (PP) wave from central to peripheral arteries in patients 24, 54, and 68 years of age. In older patients, the more rapid propagation of pulse wave reduces PP amplification, resulting in nearly identical central and peripheral BP.

Reproduced from Kelly et al. (144)
1.2.4. Non-invasive measurement of the arterial pulse wave and arterial wall properties.

The Sphygmocor system (figure 1.3), utilised in the investigations in this thesis, is a portable system based on the technique of applanation tonometry, consisting of a computer and interface board coupled to a high-fidelity piezo-electric transducer mounted in the tip of a hand-held wand. This generates a low voltage electrical current according to the pressure applied at the tip and, when applied to an artery underlying skin such that the arterial wall is flattened, circumferential pressure is equalised throughout and intra-arterial pressure equals transmural pressure at the tonometer tip (a similar principle is used when measuring intraocular pressure by applanation tonometry). The technique can be successfully employed at the site of any palpable artery to obtain the intra-arterial pressure waveform, but particularly where there is underlying bone to support the vessel being compressed.

1.2.4.1 Applanation tonometry - Pulse wave analysis

Direct measurement of ascending aortic pressure is necessarily an invasive procedure. However, applanation tonometry may be an acceptable non-invasive technique. Applanation of the carotid artery waveform, being similar to that at the ascending aorta due to its proximity, may provide a similar contour to the ascending aortic waveform. On the assumption that mean arterial and diastolic pressure remains constant throughout the arterial tree the carotid waveform may be calibrated to brachial BP, deriving carotid
systolic pressure and PP. However, DBP cannot necessarily be assumed to be a constant throughout the arterial tree as it is a function of the phasing, amplitude and frequency of incident and reflected pulse waves, differing according to the arterial site. The approach to the derivation of the ascending aortic waveform employed by the Sphygmocor system is to use a mathematical transformation function to derive the waveform by integrating a peripheral waveform (radial or carotid) and brachial BP. Ascending aortic pressure and other waveform characteristics (including AIx and Tr) can thus be derived. Mathematical transformation functions calibrated to brachial artery BP have been derived for this purpose and have been validated for use with applanation tonometry, forming the basis of central aortic pulse wave analysis from a peripheral artery using the Sphygmocor system (63). However, there has been much recent debate about the accuracy of a 'one size fits all' mathematical transformation factor for patients of different ages and with different disease states. When comparing central BP values obtained from radial applanation tonometry to invasively-measured values most investigators have found radially-derived aortic systolic values to be underestimated and diastolic values overestimated (74). This may be due in part to the routine use of brachial cuff BP measurements for calibration as intra-arterial measurements were used in the original validation studies (63) and cuff measurements may not accurately reflect intra-arterial BP values, particularly in elderly subjects (94). Some investigators suggest that, particularly for the AIx, a mathematical transformation factor adds no additional value to analysis of the pure radial artery waveform, as it is unable to introduce any new information (121). In particular, high frequency signals (1st harmonics of decomposed waveform spectra) are required to generate central AIx from the radial artery and the transformation factor has been found to
be unstable at these higher frequencies (200). A non-invasive and non-transformed measurement of central AIx may be best obtained from an artery closer to the aorta such as the carotid, although this location is inherently less stable than the radial artery to applanate (where there is immediate underlying bone). However, central AIx derived from the radial artery has been found to be reproducible with a within-observer difference of 0.5 ± 5.4% (mean difference between measurements ± standard deviation) and a between observer difference of 0.2 ± 3.8% (329). The validity of AIx and Tr has not yet been fully tested and the studies to date are discussed in Section 1.2.6.

1.2.4.2 Applanation tonometry - Pulse wave velocity

Sequential or simultaneous applanation tonometry of arterial sites with identification of the pulse wave upstroke (foot-to-foot methodology) with reference to the simultaneously-recorded ECG signal allows for calculation of arterial PWV if the distance of pulse wave travel is also known. This technique is dependent upon the acquisition of an acceptable waveform and accurate estimation of distance of pulse wave travel. Validation criteria are available for each set of waveforms acquired with the Sphygmocor system and thus poor quality waveforms can be identified and rejected. The reproducibility of this technique using Sphygmocor between the carotid and femoral arteries has been shown in one study to be 0.95 ± 15% within observers and 4.2 ± 16.8% between observers, ie. not as good as estimating the central AIx from the radial artery (328).
Figure 1.3. The Sphygmocor™ system and output.
The reproducibility of carotid to radial measurements was reported to be better in the same study (1.7 ± 9.6% within observers, 5.1 ± 12.9% between observers) possibly because good-quality recordings are more easily obtained from the radial than the femoral artery due to the proximity of underlying bone. Accurate estimation of pulse wave travel from surface markings may also be problematic, particularly for between-patient comparison studies, as this technique assumes that the vessel travels in a straight line and only within a 2 dimensional plane. This, of course, is not the case as the aorta arches anteriorly and with increasing age becomes more tortuous. Therefore the distance of pulse wave travel may be underestimated, particularly in the elderly patient. Similarly, the transit distance may be overestimated in the presence of abdominal obesity. Furthermore, the distance over which the pulse wave travels is less than that actually measured from the carotid site to the femoral or radial site as the pulse wave travels in the opposite direction in the carotid compared to the descending aorta. Thus the possibility for error in the distance calculation is significant. The disadvantage of a non-simultaneous technique such as the Sphygmocor, that takes several seconds to acquire data from each arterial site, may be that PWV changes in the short term, particularly in relation to beat-to-beat BP change. PWV has been shown to be positively related to heart rate in humans in observational and in interventional studies (172) (267). On applanation of the carotid artery, relative bradycardia may be induced as carotid baroreceptors are activated.
1.2.4.3 Other techniques

Most long-term outcome studies have used the Complior device which records waveform transmission in real time using two arterial waveform sensors, thereby potentially avoiding some of the aforementioned sources of error (14). Arterial ultrasound allows for the wall motion and luminal diameter of an arterial vessel segment to be directly imaged, along with correction for the mechanical effects of an atherosclerotic plaque, together with the calculation of regional PWV (17). Data regarding changes in arterial wall compliance can be obtained non-invasively by using a vessel wall echo-tracking ultrasound technique, coupled with a continuous measurement of finger arterial BP. This technique has been used to study the mechanics of the carotid artery particularly in relation to baroreceptor sensitivity (123;206). However, a methodological criticism is that the finger arterial BP contour may be a poor representation of that at the carotid, with differences in PP between the two sites being relevant. Furthermore, some investigators have derived carotid artery compliance by calibrating wall-track data to intermittent brachial sphygmomanometry measurements in stroke patients, thereby taking no account of the effect of short-term fluctuations in BP, well-recognised following stroke (38;255;292). Applanation tonometry may be easier to perform on the more unstable stroke patient in the acute phase of the illness than ultrasound, requiring less cooperation of the patient, being completely portable, less operator-dependent and may require a shorter training period to achieve competency.
Other investigators have measured arterial compliance based on the Windkessel model (107) which assumes the arterial system to be functionally represented by proximal and distal capacitance and resistance, as in an electrical circuit. Using this model, the peripheral arterial waveform is thought to provide information on large and small arterial wall properties. However, this model may be an oversimplification with one recent study questioning the validity of such an approach (191), finding differences in Windkessel-derived compliance values in the arm and leg thereby invalidating whole-body model assumptions and suggesting a strong influence of regional circulatory properties.

Summary box

- Applanation tonometry using Sphygmocor provides data on arterial function: the arterial waveform (pulse wave analysis), the arterial stiffness of vessel segments (pulse wave velocity) and ascending aortic BP.

- The validity of applanation tonometry to derive these variables has been called into question.

- Arterial stiffness may be measured using a variety of other techniques including ultrasound.

- However, applanation tonometry is an easily applicable technique and may be most suited to unstable patients and inexperienced investigators.
1.2.5 Relationship between arterial function and cardiovascular risk factors.

1.2.5.1 Ageing.

Ageing is the dominant process affecting arterial stiffness, wave reflections and PP. Histological studies of elastic arteries show that, with increasing age, there is thinning and fragmentation of elastin fibres (probably as a result of mechanical fatigue), smooth muscle cell degeneration and necrosis, collagen cross-linking and accumulation of advanced glycation end-products (resulting from interaction between glucose or other reducing sugars and amino acids) on both elastin and collagen fibres (84). Collagen in the human aorta is at least 500 times stiffer than elastin and more than doubles in content from age 20 to 70 years (217). This age-related change in composition and structure of the elastic arterial media increases the overall elastic modulus of the arterial wall, which is reflected in an increase in arterial stiffness and PWV, with age-related changes having been observed for both the carotid artery (41) and the aorta (216). The age-related changes in elastin and the increase in collagen are, however, not seen in muscular arteries where there is apparently no age-related increase in stiffness or PWV (41;202;216). An increase in central Alx is observed with increasing age as is an increase in PP (202), possibly in part as a result of increased central arterial stiffening.
1.2.5.2 Gender

Initial studies suggested the mean height difference between men and women accounted for the elevated AIx observed in age-matched females (119). However, post-menopausal women have been shown to have a greater PP and AIx than age and height-matched men (99) and have recently been shown to have higher levels of elastic artery stiffness. Implicating female hormonal status in the aetiology is evidence showing younger women have reduced elastic artery stiffness than age-matched men (315).

1.2.5.3 Diabetes Mellitus

Patients with types 1 and 2 diabetes mellitus, compared to healthy controls, have been shown in a number of studies to have increased stiffness of both large elastic and muscular arteries (165) (68) (272). Likely explanations include the presence of endothelial dysfunction and changes in arterial media wall mechanics via increases in advanced glycation end-product formation leading to collagen cross-linking. Dyslipidaemia and accelerated atherosclerosis may also be contributing factors. Interestingly, despite the increased central PWV in diabetics, a recent study found no increase in central AIx (157).

1.2.5.4 Sustained hypertension

Relationships between sustained hypertension and arterial wall stiffening are complex. Due to the properties of the arterial wall already described, unless isobaric distensibility is
assessed, there is a confounding effect of actual distending pressure. Due to this published valid work on the subject is surprisingly limited. Armentano et al. (12) found the effects of sustained hypertension on wall mechanics in humans to differ in relation to normotensive controls according to which large artery was studied; carotid arterial wall mechanics were found to be similar between the groups whereas femoral isobaric compliance and distensibility values were higher in the hypertensive subjects (53).

The early adaptive changes in arterial hypertension may actually reduce arterial stiffness. For example, it has been shown that despite hypertension-induced wall hypertrophy of the radial artery, wall distensibility is increased (162). In the longer term, sustained arterial hypertension leads to increases in conduit artery diameter, smooth muscle hypertrophy and, later, accelerated atherosclerosis (263), possibly related to an increase in shear stress, which may eventually increase arterial stiffness above and beyond any initial decrease.

Evidence for increased arterial stiffness as a possible predisposing factor for hypertension comes from the results of the ARIC (Atherosclerosis Risk In Communities) study (173) which showed, in a prospective follow-up study of approximately 7000 normotensive middle-aged subjects over a 6-year period, that a decreased arterial elasticity of the common carotid artery at baseline was associated with a greater risk of developing hypertension independently of other aetiological risk factors and the level of baseline BP.
1.2.5.5 Smoking

Smoking has been shown to acutely increase the stiffness of muscular but not elastic arteries, along with promoting increase in BP levels (92). Furthermore, chronic smoking, with careful correction of other associated risk factors, has been shown to increase aortic stiffness in women but not in men (287).

1.2.5.6 Obesity

Results from a recent observational study (327) found that for young adults (20 to 40 years old) and for older adults (41 to 70 years old), aortic PWV was significantly and independently correlated with higher body weight, body mass index, waist and hip circumferences and waist-hip ratio. A marked increase in PWV (0.5m/s) was seen in obese patients between 20 and 30 years of age compared to their normal-weight counterparts. In patients aged >70, obesity was not associated with further increases in arterial stiffness.

1.2.5.7 Hypercholesterolaemia and atherosclerosis

Lipid levels are probably associated with differing effects on arterial wall mechanics than the effects of overt atherosclerosis. For example, very young subjects with familial hypercholesterolaemia have been shown to have increased large artery distensibility (167), whereas other studies have shown older familial hypercholesterolaemics to have reduced distensibility (103), although controlling for the effects of subclinical atherosclerotic
disease is problematic. Wilkinson et al. (332) found higher central PP and higher AIx in middle-aged subjects with hypercholesterolaemia compared with controls, but arterial stiffness does not appear to be directly related to plasma cholesterol in elderly subjects (72). Observational work has shown increased aortic and common carotid artery stiffness to be strongly associated with atherosclerosis at various sites of the vascular tree (294;309), especially the coronary arteries (98). The cause and effect relationship between large artery stiffness and atherosclerosis appears complex. Arterial stiffness may in itself promote atherosclerosis as the stiff arterial wall is subjected to increasing intraluminal cyclical stress and/or the presence of atherosclerosis may induce increases in local stiffness. In a study of subjects with a unilateral and haemodynamically significant internal carotid artery stenosis (102), arterial distensibility at the level of the stenosing plaque was decreased on the affected side compared with the unaffected side. However, distensibility of the common carotid artery proximal to the lesion on the affected side was also lower compared to the contralateral side suggesting that the association between a plaque and arterial mechanical properties is not limited to the actual plaque site but extends beyond.

1.2.5.8 Endothelial dysfunction

Changes in arterial stiffness in association with cardiovascular risk factors such as age, hypertension, diabetes and hypercholesterolaemia may be mediated via changes in endothelial function which in turn lead to changes in the function and structure of the components of the arterial media, as well as a proinflammatory and prothrombotic state.
Endothelial dysfunction, defined as a decrease in the capacity of the endothelium to promote vessel dilatation in response to physical and chemical stimuli, is a characteristic change that occurs with increasing age and in association with other cardiovascular risk factors such as hypercholesterolaemia and diabetes. A continuous cycle promoting disease progression has been postulated (73) whereby endothelial dysfunction and damage promotes the formation of atherosclerosis which in turn increases arterial stiffness, augmenting early wave reflection to the heart and increasing PP further, which in turn causes further endothelial damage and mechanical fatigue via cyclical intraluminal stress.

Impaired vasodilatory responses may be reflected in short-term changes in vessel wall elastic modulus mediated by altered smooth muscle activity. Removal of the vascular endothelium in animals has been shown to acutely alter large artery stiffness (42), suggesting that endothelial-derived substances regulate arterial stiffness in vivo. In the longer term, endothelial dysfunction may lead to arterial remodeling via changes in extracellular matrix deposition, fibrosis and vascular cell growth. In theory, all these changes might be reflected in changes in the arterial pulse waveform and velocity with evidence for this coming from a number of studies. Endothelium-dependent vasodilatatory responses have been shown to be correlated with changes in the height of the aortic wave inflection point of the radial artery waveform (176) and the radial-derived aortic augmentation index (330). Animal studies have shown the potent endothelium-derived vasoconstrictor endothelin-1 to increase PWV in the iliac artery of the sheep. Inhibition of the endothelium-derived vasodilator nitric oxide, by inhibition of endothelial-derived
nitric oxide synthase (eNOS) using NG-monomethyl-L-arginine (L-NMMA) has been shown to increase aortic PWV, independent of BP change, in the rat (95).

A smooth muscle layer of sufficient density in the arterial media in order to effect changes in wall modulus in response to endothelial stimuli may be required if the endothelium is to have any short-term influence on arterial stiffness and this may not be the case in the elastic vessels (carotid and proximal aorta) in humans, particularly as structural changes supervene in the media with increasing age. Recent work has shown an infusion of L-NMMA does not alter aortic PWV in healthy human volunteers (aged 32 to 48 yrs) compared to blood-pressure matched control subjects (290). Although endothelial dysfunction occurs with increasing age (295), muscular arterial stiffness does not appear to increase with age (41;202;216). Endothelial dysfunction per se may be insufficient to alter elastic modulus in the absence of other changes such as atherosclerosis.

Sufficient smooth muscle activity to influence vessel mechanics may also be required if the sympathetic nervous system is to have an effect on local arterial wall dynamics. Femoral artery distensibility has been shown to increase in patients with peripheral vascular disease following lumbar sympathectomy (93) and sympathetic activation (via a cold pressor test) has been shown to decrease radial artery compliance (44), arteries in which smooth muscle cells predominate. In rats, cervical sympathectomy has been shown to be followed by an increase in carotid artery distensibility (201), but no similar studies have yet been presented for elastic arteries in humans.
1.2.5.9 Genetic factors

Much of the variability in arterial stiffness remains unexplained after accounting for the effect of cardiovascular risk factors. A study of American Indians in the Strong Heart Family study found significant contribution of genetic factors to carotid artery β index. This study and others (286) have also found a hereditary component to the aortic augmentation index, as derived from the radial artery. Genetic modulation of the extracellular matrix proteins and their regulators, including matrix metalloproteinases (MMPs), may account for some of the inter-individual differences (148).

1.2.6 Relationship between arterial stiffness and cardiovascular disease.

1.2.6.1 Cardiovascular disease

In 1999, Blacher et al. (33) reported a cross-sectional study showing that aortic arterial stiffness, as measured by Complior-derived PWV was a better correlate of cardiovascular event risk, calculated using Framingham equations, than any single cardiovascular risk factor alone, for example, hypertension, age or diabetes. A subsequent large prospective cohort study of approximately 2000 hypertensive subjects confirmed the relevance of measuring arterial stiffness in predicting patient outcome, finding that aortic PWV was a predictor of all-cause and cardiovascular mortality independently of previous cardiovascular disease, age, diabetes and PP (161). Further studies have highlighted aortic PWV as an independent risk factor for cardiovascular mortality in diabetes (68), end-stage
renal disease (34) and in older adults (196). However, there is less robust data available on
the prognostic value of indices of arterial wave reflection. To date, there is published work
suggesting carotid AIx may be a useful marker of cardiovascular risk, as it has been
shown to correlate positively with increasing cardiovascular risk score (222) and, in a
longitudinal outcome study of the very high risk group of end-stage renal failure patients,
increased carotid artery augmentation index has been found to be an independent predictor
of all-cause mortality (182). More recently, in a sample of patients referred for coronary
angiography, increased aortic AIx (as derived from the radial artery) has been found to
correlate with the degree of coronary artery disease (321), but not in patients older than 60
yrs of age. In patients with end-stage renal disease, both carotid PP (measured using
applanation tonometry) and the degree of PP amplification (brachial PP divided by carotid
PP) have been shown to be strong independent predictors of all cause (including
cardiovascular) mortality and superior in this regard to brachial PP levels (270).

1.2.6.2 Stroke

Data from the Framingham study published in 1981 (137) first suggested a relationship
between the risk of stroke and the degree of blunting of the dicrotic notch in the peripheral
pulse wave due to wave reflection early in the cardiac cycle, associated with isolated
systolic hypertension. Arterial stiffness may be a stronger risk factor for cerebrovascular
disease than for coronary heart disease. An analysis of the SMART (Second
Manifestations of Arterial Disease) study (83) showed patients with cerebrovascular
disease (qualified by a history of stroke, TIA or amaurosis fugax) to have increased
carotid stiffness compared with patients with a single diagnosis of coronary artery disease following adjustment for cardiovascular risk factors.

Observational studies have reported higher degrees of central aortic stiffness in ischaemic stroke patients, in comparison to control subjects matched for age, BP level and cardiovascular risk profile. Lehmann et al. (166) studied thoraco-abdominal aortic stiffness via Doppler ultrasound in stroke patients at least 7 days following ictus and compared the results to a group of age and sex-matched control subjects, free of cardiovascular risk factors. Arterial stiffness was found to be higher in the stroke group, although there were differences in baseline BP level between the groups, for which a linear statistical correction was made. In a study of M-mode transoesophageal ultrasound of the proximal descending thoracic aorta, Sugioka et al. (292) found that compared with a control group well-matched for BP level, age and stroke risk factors, acute stroke patients had thicker atherosclerotic plaques, and higher levels of wall stiffness, even when atherosclerotic plaque thickness was corrected for. Although these patients were ischaemic strokes, stroke aetiology or subtype was not presented in any of these studies and it is unclear whether the relationship with arterial stiffness remains true for all stroke subtypes, for all age groups or even for haemorrhagic stroke. In a prospective cohort study, Laurent et al. (163) found aortic PWV to be an independent predictor of fatal stroke in hypertensive patients with a relative risk of 1.72 for each 4 m/s increase in PWV over a median follow-up period of 8.9 yrs. However, the type of fatal stroke (haemorrhagic vs ischaemic) was not presented nor the effect on different ischaemic stroke subtypes and neither was there any data on non-fatal stroke.
The relationship between arterial stiffness and stroke is unclear. A causative link may exist between arterial stiffness and stroke via a number of mechanisms. Although brachial PP has been associated with stroke in some longitudinal studies (85;218), its predictive value remains controversial when compared to MAP (199). PP is associated with carotid artery disease, including the degree of carotid intima-media thickness, aortic and carotid atherosclerotic plaque area (273;334) and is associated with the extent of carotid plaque ulceration (183), and there is some evidence that central PP is more closely associated with these changes than brachial PP (43). Arterial stiffness has also been directly associated with the presence of aortic atherosclerotic plaque, independently of the effects of PP (344;345). Increasing PP has been shown to induce endothelial dysfunction with an impaired dilatory response to acetylcholine (266) and endothelial dysfunction per se is associated with an increased risk of stroke or TIA (298). In-vitro evidence suggests that cyclic stretching exerts a greater influence than static load on the phenotype and growth of vascular smooth muscle cells thereby influencing arterial remodelling (252) and increased PP has been shown to induce wall hypertrophy of cerebral arterioles in stroke-prone spontaneously hypertensive rats (26).

Increased arterial stiffness may reflect parallel lesions in the cerebral and peripheral vasculature, for example fibrosis, medial smooth muscle necrosis, breaks in elastin fibres, calcification and atherosclerotic plaques that give rise to an increase likelihood of stroke. Increases in cerebral arteriolar wall stiffness may limit cerebral arterial dilatation capacity leading to dysfunctional cerebral autoregulation and impaired compensation for variations in perfusion pressure. Impaired cerebrovascular reactivity has been shown to be a risk
factor for ischaemic stroke (205). In the ARIC (Atherosclerosis Risk In Communities) study (174), the prevalence and severity of cerebral white matter lesions, associated with an increased stroke risk (133), was independently associated with brachial PP.

Arterial baroreceptors may be less responsive to BP changes due to splinting of the arterial wall in association with arterial stiffness, with consequent impairment of a fundamental mechanism for BP homeostasis, a reduced restraint of sympathetic tone and a reduction in vagal activity. As well as the haemodynamic consequences, increased SNSA has also been associated with increased platelet activation (221) which may precipitate thrombosis.

Coronary heart disease and heart failure are favoured by high PP and arterial stiffness due to increased left ventricular afterload and reduced diastolic coronary perfusion, and are also risk factors for stroke (45;58), perhaps through the development of ischaemic cardiomyopathy and arrhythmogenesis.

The associated pressor BP response of acute stroke may lead to increases in arterial stiffness but other mechanisms may also play a role. For example, high levels of endothelin-1 have been found in serum following ischaemic stroke (343) and there are recognised alterations in sympathovagal balance with a predominance of sympathetic nervous system activity (22) which may alter vasomotor tone. Certainly, both endothelin-1 and the sympathetic nervous system have been shown to regulate arterial PWV in humans (44;93;194).
In the acute stroke phase, arterial stiffness may be related to abnormalities in cardiovascular regulation following stroke that confer important prognostic information, in particular increased beat to beat BP variability and decreased cardiac baroreceptor sensitivity. For example, decreased compliance of the proximal aorta may serve to buffer less effectively left ventricular ejection, leading to increases in BP variability. Also splinting of arterial baroreceptors due to barosensory arterial segment wall stiffness may be important to some of the cardiovascular instability observed following acute stroke and this is discussed in section 1.3.3.5 and researched further in this thesis.

Summary box

- Arterial stiffening, particularly for central arteries such as the aorta, occurs in association with the ageing process, sustained hypertension, diabetes mellitus and other conditions that are associated with increased cardiovascular risk, such as smoking and genetic profile.

- Arterial stiffness may be mechanistically linked to stroke via a number of pathways and may reflect parallel lesions in the cerebral vasculature.

- Assessment of central arterial stiffness appears to be a more powerful predictor of cardiovascular risk (including stroke) than conventional cardiovascular risk assessment.

- Arterial stiffness may mediate increased stroke risk through increase in PP, but other mechanisms may also be involved.
1.3. Blood pressure and acute stroke

1.3.1 Blood pressure as a risk factor for primary stroke

The continuous relationship between BP levels and the risk of first-ever stroke is now well established. Data from the Framingham study initially highlighted the importance of elevated DBP and SBP levels in predicting future stroke risk, with SBP the strongest predictor (137). Subsequently, a systematic review of 9 major prospective observational studies confirmed the relationship between increasing DBP levels and increased subsequent stroke risk (185). Importantly, there was no DBP level identified below which there was no further reduction in the risk of stroke, indicating that even for DBP levels below the diagnostic criteria for hypertension, a continuous relationship remained. For haemorrhagic stroke, a study from Eastern Asia, where the incidence of primary haemorrhagic stroke is much greater than in Western populations, confirmed a similar but stronger continuous relationship between stroke incidence and SBP and DBP levels (3). However, not all studies reach the same conclusions. The Copenhagen City Heart Study of 6545 middle-aged and elderly subjects recruited with normal SBP levels but elevated DBP levels, and studied over 12 years, reported increased SBP and PP to be independent risk factors for stroke, but not DBP (218). Similar findings were reported in the SHEP (Systolic Hypertension in the Elderly Program) study (85) and the recent prospective Brisighella Heart Study (40), with both studies reporting PP to be more important than MAP in predicting stroke risk. In contrast, however, the findings of the MRC Mild
Hypertension Trial showed MAP to be more strongly predictive of subsequent stroke risk than either PP or SBP levels (199).

Because the relationship between BP level and stroke risk is continuous and is not clarified by subdivision according to those with hypertension and those without, on a population level, the majority of patients presenting with stroke will have preceding normal BP levels. In one review, it was estimated that 80% of strokes had occurred within the 95% of the population who had a usual BP level of < 155/95 mmHg (185). The Honolulu Heart Study reported that the attributable risk of ischaemic stroke to hypertension was greater in men aged between 45 and 54 years (50%), having an overall low risk of stroke, than in men above 65 years (18%), who have a relatively higher risk suggesting that with increasing age other risk factors become more important (69). Even though the population attributable risk fraction of stroke due to hypertension may be lower than expected with increasing age, it is probably difficult to quantify due to hypertension being previously undiagnosed in some patients, definitions of hypertension varying according to the date and location of the study, the effects of regression dilution bias and, perhaps, previously poor recognition of increased PP, particularly where DBP levels are low. Importantly, however, BP levels are modifiable and remain the most effective single therapeutic method by which stroke incidence may be reduced, regardless of age. A discussion of the evidence of the effectiveness of BP reduction in altering primary stroke incidence is outside the scope of this thesis, but has been the subject of a recent review (59).
1.3.2 Blood pressure as a risk factor for recurrent stroke

It is perhaps not surprising that the continuous relationship between elevated stroke risk and BP levels is not abolished once a cerebrovascular event has occurred. A study of 2435 patients in the United Kingdom Transient Ischaemic Attack Aspirin trial found the relative risk of recurrent stroke increased according to baseline SBP and DBP level. No threshold was reported at which there was absence of further reduction in stroke risk below a certain BP level and the relationship appeared continuous to the lower quartile of BP levels studied (≤129 mmHg systolic and ≤79 mmHg diastolic) (261). However, the relationship between BP and recurrent stroke had previously been shown to be J-shaped with concerns of the effect of lower BP levels in the presence of possible impairments in cerebral autoregulatory capacity following stroke (127), but this relationship was not confirmed in the larger study.

Large trials of BP lowering in patients with a previous history of stroke or TIA, and where therapy has been commenced at a median time of several months following the event, have shown reductions in cardiovascular events with treatment. Preliminary results from the PATS (Post-stroke antihypertensive treatment) study (1) of 5665 patients with a previous stroke or TIA reported a BP reduction of 5/2 mmHg over a treatment period of two years with Indapamide alone and a 29% reduction in the risk of stroke events. In the HOPE (Heart Outcomes Prevention Evaluation) study (340) of the ACEI Ramipril versus placebo in 9297 subjects at high risk of a cardiovascular event (of which 11% had experienced a previous stroke or TIA), there was an 26% reduction in the risk of
cardiovascular mortality with Ramipril with a 3/3 mmHg reduction in BP levels compared to placebo over a five-year treatment period. In PROGRESS (Perindopril pROtection aGainst REcurrent Stroke Study) (4), in which the ACEI Perindopril was evaluated in a secondary prevention role in 6105 patients with a previous stroke or TIA, despite a reduction in BP levels of 5/3 mmHg compared to placebo there was no discernible reduction in cardiovascular events, stroke events or cardiovascular mortality over the four-year treatment period with Perindopril alone. However, when the drug was combined with the thiazide diuretic Indapamide, there was a significant reduction in cardiovascular events, all types of stroke event and cardiovascular mortality, with a BP reduction of 12/5 mmHg compared to placebo. The benefits of therapy were also seen in 'non-hypertensive' subjects (SBP ≤ 160 mmHg and DBP ≤ 90 mmHg).

1.3.3 Blood pressure following acute stroke

Whilst the majority of patients presenting with stroke may not have fulfilled current criteria for 'hypertension' prior to the event (defined by the British Hypertension Society as a SBP > 140 mmHg and/or a DBP > 90 mmHg), the majority of acute stroke patients are clearly hypertensive on admission to hospital, with higher levels being observed in patients with primary intracerebral haemorrhage (207). In the International Stroke Trial (IST), which is by far the largest single study of BP following ischaemic stroke and outcome comprising 19435 patients presenting acutely (within the first 48 hours), a single brachial BP measurement was recorded at a median time of 20 hours following symptom onset with 82% of patients having a SBP ≥ 140 mmHg and 56% a SBP ≥ 160 mmHg (2).
The natural history of BP levels following stroke is for a spontaneous decline to occur during the first few days, with the greatest falls associated with the highest baseline BP levels (49), and levels usually reaching a plateau by day 5. However, BP decline may be more marked during the first few hours in some patients. In one small study, where BP profiles were measured from a mean time of 19 minutes following symptom-onset (by a mobile emergency team), 95% of patients with an elevated SBP $\geq 160$ mmHg at baseline were reported to undergo a significant and spontaneous decline in both SBP and DBP levels during the first 90 minutes after the onset of stroke (mean change in SBP, 29 mmHg and DBP, 10 mmHg) (50). However, the results of this particular study may have been confounded by non-standardised BP measurement, the stress of removal of the patient and that observations were taken within the setting of a thrombolysis trial where reductions in BP may have been desirable and may therefore be biased. Albeit the majority of stroke patients experience some reduction of BP levels in the acute phase of stroke, approximately two thirds of patients followed up on discharge at one month post-stroke in one prospective study were reported as having elevated BP levels similar to those on admission and levels remained elevated for at least the following year (55).

The origins of elevated BP levels following stroke are unclear. The BP response to acute hospitalisation (alerting effect) in stroke patients and control patients has been studied, with the stroke group reported to have excessive BP levels on admission but similar BP levels to the controls by day 7 thereby minimising this factor, but not completely (49). Post-stroke alterations in autonomic nervous system activity have been recognised with associated increased catecholamine, glucocorticoid and mineralocorticoid release. Raised
intracranial pressure in relation to stroke may also provoke a pressor response via the Cushing reflex.

1.3.4 Blood pressure following acute stroke and outcome

In the IST (figure 1.4), high or low SBP was associated with an impaired short (14 day) and long-term (6 month) outcome in a ‘U-shaped’ relationship. For every 10 mmHg increase in SBP above 150 mmHg, the risk of early death increased by 3.8%, there was an increase in the frequency of early stroke recurrence by 4.2% and there was a non-significant increase of 1.1% in 6-month death or dependency, independently of age, time to BP measurement, level of consciousness and the presence of atrial fibrillation. In the estimated 32% of patients with a SBP level below 150 mmHg (of which only 5% had a SBP level < 120 mmHg), for each 10 mmHg decrease in SBP there was a corresponding 17.9% increased risk of early death and an increased risk of death or dependency at 6 months of 3.6%. Whilst the most severe stroke syndrome (total anterior circulation stroke - TACS) was associated with low BP, the relationships remained significant following adjustment for this factor. It is likely that, whilst reporting significant findings, the IST may have under-reported the strength of the BP relationship with outcome as it was subject to the effects of regression dilution bias based on a single and non-standardised casual BP measurement. A study of repeated BP measurement following acute ischaemic stroke in the first 24 hours following hospital admission, overcoming potential sources of bias by using a validated, automated BP monitor, reported an odds ratio of 1.88 for death or dependency at 30 days for each 10 mmHg increase in 24-hour SBP, and an increased
hazards ratio of 2.41 for death when admission systolic 24-hour BP levels were $\geq 160$ mmHg over a median follow-up period of 2.5 years (254;257). Prior to these studies, previous investigators had reported similar relationships to the IST (48;136), and also for primary intracerebral haemorrhage (71), but this was not a consistent finding with some studies reporting absence of (39;54) or even a positive relationship (281) between BP and stroke outcome. The timing and method of BP measurement and study sample size varies greatly between these smaller studies, and a recent meta-analysis of 32 of them, where BP was measured within 7 days of ictus, found elevated MAP and DBP (but not SBP) levels to predict an adverse outcome following acute ischaemic stroke and elevated SBP and MAP level to predict adverse outcome following primary intracerebral haemorrhage (333). Recent work suggests that admission PP may be more important than MAP in predicting stroke outcome (13). Wide variation in perfusion pressure with each cardiac cycle might have particular relevance following stroke due to the impaired cerebral compensatory mechanisms, with a greater variability in cerebral blood flow having adverse consequences for the viability of ischaemic neuronal tissue.
Figure 1.4. Relationship between SBP level on admission with acute ischaemic stroke and stroke outcome. Data from the International Stroke Trial (170).
The mechanisms by which this might occur are discussed further in Chapter 1.3.3.2.

However, the relationship between increased PP and stroke outcome might be confounded by other associated factors, such as the degree of endothelial dysfunction, atherosclerotic burden and arterial stiffness.

The mechanisms by which elevated BP levels lead to impaired short-term outcome following stroke have not been fully elucidated. In the IST (170), early stroke recurrence and cerebral oedema formation were correlated with SBP levels and accounted for most of the early death and disability, although there was no association reported with haemorrhagic transformation of the infarct. A recent study of both ischaemic and primary haemorrhagic stroke found 24-hour BP levels, but not casual BP measurements, performed in the acute stroke phase to be independently associated with cerebral oedema formation (311), although the cause and effect relationship remains unclear. This is also the situation in studies of primary intracerebral haemorrhage, where haematoma expansion is associated with an impaired outcome (51), and positive relationships have been reported between haematoma expansion and admission SBP levels (143). However, the pressure effects of haematoma causing a pressor BP response via the Cushing reflex may confound this relationship.

A recently-published study reported spontaneous SBP reduction during the first 24 hours following acute ischaemic stroke to be independently associated with an adverse outcome at 3 months follow-up (226). Cerebrovascular autoregulation (CA) is impaired following acute stroke and cerebral blood flow (CBF) is therefore very sensitive to changes in
systemic BP levels. This may be particularly important for rapid changes in systemic BP levels that occur over periods of seconds, as it has been shown that dynamic CA is more impaired than static CA post-stroke (75). Any reduction in CBF may have potential consequences for the viability of the ischaemic but not yet infarcted neuronal tissue if systemic BP levels rapidly fall. However, careful scrutiny of this study reveals that approximately 60% of patients in this study received one or more antihypertensive drugs, some of which may have had adverse effects on cerebral blood flow. In contrast, other studies have found improved outcome with spontaneous BP falls in the acute stroke period (60), but again have not controlled well for the effects of any immediate hypotensive therapy and it is difficult at the present time to make conclusions about the prognostic significance of an early spontaneous SBP fall.

Summary box

• Elevated BP levels are a powerful risk factor for primary and recurrent ischaemic and haemorrhagic stroke

• BP reduction is the single most effective strategy for reduction of risk of primary and recurrent stroke

• Elevated BP levels during the acute stroke phase are associated with impaired short and medium-term outcomes
1.3.5 Cardiovascular haemodynamic stability and stroke

1.3.5.1 Diurnal blood pressure variability

It is increasingly recognised that, independently of the absolute level of BP, day-night BP variability is also predictive of subsequent cardiovascular risk. The usual 24-hour BP variability pattern, with morning BP levels being higher than those in the evening with a further decrease at night time, appears to confer a favourable prognosis in terms of end organ damage and cardiovascular mortality, when compared to subjects lacking a normal BP decrease at night (10% SBP decrease or absolute 10 mmHg day minus night SBP fall). Lack of a night time BP fall has been shown to be associated with an increased prevalence of hypertensive target organ damage which confers excess cardiovascular risk, for example, left ventricular hypertrophy (129). Furthermore, an excessive nocturnal BP fall, as well as no fall or an elevation in night time BP level in hypertensive patients has been shown to have adverse effects on the brain, with one study correlating abnormal night time BP patterns with the level of asymptomatic ischaemic change (in the form of white matter lesions detected by magnetic resonance imaging), with increases being seen in patients with an excessive fall, absence or rise in BP levels at night (138). Periods of nocturnal hypotension on a background of daytime hypertension might have deleterious effect due to a hypertension-induced right shift in the cerebral autoregulatory curve, and thus modest falls in systemic BP may lead to marked reductions in cerebral blood flow. A number of investigators have found the night time fall in BP levels to be reduced or absent following stroke (179), especially in the presence of cortical infarct or primary
haemorrhage (76), and the absence of a night time BP fall following stroke has been reported to be associated with a decreased odds of short-term recovery (31). Lack of nocturnal BP fall has been correlated with elevated plasma catecholamine levels and may be associated with increased activity of the sympathetic nervous system (274).

1.3.5.2 Short-term blood pressure variability

Increased beat-to-beat BP variability (BPV) has been observed with increasing age and in subjects with hypertension. Although BPV increases with higher mean absolute BP levels, it is recognised that, independent of the mean BP level, the degree of BPV is related to the degree of target organ damage in hypertensive patients and the risk of subsequent cardiovascular events (145;235). In one study with relevance to stroke aetiology, an increase in carotid intima-media thickness (utilised as a surrogate marker for early atherosclerosis) over a 3-year follow-up period was found to be more strongly related to increased daytime systolic BPV at baseline than absolute BP levels (275).

Following stroke, increased BPV may have particular consequences for the evolution of stroke pathology, and the resulting degree of neurological damage. A facilitating mechanism might be the recognised impairment in cerebrovascular autoregulation (CA) that occurs following acute stroke, particularly for beat-to-beat changes in BP (dynamic CA). Both increased beat-to-beat BPV and impairment in dynamic CA have been shown to remain impaired for at least the first 20 to 30 days following stroke (78;255). Immediately following ischaemic stroke, the core of infarcted and therefore unrecoverable
neuronal tissue may be surrounded to a variable extent by a zone of ischaemic and non-functioning neuronal tissue, the "ischaemic penumbra", to which blood supply has been critically reduced but not to sufficient degree to precipitate immediate infarction. The size and potential viability of the penumbra is likely to be dependent upon the location and size of vessel occlusion, the degree of collateral flow and other physiological factors (for example, body temperature, metabolic demand and local gene expression) (105). As CBF exists in a pressure-passive relationship with systemic arterial pressure following stroke, the ischaemic penumbra is likely to be acutely vulnerable to systemic BP change. In theory, even short-term reductions in CBF may precipitate penumbral infarction. Conversely, rapid rises in CBF may promote viability of the penumbra, but observational studies (170;311) suggest also an increased risk of vasogenic cerebral oedema and possible haemorrhagic transformation of the infarct. It appears possible that reperfusion injury may also occur if blood flow to neuronal tissue undergoes cyclical reduction and increase secondary to fluctuating BP levels. Watson et al. (320) found in a rat model of stroke that only intermediate levels of ischaemia were required to produce reperfusion injury, ie. transient occlusion of the middle cerebral artery followed by restoration of blood flow resulted in a larger infarct, than when the vessel was permanently occluded. A serial MRI study in the acute phase of cerebral infarction has shown the reduction in diffusion-weighted coefficient, indicating cytotoxic oedema and at maximum reduction probably the extent of unrecoverable tissue, is at a peak at 2.8 days (range 1.6 to 5.3 days) (224) suggesting that CBF fluctuation following the onset of stroke may have important effects on the final infarct size for many hours following the onset of stroke.
A study comparing the degree of systolic beat-to-beat BPV in acute ischaemic stroke patients to control subjects matched for age and gender, and measured as the standard deviation of SBP continuously recorded over a 30-minute period using a validated non-invasive finger photoplethsmograph device (Finapres), found systolic beat-to-beat BPV was significantly greater in the stroke patients and remained elevated at 10-14 days following stroke-onset (255). A subsequent and larger study evaluated the effects of beat-to-beat BPV on short-term outcome following stroke (77), via analysis of two 5-minute Finapres recordings, and found increased beat-to-beat BPV for MAP and DBP to independently predict the likelihood of death or disability at 30-days post-stroke with an odds ratio of 1.38 for an adverse outcome with each 10-mmHg increase in beat-to-beat MAP variability. Admission beat-to-beat SBP levels were higher in the dead or dependent patients but no significant association was found for systolic beat-to-beat BPV and outcome. Thus, from the available evidence, it would seem reasonable to target BPV, as well as absolute BP level for antihypertensive drug trials in the acute phase of stroke.

1.3.5.3 The arterial baroreflex

The principal beat-to-beat neural reflex responsible for the homeostasis of arterial BP levels is the arterial baroreflex, a schematic diagram of which is shown in Figure 1.5. Baroreceptor sensory nerve endings lie in the adventitial layer in the carotid sinus and the aortic arch in a circumferential arrangement in high density, with scattered baroreceptors present elsewhere in the large arteries. Sensitive to stretch, they depolarise in response to increasing distension usually induced by an increase in luminal pressure and adjust rapidly
to steady state BP levels in humans. Baroreceptors are much more sensitive to dynamic changes in BP levels (occurring over seconds and minutes) than over a longer period and reset to tonic activity when altered BP levels have been sustained over several hours, although sensitivity varies according to the absolute baseline BP level. Baroreceptor afferent activity, via the glossopharyngeal nerve from the carotid sinus and via vagal afferents from the aortic arch, is received by the nucleus tractus solitarius (NTS), in a loosely defined area in the medulla termed the central vasomotor center. The current understanding of the neuroanatomy of this region (245) is that excitatory inputs project from the NTS to the caudal ventrolateral medulla (CVLM) from where inhibitory inputs project to the rostral ventrolateral medulla (RVLM). The RVLM contains excitatory neurons that are continually tonically active which, together with neurons from other areas including the hypothalamus and pons, are the precursors of sympathetic nervous activity. The RVLM receives excitatory and inhibitory traffic from higher centers including the cortex and the hypothalamus. Both the CVLM and RVLM are thought to receive and project neuronal connections with the ventral respiratory group of neurons including pre-Botzinger neurons responsible for respiratory rhythmicity. They also receive input from cardio-pulmonary receptors also involved in BP homeostasis. Baroreceptor afferent nerve traffic leads to a reflex inhibition of tonic sympathetic nervous system output and an increase in parasympathetic nervous system activity.
Figure 1.5. Diagram of the cardiac arterial baroreflex.

IX – Glossopharyngeal nerve
X – Vagus nerve
SNS – Sympathetic efferents
BP reduction is therefore achieved by the change in autonomic balance resulting in negative cardiac chronotropic effect and consequent reduction in cardiac output and by resistance vessel (arteriolar) smooth muscle relaxation thereby decreasing total peripheral resistance. The ability of the reflex to effect changes in the target organs (heart and resistance blood vessels) in response to a change in carotid sinus and aortic arch arterial BP is thus dependent on a number of stages, abnormalities of which at any point (afferent, central or efferent) may become the overall rate-limiting step, thus decreasing the overall sensitivity of the reflex.

Initial studies to measure cardiac baroreceptor sensitivity involved intravenous injection of a pressor or depressor agent with minimal influence on PI, for example phenylephrine or sodium nitroprusside, coupled with intrarterial measurements of BP. Cardiac BRS was assessed from the slope of the change in ECG R-R wave interval (the pulse interval) per unit change in SBP (the Oxford technique) (285). However, intravenous drugs may influence cardiac BRS independently of BP, leading to errors in BRS calculation. For example, phenylephrine might directly activate the baroreflex via alpha-receptor-induced vasoconstriction of the aortic arch or carotid sinus. The Oxford technique is not free of risks to the subject, for example cardiac arrhythmias may be precipitated by intravenous phenylephrine. As a result, non-invasive techniques to manipulate BP have been explored, for example the neck suction method to increase carotid transmural pressure and thereby mimicking a pressor stimulus on the carotid baroreceptors (88), the valsalva method utilising forced expiration against a closed glottis to promote BP change (142), and lower body negative pressure to induce hypotension (335). Estimation of spontaneous cardiac
baroreflex sensitivity (cardiac BRS), without BP manipulation, is now well-established using any non-invasive method of assessing beat-to-beat BP levels, or carotid sinus or aortic arch distension and the pulse interval. Non-invasive techniques of measuring spontaneous cardiac BRS have benefits over techniques where BP is manipulated, as they are not confined to the laboratory setting, can be conducted on a wide range of subjects, and can be used on unstable patients without the potential of causing harm. Spontaneous cardiac BRS measurements have been shown to correlate well with invasive measures over a wide range of subjects, including elderly (244), chronic heart failure (66), hypertensive (130) and post-myocardial infarction patients (246), although good correlation has not been found in all studies (180). Spontaneous BRS results might be more applicable to a clinical setting where a similar measurement may be relatively easily reproduced outside of a research study and certainly measurements obtained in this way have been shown to convey important prognostic information (156;258).

Computer-based analysis of spontaneous SBP and pulse interval traces to derive cardiac BRS can be performed in the time-domain using a sequence analysis of beat-to-beat SBP change and corresponding PI change, calculating the slope of the change in PI per unit change in SBP. Alternatively analysis in the frequency domain may be made using the principle that any waveform can be decomposed into a multiple of sine waves at varying frequency, amplitude and phase. A mathematical algorithm such as Fast Fourier Transformation (FFT) may derive component spectra of PI and SBP waveforms. Using this method rhythmic patterns in SBP and PI can be identified and classified according to their power and frequency (253). The ratio of the power of SBP and PI spectra in the
lower frequency band has been shown to represent cardiac BRS (253). Each of these methods are used in this thesis and are described further in the methodology sections of the results chapters. It should be highlighted that with all of these methods, only one afferent limb of the reflex is studied, the heart rate response (cardiac BRS), whereas changes in resistance vessels may differ. Control of muscle sympathetic nervous system activity in relation to the arterial baroreflex may be directly assessed using superficial micro-electrodes, usually in the peroneal nerve (91).

A study using a frequency domain analysis technique to non-invasively measure spontaneous BRS in 37 patients with ischaemic or haemorrhagic stroke within 72 hours of stroke-symptom onset and 37 control subjects matched for gender, age and BP found cardiac BRS to be significantly impaired in the stroke group compared with the control group (259). Subsequent follow-up of these and other stroke patients found an impaired cardiac BRS below the median level (< 5 ms/mmHg) in the acute stroke phase to be predictive of subsequent death in the long-term (28% versus 8% mortality rate during median follow-up period of 4.1 years), independently of age, BP level, stroke severity or stroke subtype (258). The cause of death of the subjects in this study was, in the majority of cases due to coronary artery disease rather than recurrent stroke. That relationships between impaired cardiac BRS and short-term outcome did not achieve statistical significance is supported by the weak and not statistically significant negative association between admission cardiac BRS and beat-to-beat BPV, in the presence of a strong and highly significant positive relationship between cardiac BRS and PI variability, suggesting the presence of additional factors driving the prognostically-significant BP variability in
the acute stroke phase. This might be related to respiratory activity (306) or the reduced buffering of left ventricular ejection volumes due to decreased large artery compliance. Interestingly, recent work in the rat has shown that arterial baroreceptors may modulate cerebral blood flow through direct connections with pontine parasympathetic neurons, and thus impairment of cardiac BRS may itself reduce cerebral blood flow perhaps via a right-shift of the cerebral autoregulatory curve (8).

Association between impairment of cardiac BRS and impaired patient outcome is not a new finding. In patients following a recent myocardial infarction, the ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) study (156), found impaired cardiac BRS at baseline to be an independent risk factor for subsequent cardiac mortality (mean follow-up of 21 months), independently of the degree of LV dysfunction and prevalence of ventricular arrhythmia. The Hoorn Study (100), found impaired BRS and other measures of autonomic dysfunction to be independent predictors of cardiovascular death especially in subjects with diabetes, hypertension or a history of cardiovascular disease. Impaired BRS has been suggested, from the results of a cross-sectional study, to be an integrative variable of established and independent cardiovascular risk factors in hypertensive subjects including age, heart rate, serum cholesterol and left ventricular hypertrophy (159).
1.3.5.4. Central nervous system influences on arterial baroreflex-mediated cardiovascular responses following stroke

The aetiology of impaired cardiac BRS following stroke has been the subject of recent speculation (229), as it is unknown whether it arises as a result of the acute neurological disturbance, or is present prior to stroke-onset. That the balance of cardiac autonomic tone appears to be affected by the location of stroke in humans supports the hypothesis that changes in cardiac BRS are initiated by the onset of stroke. Sander et al. (274) found the largest increase in sympathetic nervous system activity (SNSA), represented by increases in serum norepinephrine levels, to occur following infarction of the insular cortex compared with other cortical areas. Furthermore, infarction of this area was more closely associated with QT prolongation and cardiac arrhythmias. Robinson et al. (259), found patients with right hemispheric cortical stroke to have increases in SNSA, as evidenced by an increase in low frequency to high frequency ratio for PI variability, compared with those with left hemispheric stroke. Other investigators have found reductions in low frequency heart rate variability following right cortical stroke compared to left, particularly where the infarct is in the right insular cortex (22;301). Thus the right insular cortex may be important in regulating cardiac autonomic tone in humans and disruption of its function by stroke may lead to autonomic imbalance in favour of increased SNSA. Korpelainen et al. (153) also found decreased HR variability following stroke (although did not evaluate hemispheric differences) and studied the patients again 6 months later. HRV remained decreased at 6 months although there were slight increases in PIV across all the methods used (low-frequency power, standard deviation of all R-R intervals and
Poincare plots). Other studies support the dominance of the right hemisphere in the sympathetic autonomic control of heart rate. Yoon et al. (338) studied the variability of heart rate before and after hemispheric inactivation by intracarotid injection of amobarbital in patients with temporal lobe epilepsy. Inactivation of the left hemisphere shifted cardiac autonomic tone in favour of sympathetic activity, whereas no such effect was seen with right hemispheric inactivation. Hilz et al. (120) measured cardiac BRS following hemisphere inactivation in epilepsy patients using a similar method and found augmented parasympathetic activity and an increase in cardiac BRS following right hemisphere inactivation. There are, of course, inconsistencies in the above evidence. If inactivation of the right insular cortex inhibits SNSA in humans then it does not necessarily follow that stroke in this area should increase SNSA. The processes affecting the insular cortex following pharmacological inactivation and ischaemic stroke are likely to be very different apart from any baseline differences in the patients studied. It is possible that the presence of stroke may activate hemispheric centres by local pressure or depolarising effects as well as inactivate them. Furthermore, cardiac autonomic innervation is asymmetric and this may be important in explaining some of the incongruity; the left stellate ganglion is dominant for cardiac sympathetic innervation in humans, and the left vagus principally innervates the atrioventricular node and the right the sino-atrial node. It might be expected that stroke involving the nuclei responsible for baroreflex function situated in the medulla would alter cardiac BRS and case reports exist of baroreflex failure in such a setting (32;243).
1.3.5.5 Properties of the arterial baroreceptor following stroke

The degree of baroreceptor deformation in response to a given change in arterial BP is dependent upon the mechanical properties of the arterial wall in which it is situated. Studies examining elastic artery compliance using direct ultrasound visualisation of arterial diameter in relation to finger arterial pressure and comparing this with measures of cardiac BRS in the young and elderly, and in healthy and hypertensive subjects have found cardiac BRS to be significantly and positively correlated with both carotid artery and aortic arch distensibility (38;158;169;206). In these studies, decreases in both variables were observed to occur with age, and the reduction in distensibility was more marked in the carotid sinus. In a study of patients with coronary artery disease (302), carotid distensibility and cardiac BRS were positively correlated and there was a reduction in both carotid distensibility and cardiac BRS in the subjects with ≥75% stenosis of a coronary artery compared to patients with less severe coronary artery disease. However, these studies have been unable to demonstrate a causal relationship. A recent paper (180) has questioned the nature of the association between these two variables, suggesting that increased barosensory vessel wall stiffness and decreased cardiac BRS, as measured using spontaneous non-invasive baroreflex assessment, decrease in parallel with age and may not be causally related, merely that spontaneous BRS measurements more likely reflect reduced parasympathetic activity with increasing age, whereas only invasive measurements using pressor and depressor agents (modified Oxford technique) demonstrate true baroreceptor activity and show no correlation with wall stiffness. In certain hypertensive groups, for example in pre-eclampsia the relationship between
impairment in cardiac BRS and arterial stiffness is less clear (197). A number of investigators (123;124;141;152) have attempted to separate the mechanical component (BP/barosensory vessel diameter relationship) from the neural component (baroreceptor discharge/efferent activity relationship) of the baroreflex arc using direct visualisation of the carotid sinus with ultrasound together with pulse interval analysis. Using this technique, age-related declines in both the mechanical and neural components of the baroreflex arc have been observed, supporting the notion that, independently of alterations in barosensory vessel wall mechanics, there is a change in autonomic cardiovascular control with age.

A methodological problem when considering studies utilising finger arterial BP measurement as a index of luminal pressure in the barosensory vessels is that the effects of pulse wave reflection may serve to amplify peripheral PP and will give rise to a different pulse waveform and BP values at the finger to that at the central barosensory vessels thus influencing the measure of cardiac BRS. In fact, one study found much better coherence between pulse interval change and carotid distension variables than finger arterial pressure measurement (152). A recent study failed to find an association between carotid arterial stiffness and baroreflex activity in elderly patients using finger arterial BP and carotid ultrasound techniques although there was a relationship found with SBP levels and BRS, suggesting other mechanisms than barosensory arterial stiffness might be important (209).
The relationship between cardiac BRS and arterial stiffness in stroke patients has not yet been explored or the extent to which the acute neurological disturbance may influence this relationship.

1.3.5.6 Autonomic innervation of myocardium and arteriolar smooth muscle following stroke

There is evidence for concomitant myocardial damage in association with acute stroke, probably resulting as a consequence of increased catecholamine levels resulting from increased SNSA (211). Cechetto et al (56) found subendocardial pathology to be more frequent in rat hearts following middle cerebral artery occlusion involving the insular cortex compared to cerebral infarction not involving the insular cortex. While ECG abnormalities are common in humans following stroke, attributing them to myocardial ischaemia has been difficult because of the relative non-specificity of a rise in ‘cardiac enzymes’. However, a recent study showed associated myocardial infarction to be common in the presence of stroke, identifying 17% of patients in an acute stroke series to have significantly elevated serum troponin T levels, in the absence of other evidence of acute myocardial infarction (131), and this was an independent predictor of in-hospital death. Myocardial infarction or ischaemia may blunt cardiac responses to autonomic innervation, and thus reduce cardiac BRS. Pomidossi et al. (247) studied cardiac BRS by monitoring pulse interval change in relation to a depressor SBP response induced by a bolus of intravenous nitroglycerine in patients with myocardial ischaemia during and after episodes of spontaneous and catheter-induced angina, characterized by ECG ST-segment
depression. Cardiac BRS was significantly reduced during the ischaemic phase compared to 30 minutes after recovery.

Robinson et al. (256) studied forearm vasomotor responses to lower body negative pressure (thereby inducing a fall in systemic BP levels) in the acute and subacute stroke period and found forearm vascular resistance did not significantly increase, whereas it did in a control group despite similar depressor BP responses. Heart rate responses remained similar between the two groups. Whilst this observation may have been due to a lack of arterial-baroreflex and cardiopulmonary receptor-induced vasoconstriction, the efferent pathway may itself have been impaired or resistance vessels may have been already maximally constricted. Nevertheless, alterations in peripheral vasomotor tone do not appear to be available to stroke patients in order to compensate for changes in arterial BP and it may be that change in cardiac output is the dominant mechanism, even though this response is impaired as already described.
Summary box

• Increased beat-to-beat BP variability, particularly for DBP and MAP levels, in the acute stroke phase is associated with an impaired short-term outcome following stroke.

• BP variability may be related to cardiac BRS during the acute stroke phase but other factors may have influence such as respiratory activity and arterial compliance.

• Cardiac BRS is impaired following acute stroke compared to control subjects.

• Impaired spontaneous cardiac BRS during the acute stroke phase, measured using a non-invasive technique, has long-term prognostic significance.

• The degree of cardiac BRS impairment appears to be dependent upon the location, size and laterality of the stroke lesion.

• Reduced baroreceptor afferent activity, due to increased central arterial stiffness, is related to the degree of cardiac BRS impairment in some patient groups, for example in the elderly and patients with coronary artery disease.

• The relationship between arterial stiffness and cardiac BRS in stroke patients is unknown.

• Other mechanisms may also contribute to impaired cardiac BRS levels following stroke such as concomitant myocardial ischaemia.
1.3.6 Blood pressure reduction in acute stroke

There is established evidence for the beneficial role of BP reduction commenced several weeks following the index event (at least 2 weeks after), with the degree of vascular protection being related to the degree of BP reduction (250), and this has been shown for several drugs including thiazide diuretics (1) and ACE inhibitor – based therapy (4).

However, the current management of hypertension immediately following acute stroke is a matter of debate, as reflected in a 1995 UK-based survey of clinical practice. Conducted by the Stroke Association, the survey found that 6% of physicians would start antihypertensive therapy on admission, 21% would wait a few hours, and the rest would wait anything from a few days to a few weeks (177). This varying practice is not surprising given, firstly, the lack of available evidence that immediate BP reduction is of benefit following acute stroke and secondly, concerns that, as cerebral autoregulatory capacity appears to be impaired following stroke (75), BP reduction might actually be harmful by reducing cerebral blood flow to ischaemic areas thereby extending stroke. Furthermore, the natural history of BP changes following stroke is for a spontaneous reduction to occur during the first 4 to 10 days.

Arguments against pursuing an aggressive BP lowering strategy are supported by the observation from the IST data that there was an adverse short and long-term outcome for patients with a low BP level on admission (18.4% of ischaemic strokes). For SBP levels < 150 mmHg, every 10 mmHg fall was associated with an increased risk of early death of 17.9%. Thus BP reduction may be best aimed at achieving SBP levels around 150mmHg.
Smaller observational studies have also reported adverse post-stroke outcomes related to low admission BP (136;230;281). Furthermore, a recent study found the extent of the fall in SBP during the first 24 hours following stroke onset to be an independent predictor of an adverse short-term outcome (226). However, another similar study found an early fall in MAP to be associated with an improved short-term outcome (60). The discrepancy between these results may be partly explained by these studies not being purely observational; a number of patients in each study received open-label antihypertensive therapy at the discretion of the supervising physician. Furthermore, differences in stroke type and BP measurement technique may have been important confounding variables. In addition, drug effects on cerebral blood flow were not recorded.

A recent Cochrane review of interventions for deliberately altering BP in acute stroke (6) concluded that there was insufficient trial evidence available to evaluate the effect of altering BP on outcome during the acute phase of stroke. A meta-analysis of available trials is reproduced in figure 1.6. A recent scientific statement from the American Stroke Association (7) concluded that in the management of acute stroke 'in most circumstances, the BP levels should generally not be lowered'. Circumstances where acute BP reduction may be desirable include peri-stroke vascular emergencies such as aortic dissection, severe left ventricular failure or hypertensive encephalopathy, or, in the case of primary intracerebral haemorrhage, where BP levels are persistently > 200/120 mmHg. However, the evidence-base for benefits of BP lowering, or at least giving drugs with beneficial cardiovascular effects in the acute phase of stroke, is now increasing. It might be proposed that an ideal antihypertensive agent for use in the acute phase of stroke would reduce
arterial BP levels promptly, whilst maintaining or improving cerebral blood flow (this may be achieved in part by altering the limits of cerebral autoregulation), and would lead to decreases in beat-to-beat BPV and an increase in cardiac BRS. Furthermore, preservation of diurnal BP pattern might also be beneficial.

To date, a number of small trials have been published evaluating antihypertensive therapy in the acute phase of stroke and these are subsequently described. There are now three large and ongoing UK-based multicentre studies underway specifically evaluating the effect of a number of different antihypertensive therapies (260) and these are described on section 7.2.3.
Figure 1.6. Cochrane meta-analysis of interventions to lower blood pressure in acute stroke (6).

<table>
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<th>Study</th>
<th>Lower BP n/N</th>
<th>Higher BP n/N</th>
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<th>Weight (%)</th>
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<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
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<td>4.61 [0.17, 122.46]</td>
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<td>11.0</td>
<td>4.61 [0.17, 122.46]</td>
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<tr>
<td>02 Calcium channel blockers (po)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Uzuner 1995</td>
<td>4/38</td>
<td>0/30</td>
<td></td>
<td>67.7</td>
<td>0.85 [0.17, 2.46]</td>
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<td>67.7</td>
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<tr>
<td>x Dyker 1997</td>
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<td></td>
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<tr>
<td>Bath 2000</td>
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<td></td>
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1.3.7 Antihypertensive drug trials following acute stroke

1.3.7.1 Beta-blockers

The principal theoretical basis for testing beta-blockers in acute stroke is that they might ameliorate catecholamine-induced cardiac and neurological damage, and reduce the metabolic demands of the ischaemic brain. In the BEST trial (21), therapy with atenolol or propranolol commenced within 48 hours of symptom-onset was associated with a significant BP reduction, but there was a non-significant increase in mortality and a decrease in neurological and functional outcome at 6 months compared with placebo. Labetalol has been tested in a controlled trial of 10 patients with primary intracerebral haemorrhage, achieving a significant BP reduction with no reported adverse effects (238). Studies in healthy humans suggest labetalol may not alter regional or global cerebral blood flow or cerebral autoregulation (227;278) and the drug has been employed, although in a non-randomised manner, for the treatment of hypertensive acute stroke patients prior to thrombolysis in the NINDS trial (52). Labetalol is currently being evaluated in the multicentre CHHIPS trial (260).

1.3.7.2 Calcium channel blockers

Calcium channel blockers have been more widely studied in acute ischaemic stroke. Theoretical benefits are that they may have a cerebroprotective effect by limiting post-ischaemic cellular calcium influx, that they have a preferential vasodilator action on cerebral blood vessels and that they have been used successfully (particularly nimodipine)
in the treatment of subarachnoid haemorrhage. However, a recent review of 47 trials found no overall benefit of treatment on stroke outcome (122). In fact, in a subgroup analysis of one of the larger trials, INWEST, DBP reduction with high-dose intravenous nimodipine within 24 hours of symptom onset was found to be associated with early neurological deterioration (9), and a trend to an adverse outcome with CCBs is reported in the Cochrane review (6). A small study of cerebral blood flow using single photon emission computed tomography (SPECT) (181) in acute stroke patients with hypertension highlighted the variable effects of CCB therapy on middle cerebral artery blood flow when initiated within 72 hours following stroke. There was no overall change in CBF by day 3 of treatment, despite significant MAP reduction in all patients but 3 out of the 5 pts treated with the CCB underwent a reduction in cerebral blood flow.

1.3.7.3 Nitrates

Nitric oxide is a potent vasodilator of large cerebral arteries but this effect may not necessarily be beneficial. Intravenous sodium nitroprusside has been shown to increase intracranial pressure in non-stroke patients with large mass-producing lesions, particularly with a BP fall of 20% or more (67). A transdermal nitric oxide donor in the form of a glyceryl trinitrate patch is being evaluated in acute stroke administered within 72 hours of symptom-onset inducing a reduction in arterial BP, and to date having been reported to have no effect on cerebral blood flow (25). Nitrate therapy may be limited by the development of tachyphylaxis.
1.3.7.4 Thiazide diuretics

The value of thiazide diuretics in BP lowering in acute stroke may be limited by the time lag of several days from the initiation of therapy to a significant BP reduction. A small study evaluated oral Bendrofluazide in acute stroke (initiated within 72 hours of symptom-onset) and found no effect on BP, beat-to-beat BPV, regional CBF or CA (87).

1.3.7.5 Other drugs

Although not a study specifically designed with the aim of lowering BP levels, the IMAGES (Intravenous Magnesium Efficacy in Stroke) trial (208) of 2589 patients randomised within 12 hours of acute stroke to receive a 24 hour infusion of intravenous magnesium sulphate (infarct or haemorrhage) reported a 4/3 mmHg reduction in BP levels by the end of the infusion with the active agent compared to placebo but also a trend to an adverse 90-day outcome in the treated group. However, treatment appeared to have beneficial effects on outcome for lacunar stroke.

1.3.7.6 Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers.

Previous studies of ACEI therapy in acute stroke comprise mostly small studies evaluating CBF with the initiation of therapy at a median time of several days following stroke-symptom onset and in patients with very mild strokes (86;181;317) and these trials are subsequently discussed. No studies to date report the effects of either ACEI or ARB
therapy commenced within the first 24 hours following stroke. However, amongst the many trials showing neutral outcomes or trends to adverse effect of antihypertensive therapy commenced in the acute stroke phase one recent study has shown apparent improvement in patient outcome. The ACCESS study (277) was a randomised, double-blinded, placebo-controlled study of the ARB, Candesartan, evaluating initiation of therapy within 72 hours in 342 hypertensive acute ischaemic stroke patients. Those randomised to the placebo arm, received placebo for the first 7 days and subsequently all participants with 24-hr automated casual BP mean values of >135/85 mmHg received a Candesartan-based BP-lowering regime for at least the next 1 year. The trial was terminated prematurely as it demonstrated a significant reduction in vascular events at 1 year with treatment. However, there was no observable difference in BP response between the active and placebo groups in the acute phase, and the study was limited to patients with SBP in excess of 180 mmHg (equivalent to only 15% of stroke admissions in the IST, compared with 81% with SBP ≥ 140 mmHg).

1.3.8 Theoretical benefits of inhibition of the renin-angiotensin system following acute stroke

1.3.8.1 Cerebral blood flow and autoregulation

Studies in subjects with or without a history of stroke show ACEI to increase or maintain CBF in association with a reduction in BP levels. Britton et al. (47) reported a group of hypertensive patients with established cerebrovascular disease already on pre-existing and
established antihypertensive (non-ACEI) therapy when switched to treatment with captopril underwent an increase in cerebral blood flow (measured using a surface gamma camera following 99-Technetium venous injection) with a BP reduction compared to a control group remaining on pre-existing (non-ACEI) therapy. An increase in CBF following 4 weeks duration of ACEI therapy with Alacepril was also found in stroke patients, commenced more than 3 months after the index event (213). Using a xenon-inhalation technique to measure cerebral blood flow, this study showed equivalent increases in blood flow in both the affected and unaffected hemispheres compared to control subjects. A reduction in MAP was reported by one study in a group of 5 patients (181) treated with clonidine (2 patients) or captopril (3 patients) within 72 hours of ischaemic stroke over a 3 day period. Overall there was an increase in CBF in every patient by day 3, statistically significant for the group, although the analysis for the captopril group alone was not reported. In one placebo-controlled study of 28 ischaemic stroke patients (86), ACEI therapy (4mg Perindopril once-daily) commenced in the subacute stroke phase (2 to 7 days following symptom-onset), led to no change in MCA flow over the course of two weeks of therapy despite an approximate 20mmHg reduction in SBP. Furthermore, a significant BP reduction of 18/11 mmHg had occurred by hour 4 of treatment, but importantly there was no corresponding change in the cerebral blood flow or resistance index (a measure of arterial tone and distensibility) at this time. However, patients in this study had very mild strokes and were perhaps poorly representative. Another study measuring regional CBF response to captopril as soon as one hour following therapy in 12 ischaemic stroke patients recruited within 5 days of stroke-onset (mean time 2 days) also reported no change in CBF using a SPECT method,
although, perhaps as expected, neither was there any significant change in arterial BP by this time (317). In the presence of severe stenotic or occlusive carotid disease, regional and global cerebral blood flow has also been shown to be maintained with ACEI in stroke patients (319), and in elderly subjects without stroke (239). It appears that ACEI therapy may shift the upper and lower limits of the cerebral autoregulatory curve towards lower BP levels as has been shown in studies of the spontaneously hypertensive rat following intravenous injection of captopril (23) and this drug has been shown in-vitro to dilate feline pial cerebral arteries (323). A recent study in patients with a recent history of lacunar stroke (previous 3 to 12 months) found treatment with perindopril for a duration of 14 days increased middle cerebral artery blood flow in response to acetazolamide, indicating an improvement in the capacity of cerebral resistance vessels to vasodilate to this stimulus (probably increased arterial CO$_2$ concentration) (318). Similar findings have been shown after treatment with perindopril for one year in ischaemic stroke patients (118). To date, it must be emphasised that studies evaluating cerebral blood flow and responses to ACE inhibition or ARB therapy involve mild strokes (mostly lacunar) and/or a considerable time interval between qualifying stroke event and patient recruitment and, although changes in cerebral autoregulation are recognised in subjects with mild stroke, drug effect on CBF and dynamics in the presence of more severe and recent stroke is currently unknown.

A postulated mechanism by which the limits of CA are altered by ACEI is through the inhibition of angiotensin II, which has been shown to regulate cerebral blood flow (268). Alternatively, ACEI may reduce cerebral perivascular sympathetic tone thereby leading to
vasodilatation. However, against this hypothesis is that drug effect on CBF autoregulation has been shown to remain present in rats subjected to sympathetic denervation (316). ACEI has been shown to up-regulate vascular endothelial-derived nitric oxide synthase (eNOS) (178). The NO synthase inhibitor L-NMMA has been shown to reduce CBF suggesting a role for NO in maintaining cerebral blood flow (325). There is also some evidence for NO, in particular, being involved in static and dynamic cerebral autoregulatory mechanisms. Inhibition of eNOS activity using the inhibitors nitro-L-arginine and L-NMMA in rats has been shown to raise the lower limit of BP for cerebral autoregulation (135) and attenuate the control of short-term changes in cerebral vascular resistance in response to rapid changes in cerebral perfusion pressure, i.e. dynamic cerebral autoregulation (297). Attenuated dynamic cerebral autoregulatory responses have also been shown in human volunteers following L-NMMA infusion (326). Accumulation of bradykinin following ACEI may also be important to lowering the lower limit of CA, as an inhibitor of bradykinin in a rat model of stroke has been shown to abolish the autoregulatory response to captopril (296). The mechanism by which ACEI alters the CA curve may therefore be via a variety of mechanisms perhaps leading to a reduction in large and medium cerebral artery vascular tone. As CBF remains a near-constant, this dilatation may be accompanied by a compensatory constriction of the smaller cerebral resistance vessels. The dilatatory reserve capacity of the smaller vessels will then be greater as systemic BP decreases. Evidence for small cerebral artery vasoconstriction with ACEI therapy is presented by one clinical study reporting an increase in MCA resistance index with lisinopril (80).
Angiotensin (AT$_1$-subtype) receptor blockers may not have the same effect as ACEI on CBF. In studies of spontaneous hypertensive rats (90), an experimental antagonist did not appear to alter the limits of CA, but a different experimental antagonist was found to have a similar response to ACEI in another study (313). This disparity may be explained due to different angiotensin (AT) - receptor subtypes appearing to have differing effects on the cerebral circulation. AT$_1$ receptors appear to constrict cerebral arterioles, thereby reducing CBF (155), whereas the AT$_2$ receptor has been shown to extend the upper limit of the CA curve and the AT$_4$ receptor has been shown to increase CBF (214). However detailed studies of selective blockade of the AT receptor family in humans are currently lacking, although there might be theoretical benefits to selective AT$_1$ receptor blockade, leaving AT$_2$ receptors unopposed.

There is some evidence that activation of the renin-angiotensin system may contribute to neuronal damage following stroke. Pre-treatment of rats with captopril prior to carotid artery ligation leads to an improved neurological outcome on day 3, decreased brain lactate levels and increased ATP levels compared to placebo (269;322). Similar results have been shown in rats with selective AT$_1$-blockade pre-treatment (113;219). Interestingly, long-term inhibition of AT$_2$ receptors appears to block the beneficial effects of AT$_1$-receptor blockade. Activation of AT$_2$ receptors in brain tissue that has undergone ischaemic injury may initiate neuroregeneration or induce apoptosis in severely damaged neurons (342).
1.3.8.2 Haemodynamic stability and cardiovascular reflexes

The majority of research studies on the cardiac baroreflex following treatment with ACEI report increases in BRS. Increase in cardiac BRS with ACEI treatment is observed in groups where cardiac BRS would ordinarily be impaired at baseline, for example in chronic renal failure (175), diabetic autonomic neuropathy (151), following myocardial infarction (192) and in the elderly (210). Some studies report an ACEI-induced resetting of the cardiac baroreflex following a short treatment period. For example, Yee et al. (337) examined the function of a single-dose of enalapril or losartan on the arterial baroreflex (measured by the heart rate response to a pressor stimulus following intravenous phenylephrine) in healthy young volunteers and found a significant increase in cardiac BRS with both drugs when compared to placebo. This finding is not restricted to younger subjects; in a study of 5 hypertensive elderly subjects, 7 days of enalapril therapy also increased cardiac BRS compared to placebo (210). Resetting of, and increases in, cardiac BRS have also been reported with beta-blockers, calcium channel blockers (CCB) and thiazide diuretics. However, one study directly comparing the effects of a one year duration of therapy with each of these 4 drug classes reported a more rapid increase in baroreceptor sensitivity with ACEI and CCB compared to beta-blocker and thiazide diuretic, although a similar increase in cardiac BRS was achieved with each class by the end of the study period (125). The mechanism by which ACEI improve BRS has not yet been fully elucidated. Recent work has shown improvement in cardiac BRS by ACEI or ARBs may be mediated via blockade of AT₁ receptors in medullary nuclei (89;220). Angiotensin II has been shown to inhibit cardiac parasympathetic activity and support
SNSA in animal models (249;336). ACEI may also increase the compliance of the baroreceptor-containing carotid sinus and aortic arch (307), rendering baroreceptors more sensitive to changes in BP levels and this is discussed in detail later. Perhaps in keeping with effects on the arterial baroreflex, the majority of studies examining changes in sympathovagal balance with ACEI therapy report an enhancement of vagal activity, and a reduction in sympathetic nervous system activity (SNSA) from baseline (10;57;231;241;271), associated with an increase in heart rate variability (151). Veerman et al. (310), in a study of the ACEI, spirapril in hypertensive patients and utilising power spectral analysis to assess SBP variability found a significant reduction in relative power in the mid-frequency band (0.08 - 0.12 Hz) compared to placebo following only a single dose. This decrease was sustained following 8 weeks of treatment. Changes in SBP variability in the low to mid frequency band appear to be mediated by SNSA (237). Furthermore, in this study, there was no change in the high-frequency band of SBP variability suggesting no change in cardiac vagal activity. In rats, activation of the renin-angiotensin system using an isoprenaline infusion has been shown to increase SBP variability in the low-frequency band, and this may be blocked using the AT\(_1\) receptor antagonist, valsartan (35). Abolition of NO activity using L-NMMA in rats has been observed to increase LF SBP oscillations, perhaps via increased vasoconstricting ability of angiotensin II unopposed by the endogenous vasodilator NO. LF SBP fluctuations were returned to normal, however, with the AT\(_1\) receptor antagonist, losartan (112). However, a substudy of the ATLAS Trial (Assessment of Treatment with Lisinopril And Survival in heart failure) showed from 24-hour ambulatory monitoring results that there was an increased variability in SBP with following 4 weeks therapy with a high dose of Lisinopril.
(35mg) compared to a lower dose (5mg) (104). However, at the sampling frequency of every 15 minutes (ie. 0.001 Hz), this may have represented increased power in a very low frequency band influenced by factors other than the autonomic nervous system. With regard diurnal BP variability, ACEI have been shown not to effect an excess fall in nighttime arterial pressure compared to placebo, with long-acting or twice daily formulations having equivalent BP reduction during both day and night (203;236).

1.3.8.3 Arterial stiffness and pulse wave reflection

ACEI, in common with other antihypertensive agents, may reduce arterial stiffness simply via MAP reduction thereby influencing arterial wall modulus. Studies evaluating the direct effects on arterial wall mechanics independent of BP therefore need to control for this factor and, furthermore, it is insufficient to make a linear correction for the effects of BP, as the relationship between BP and arterial wall modulus is non-linear. A number of studies involve head-to-head comparisons of ACEI versus a non-ACEI comparator drug titrated to achieve an equivalent BP reduction to the ACEI, and from these studies, valid observations may be made about non-BP ACEI effects. However, many of these studies are small and many may be underpowered to detect differences between drugs (79;184). Furthermore, they are largely of short duration and long-term effects cannot be inferred because counter-regulatory mechanisms may subsequently develop and negate any long-term effect on arterial stiffness. Additionally, beta-blockers have often been used as the comparator drug perhaps emphasising not so much beneficial effects of ACEI but the
limitations of beta-blockers, particularly with regard central wave reflections and central arterial pressure.

As previously discussed, reductions in aortic augmentation index may occur secondary to changes in heart rate, left ventricular ejection time and the position of peripheral reflecting sites as well as due to changes in arterial PWV and cannot be inferred as directly representative of changes in arterial ‘stiffness’. However, a direct reduction in aortic augmentation index, perhaps separate from the effects on arterial stiffness, may be desirable, leading to a reduction in central PP. It is an attractive concept that isolated systolic hypertension might be best treated with drugs that delay the return of the reflected pulse wave. Intravenous angiotensin II has been shown to increase AIx and decrease Tr in healthy volunteers (331), and its effects on the central pulse wave may be independent of aortic PWV and related to changes in peripheral vascular tone. This was shown by Kelly et al. (144) who demonstrated infusions of nitroglycerine and angiotensin II in human volunteers significantly decreased and increased respectively AIx but did not change aortic PWV. Incidentally, this study also reported a greater increase in brachial PWV than aortic PWV in response to intravenous angiotensin II, suggesting that the influence of the endothelium on arterial stiffness, at least in the short term, is not equivalent for central and peripheral arteries. In patients with essential hypertension, a number of studies of ACEI on AIx report reductions independent of BP following varying lengths of therapy, for example: oral captopril 100mg daily for 4 weeks (187), iv. captopril mean single dose 11mg and Fosinopril 10mg for 8 weeks (300), oral fosinopril 10 to 20mg for 8 weeks (64).
Some studies suggest that ACEI are more efficacious in lowering AIx than some other antihypertensive drugs, in particular beta-blockers (64;79).

Effects of ACEI on the more direct measure of arterial wall stiffness, ie. PWV, has been studied. Reductions in aortic PWV: oral quinapril 20mg single-dose (304), oral captopril 100mg daily for 4 weeks (187), Lisinopril 10 to 30mg for 8 weeks (282) and brachial PWV: iv. enalaprilat single dose (171), Perindopril 2 to 8mg daily for 8 weeks (16) have been reported. Comparison studies of the effectiveness of other drugs are at variance with some reporting comparable effects of CCB, thiazide diuretics, beta-blockers and ACEI on central arterial stiffness (79;276;303), and others reporting an increased efficacy of ACEI over thiazide diuretics (307) and beta-blockers (20;184).

Particular interest has centred on the effectiveness of a low-dose ACEI/thiazide combination on arterial haemodynamics. Compared to atenolol, a combination of perindopril 2mg and indapamide 0.625mg has been shown to decrease SBP and PP in association with a reduction in AIx, in the presence of unchanged aortic PWV (15) in hypertensive patients. However, it is possible that finding may have simply been a reflection of beta-blocker induced HR changes rather than any particular potent effect of the combination of the vasodilator indapamide and ACE on altering peripheral reflecting sites. It is appropriate to reflect at this point on the results of the LIFE study (70) which showed Atenolol to be less effective in reducing cardiovascular endpoints, particularly stroke, than Losartan for similar brachial BP reduction and that a potential underlying mechanism may have been the inability of the beta-blocker to reduce central AIx to a
similar extent as with ARB therapy, although much debate has taken place about the basis for the findings in this particular trial. Additionally, in the PROGRESS study (4) only significant reductions in vascular events were observed in patients receiving both Perindopril and Indapamide rather than Perindopril alone despite a significant BP reduction with Perindopril alone, although this may have been related to differences in BP lowering.

It has been suggested that ACEI may reduce arterial stiffness independently of BP reduction by effects on endothelial function and, in the longer term, via vascular remodelling. Endogenous angiotensin II may alter arterial wall modulus via endothelial effects including by the direct effects of vasoconstriction and promotion of oxidative stress inducing endothelial dysfunction via degradation of nitric oxide by reactive oxygen species (288). Furthermore, sympathetic vascular tone may be increased by central All effects. Blockade of All production either by inhibition of ACE or All receptor blockade has been shown to reduce oxidative stress levels in subjects with essential hypertension (27). A recent parallel group study (101) found in patients with essential hypertension that, with an equivalent BP reduction between drugs, vessel wall oxidative stress was reduced by ARB, ACEI and CCB therapy but only the ACEI (perindopril) increased flow-mediated dilatation in the brachial artery. Differences between the ARB and ACEI suggest that perhaps bradykinin-related mechanisms may be important, highlighting that similar pharmacological effects cannot necessarily be inferred for both ACEI and ARBs. Bradykinins may induce endothelial cyclic GMP promoting NO synthesis and ACEI have
also been shown to directly induce the expression of eNOS (178). ACEI has been shown to prevent the age-associated decline in endothelium-derived hyperpolarizing factor (111).

Longer-term remodelling of arterial structure has been shown with ACEI. In one study, carotid artery compliance was increased and radial artery wall hypertrophy decreased by an ACEI-based BP-lowering regime over a 9 month treatment period (106). Other studies have shown similar changes following long-term ACEI treatment in the carotid artery but it is possible that regression of hypertension-related structural changes in the conduit arteries could be related to BP reduction rather than the drug (289).

The influence of genetic factors in the vascular response to ACEI may also be important. For example in one study (28), perindopril was more efficacious at improving arterial stiffness compared to nitrendipine in patients carrying the C allele of the A1166C polymorphism of the AT₁ receptor, whereas in the patients homozygous for the M allele the reverse was true.

1.3.8.4 BP reduction and time-course with oral Lisinopril

Lisinopril is an orally active, non-sulphhydryl angiotensin-converting enzyme inhibitor that is not metabolized or bound to protein giving peak serum concentrations occurring 6 to 8 hours after oral dosing (109). A single dose of oral Lisinopril, in untreated patients with mild to moderate essential hypertension, has been shown in a study of 83 patients to produce a peak SBP reduction by hour 4.5 to 5, and a peak DBP reduction by hour 4, with
no associated changes in heart rate (65). The time to peak SBP reduction by hour 4.5 to 5 was similar for a wide range of doses from 2.5mg to 80mg although, unsurprisingly, the degree of BP reduction by hour 4 was dose-dependent, as was the mean BP reduction over 24 hours. The peak SBP reduction with the first dose of 2.5mg in this study was 16/13 mmHg, and for 10mg, 27/21 mmHg, although no instances of symptomatic first-dose hypotension were recorded at any dose, neither was there any asymptomatic abrupt drop in BP at other times. A similar pharmacodynamic profile for oral Lisinopril has been reported by other studies (134;198). One study found that, at a low dose of Lisinopril (≤ 10mg) the first-dose antihypertensive effect was only significant for the first 12 hours (283). However, other studies have found that the hypotensive effect of sustained daily dosing of Lisinopril over 5 to 8 days is present at 24 hours post-dose for doses between 2.5mg and 10mg (65;82;283). Hence, an oral dose of 5mg Lisinopril may result in a prompt BP reduction following stroke within the first few hours and may result in sustained BP reduction over the subsequent 24-hour period.
Summary box

- BP reduction in the acute phase of stroke is not currently recommended due to the lack of available trial evidence showing benefit.

- To date, small trials of BP reduction in the acute stroke phase have shown no benefit on outcome, or no change in BP levels.

- ACEI or ARB therapy shows promise as treatment for hypertension in the acute stroke phase as cerebral blood flow appears to be maintained despite concomitant BP reduction, and there might be other beneficial effects on systemic and cerebral vascular function.

- Oral Lisinopril 5mg may suitable for use as treatment for hypertension during the acute stroke phase as in trials of hypertensive patients without cerebrovascular disease show BP reduction to be achieved within the first few hours and maintained over the subsequent 24-hour period.
PHASE I

2. CENTRAL ARTERIAL STIFFNESS FOLLOWING ACUTE ISCHAEMIC STROKE AND RELATIONSHIP WITH STROKE AETIOLOGY
2.1 Background and aims

Investigation of arterial wall properties in stroke patients is currently limited to analysis of the central elastic arteries (aorta and carotid) with studies reporting increased wall stiffness in patients with established cerebrovascular disease and in the acute phase of stroke in comparison to control subjects (166). This difference remains following correction for stroke risk factors including age and BP level (83;292). In one prospective follow-up study of hypertensive individuals (163), increased aortic PWV was found to be associated with an increased risk of subsequent death from stroke from any cause (presumably ischaemic and haemorrhagic stroke, although the predictive power for each subtype is not reported). However, a number of questions regarding arterial stiffness and stroke remain unresolved.

Ischaemic stroke is a heterogeneous disorder. Small or large vessels may be affected, with local thrombosis or thromboembolism from artery to artery or cardiac embolism. Arterial stiffness may therefore not be associated with all aetiological subtypes of ischaemic stroke. Major risk factors for lacunar and atherothrombotic stroke, for example: hypertension, ageing and diabetes, are associated with central elastic arterial stiffening (165;202;332) but major risk factors for cardioembolic stroke, for example: atrial fibrillation, valvular heart disease and left ventricular dysfunction, may have a much weaker association with arterial stiffness.
To date, it is unknown which measures of arterial stiffness, other than aortic PWV, might prove to be risk factors for stroke. For example, no data are yet available on the properties of the arterial pulse wave or medium-sized (muscular) arterial function in stroke patients. Radial pulse wave analysis is a particularly attractive technique as it is quick to perform, requires only a single arterial site to be studied and is less intrusive than other arterial stiffness measurements.

Cardiovascular risk factors for stroke of large artery or lacunar origin, for example, ageing and diabetes, appear to be associated with preferential stiffening of central over peripheral arteries (146, 202). It might be expected therefore that there is a greater increase in central arterial over peripheral arterial stiffness in stroke patients compared to control subjects, and that peripheral arterial stiffness has a weaker relationship with stroke risk. However, arterial stiffness might be increased as a consequence of the recognised neurohumoral effects of stroke and this might be particularly true for peripheral vessels such as the brachial artery, due to its greater smooth muscle component. For example, serum levels of the potent vasoconstrictor endothelin-1 are found to be increased in the acute stroke phase (343) and this peptide has been shown to increase PWV in humans and animals (194, 314). The sympathetic nervous system has been shown to to be increased in activity following acute stroke (22) and to regulate arterial distensibility in the human radial and femoral artery (93). If these peri-stroke mechanisms are important determinants of increased arterial stiffness in the acute stroke phase, this might explain some of the observations of previous studies.
In this study, central (elastic) and peripheral (muscular) arterial stiffness and the central arterial waveform are evaluated using a non-invasive technique in patients with acute ischaemic stroke and in a group of control subjects matched as closely as possible to the stroke group for cardiovascular risk factors.

The study hypotheses are:

a) patients with stroke of ‘arterial’ origin have increased large arterial stiffness when compared to matched control subjects.

b) patients with stroke of ‘cardiac’ origin do not have increased arterial stiffness compared to matched control subjects.

c) peripheral arterial stiffness and peripheral pulse wave analysis (indices of arterial stiffness) will distinguish stroke patients from control subjects.

2.2 Methods

2.2.1 Subjects

Stroke patients admitted to the acute stroke units of University Hospitals Leicester NHS Trust and with neuroradiologically-confirmed acute ischaemic stroke were studied within 72 hours following the onset of symptoms. Patients with a requirement to continue antihypertensive therapy or medication with effects on cardiovascular or autonomic function were excluded, otherwise all such medication was discontinued immediately.
following admission to hospital. Unconscious patients or those with neurological signs lasting <24 hours were excluded, as were those patients with a concomitant acute coronary syndrome. Aetiological stroke subtype was determined retrospectively from the case notes taking account of findings on clinical history, clinical examination, cardiovascular and neuroradiological investigation results using a computer-based modified TOAST (Trial of Org – 10172) algorithm (108), thereby classifying patients into large artery (atherothrombotic), small artery (lacunar), cardioembolic, other (e.g. vasculitis) or unclassified ischaemic stroke.

Control subjects with no history of previous stroke or TIA, with no evidence of cerebrovascular disease on neurological examination, but possessing cardiovascular risk factors were recruited from the hypertension and the surgical pre-assessment outpatient clinics. Where control subjects were taking medication known to affect the cardiovascular system, this was omitted on the day of the recording. Stroke patients and control subjects with renal failure (creatinine > 200 umol/L), severe aortic stenosis (peak gradient >50mmHg), pre-evident carotid stenosis > 70% or cardiac arrhythmia (e.g. atrial fibrillation) were excluded.

2.2.2 Protocol

Subjects were studied in the supine position in a cardiovascular research laboratory or at the bedside with external stimuli (background noise and lighting) minimized and at least 2
hours following a light meal, having abstained from all caffeinated products, smoking and alcohol for at least 4 hours prior. All subjects were asked to micturate before the study.

Casual oscillometric brachial BP was measured at least three times in quick succession using a monitor validated according to British Hypertension Society criteria (A&D UA-767, A&D Company Limited, Tokyo, Japan) (262), in the non-hemiparetic limb. The mean of the latter two recordings (where difference in BP was \( \leq 10 \) mmHg for SBP and DBP) was used in the analysis, and in the calibration of subsequent arterial tonometric recordings. MAP was calculated as DBP plus one third of PP.

2.2.2.1 Pulse wave velocity and pulse wave analysis

Applanation tonometry of the carotid, femoral and radial arteries was conducted using a high-fidelity micromanometer (SPT-301B; Millar Instruments, Texas, USA) coupled to the Sphygmocor™ system (Sphygmocor; PWV Medical, Sydney, Australia) to estimate carotid to femoral pulse wave velocity (PWVcf), carotid to radial pulse wave velocity (PWVcr) and arterial waveform characteristics (AIx and Tr) at the radial and carotid arteries (see Section 1.2.4). Arterial PP contours and 3-lead surface ECG were recorded synchronously. Pulse transit length was estimated by subtracting the sternal notch to carotid applanation point distance from the sternal notch to femoral and radial applanation point distance and a foot-to-foot methodology was employed to determine pressure contour transit time in relation to the ECG R-wave. Pulse wave data were obtained for the ascending aorta via radial artery applanation (in the non-hemiparetic limb) and the use of a
generalised transfer function incorporated in the Sphygmocor software (version 5.01). The carotid artery was also planated directly and the AIx was measured, without use of a transformation function. The aortic AIx was also derived using the proprietary transformation function with carotid data. All AIx values were corrected for heart rate using an algorithm based on previous studies (0.6% increase per 1 beat-per-minute decrease in heart rate) (225). PWV recordings with >5% standard deviation of the mean time between R-wave and pulse foot for the waveform sequence and pulse wave analysis recordings with >10% variation in pulse height or diastolic variability were rejected automatically by the software and the measurement repeated. Waveforms of sufficient quality to be used for pulse wave analysis could not be obtained for a small number of patients and controls (see Table 2). Qualifying recordings were performed in triplicate and mean values taken for subsequent data analysis.

2.2.3 Statistical methods

Data were analysed using SAS version 8.0 and SPSS version 11.5 and employing the Mann-Whitney U test for continuous data and the Chi squared test for categorical data. The relationship of arterial stiffness with multiple variables was explored using a multiple linear regression model with logarithmic transformation on the response variable (arterial stiffness) to establish the fit for inherent non-linearity. Statistical significance was taken at the 5% level.
2.3 Results

Twenty-nine ischaemic stroke patients (22 male; mean age, 68 ± 9 years) and twenty-nine control subjects (17 male; mean age, 65 ± 10 years) were included. Stroke patients were studied at a median time of 24 hours following the onset of stroke-symptoms (interquartile range 19 to 34, range 10 to 72 hours).

2.3.1 Arterial stiffness following ischaemic stroke

The demographics of the subjects are shown in table 2.1. PWVcf, PWVcr and pulse wave analysis results are presented in table 2.2. Figures 2.1 and 2.2 show the distribution of PWV values and radially-derived pulse wave analysis data between the groups. PWVcf, but not PWVcr, was significantly increased in the ischaemic stroke patients (p<0.05). There was no significant difference in any value of central Tr or Alx, from either aorta or carotid artery, whether measured directly or indirectly, or whether the result was corrected for heart rate.
Table 2.1. Demographics of ischaemic stroke patients and control subjects.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ischaemic Stroke, n=29</th>
<th>Control, n=29</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>68.2 ± 8.6</td>
<td>64.8 ± 9.7</td>
<td>NS</td>
</tr>
<tr>
<td>Gender</td>
<td>22M : 7F</td>
<td>17M : 12F</td>
<td>NS*</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>165.7 ± 8.6</td>
<td>163.8 ± 10.5</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>79.5 ± 14.9</td>
<td>76.7 ± 14.6</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiovascular variables (mmHg):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>154.3 ± 22.1</td>
<td>142.1 ± 18.1</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>MAP</td>
<td>106.3 ± 15.8</td>
<td>100.9 ± 11.9</td>
<td>NS</td>
</tr>
<tr>
<td>DBP</td>
<td>82.3 ± 14.9</td>
<td>80.3 ± 10.6</td>
<td>NS</td>
</tr>
<tr>
<td>PP</td>
<td>72.0 ± 16.8</td>
<td>61.7 ± 14.0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>71.6 ± 12.0</td>
<td>64.6 ± 10.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Past Medical History*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current BP lowering therapy</td>
<td>18 (62)</td>
<td>16 (55)</td>
<td>NS*</td>
</tr>
<tr>
<td>Lipid-lowering therapy</td>
<td>6 (21)</td>
<td>5 (17)</td>
<td>NS*</td>
</tr>
<tr>
<td>Hypertension</td>
<td>21 (72)</td>
<td>15 (52)</td>
<td>NS*</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>7 (24)</td>
<td>2 (7)</td>
<td>NS*</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>6 (21)</td>
<td>4 (14)</td>
<td>NS*</td>
</tr>
<tr>
<td>Previous stroke or TIA</td>
<td>8 (28)</td>
<td>0 (0)</td>
<td>†*</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>2 (7)</td>
<td>2 (7)</td>
<td>NS*</td>
</tr>
<tr>
<td>Smoker in last 5 years</td>
<td>10 (35)</td>
<td>4 (14)</td>
<td>NS*</td>
</tr>
</tbody>
</table>

Data presented as mean ± standard deviation and absolute number (percentage).
* \( \chi^2 \) test used for differences († insufficient data for test).
Table 2.2. Pulse wave velocity and aortic and carotid waveform data.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ischaemic Stroke</th>
<th>Control</th>
<th>Mann-Whitney U test (P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pulse wave velocity</strong></td>
<td>n=29</td>
<td>n=29</td>
<td></td>
</tr>
<tr>
<td>PWV – carotid to femoral (m/s)</td>
<td>11.4 ±3.0</td>
<td>9.6 ±1.7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>PWV – carotid to radial (m/s)</td>
<td>9.0 ±1.3</td>
<td>8.6 ±1.5</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Radially-derived aortic indices of wave reflection</strong></td>
<td>n=28</td>
<td>n=28</td>
<td></td>
</tr>
<tr>
<td>AIx (%)</td>
<td>23 ±9</td>
<td>27 ±10</td>
<td>NS</td>
</tr>
<tr>
<td>AIx – HR corrected (%)</td>
<td>23 ±9</td>
<td>25 ±9</td>
<td>NS</td>
</tr>
<tr>
<td>Tr (ms)</td>
<td>137 ±12</td>
<td>141 ±11</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Carotid-derived indices of wave reflection (%)</strong></td>
<td>n=27</td>
<td>n=26</td>
<td></td>
</tr>
<tr>
<td>Carotid AIx</td>
<td>122 ±24</td>
<td>135 ±28</td>
<td>NS</td>
</tr>
<tr>
<td>Carotid AIx – HR corrected</td>
<td>119 ±23</td>
<td>126 ±24</td>
<td>NS</td>
</tr>
<tr>
<td>Aortic AIx</td>
<td>30 ±12</td>
<td>36 ±13</td>
<td>NS</td>
</tr>
<tr>
<td>Aortic AIx – HR corrected</td>
<td>29 ±11</td>
<td>33 ±12</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data presented as mean ± standard deviation.
*No waveform data for one stroke and one control subject
†No waveform data for two stroke and three control subjects
Figure 2.1. Box and whisker plots of PWV distribution between ischaemic stroke patients and control subjects.

- Outlier value (1.5 - 3 times interquartile range)
- † - $P<0.05$ compared to control (Mann-Whitney U test)
Figure 2.2. Box and whisker plots of aortic pulse wave data derived from the radial artery between ischaemic stroke patients and control subjects.

Aortic Alx

\[ P = \text{NS, Mann-Whitney U test} \]

Aortic Tr

\[ P = \text{NS, Mann-Whitney U test} \]

o - outlier value (1.5 - 3 times interquartile range)
2.3.2 Effect of ischaemic stroke subtype

Stroke subtype classification identified 7 (24%) lacunar, 7 (24%) cardioembolic, 2 (7%) atherothrombotic, 0 (0%) other and 13 (45%) unclassified ischaemic strokes. Analysis of arterial stiffness values across the stroke subtypes is presented in tables 2.3 and 2.4, and figure 2.3. Furthermore the data are examined according to cardioembolic and non-cardioembolic (all other strokes) subgroups. The cardioembolic strokes had similar central and peripheral PWV values to the control subjects and there were no significant differences in any other measured baseline variables, e.g. age and MAP that might have accounted for this observation (Table 2.3). Significantly elevated PWVcf values were found in the non-cardioembolic stroke group in comparison with control subjects but there were also significant differences in SBP and PP (Table 2.4).

Acknowledging that cardioembolic strokes had similar baseline cardiovascular risk data to the control subjects, the multiple regression model analysis was conducted with and without these patients. The results of the non-linear regression models, including the effects of stroke, age, MAP level, heart rate, body mass index and all other cardiovascular risk factors including diabetes on PWVcf are presented in table 2.5. For all strokes combined, stroke status was found not to be a significant independent predictive variable of PWVcf but when cardioembolic strokes were excluded, stroke status was significantly independently related to PWVcf ($P=0.05$). Age, MAP level and diabetes were also independent predictors of the PWVcf value (Table 2.5). No significant relationship was found between stroke and PWVcr, Tr or AIx in separate regression analyses.
Figure 2.3. Box and whisker plots of arterial stiffness in control subjects and patients according to ischaemic stroke subtype

- Pulse wave velocity (carotid-femoral)
- Pulse wave velocity (carotid-radial)

- ○ - outlier value (1.5 – 3 times IQR), * - outlier value (>3 times IQR)
- † - P<0.05 compared to control group (Mann-Whitney U test)

N = 29 29 7 7 7 7 2 2 13 13
Table 2.3. Baseline demographic and cardiovascular data between control and cardioembolic ischaemic stroke subjects.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Cardioembolic stroke subtype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>29</td>
<td>7</td>
</tr>
<tr>
<td>Age (years)</td>
<td>65 ± 10</td>
<td>66 ± 8</td>
</tr>
<tr>
<td>SBP</td>
<td>142 ± 18</td>
<td>143 ± 24</td>
</tr>
<tr>
<td>MAP</td>
<td>101 ± 12</td>
<td>101 ± 20</td>
</tr>
<tr>
<td>DBP</td>
<td>80 ± 11</td>
<td>80 ± 22</td>
</tr>
<tr>
<td>PP</td>
<td>62 ± 14</td>
<td>64 ± 20</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>65 ± 10</td>
<td>71 ± 10</td>
</tr>
<tr>
<td>Past history: diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>diabetes</td>
<td>2 (7%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>hypertension</td>
<td>15 (52%)</td>
<td>4 (57%)</td>
</tr>
<tr>
<td>ischaemic heart disease</td>
<td>4 (14%)</td>
<td>2 (29%)</td>
</tr>
<tr>
<td>smoker</td>
<td>4 (14%)</td>
<td>2 (29%)</td>
</tr>
<tr>
<td>Previous antihypertensive therapy</td>
<td>16 (55%)</td>
<td>5 (71%)</td>
</tr>
<tr>
<td>PWV – carotid to femoral (m/s)</td>
<td>9.6 ± 1.7</td>
<td>9.5 ± 2.4</td>
</tr>
<tr>
<td>PWV – carotid to radial (m/s)</td>
<td>8.6 ± 1.5</td>
<td>8.5 ± 1.8</td>
</tr>
<tr>
<td>Radially derived - Alx (%) – HR corrected</td>
<td>25 ± 9</td>
<td>23 ± 9</td>
</tr>
<tr>
<td>Tr (ms)</td>
<td>141 ± 11</td>
<td>138 ± 14</td>
</tr>
<tr>
<td>Stroke severity (NIHSS)</td>
<td>-</td>
<td>12 ± 5</td>
</tr>
</tbody>
</table>
Table 2.4. Baseline demographic and cardiovascular data between control and non-cardioembolic ischaemic stroke subjects.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Ischaemic stroke subtype</th>
<th>Non-cardioembolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>29</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>65 ± 10</td>
<td>69 ± 9</td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>142 ± 18</td>
<td>158 ± 21 *</td>
<td></td>
</tr>
<tr>
<td>MAP</td>
<td>101 ± 12</td>
<td>108 ± 14</td>
<td></td>
</tr>
<tr>
<td>DBP</td>
<td>80 ± 11</td>
<td>83 ± 13</td>
<td></td>
</tr>
<tr>
<td>PP</td>
<td>62 ± 14</td>
<td>75 ± 15 *</td>
<td></td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>65 ± 10</td>
<td>72 ± 13</td>
<td></td>
</tr>
<tr>
<td>PWV – carotid to femoral (m/s)</td>
<td>9.6 ± 1.7</td>
<td>12.0 ± 2.9 *</td>
<td></td>
</tr>
<tr>
<td>PWV – carotid to radial (m/s)</td>
<td>8.6 ± 1.5</td>
<td>9.2 ± 1.1</td>
<td></td>
</tr>
<tr>
<td>Radially derived - Alx (%) – HR corrected</td>
<td>25 ± 9</td>
<td>23 ± 9</td>
<td></td>
</tr>
<tr>
<td>Tr (ms)</td>
<td>141 ± 11</td>
<td>136 ± 12</td>
<td></td>
</tr>
</tbody>
</table>

*P<0.05 compared to control subjects
Table 2.5. Multiple regression analysis for PWVcf (logarithmic transformation) for a) entire data set and b) excluding cardioembolic strokes.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate</th>
<th>P  value</th>
<th>Variable</th>
<th>Estimate</th>
<th>P  value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PWVcf</td>
<td></td>
<td></td>
<td>PWVcf</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>0.04</td>
<td>NS</td>
<td>Ischaemic stroke</td>
<td>0.07</td>
<td>0.05</td>
</tr>
<tr>
<td>MAP</td>
<td>0.01</td>
<td>&lt;0.01</td>
<td>MAP</td>
<td>0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age</td>
<td>0.02</td>
<td>&lt;0.01</td>
<td>Age</td>
<td>0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.18</td>
<td>&lt;0.01</td>
<td>Diabetes</td>
<td>0.15</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Adjusted R²</td>
<td>0.68</td>
<td></td>
<td>Adjusted R²</td>
<td>0.73</td>
<td></td>
</tr>
</tbody>
</table>

Data included in model: ischaemic stroke (Y/N), age, MAP, heart rate, gender, stroke severity, past history of diabetes, coronary artery disease, stroke, hypertension, peripheral vascular disease, height, weight.
2.4 Discussion

2.4.1 Arterial stiffness following ischaemic stroke

This study confirms the findings of previous investigations showing central arterial stiffness to be increased in acute ischaemic stroke patients (166;292). In keeping with the findings of other studies (163) the results suggest central arterial stiffness is a risk factor for ischaemic stroke, as it appears independent of the effects of other cardiovascular variables in the acute stroke period. Central arterial stiffness might be further along the mechanistic pathway for stroke of arterial origin, via a number of potential mechanisms and these are discussed extensively in section 1.2.6, but briefly, central arterial stiffness gives rise to an increase in PP which has been shown to be associated with increased carotid intima-media thickness and is correlated with the extent of carotid plaque ulceration (183). Increased brachial PP has also been found to be associated with cerebral white matter lesions, associated with small vessel ischaemia (173).

Central elastic arteries appear to be preferentially affected by stiffening processes in relation to cardiovascular risk factors more than peripheral muscular arteries (41) (146) and this is shown for the first time in stroke patients. Furthermore, the data suggest that any acute humoral or autonomic effect is unlikely to lead to changes in arterial stiffness in the acute stroke phase, as patients with stroke of cardioembolic origin of moderate neurological severity appear to have similar values of aortic stiffness to stroke-free control subjects. This may not be surprising in the light of recent studies that show stiffness of the human aorta to be relatively unresponsive to acute manipulation of endothelial function.
(for example, inhibition of nitric oxide) (290). However, that there is no change either in peripheral arterial stiffness or pulse wave analysis suggests there is no increase in arterial stiffness in association with acute stroke per se, although the dataset is small and neither sympathetic tone nor circulating vasoconstrictor levels were measured in the study. Previous investigators have stated that an assessment of central arterial stiffness might add additional prognostic information to conventional cardiovascular risk assessment (161). If this is confirmed, a more widely available and portable method requiring less training and expertise such as the one employed in this study may be preferable.

It was expected that pulse wave analysis might provide useful discriminatory variables between acute stroke and control subjects. Tr has been previously used as a surrogate marker of central arterial stiffness (331), being influenced less by heart rate than AIX. However, despite differences in this value between stroke and control subjects, the absolute difference remained small and did not achieve statistical significance, thus the sensitivity of this measurement may not be as good as that for PWVcf. AIX, however measured, did not appear to be a useful variable discriminating between stroke and control subjects. Despite radial-derived central AIX theoretically being a marker of systemic arterial stiffness, the number of published studies relating AIX to outcome is currently limited to studies of the carotid waveform in high risk groups (222). Perhaps wider application is limited because AIX is highly dependent upon the heart rate and location and efficiency of reflecting sites, and that radial tonometric measurements of central augmentation index may not be accurate. Errors in calculating the aortic AIX from the radial artery are likely to arise as it depends on the 1st harmonic of the spectral
components of the radial waveform that have been shown to be highly variable between recordings (200). Carotid AIx measures may be a better approximation of aortic AIx but no difference was found between the groups in this study. Because of the influence of many cardiovascular variables on AIx, not least the heart rate, the presence of acute stroke with an associated tachycardia (which reduces AIx) may have masked any true differences in this variable between the groups. It remains to be found if, in a prospective cohort study, AIx or Tr confer any predictive value for stroke. However, a recent study highlights the poor predictive value of aortic AIx finding that, in diabetic patients, there is an increase in aortic PWV but no change in AIx in comparison to control subjects (157).

### 2.4.2 Effects of ischaemic stroke subtype

Central arterial stiffness is increased in ischaemic strokes of arterial or unknown origin but this does not appear, from the data presented, to be true for stroke of cardioembolic origin. Risk factors for stroke may have different relationships with the ischaemic stroke subtypes. For example, hospital-based studies have found lacunar (small-vessel) stroke to be particularly associated with a history of hypertension and diabetes (339), and these risk factors have also been found to be important for atherothrombotic (large vessel) stroke together with male sex, smoking and hypercholesterolaemia (324). A family history of vascular disease (stroke or myocardial infarction) appears to be important for all stroke subtypes, but appears less so for cardioembolic stroke, where age is a predominant risk factor (279). A recent meta-analysis of population-based studies evaluating risk factors for the different ischaemic stroke subtypes (280) found only a weak relationship for lacunar
stroke with hypertension, to have no link with diabetes and to be more common in females. This study also found cardioembolic stroke was associated with lower SBP levels and lower cholesterol levels, than the other stroke subtypes and there was no relationship with diabetes. A history of smoking was found to be as likely for both small and large vessel ischaemic stroke, but was less common in cardioembolic stroke. It might be expected therefore that cardioembolic stroke, in comparison to the other ischaemic subtypes, might be associated with lower levels of arterial stiffness. Furthermore, a history of cardiac arrhythmia (e.g., atrial fibrillation), left ventricular dysfunction or valvular heart disease is not recorded in these studies and may be predominant in the stroke aetiology of these patients.

2.4.3 Study limitations

There are a number of acknowledged limitations to this study. It is acknowledged that the study population was relatively small and the results require confirmation in a larger study. Although there were baseline differences in some of the cardiovascular risk factors between stroke and control groups (i.e., age and MAP level) these were corrected for in the statistical analysis, but the possibility of these differences having relevance to the study findings cannot be absolutely discounted. It is possible that inadequate recording of stroke risk factors may have influenced the results. For example, a more accurate assessment of the degree of recent glycaemic control, duration of diabetes or pre-existing hypertension or LDL-cholesterol levels may have lead to displacement of arterial stiffness from the regression model. The degree of aortic atherosclerotic plaque was not assessed in the
subjects and it is possible that atherosclerotic burden could simply account for the changes in PWV in relation to stroke. However, one study reporting increased aortic wall stiffness in ischaemic stroke used an M-mode Doppler ultrasound technique and was able to exclude the confounding effects of atheroma (292).

Labelling of patients as non-cardioembolic according to stroke aetiological subtype and assuming them to have been of arterial origin might have been flawed as it cannot automatically be assumed the stroke in these patients was necessarily of arterial origin, although it is reasonable to assume that the majority were. There were an unusually small number of patients where large artery atherosclerosis could be attributed as the cause of the stroke using the TOAST criteria (although 52% of study patients had carotid duplex performed after the event). Insufficient data were available to accurately classify every patient. However the proportion of the patients (45%) remaining unclassified according to TOAST criteria was similar to much larger population-based studies using retrospective TOAST classification finding approximately 40% of ischaemic stroke aetiology to remain unclassified (150; 242). It is highly likely that some patients with cardioembolism as the source of their stroke were included in the ‘non-cardioembolic’ group. In a Western population coronary artery disease is common and is associated with arterial stiffness (195), and may be the underlying cause of a number of cardioembolic strokes through the promotion of arrhythmia and left ventricular dysfunction due to ischaemic cardiomyopathy. Despite the arguments above, it might therefore be surprising that arterial stiffness was not apparently increased in the cardioembolic stroke group. Although there may be differences in cardiovascular risk prevalence between large and small artery
infarcts, where for large artery infarcts male sex, smoking and diabetes is more common
(280), this study was underpowered to evaluate differences in arterial stiffness level
between these two subtypes and further investigation is required evaluating arterial
function in more accurately-defined aetiological subgroups but such a study would need to
be much larger than the current work.

Patients with persistent atrial fibrillation and an acute stroke (where cardioembolism is
very likely as aetiology and comprising approximately 15% of strokes) were unable to
participate in the study because arterial stiffness measurements required the presence of
sinus rhythm, and therefore this common subgroup was excluded. It cannot be discounted
that arterial stiffness would have been increased in this group. Lastly, no data is presented
on haemorrhagic stroke.

2.5 Summary

This study supports the hypothesis that central arterial stiffness is an independent risk
factor for stroke, together with age, MAP and diabetes, finding an increase in central
arterial stiffness as measured by aortic PWV in stroke patients following correction for
other cardiovascular risk factors. No difference is found in other measures of arterial
function (muscular artery PWV, central Alx or Tr) between stroke and control subjects.
Evidence is presented showing increased arterial stiffness may not be a risk factor for all
stroke subtypes, in particular, not cardioembolic stroke.
2.6 Conclusions

- Central but not peripheral arterial stiffness is increased in acute ischaemic stroke of non-cardioembolic origin compared to control patients without cerebrovascular disease.

- This relationship is independent of other confounding variables including blood pressure.

- Measures of pulse wave analysis (Alx and Tr) do not appear to distinguish stroke patients from matched-control subjects.
3. THE RELATIONSHIP BETWEEN CARDIAC BARORECEPTOR SENSITIVITY AND CENTRAL ARTERIAL STIFFNESS FOLLOWING ACUTE ISCHAEMIC STROKE
### 3.1 Background and aims

An increase in MAP and DBP beat to beat variability, as assessed by the standard deviation of a 10-minute continuous non-invasive arterial BP recording within 72 hours of stroke symptom-onset, is associated with an increased risk of death or disability at 30 days (77). It is likely that increases in BP variability are, at least partly, a consequence of the attenuated cardiac baroreceptor sensitivity (BRS) observed immediately following ischaemic stroke (259), leading to impaired homeostasis of BP levels. Impairment of spontaneous cardiac BRS, assessed by power spectral analysis of 10 minutes continuous BP and pulse interval (PI) data within 72 hours of stroke, has been shown to be predictive of cardiovascular death during long-term follow-up, independently of age, BP level, stroke severity or stroke subtype.

The aetiology of impaired cardiac BRS following stroke has been the subject of speculation (229), as it is unknown whether it arises as a direct result of the acute neurological disturbance, or is due to other cardiovascular factors. Impairment in cardiac BRS appears to be dependent upon stroke lesion location (341), and sympathetic predominance has been shown following right compared to left-sided hemispheric stroke (259). However, studies in hypertensive subjects, the elderly and in subjects with coronary artery disease (groups with an elevated risk of stroke) have demonstrated associations between decreased cardiac BRS and reduced carotid sinus and aortic arch distensibility (38;147;206;302). Increased large artery stiffness in hypertensive subjects, as well as those with diabetes and renal disease, is an independent predictor of cardiovascular risk (33;34;68) and has recently been identified as an independent risk factor for fatal stroke (163). Observational studies
have reported higher degrees of aortic stiffness in stroke patients, in comparison to control subjects matched for age, BP level and cardiovascular risk profile (166;292).

The aim of this analysis was to determine the relationship between cardiac BRS and the degree of large artery (aortic) stiffness in patients during the acute ischaemic stroke phase and in comparison to a group of control subjects free of history of stroke or TIA but matched as closely as possible to the stroke group for other stroke risk factors, and to evaluate the effects of stroke per se on cardiac BRS levels when considering other cardiovascular variables such as arterial stiffness. The study hypothesis was that cardiac BRS and aortic PWV would be negatively correlated in stroke patients.

3.2 Methods

3.2.1 Subjects

31 patients admitted to the acute stroke units of University Hospitals Leicester NHS Trust and with neuroradiologically-confirmed ischaemic stroke were studied within 48 hours of stroke symptom-onset (if the patient first noticed stroke symptoms on waking, the time of stroke onset was taken as the time of onset of sleep) and at 14 ± 2 days post-stroke, as participants of the COSSACS (Continue Or Stop post-Stroke Antihypertensives Collaborative Study) or CHIPS (Control of Hypertension Immediately Post Stroke pilot) studies. Patients were either randomised to continue or stop pre-existing antihypertensive therapy (COSSACS) or oral Lisinopril 5mg daily or placebo (CHIPS pilot) immediately following the first study measurements until day 14 post-stroke. Active therapy was received by 7 COSSACS and 6 CHIPS patients. 26
control subjects were recruited from the hypertension and pre-surgery assessment out-patient clinics and studied on a single occasion. Control subjects were matched as closely as possible to the stroke group for ischaemic stroke risk factors but had no history of previous stroke or transient ischaemic attack and no signs of cerebrovascular disease on neurological examination.

3.2.2 Protocol

Stroke type according to the Oxfordshire Community Stroke Project (OCSP) classification and stroke severity according to the National Institutes of Health Stroke Scale (NIHSS) were recorded. Apart from study medication, all drugs with effects on cardiovascular or autonomic function were discontinued immediately following admission to hospital. Control subjects were asked to omit any antihypertensive medication at least 24 hours prior to the study. Unconscious patients or those with neurological signs lasting <24 hours were excluded, as were those with a concomitant acute coronary syndrome, cardiac failure or cardiac arrhythmia.

Subjects were studied at the bedside or in a dedicated cardiovascular research laboratory in the supine position with external stimuli (background noise and lighting) minimized and at least 2 hours following a light meal, having abstained from all caffeinated products, smoking and alcohol for at least 4 hours prior. All subjects were asked to micturate before the study.
Casual oscillometric brachial BP in the non-hemiparetic limb was measured at least three times in quick succession as previously described in Chapter 2. Aortic PWV was performed as described previously in Chapter 2 and Chapter 1.2.4.

### 3.2.2.1 Cardiac BRS

A 10-minute continuous recording of pulse interval (PI) from 3-lead surface ECG and finger arterial BP using a Finapres™ device (Finapres 2300, Ohmeda, USA) was conducted. The Finapres beat-to-beat BP monitor (figure 3.1) is a photoplethysmographic device involving an inflatable cuff fully wrapped around the middle phalanx of a finger, usually the middle finger. On initialisation of the device, the finger artery is fully unloaded, and then loaded to arterial occlusion with stepwise increasing pressure automatically applied to the cuff. An infrared signal is transmitted through the finger pulp from one side of the cuff to the other. The changes in infrared transmission are correlated to cuff pressure using this initial calibration technique (Physiocal). The finger arterial BP waveform is derived by the degree of inflation of the cuff required to keep the infrared signal constant, ie. to keep finger volume constant. This method of measuring finger arterial BP was first described as the volume clamp method in 1973 by Penaz (240). The system has a fast acting servo allowing rapid changes in finger volume, ie. those occurring with each cardiac cycle, to be tracked. Non-invasive measurements obtained using this device have been shown to correlate well with intra-arterial measurements in a wide group of subjects, including the elderly (264;284), and in particular in monitoring beat-to-beat changes in BP (291). BPV and cardiac BRS calculated from concurrent Finapres and intra-arterial
measurements give very similar results (233) but with a tendency to overestimate SBP variability (228).

Allowing a minimum of 5 minutes of recalibration to occur, such that Physiocal did not initiate until at least every 60 cardiac cycles, recalibration was disabled and a continuous recording of finger arterial BP made for 10 minutes. The arterial pressure waveform together with the analogue ECG signal were converted to a digital signal using a dedicated PC fitted with an analogue to digital converter board at 500 Hz and saved as a file for off-line analysis. This was performed using software specially written for the department by Professor R. Panerai in the Department of Medical Physics at Leicester University.
Figure 3.1. Finapres 2300, Ohmeda for non-invasive estimation of finger arterial BP
Recordings were used for cardiac BRS estimation were inspected manually for the presence of ectopic beats. If these exceeded >2% of cardiac cycles the recording was rejected. Where there were ≤2% ectopics, these were manually removed using the software and a straight line was interpolated by the computer. The tracings were then resampled and subject to fast fourier transformation (FFT). Spectral analysis techniques, in this case FFT, decompose the SBP and PI tachograms into their oscillatory components in terms of their frequency and amplitude spectra and require stationary conditions (i.e. no slow trends or step changes in the parameter), strict periodicity of the data and are frequently used with an apriori selection of the number and frequency range of oscillatory components. In this work, data segments of 256 points were used divided into 2 segments. The power spectra were smoothed with a 13-point triangular window. This produced estimates of power spectra of PI and SBP, coherence function, and frequency response between PI and SBP with 58 degrees of freedom. Coherence between BP and PI variability reflects the amount of linear coupling between the two spectra and is therefore comparable to the correlation coefficient in regression analysis. A coherence value >0.40 was considered significant, in keeping with previous studies (232;259). Power spectral analysis estimates of PI variability and SBP variability were obtained by calculation of the square root of the powers of PI and SBP respectively for the low frequency bands (LF) bands (0.05 to 0.15 Hz) and the square root of the ratio between the powers as cardiac BRS. Cardiac BRS assessed in this way compares well with estimation of gain of the baroreceptor using pharmacological methods (253). Normalised low frequency (LF) and high frequency (HF – 0.15 to 0.40 Hz) powers for PI were calculated and the ratio used as an index of sympathovagal balance (189).
3.2.3 Statistical methods

The Wilcoxon Signed Rank Test and the Mann-Whitney U Test were used to compare the levels of clinical parameters between stroke and control subjects and between the active and the placebo subgroups among the stroke patients. An integrative variable of previous cardiovascular history was created, being positive where there was an established history of at least one of: diabetes mellitus, coronary artery disease (previous angina, myocardial infarction or abnormal coronary angiographic findings), hypertension, previous stroke or transient ischaemic attack. This permitted analysis of the combined effect of previous cardiovascular history on cardiac BRS levels and inclusion of all the categorical risk factors would have introduced problems in model fitting with respect to sample size. The relationship of cardiac BRS with clinical variables and cardiovascular risk factors was studied using Spearman Rank Correlation for bivariate analysis and a Quantile Regression Method (QR) for multivariate analysis. The QR method allows complete statistical analysis of the stochastic relationships among clinical parameters and possible multicollinearity among the risk factors does not affect the estimation or the inference procedure in this robust QR modelling approach. The inclusion of clinical parameters in the regression models was based on the model Objective Function and the Sum of Squared Errors (SSE). The normality of regression residuals was tested using the Jarque-Bera Asymptotic Lagrange Multiplier Normality Test (Jarque-Bera $\chi^2$ Test) (132). Statistical significance was taken at the 5% level. Statistical analyses were performed using SPSS 11.5 (SPSS Inc., USA) and SHAZAM (SHAZAM Project, University of British Columbia, Canada) computational softwares.
3.3 Results

Subject demographic and cardiovascular data are shown in tables 3.1 and 3.2, showing the two groups were well-matched for cardiovascular parameters and risk factors and, as expected from previous studies (259;292), the stroke patients had significantly lower cardiac BRS levels and significantly elevated PWVcf levels compared to the control subjects. Clinical diagnosis of stroke-subtype by the OCSP (Oxford Community Stroke Project) classification (18) identified 2 total anterior circulation, 10 partial anterior circulation, 17 lacunar and 2 posterior circulation infarcts. The changes in stroke patient cardiovascular data between the first and second studies are shown in table 3.2. As expected, there was a significant reduction in SBP levels during the acute stroke phase. Simple correlation coefficients between cardiac BRS values and other cardiovascular factors in the control and stroke patients at baseline and on day 14 are shown in table 3.3 and scatterplots in figure 3.2. In this analysis, cardiac BRS was significantly associated with age, heart rate and PWVcf level at baseline and with SBP and PWVcf level on day 14. Analysis of the effect of antihypertensive therapy continued during the acute stroke phase revealed no significant confounding effect on the distribution of values or relationship between values for cardiac BRS and PWVcf at day 14. In the quantile regression models (table 3.4), evaluating the influence of all measured variables on cardiac BRS in the stroke patients at baseline and on day 14, cardiac BRS was independently related to age, cardiovascular history, heart rate and PWVcf, but no BP parameter. In the study as a whole, stroke status (stroke or control) was not significantly related to cardiac BRS level.
Table 3.1. Characteristics of study subjects.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Stroke, n=31</th>
<th>Control, n=26</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>66.6 ± 8.8</td>
<td>63.1 ± 9.4</td>
<td>NS*</td>
</tr>
<tr>
<td>Body mass index†</td>
<td>27.8 ± 5.1</td>
<td>28.5 ± 5.1</td>
<td>NS*</td>
</tr>
<tr>
<td>Gender - male</td>
<td>20 (65%)</td>
<td>16 (62%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Previous history:**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Stroke/TIA</th>
<th>Control</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke / TIA</td>
<td>6 (19%)</td>
<td>0 (0%)</td>
<td>‡</td>
</tr>
<tr>
<td>Hypertension</td>
<td>23 (74%)</td>
<td>13 (50%)</td>
<td>NS</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>4 (13%)</td>
<td>4 (15%)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3 (10%)</td>
<td>1 (4%)</td>
<td>‡</td>
</tr>
<tr>
<td>Smoker</td>
<td>7 (23%)</td>
<td>3 (12%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Previous drug therapy:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Stroke</th>
<th>Control</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>9 (29%)</td>
<td>5 (19%)</td>
<td>NS</td>
</tr>
<tr>
<td>Lipid-lowering therapy</td>
<td>2 (6%)</td>
<td>6 (23%)</td>
<td>NS</td>
</tr>
<tr>
<td>Calcium antagonist</td>
<td>1 (3%)</td>
<td>6 (23%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Thiazide diuretic</td>
<td>9 (29%)</td>
<td>5 (19%)</td>
<td>NS</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>4 (13%)</td>
<td>2 (8%)</td>
<td>‡</td>
</tr>
<tr>
<td>Angiotensin-receptor blocker</td>
<td>2 (6%)</td>
<td>3 (12%)</td>
<td>NS</td>
</tr>
<tr>
<td>Alpha-blocker</td>
<td>0 (0%)</td>
<td>1 (4%)</td>
<td>‡</td>
</tr>
<tr>
<td>β-blocker</td>
<td>11 (35%)</td>
<td>6 (23%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Continuous data presented as mean ± standard deviation, categorical data as n (%).

χ² test except * Mann-Whitney U test

‡ χ² test inapplicable due to low n (%).

† Body mass index (weight(kg)/height(m)²)
Table 3.2. Cardiovascular variables of study subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Stroke Baseline (&lt;48 hrs)</th>
<th>Stroke Follow-up (Day 14)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ctrl vs Stroke baseline</td>
<td>Ctrl vs Stroke (follow-up)</td>
<td>Stroke baseline vs follow-up*</td>
<td></td>
</tr>
<tr>
<td>Casual brachial blood pressure, mmHg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>147.7 ± 17.6</td>
<td>155.5 ± 19.7</td>
<td>147.4 ± 19.7</td>
<td>NS</td>
</tr>
<tr>
<td>Mean arterial</td>
<td>106.1 ± 10.0</td>
<td>108.8 ± 15.6</td>
<td>103.6 ± 13.1</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic</td>
<td>85.4 ± 8.7</td>
<td>85.5 ± 15.4</td>
<td>81.7 ± 11.8</td>
<td>NS</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>62.4 ± 15.6</td>
<td>70.0 ± 13.9</td>
<td>65.7 ± 15.2</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>64.8 ± 11.7</td>
<td>68.8 ± 13.9</td>
<td>66.4 ± 9.5</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac BRS (LF), ms/mmHg</td>
<td>6.5 ± 4.2</td>
<td>4.3 ± 2.3</td>
<td>4.9 ± 2.6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LF:HF ratio for PI</td>
<td>3.0 ± 2.9</td>
<td>3.1 ± 2.2</td>
<td>2.7 ± 2.2</td>
<td>NS</td>
</tr>
<tr>
<td>PWVcf, m/s</td>
<td>9.7 ± 1.9</td>
<td>11.2 ± 2.4</td>
<td>10.5 ± 2.2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Stroke severity (NIHSS)</td>
<td>-</td>
<td>8.3 ± 4.4</td>
<td>4.0 ± 3.1</td>
<td>-</td>
</tr>
</tbody>
</table>

Mann–Whitney test except * Wilcoxon test
NIHSS – National Institutes of Health Stroke Severity
Table 3.3. Correlation coefficients (r) for cardiac BRS in study subjects.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control group</th>
<th>Stroke group</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (&lt;48hrs)</td>
<td>Follow-up (Day 14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>-0.15</td>
<td>-0.40*</td>
<td>-0.24</td>
<td></td>
</tr>
<tr>
<td>Body mass index</td>
<td>-0.18</td>
<td>0.09</td>
<td>-0.18</td>
<td></td>
</tr>
<tr>
<td>Stroke severity (NIHSS)</td>
<td>-0.18</td>
<td>-0.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td>-0.16</td>
<td>-0.32</td>
<td>-0.40*</td>
<td></td>
</tr>
<tr>
<td>Mean arterial BP</td>
<td>-0.11</td>
<td>-0.25</td>
<td>-0.32</td>
<td></td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>-0.05</td>
<td>-0.13</td>
<td>-0.21</td>
<td></td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>-0.11</td>
<td>-0.22</td>
<td>-0.35</td>
<td></td>
</tr>
<tr>
<td>Heart rate</td>
<td>-0.24</td>
<td>-0.50**</td>
<td>-0.34</td>
<td></td>
</tr>
<tr>
<td>LF:HF ratio for PI</td>
<td>-0.22</td>
<td>0.07</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>PWVcf</td>
<td>-0.27</td>
<td>-0.51**</td>
<td>-0.54**</td>
<td></td>
</tr>
</tbody>
</table>

*P<0.05, **P<0.01, Spearman rank correlation
Table 3.4. Results obtained from the quantile regression models of stroke patient data and of all subjects combined. Cardiac BRS as dependent variable.

<table>
<thead>
<tr>
<th>Variables/Criteria</th>
<th>Baseline (&lt;48hrs)</th>
<th>Follow-up (day 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate Value</td>
<td>P</td>
</tr>
<tr>
<td><strong>Stroke patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>-0.16</td>
<td><strong>0.05</strong></td>
</tr>
<tr>
<td>Cardiovascular history (Y/N)</td>
<td>-0.41</td>
<td><strong>&lt;0.05</strong></td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>-0.19</td>
<td><strong>&lt;0.01</strong></td>
</tr>
<tr>
<td>Carotid-femoral PWV (m/s)</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td>Sum of squared errors</td>
<td>1.03 (2)</td>
<td>1.47 (2)</td>
</tr>
<tr>
<td>Jarque-Bera $\chi^2$ (df)</td>
<td>0.40 (0.31)</td>
<td></td>
</tr>
<tr>
<td>Skewness (SE)</td>
<td></td>
<td></td>
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<tr>
<td><strong>All subjects</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute stroke (Y/N)</td>
<td>-0.82</td>
<td>NS</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>-0.09</td>
<td><strong>&lt;0.01</strong></td>
</tr>
<tr>
<td>Cardiovascular history (Y/N)</td>
<td>-0.35</td>
<td><strong>&lt;0.01</strong></td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>-0.17</td>
<td><strong>&lt;0.01</strong></td>
</tr>
<tr>
<td>Carotid-femoral PWV (m/s)</td>
<td>-0.59</td>
<td><strong>&lt;0.01</strong></td>
</tr>
<tr>
<td>Sum of squared errors</td>
<td>0.35</td>
<td></td>
</tr>
<tr>
<td>Jarque-Bera $\chi^2$ (df)</td>
<td>1.66 (2)</td>
<td></td>
</tr>
<tr>
<td>Skewness (SE)</td>
<td>0.44 (0.38)</td>
<td></td>
</tr>
</tbody>
</table>

Data entered into models included age, peripheral SBP, MAP and DBP, heart rate, history of cardiovascular disease (hypertension, diabetes, coronary artery disease and stroke or transient ischaemic attack), pulse wave velocity, stroke severity, body mass index and gender.
Figure 3.2. Scatterplots of carotid-femoral pulse wave velocity and cardiac BRS (LF) in control subjects (a), stroke patients within 48 hours (b), at day 14 (c).

a. $r = -0.27$, NS

b. $r = -0.51$, $P<0.01$

c. $r = -0.54$, $P<0.01$

$r$ - Spearman correlation coefficient
3.4 Discussion

3.4.1 Stroke patients

This study shows that, immediately following cerebral infarction and at 14 days post-stroke when BP levels have decreased (117), depressed cardiac BRS levels are associated with increased large artery stiffness, and this relationship is independent of other cardiovascular variables including BP. Wall stiffness of the barosensory arterial vessels of stroke patients may limit baroreceptor stretch in response to changes in BP thereby accounting for, at least in part, the reduced cardiac BRS levels observed immediately after ischaemic stroke. Increased arterial stiffness is associated with the presence of atherosclerosis (309) and baroreceptor function has been shown to be affected, independently of mechanical effects, by a number of atherosclerosis-associated mechanisms including altered paracrine activity, activated platelets and the effects of oxygen-derived free-radicals (61). Increased arterial stiffness for dynamic BP changes (168) may alter the frequency of baroreceptor afferent activity, usually coupled to pulsatile pressure, to which the central vasomotor nuclei alter cardiac autonomic tone in response (62). However, the relationship between PWVcf and cardiac BRS may arise via mechanisms other than attenuation of baroreceptor function. For example, increased PWVcf has been shown to correlate with coronary artery disease severity (149) and may reflect latent cardiac ischaemia resulting in a decrease in cardiac chronotropic response to autonomic innervation.
3.4.2 All subjects

Analysis of data from stroke and control groups combined, allowing the effect of cerebrovascular disease per se to be explored as well as that of cerebrovascular risk factors, suggests cerebral infarction may be unrelated to the level of cardiac BRS when other cardiovascular risk factors including large artery stiffness are considered. Several studies report increased arterial stiffness in stroke patients (83;166;292). However, other evidence suggests a direct influence of stroke per se on cardiac BRS levels. For example, brainstem infarction affecting central vasomotor nuclei has been shown to cause baroreflex failure (243), lesions in the insular cortex alter BRS in rats with asymmetric responses between the right and left hemispheres (341) and studies in stroke patients have reported asymmetrical cardiac autonomic responses to cortical infarction (22). Furthermore, arterial stiffness and cardiac BRS have been found to be unrelated in some hypertensive conditions, for example pre-eclampsia (197). Larger studies have confirmed the relationship between cardiac BRS and arterial stiffness in individuals with essential hypertension (159;267), and it was unlikely that a similar relationship would have been shown in our control group due to a limited sample size.

3.4.3 Cardiac BRS and outcome

Acute ischaemic stroke patients with depressed cardiac BRS levels have an increased cardiovascular mortality in the long-term compared to those with higher levels (258) and elevated large artery stiffness is also associated with increased cardiovascular mortality in patients with essential hypertension (161) and diabetes (68). Increased arterial stiffness may offer additional prognostic information in stroke patients and a further study is required to compare the predictive properties of these two variables on
stroke outcome. Interestingly, beta-blocker therapy appears to be less effective in reducing post-stroke cardiovascular events than other classes of antihypertensive therapy (250), although might be expected to have benefit where sympathetic nervous system activity predominates as a result of impaired cardiac BRS. Furthermore, head-to-head comparison studies have reported beta-blockers to be less effective in reducing large artery stiffness than other antihypertensive drugs (20;251).

3.4.4 Study limitations

It is a limitation of the study that the measure of arterial stiffness encompassed the whole of the arterial length between the common carotid and proximal femoral artery and not specifically the barosensory arterial segments in the aortic arch and carotid sinus. However, studies have shown close correlation between PWVcf and both common carotid artery stiffness and aortic arch elastic modulus in other patient groups (128;212). As a further limitation to our study, it should be noted that our study groups were relatively small, and our data may therefore need to be confirmed in larger patient populations. This would also allow further exploration of individual aspects of past cardiovascular history, in particular previous stroke and diabetes on cardiac BRS levels in acute stroke patients.

3.5 Summary

This study has shown the impairment in cardiac BRS immediately following ischaemic stroke is related to increased large artery stiffness, suggesting that the reduction in cardiac BRS observed in ischaemic stroke patients within the first few hours is associated with increased stiffness of the large artery wall and that this relationship
exists at least up to 14 days following stroke. Further studies are needed to evaluate the contributory role of neurological and cardiovascular effects on cardiac BRS level across the stroke subtypes and consider the effects of anti-hypertensive drugs on arterial stiffness and cardiac BRS levels in the acute stroke phase and the subsequent effect on prognosis.

3.6 Conclusions

- Cardiac BRS and aortic PWV are inversely correlated during the acute stroke phase independently of other cardiovascular risk factors

- When all cardiovascular variables are considered, the cardiac BRS level appears to be sufficiently explained by age, previous cardiovascular history, heart rate and central arterial stiffness with the presence of ischaemic stroke not a relevant variable
4. LARGE ARTERY STIFFNESS AND
CARDIOVASCULAR REFLEXES IN RELATION TO
BLOOD PRESSURE LEVELS AND VARIABILITY
FOLLOWING ACUTE STROKE
4.1 Background and aims

4.1.1 Arterial stiffness

Arterial stiffness is elevated in acute stroke patients compared to control subjects matched for cardiovascular risk factors including BP level (Chapter 2) and is related to cardiac BRS (Chapter 3). PWV, according to the Moens-Kortweg equation (Chapter 1.2.2), is dependent upon both arterial distension pressure and the elastic modulus of vessel wall components. In the presence of advanced diseased-induced structural changes in the artery, PWV may be less dependent upon arterial distension pressure and therefore may not necessarily decrease in parallel with BP reduction. In one study of hypertensive patients with end-stage renal disease that evaluated the differential effects of combination antihypertensive therapy on BP and arterial stiffness, aortic PWV increased or remained unchanged in one third of patients reaching the target BP reduction (114), and these patients were subsequently found to have an impaired short-term survival. The natural history of arterial stiffness in relation to the recognised changes in BP during the acute phase of stroke is currently unknown.

4.1.2 Beat-to-beat BP variability

Beat-to-beat BP variability, as calculated from the standard deviation of a 10-minute continuous non-invasive measure of finger arterial BP, is increased in acute stroke patients compared to control subjects and this persists throughout the acute stroke phase (255), although the underlying mechanism is unclear. There might be a relationship with impaired cardiac BRS, but this has not yet been demonstrated for acute stroke patients. One study found that while beat-to-beat PI variability and cardiac
BRS were strongly positively correlated immediately following stroke, there was no significant relationship between beat-to-beat BP variability and cardiac BRS (259). Arterial stiffness might contribute to increased beat-to-beat BP variability due to decreased buffering of left ventricular ejection volume which might be more variable in stroke patients due to increase in the activity of the sympathetic nervous system (22). A number of investigators have suggested a link between arterial stiffness and BPV in hypertensive subjects. For example, PP, an index of arterial stiffness, has been found to be associated with the variability of BP measurements in 24 hour ambulatory recordings (126;305) and with beat-to-beat SBP variability (312). The authors suggest that the aetiological pathway is via impairments in cardiac BRS due to splinting of arterial baroreceptors as a result of increased arterial stiffness, although this mechanism does not appear, as far as can be ascertained from the literature, to have yet been demonstrated.

This chapter explores the dynamic relationship between arterial stiffness and BP levels and the inter-relationships between arterial stiffness, cardiac BRS and beat-to-beat BP variability in the acute stroke period. These associations are important to understand if antihypertensive therapy is to be employed in the acute phase of stroke with the aim of improving some of these prognostically-important parameters.

The study hypotheses are a) arterial stiffness changes in parallel with BP level following acute stroke and b) beat-to-beat BP variability following acute stroke is a function of cardiac BRS, which, in turn, is related to central arterial stiffness.
4.2 Methods

4.2.1 Subjects

Patients presenting to University Hospitals Leicester NHS Trust with symptoms of acute stroke were recruited within 24 hours of symptom-onset and studied within 72 hours of ictus and again on day 14. Patients enrolled into the placebo arm of the CHIPS (Control of Hypertension Immediately Post-Stroke) pilot study (Chapter 5) were also included in the analysis. Patients with atrial fibrillation or requirement to continue or start medication known to affect the cardiovascular system were excluded (except for those taking lipid-lowering therapy where this was continued), otherwise all such medication was withdrawn for the first 14 days. Patients with neuroradiologically-confirmed acute ischaemic or haemorrhagic stroke were included, with those with non-stroke diagnoses or TIA subsequently excluded from the study. Patients were studied in an environment as previously described in Chapter 2.

4.2.2 Protocol

Cardiovascular measurements were performed at baseline and day 14 following stroke. Methodology has been previously described (Chapters 2 and 3) but briefly, casual brachial BP (A&D UA-767) was recorded in the unaffected arm where there was acute hemiparesis. PWV between the carotid and femoral arteries and central aortic waveform data were obtained from the radial artery. A 10-minute continuous beat-to-beat BP recording using a Finapres device was conducted together with 3-lead surface ECG to derive BP and PI variability and cardiac BRS. For BP and PI variability, the standard deviation of the parameters was taken for the entire recording, with no prior
removal of ectopic beats. To derive cardiac BRS, the unedited recording was analysed in the time domain. Tachograms unedited for ectopic beats were used for assessment of cardiac BRS using a time domain method whereby consecutive sequences of spontaneous and transient pressor or depressor SBP variation of at least 3 beats in length were identified and the simultaneous PI response measured. The slope of SBP change versus PI change was calculated for each sequence by linear regression analysis. A sequence identified as indicating cardiac baroreceptor reflex activity consisted of a simultaneous increase (pressor BRS) or decrease (depressor BRS) in SBP and PI. The mean slope was calculated for all the pressor and depressor sequences, with the average of these two values taken as cardiac BRS (cardiac BRS, sequence). The sequence method has been utilised in a number of previous studies (159;234) and has been shown to represent baroreceptor modulation of the sinus node (30). Estimates based on the EuroBaVar dataset (160), a standard dataset used to evaluate different methods of spontaneous cardiac BRS measurement, report a correlation coefficient of 0.77 between time and frequency domain methods of cardiac BRS calculation.

Stroke subtype (either cortical, subcortical infarct or primary intracerebral haemorrhage) was made according to the Oxfordshire Community Stroke Project classification (18) using the neuroimaging results and the findings on neurological examination.

4.2.3 Statistical methods

The relationship between change in BP levels and other cardiovascular variables was principally analysed according to MAP level. Data are presented as mean ± standard
deviation. Statistical analysis was performed using SPSS Version 11.5, using Wilcoxon Paired Ranks Test for the changes in paired cardiovascular variables over time, Spearman’s Rank Correlation Coefficient (r) to study bivariate relationships and Multiple Linear Regression to evaluate the relationships between multiple variables. Statistical significance was taken at the 5% level.

4.3 Results

19 acute stroke patients were studied. Baseline demographic and cardiovascular data of the subjects are presented in Tables 4.1 and 4.2.

4.3.1 The relationship at baseline and on day 14 of the acute stroke phase between BP, cardiac BRS and BP variability.

The relationships between the changes in PWVcf, cardiac BRS and MAP between baseline and day 14 post-stroke are shown in Figure 4.1. Changes in both cardiac BRS and PWVcf were significantly correlated with changes in MAP. Correcting for the effects of MAP on both cardiac BRS and PWVcf by multiple linear regression, the relationship between the change in cardiac BRS and change in PWVcf did not remain statistically significant (r=-0.026, NS). No correlation was seen between the change in MAP and the change in AIx (r=0.17, NS), but the relationship between the changes in MAP and Tr was statistically significant (r=0.45, P=0.05). No correlation was seen between the change in MAP, cardiac BRS or PWVcf and the change in any parameter of beat-to-beat BPV.
Table 4.1. Baseline demographics of patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Stroke, n=19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>72.4 ± 9.4</td>
</tr>
<tr>
<td>Gender</td>
<td>14 M:5 F</td>
</tr>
<tr>
<td>Body mass index [wt (kg) / h (m)^2]</td>
<td>27.5 ± 4.9</td>
</tr>
<tr>
<td>Stroke severity (NIHSS)</td>
<td>9.7 ± 5.3</td>
</tr>
<tr>
<td>Time from stroke onset to baseline study (hrs)</td>
<td>31 ± 18</td>
</tr>
<tr>
<td>Stroke subtype</td>
<td></td>
</tr>
<tr>
<td>Cortical</td>
<td>8</td>
</tr>
<tr>
<td>Subcortical</td>
<td>9</td>
</tr>
<tr>
<td>Primary haemorrhage</td>
<td>2</td>
</tr>
</tbody>
</table>
Table 4.2. Cardiovascular data of subjects at baseline and day 14, n=19.

<table>
<thead>
<tr>
<th>Cardiovascular variable</th>
<th>Baseline (first 72 hours)</th>
<th>Day 14</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brachial BP (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>164.3 ± 21.1</td>
<td>161.6 ± 27.3</td>
<td>-2.7 ± 21.0</td>
</tr>
<tr>
<td>MAP</td>
<td>111.5 ± 11.9</td>
<td>109.2 ± 15.1</td>
<td>-2.2 ± 16.4</td>
</tr>
<tr>
<td>DBP</td>
<td>85.1 ± 11.2</td>
<td>83.1 ± 10.6</td>
<td>-2.0 ± 15.4</td>
</tr>
<tr>
<td>PP</td>
<td>79.3 ± 20.2</td>
<td>78.5 ± 20.9</td>
<td>-0.7 ± 13.1</td>
</tr>
<tr>
<td>BP variability (Finapres) (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBPV</td>
<td>10.5 ± 3.4</td>
<td>9.8 ± 4.8</td>
<td>-0.7 ± 5.0</td>
</tr>
<tr>
<td>MAPV</td>
<td>6.6 ± 1.9</td>
<td>6.3 ± 3.5</td>
<td>-0.3 ± 3.4</td>
</tr>
<tr>
<td>DBPV</td>
<td>4.8 ± 1.4</td>
<td>4.5 ± 2.5</td>
<td>-0.3 ± 2.6</td>
</tr>
<tr>
<td>PI (ms)</td>
<td>936 ± 124</td>
<td>902 ± 150</td>
<td>-34 ± 141</td>
</tr>
<tr>
<td>PIV (ms)</td>
<td>60 ± 43</td>
<td>54 ± 52</td>
<td>-6 ± 39</td>
</tr>
<tr>
<td>PWVcf (m/s)</td>
<td>12.6 ± 1.9</td>
<td>12.5 ± 2.9</td>
<td>-0.0 ± 2.3</td>
</tr>
<tr>
<td>Aortic AIx from radial (%)</td>
<td>27.5 ± 7.3</td>
<td>27.6 ± 7.8</td>
<td>0.0 ± 5.6</td>
</tr>
<tr>
<td>Aortic Tr from radial (ms)</td>
<td>134 ± 10</td>
<td>134 ± 11</td>
<td>0 ± 7</td>
</tr>
<tr>
<td>Cardiac BRS (ms/mmHg)</td>
<td>7.1 ± 5.8</td>
<td>4.9 ± 5.2</td>
<td>-2.2 ± 6.2</td>
</tr>
<tr>
<td>Stroke severity (NIHSS)</td>
<td>9.7 ± 5.3</td>
<td>5.8 ± 4.8</td>
<td>-3.9 ± 2.7*</td>
</tr>
</tbody>
</table>

Data presented as mean ± standard deviation. *P<0.01 (Wilcoxon test). All other differences were non-significant.
4.3.2 The relationship between beat-to-beat BP variability, arterial stiffness and cardiac BRS in the acute stroke phase

The correlation between beat-to-beat MAP variability and arterial stiffness versus cardiac BRS at baseline and on day 14 is shown in figure 4.2. MAP variability was much more closely correlated with PWVcf at baseline and on day 14 (p<0.01) than with cardiac BRS (p=NS). Spearman’s rank correlation coefficients for absolute BP and PI levels and their beat-to-beat variability with arterial stiffness and cardiac BRS are shown in Table 4.3. Parameters of beat-to-beat BP variability were correlated with arterial stiffness at baseline and on day 14, whereas no such relationship was demonstrated with cardiac BRS. However, PI variability was significantly correlated to cardiac BRS but not arterial stiffness.

In a multiple linear regression analysis correcting for the effects of absolute BP levels, age, cardiac BRS and PI (table 4.4), the association of PWVcf and beat-to-beat MAP variability remained independent at both baseline and at day 14. All indices of beat-to-beat BP variability (SBP, MAP and DBP) were found to be independently related to PWVcf at both baseline and day 14 (p<0.05), when correcting for absolute levels and cardiac BRS.
Figure 4.1. Scatter plots to show relationships between changes in PWVcf, MAP and cardiac BRS during the first 14 days following acute stroke. Spearman's rank correlation coefficient (r). Variables presented as day 14 data minus baseline data. Negative sign indicates MAP fall.

$r=0.67, P<0.01$

$r=0.59, P<0.01$

$r=0.52, P<0.02$
Table 4.3. Associations between Finapres BP parameters, beat-to-beat BP variability, central arterial stiffness and cardiac BRS, n=19.

<table>
<thead>
<tr>
<th></th>
<th>PWV carotid-femoral</th>
<th>Cardiac BRS, sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>baseline</td>
<td>Day 14</td>
</tr>
<tr>
<td><strong>Absolute levels</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI, ms</td>
<td>-.170</td>
<td>.200</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>.254</td>
<td>.551*</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>-.025</td>
<td>.526*</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>-.214</td>
<td>.237</td>
</tr>
<tr>
<td>PP, mmHg</td>
<td>.198</td>
<td>.572*</td>
</tr>
<tr>
<td><strong>Variability</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI variability, ms</td>
<td>-.105</td>
<td>.060</td>
</tr>
<tr>
<td>SBP variability, mmHg</td>
<td>.372</td>
<td>.482*</td>
</tr>
<tr>
<td>MAP</td>
<td>.596**</td>
<td>.618*</td>
</tr>
<tr>
<td>DBP</td>
<td>.363</td>
<td>.626*</td>
</tr>
</tbody>
</table>

Spearmans rank correlation. * P<0.05, **P<0.01
Figure 4.2. Scatterplots of beat-to-beat MAP variability with central arterial stiffness (PWVcf) and cardiac BRS. Spearman’s rank correlation coefficient.

Baseline

Day 14

Baseline Day 14

5 10 15 20
PWVcf (m/s)

5 10 15 20
PWVcf (m/s)

Cardiac BRS, sequence (ms/mmHg)

Cardiac BRS, sequence (ms/mmHg)

$r=0.596, P<0.01$

$r=0.618, P<0.01$

$r=0.172, P=NS$

$r=0.054, P=NS$
Table 4.4. Results of multiple linear regression of related cardiovascular variables to beat-to-beat MAP variability (mmHg) at baseline and day 14 following stroke.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th></th>
<th>Day 14</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coefficient</td>
<td>P Value</td>
<td>Coefficient</td>
<td>P Value</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>0.01</td>
<td>NS</td>
<td>-0.03</td>
<td>NS</td>
</tr>
<tr>
<td>PWVcf (m/s)</td>
<td>0.67</td>
<td>&lt;0.05</td>
<td>1.39</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SBP - Finapres (mmHg)</td>
<td>-0.01</td>
<td>NS</td>
<td>-0.11</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>DBP - Finapres (mmHg)</td>
<td>0.02</td>
<td>NS</td>
<td>0.02</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac BRS (ms/mmHg)</td>
<td>0.09</td>
<td>NS</td>
<td>-0.00</td>
<td>NS</td>
</tr>
<tr>
<td>Pulse interval (ms)</td>
<td>-0.01</td>
<td>NS</td>
<td>0.00</td>
<td>NS</td>
</tr>
</tbody>
</table>

Beat-to-beat MAP variability as dependent variable. All covariates in model are listed.
4.4 Discussion

4.4.1 Arterial stiffness, cardiac BRS and BP levels

The relationship between the change in BP levels during the first 14 days following stroke and other cardiovascular variables was principally analysed according to MAP, as this parameter was considered to be the arterial distending pressure, and independent of arterial stiffness, whereas SBP, DBP or PP are variables influenced by arterial stiffness levels (216). No significant reduction in BP level was observed during the 14 day study period, whereas this might have been expected considering the findings of previous studies of the natural history of BP changes during the acute stroke phase (49;117).

Nevertheless, individual patient data analysis to evaluate the effects of changing BP levels on other cardiovascular parameters, with a variety of BP responses during the acute stroke period allowed exploration of the dynamic relationship between cardiovascular variables. Despite arterial stiffness being increased in stroke patients compared to matched control subjects (Chapter 2), indicating a higher degree of arterial dysfunction and structural change, the change in arterial stiffness during the acute stroke phase was closely related to the change in MAP level. Changes in cardiac BRS were also shown to be related to, at least in part, the changes in MAP level during the acute stroke phase. On the basis of these results, and independently of any drug-specific effects on arterial stiffness or cardiac BRS levels, BP lowering per se within the acute stroke phase might be expected to favourably influence these parameters. This might be particularly important for cardiac BRS, which has been shown to have long-term prognostic significance (258) following stroke. In
patients with end-stage renal failure the persistence of aortic stiffness reversibility in response to BP lowering appears to have a beneficial and BP-independent impact on the survival of these patients (114). Although the data did show a relationship between the change in arterial stiffness and the change in cardiac BRS during the acute stroke phase, this was not found to be independent of MAP level. This is not entirely surprising given the relatively small patient numbers in this study and it has already been shown in this thesis (Chapter 3) that at baseline and at day 14 following stroke, the relationship between PWVcf and cardiac BRS levels is independent of BP.

4.4.2 Beat-to-beat BP variability

There is an increasing body of evidence that increased beat-to-beat BP variability cannot be directly attributed to impaired cardiac BRS in stroke patients. Robinson et al. (259) did not show a relationship between BP variability (as assessed by the low frequency spectral power of SBP during a 10-minute recording) and cardiac BRS in the acute stroke phase but there was a clear relationship with PI variability, and the findings are replicated in this study. Mancia et al. (190), in a study of normotensive and hypertensive individuals, found no significant correlation between beat-to-beat BP variability and cardiac BRS, although such a relationship might be expected to be stronger in the presence of depressed cardiac BRS levels as found following stroke. Recent evidence has shed light on other contributing factors to increased beat-to-beat BP variability in the acute stroke phase with disordered respiratory activity, in particular upper airway obstruction, being important (306). The present work shows a positive relationship between beat-to-beat BP variability
and large artery stiffness. The proposed mechanism for this is a reduction in buffering of left ventricular ejection volume due to decreased central aortic compliance, as has been postulated by previous authors (126) and not via cardiac BRS reduction through baroreceptor splinting or the central effects of stroke as previously suggested (312).

4.4.3 Study limitations

There are a number of potential criticisms of this work. Given the small patient numbers and the relatively large number of studied covariates including multiple comparisons the presented findings should be considered exploratory. Only an interventional study will determine whether therapeutic reductions in MAP bring about improvement in other cardiovascular parameters in the acute stroke period. Certain drugs, for example ACEI, may have additional mechanisms of action on these values over and above any BP lowering effect, for example by altering endothelial function and nitric oxide activity (178), but the opposite may be true for other drugs, for example beta-blockers which have been shown to have less favourable effects on arterial stiffness (184). The finding of a strong correlation between cardiac BRS and arterial stiffness with MAP levels also highlights the necessity of controlling for any change in MAP if therapeutic effects on arterial stiffness via other mechanisms are to be evaluated.
4.5 Summary

The natural history of arterial stiffness and cardiac baroreceptor sensitivity closely follows the natural history of arterial BP during the first 14 days following acute stroke. As a result, antihypertensive therapy for the treatment of hypertension in the acute stroke phase in lowering BP levels might be expected to improve these other haemodynamic parameters, but this requires further evaluation. Finding a relationship between beat-to-beat BPV and cardiac BRS in acute stroke patients has again proved elusive. An association between arterial stiffness and beat-to-beat BPV has been demonstrated in this study, independently of other cardiovascular factors, and this may be an important contributory mechanism to the prognostically-important beat-to-beat fluctuations in BP that occur following acute stroke. These preliminary results require reproduction in a larger study.

4.6 Conclusions

- Arterial stiffness and cardiac BRS are BP-dependent variables in the acute phase of stroke (first 14 days).

- Beat-to-beat BPV is more closely related to central arterial stiffness than cardiac BRS in the acute stroke phase.
PHASE II

5. THE EFFECT OF ORAL LISINOPRIL ON BLOOD PRESSURE LEVELS IN THE ACUTE AND SUB-ACUTE PHASES OF STROKE
5.1 Background and aims

The relationship between BP level on hospital admission following acute stroke and short (2-weeks) and medium-term outcome is U-shaped and is discussed in detail in Chapter 1.3.3. The majority of stroke patients admitted to hospital (over 80%) have a SBP level of $\geq 140$ mmHg. There is well-established evidence that pharmacological BP reduction induced several weeks following the index event (at least 2 weeks post-ictus) reduces subsequent cardiovascular events with the degree of vascular protection appearing to be related to the degree of BP reduction. This benefit from BP lowering has been shown for several drugs including thiazide diuretics and ACE inhibitors (ACEI) (1;4), but there is continued debate about whether to treat elevated BP levels within the first few hours or days following a stroke (6). Uncertainty is based on the observation that there is impairment of cerebral autoregulation following acute stroke and a fall in systemic BP levels may therefore result in a fall in cerebral perfusion pressure and CBF, decreasing further perfusion of the ischaemic penumbra and extending infarct size. A number of small and relatively underpowered trials of antihypertensive therapy within the first 72 hours of stroke have suggested this might be a valid concern with some trials showing trends to adverse outcome with antihypertensive therapy (9). The remainder shown either no effect of treatment on BP levels, or no effect on stroke outcome or neither (21;87;277). ACEI therapy has yet to be studied for the treatment of hypertension immediately following stroke (within the first 24 hours of symptom-onset) although such therapy has been shown to reduce BP levels and preserve CBF when commenced during the sub-acute phase of stroke (>72 hours following ictus) (86;248). There is evidence from studies in essential
hypertension that once-daily oral Lisinopril 5mg may provide sufficient and sustained lowering of BP levels (65;109).

The study hypothesis was that once-daily oral therapy with the ACEI Lisinopril commenced within 24 hours of stroke onset would result in prompt and sustained reduction in BP levels during the immediate, acute and subacute phases of stroke and be well-tolerated with no evident adverse effect in terms of neurological function and patient outcome. This was tested in a double-blinded placebo-controlled parallel-group study (CHIPS – Control of Hypertension Immediately Post Stroke).

5.2 Methods

5.2.1 Subjects

Patients presenting to University Hospitals Leicester NHS Trust with the onset of symptoms of acute stroke within the previous 24 hours (where stroke occurred during sleep the time of onset was deemed to be when the patient retired the previous evening) underwent casual brachial BP monitoring (A&D UA-767) whilst in the supine position. BP levels were recorded every 5 minutes for a duration of 30 minutes. Patients with a mean SBP level ≥140 mmHg or DBP level ≥90 mmHg were invited to participate in the study. An assessment of swallowing status was made at the bedside according to standard protocol (186) and dysphagic patients were excluded. Patients with established severe (>70%) carotid stenosis, significant aortic stenosis (peak gradient > 50mmHg), plasma
creatine > 200 umols/L, signs of severe dehydration, known adverse reaction to ACEI therapy or a pre-stroke modified Rankin score of >2 were excluded. Subjects with a requirement to continue previous medication known to have antihypertensive properties, for example beta-blockers and nitrates for coronary artery disease, were also excluded from the study. Otherwise, all existing antihypertensive medication was discontinued and no novel medication known to affect the cardiovascular system other than the study drug was introduced during the subsequent 14 days. However, where patients were previously taking lipid-lowering therapy this was continued. Patients with a non-stroke diagnosis or transient ischaemic attack (TIA) were subsequently withdrawn from the study.

5.2.2 Drug administration

Patients were randomised according to their order of entry into the study, and provided with pre-prepared and numbered but otherwise identical study packs containing capsules of either Lisinopril 5mg or placebo. The sequential randomised order of study packs had been pre-determined by a research pharmacist (not otherwise involved with the conduct of the study) using a table of random numbers. Both the investigator and patient were blinded to the contents of the study packs until the last participant had completed the study. Following the initial neurological and cardiovascular assessments drug therapy was administered within 24 hours of stroke symptom-onset. Therapy was continued once-daily and administered at approximately the same time each day for the next 14 days. On day 7, where brachial SBP levels were ≥140 mmHg or DBP ≥90 mmHg, therapy was doubled for the subsequent 7 days (two Lisinopril 5mg [10mg] or two placebo capsules). Following
neurological, functional and cardiovascular assessment, study medication was discontinued following day 14 and subsequent drug therapy was at the discretion of the supervising physician.

5.2.3 Assessment of BP levels

Immediately prior to randomisation and drug administration recordings of casual brachial BP and finger arterial beat-to-beat BP were conducted. At least three casual brachial BP measurements with the cuff placed, where there was hemiparesis, on the non-hemiparetic arm were made in quick succession with the mean of the latter two recordings (where difference in BP was ≤10 mmHg for SBP and DBP) taken for analysis. Subjects in sinus rhythm and with an ectopic beat rate of <2%, underwent a 10-minute non-invasive continuous finger arterial BP recording on the non-hemiparetic hand using a Finapres device, the methodology having been previously described (Chapter 3). A British Hypertension Society validated automated 24-hour BP monitor (Spacelabs 90207, Redmond, USA) (223) was initialised to record brachial BP every 30 minutes for 24 hours following the first dose using a cuff of the appropriate size on the hemiparetic arm, with an initial recording being made just prior to first dose administration. On day 7 of the study the casual brachial BP measurements were repeated and on day 14, brachial BP, beat-to-beat BP and 24 hr automated BP recordings were repeated. Patients were excluded from 24-hour BP analysis if they were unable to tolerate ≤ 12 hours BP monitoring at randomisation and on day 14.
5.2.4 Assessment of outcome

Prior to initial dosing, stroke severity was assessed using the National Institutes of Health Stroke Severity score. Assessment of functional status was made using the Barthel score and modified Rankin index (see Appendix) and required evaluation by the multidisciplinary team (physiotherapist, occupational therapist and nursing staff) within the first 24 hours following administration of the first dose of study drug. These assessments were repeated on day 14 of the study and at 20 weeks following ictus.

5.2.5 Safety considerations

A 30% fall in SBP levels within 12 hours of the first dose of test drug would require withdrawal of the patient from the study. As part of the ethical committee requirement, patients with primary intracerebral haemorrhage with SBP levels persistently $\geq 200$ mmHg during the course of the treatment phase were also withdrawn. Serum creatinine level was measured on day 3 and day 7 of the study and at other times according to clinical requirement. A doubling of serum creatinine necessitated withdrawal of the patient from the study.

5.2.6 Statistical methods

The first-dose response curves obtained by automated BP monitoring (Spacelabs) were assessed using an area under the curve (AUC) analysis (193) with active and placebo areas
compared with Student's t-test. Differences in other parameters between the two groups were assessed using the Mann-Whitney U test and the $\chi^2$ test. Multiple linear regression was used to correct for differences in baseline BP levels between the two groups. 20-week survival analysis was conducted using the Log Rank test. Statistical significance was taken at the 5% level. SPSS Version 11.5 was used for statistical analysis.

5.3 Results

47 patients were recruited to the study. Patient demographic and cardiovascular information at baseline (prior to randomisation) is presented in Table 5.1. Complete data collection for all participants was not possible due to some early study withdrawals and intolerance of automated BP recording in some patients. This is subsequently described in more detail.

5.3.1 BP response to first dose

38 patients tolerated automated brachial BP monitoring for the first 16 hours following the initial dose and the data from these patients is presented in Table 5.2. 7 patients were unable to tolerate monitoring for more than 8 hours and in 2 there was machine failure (one kinked cuff inflation tube, one monitor malfunctioned after getting wet). Insufficient data were available for analysis beyond 16 hours as the number of participants developing intolerance or absent readings increased markedly beyond this time.
Table 5.1. Baseline data of all participants in the CHIPS pilot.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lisinopril, n=21</th>
<th>Placebo, n=26</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>70 ± 13</td>
<td>74 ± 9</td>
<td>NS</td>
</tr>
<tr>
<td>Gender</td>
<td>9M :12F</td>
<td>19M :7F</td>
<td>NS</td>
</tr>
<tr>
<td>Stroke type</td>
<td>19 infarct : 2 PICH</td>
<td>23 infarct : 3 PICH</td>
<td>NS</td>
</tr>
<tr>
<td>OCSP classification</td>
<td>6 LACI, 6 PACI, 5</td>
<td>10 LACI, 7 PACI, 2</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>TACI, 2 POCI, 2 PICH</td>
<td>TACI, 4 POCI, 3 PICH</td>
<td></td>
</tr>
<tr>
<td>Stroke severity (NIHSS)</td>
<td>12 ± 7</td>
<td>11 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td>Time to randomisation</td>
<td>18 ± 6</td>
<td>19 ± 5</td>
<td>NS</td>
</tr>
<tr>
<td>from stroke onset (hrs)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*Systolic BP (mmHg)</td>
<td>180.3 ± 18.7</td>
<td>168.7 ± 20.2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Mean arterial BP (mmHg)</td>
<td>119.9 ± 12.5</td>
<td>114.7 ± 12.4</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>89.7 ± 13.0</td>
<td>87.7 ± 11.7</td>
<td>NS</td>
</tr>
<tr>
<td>Pulse pressure (mmHg)</td>
<td>90.6 ± 18.3</td>
<td>81.0 ± 18.2</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>72.8 ± 10.0</td>
<td>67.1 ± 13.1</td>
<td>NS</td>
</tr>
</tbody>
</table>
Table 5.1. Continued

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lisinopril, n=21</th>
<th>Placebo, n=26</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any antihypertensive therapy immediately prior to stroke</td>
<td>9 (42%)</td>
<td>15 (58%)</td>
<td>NS</td>
</tr>
<tr>
<td>Drug class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>1 (5%)</td>
<td>5 (19%)</td>
<td>†</td>
</tr>
<tr>
<td>Thiazide diuretic</td>
<td>4 (19%)</td>
<td>9 (33%)</td>
<td>NS</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>4 (19%)</td>
<td>3 (11%)</td>
<td>NS</td>
</tr>
<tr>
<td>Angiotensin-receptor blocker</td>
<td>1 (5%)</td>
<td>2 (8%)</td>
<td>‡</td>
</tr>
<tr>
<td>Alpha-blocker</td>
<td>0 (0%)</td>
<td>4 (15%)</td>
<td>‡</td>
</tr>
<tr>
<td>β-blocker</td>
<td>3 (14%)</td>
<td>8 (30%)</td>
<td>NS</td>
</tr>
<tr>
<td>Dose increase required on day 7</td>
<td>10/20 (50%)</td>
<td>15/23 (65%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Results presented as mean ± standard deviation or number (percentage)

NIHSS- National Institutes of Health Stroke Severity score

OCSP – Oxford Community Stroke Project classification


Haemorrhage: PICH – primary intracerebral

‡ insufficient sample size to apply χ² test.

* BP data from casual brachial measurements (A&D UA-767)
Table 5.2. Baseline (pre-randomisation) demographics and cardiovascular variables of the 38 study subjects undergoing at least 16 hours automated BP monitoring following initial dose.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Active group, n=19</th>
<th>Placebo group, n=19</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>71 ± 14</td>
<td>74 ± 9</td>
<td>NS</td>
</tr>
<tr>
<td>Gender</td>
<td>11F : 8M</td>
<td>4F : 15M</td>
<td>NS</td>
</tr>
<tr>
<td>Stroke subtype (OCSP)</td>
<td>4 LACI</td>
<td>7 LACI</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7 PACI</td>
<td>6 PACI</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 TACI</td>
<td>1 TACI</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>2 POCI</td>
<td>4 POCI</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 PICH</td>
<td>1 PICH</td>
<td></td>
</tr>
<tr>
<td>Time from stroke-onset to first dose (hrs)</td>
<td>18 ± 6</td>
<td>19 ± 4</td>
<td>NS</td>
</tr>
<tr>
<td>Stroke severity (NIHSS)*</td>
<td>13 [6, 9]</td>
<td>11 [8, 14]</td>
<td>NS</td>
</tr>
<tr>
<td>Barthel index*</td>
<td>10 [2, 14]</td>
<td>6 [5, 8]</td>
<td>NS</td>
</tr>
<tr>
<td>Modified Rankin score*</td>
<td>4 [4, 5]</td>
<td>4 [4, 5]</td>
<td>NS</td>
</tr>
<tr>
<td>Pre-randomisation blood pressure – automated cuff data (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>173.8 ± 19.4</td>
<td>168.3 ± 14.5</td>
<td>NS</td>
</tr>
<tr>
<td>Mean arterial</td>
<td>119.6 ± 13.6</td>
<td>117.6 ± 12.5</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic</td>
<td>92.5 ± 14.0</td>
<td>92.3 ± 14.1</td>
<td>NS</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>81.3 ± 17.8</td>
<td>76.0 ± 14.4</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>72.8 ± 9.4</td>
<td>74.4 ± 16.0</td>
<td>NS</td>
</tr>
</tbody>
</table>

Variables presented as mean ± standard deviation except * median [interquartile range]
Figure 5.1. Hourly-automated brachial BP and heart rate profile following first dose according to treatment group (Mean ± SE).

* p<0.05 for area difference compared to placebo. No difference in HR between groups.
Figure 5.2. Casual brachial and finger arterial BP (Mean ± SE). Data are presented as changes from baseline with actual baseline data displayed in table.

**CASUAL BP** (lisinopril 23, placebo 17)  

**FINAPRES BP** (lisinopril 10, placebo 10)

<table>
<thead>
<tr>
<th>Day</th>
<th>Casual BP reduction (SBP/DBP) compared to placebo (mean ± SE):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 7</td>
<td>-23±8/11±4 mmHg</td>
</tr>
<tr>
<td>Day 14</td>
<td>-21±8/6±4 mmHg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Day 14</th>
<th>Finapres BP reduction (SBP/DBP) compared to placebo:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 14</td>
<td>-22±13/6±10 mmHg</td>
</tr>
</tbody>
</table>

* p<0.05 for difference in BP between groups, Mann Whitney U test. † Mean ± SD.

<table>
<thead>
<tr>
<th>Baseline BP (mmHg)†</th>
<th>Casual</th>
<th>Finapres</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lisinopril, n=23</td>
<td>Placebo, n=17</td>
</tr>
<tr>
<td>SBP</td>
<td>183.4 ± 18.1</td>
<td>168.5 ± 21.7</td>
</tr>
<tr>
<td>DBP</td>
<td>91.2 ± 13.2</td>
<td>87.6 ± 12.7</td>
</tr>
</tbody>
</table>
Figure 5.3. 24-hour automated mean BP (Mean ± SE). Data are presented as changes from baseline with actual baseline data displayed in table.

<table>
<thead>
<tr>
<th>Baseline variable</th>
<th>Casual</th>
<th>Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>156.4 ± 21.9</td>
<td>157.3 ± 16.2</td>
<td>NS</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>84.7 ± 12.9</td>
<td>85.8 ± 11.1</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>72.0 ± 10.7</td>
<td>64.8 ± 10.6</td>
<td>NS</td>
</tr>
</tbody>
</table>

24hr automated BP reduction compared to placebo (mean ± SE):
Day 14 – 13±5/4±3 mmHg

HR reduction compared to placebo
Day 14 – 6±3 bpm

* p<0.05 for difference in BP between groups, Mann Whitney U test. † Mean ± SD.
There was a small and non-significant difference in baseline SBP levels between the Lisinopril and placebo groups undergoing continuous BP monitoring following the first-dose (5.5 ± 5.6 [S.E.] mmHg) and, for the purposes of clarity, the changes from baseline for the first-dose BP and heart rate responses are displayed in Figure 5.1, although similar results are obtained whether the data are analysed according to changes from baseline or absolute values.

In the AUC analysis, during the immediate phase following drug administration (between hour 0 and hour 4) the sum of SBP, MAP and DBP levels were not significantly different between the Lisinopril group and the placebo group (SBP p=0.19, MAP p=0.85, DBP p=0.54 for group area differences). However, at hour 4, BP levels were at a significantly lower level in the Lisinopril group in comparison to the placebo group (SBP reduction 20 ± 6 mmHg [mean ± SE] [p<0.01], MAP reduction 11 ± 3 mmHg [p<0.01] and DBP reduction 7 ± 3 mmHg [p<0.05]). These were the maximum reductions with respect to placebo achieved following the first-dose. In the lisinopril group the SBP change from baseline at hour 4 ranged from -55 to +19 mmHg (-28 to +13%), and the DBP change from -28 to +16 mmHg (-25 to +23%). In the AUC analysis of BP levels between hour 0 and hour 12, SBP levels but not MAP or DBP were significantly reduced in the Lisinopril group compared to placebo (p<0.05, p=0.15, p=0.44, respectively). During the entire first-dose monitoring period (hour 0 to 16), the difference in SBP, MAP and DBP between groups did not achieve statistical significance (p=0.08, p=0.25, p=0.58, respectively). Heart rate was unaffected by treatment (p=0.61).
To explore the effects of pre-stroke antihypertensive treatment on the BP profile immediately following randomisation into the study the results were analysed according to the presence or absence of previous antihypertensive therapy and the number of antihypertensive drugs being taken prior to hospital admission. No relationship was found between BP profile and previous antihypertensive drug therapy, in particular the peak in SBP and DBP levels at hour 4 in the placebo group could not be attributed to the withdrawal of previous antihypertensive drug therapy.

5.3.2 BP response during the acute and subacute stroke phase

7 patients did not complete 14 days of therapy (see outcome section for details). Of those completing the course of therapy, all took >90% of the prescribed doses. The results of BP changes from baseline are displayed in Figure 5.2. The natural fall in BP levels during the acute stroke phase is shown in the placebo group, in keeping with the findings of other studies (116). However, significant SBP reduction was observed, over and above the natural fall in BP levels, on days 7 and 14 in the Lisinopril group with respect to the placebo group, and there was a significant reduction in DBP levels on day 7 in the Lisinopril group compared to the placebo group. Due to the significant difference in casual brachial SBP levels between Lisinopril and placebo groups at baseline (table 5.1), occurring purely by chance, the data were analysed using multiple regression analysis taking into account these baseline differences. In this analysis, SBP reduction was independently related to treatment with Lisinopril at both day 7 (p<0.05) and day 14 (p<0.05) and DBP reduction was independently related to Lisinopril treatment at day 7 (p<0.05) but not at day 14 (p=0.19).
5.3.3 Finapres BP levels

Results are presented for the 20 subjects with acceptable Finapres recordings at both baseline and day 14 in Figure 5.2. An acceptable recording comprised a stable beat-to-beat BP trace for at least 10 minutes, with < 2% ectopic beats and the presence of sinus rhythm. The natural fall in BP levels is observed in the placebo group. However, the Lisinopril group underwent additional and significant reduction in SBP levels by day 14 (p<0.05).

5.3.4 24-hour automated BP levels

24-hour automated BP data is presented for the 31 subjects for whom >12 consecutive hours of data were collected at both baseline and on day 14 (Figure 5.3). There was a significant reduction in SBP levels (p<0.05) in the Lisinopril treated group compared to placebo. Analysis of the 24-hour BP data showed a significant fall in daytime and a trend to a fall in night-time BP levels but there was no change in the diurnal ratio (ratio of daytime to evening BP levels) with therapy.

5.3.5 Outcome data

Of the 7 patients (15%) unable to complete 14 days of therapy, 4 were randomised to lisinopril and 3 to placebo. In the lisinopril group, the reasons for discontinuation of therapy were: 1) the development of hydrocephalus secondary to primary intracerebral haemorrhage necessitating transfer to a neurosurgical unit, 2) fluctuating dysphagia in the
setting of an otherwise unchanged stroke severity score, 3) the development of a severe pneumonia and 4) the development of small bowel pseudo-obstruction. In the placebo patients, one death occurred (cause of death: 1a, stroke) during the treatment period and two patients with primary intracerebral haemorrhage developed sustained SBP levels of $\geq 200$ mmHg necessitating early study withdrawal. Of those completing therapy, stroke severity and functional status measures at the beginning of the treatment period were similar with no significant differences observed between groups at day 14 (table 5.3). All study participants were followed up with regards outcome on an intention-to-treat basis over a 20-week follow-up period. Figure 5.4 shows survival curves for each group indicating the proportion of dead or dependent patients (those with a modified Rankin score of $>2$), there being no significant difference between these curves. Subgroup analysis of day 14 and 20 week outcome divided according to cortical and sub-cortical stroke showed no trend to adverse outcomes in either group. With regard safety of therapy, no participant had a recognised adverse drug-related reaction. No patient had a significant increase (doubling or more) of serum creatinine during the treatment phase and no patient exhibited a significant ($>30\%$) fall in SBP levels on receiving the first dose of study drug.
Table 5.3. Outcome variables in survivors followed up on day 14, n=40

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>Placebo group, n=23</th>
<th>Active group, n=17</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Day 14</td>
</tr>
</tbody>
</table>

Variables presented as median [interquartile range]
NIHSS – National Institutes of Health Stroke Severity scale
No significant differences between groups

Figure 5.4. Proportion dead or dependent over a 3-month period (modified Rankin >2) by treatment group (n=47). Log rank test, NS.
5.4 Discussion

This is the first study to the authors knowledge evaluating the effects of an oral ACEI administered early following the onset of acute stroke (within the first 24 hours), in patients with moderate to severe neurological severity or in patients with haemorrhagic stroke.

5.4.1 First dose response

Compared to placebo-treated patients, the first-dose antihypertensive effect of 5mg oral Lisinopril did not result in an instantaneous or excessive (>30%) fall in SBP levels in any patient with BP reduction reaching a peak by 4 hours following administration. BP reduction remained statistically significant with therapy up to 12 hours following administration. A gradual as opposed to a more rapid fall in BP levels over the first few hours of stroke may be desirable to avoid fall in CBF, more likely to occur following stroke due to impairment of dynamic cerebral autoregulatory capacity (75). Additionally, that the BP fall was sustained for at least 12 hours following a single dose might be equally important to reducing perturbations in CBF. Drugs that induce precipitous and/or short-term falls in BP levels have been implicated in the adverse outcome observed in some studies of antihypertensive therapy in the acute stroke phase, particularly intravenous and oral CCBs (9;140).

The presented results are broadly similar to those of Dyker and colleagues (86) reporting the antihypertensive effect of oral Perindopril 4mg administered between 72 and 96 hours of stroke onset. A maximum BP reduction of 18/11mmHg (compared to placebo) by hour 6 was found which remained significant at 24 hours following
administration (absolute BP at this time not reported). The BP and heart rate changes demonstrated are also in keeping with studies of the clinical pharmacology of Lisinopril in subjects with essential hypertension but without history of cerebrovascular disease (109). Cirillo et al. (65) observed the first-dose peak antihypertensive effect of oral Lisinopril to occur between 4 and 6 hours following administration for both SBP and DBP levels and the timing was not dose-related. However, the magnitude of the antihypertensive effect over 24 hours (AUC with respect to placebo) was found to be related to the dose and greater reductions were observed in SBP than DBP levels. For example, 2.5mg of Lisinopril was associated with a 16/13 mmHg BP reduction at 5 hours and 4/4 mmHg at 24 hours. A 10mg dose lead to a 27/21 mmHg reduction by hour 4 and 12/8 mmHg reduction at 24 hours. A 20/7 mmHg reduction by 4 hours in the present study is in keeping with these results, although DBP reduction appears less marked.

Differences in antihypertensive response to Lisinopril in acute stroke patients compared to subjects with essential hypertension might be expected as the underlying aetiology of the raised BP level is likely to be different. For example, in acute stroke patients high renin activity is expected in association with increased activation of the sympathetic nervous system (22).

The present study showed that with a 5mg Lisinopril dose there was no significant antihypertensive effect beyond 12 hours following administration and this might be relevant if 24-hour BP reduction is to be achieved in stroke patients with a single dose. Whilst it is accepted that the present study might have been underpowered to detect BP changes beyond 12 hours, in the study by Dyker et al. (86) fewer patients were
recruited (24 patients, 12 in each group) yet significant BP reduction up to 24 hours following a single dose was reported. However, the Dyker study recruited only patients with very mild stroke (NIHSS score <4) and during the subacute stroke phase (2 to 7 days post-ictus). The dose to peak effect is longer with Perindopril (8-10 hrs) than Lisinopril (4-6 hrs) in patients with essential hypertension (109;164). Beat-to-beat BPV may have been greater in the more severe strokes presented in the current study, providing a diluting effect on the observations and the pharmacokinetics of ACE inhibitors in the acute stroke phase are incompletely understood.

In the placebo group, a rise in SBP and DBP levels was observed during hour 4. This could not be explained by the withdrawal of previous antihypertensive therapy, although it might be expected that patients previously taking several antihypertensive drugs prior to stroke and undergoing sudden withdrawal of such therapy may exhibit a pressor response. This might have consequences for stroke evolution and the effects of sudden antihypertensive drug withdrawal need to be evaluated in a larger study.

5.4.2 Casual brachial, Finapres and 24-hr BP levels during the 14 day period

Data from the placebo-treated patients show the natural fall in BP levels that is expected to occur during the first few days of stroke, in keeping with other studies (49;116). However, once-daily therapy with Lisinopril gave rise to an additional reduction in BP levels over and above that occurring naturally and appeared to have a sustained effect during the first 14 days, however BP was measured. No reflex tachycardia was observed following repeated dosing.
No data is available from the Dyker publication (86) describing levels of BP reduction following 2 weeks of therapy with Perindopril and few data exist from other stroke trials assessing other BP-lowering therapy, for example CCBs. A Cochrane systematic review of vasoactive drugs in acute stroke (5), utilising individual patient data, reported the effects of various therapies on BP levels in the early phase (<24 hours following administration) and late phase (24 to 72 hours following administration). In the meta-analyses, oral CCBs lead to an approximate 5/2 mmHg BP reduction in the early phase and 4/1 mmHg BP reduction in the late phase. Beta-blockers were found to reduce BP by approximately 10/3 mmHg in the acute phase and 8/6 mmHg in the late phase.

In hypertensive subjects without cerebrovascular disease, results from 24-hour BP monitoring have shown a 4/4 and 10/6 mmHg reduction with 2.5 and 10mg of Lisinopril respectively on day 7 of once-daily dosing (65). Greater reductions in Finapres and casual BP levels are shown in this study, and this may be due to the timing of drug administration with respect to casual and Finapres measurements with some measurements being performed a few hours following the previous drug dose when antihypertensive effect may have been at or near maximum. 24-hour BP reduction is less marked than casual and Finapres measurements and is in keeping with the degree of BP reduction seen in non-stroke subjects (65).

5.4.3 Outcome

Therapy appeared to be well-tolerated and no patients were withdrawn from the study due to a recognised adverse drug reaction. Despite significant therapy-related falls in
BP levels, neurological outcome and functional status on day 14 and functional status over a 20-week follow-up period appeared to be similar between the groups. Although the study was not powered to detect differences in outcome between groups, it is reassuring that there was no divergence of the survival curves. On the basis of these results, larger phase III studies are now ongoing (COSSACS and CHHIPS (260)) with recruitment targets of sufficient size to evaluate the effects of antihypertensive therapy commenced within 24-hours of acute stroke on short, medium and long-term outcome.

5.4.4 Study limitations

By pure chance, the baseline casual SBP levels were statistically different between the treatment groups. This made analysis of subsequent BP change difficult as it is recognised that greater BP falls are expected in those with the highest levels during the acute stroke phase (50). To some extent, this difference was corrected for using multiple regression analysis. Nevertheless, the BP reduction in the treated group, particularly for casual BP data may have been over-estimated. Although every attempt was made to perform day 7 and day 14 follow-up measurements several hours following previous drug dosing, this was not always possible, and the lack of consistency of timing of day 7 and day 14 cardiovascular assessments in relation to the timing of drug therapy is a valid criticism of study methodology. The practicalities of conducting the study across several hospital sites and wards by a single investigator made timing in relation to drug therapy on day 7 and day 14 difficult to control for. This may explain why there is a greater reduction in casual and finapres BP levels at day 14 than 24-hour BP levels.
Compared to the distribution of unselected hospital stroke admissions according to stroke subtype, where approximately 24% of patients have a lacunar stroke syndrome according to the OCSP (19;170), lacunar stroke patients were slightly over-represented in this study (40% in the placebo group and 32% in the lisinopril group). This may have been due to only patients being able to swallow being recruited (see Appendix 1).

Although Dawson et al. (75) found there was global dysregulation of cerebral autoregulatory capacity involving both the affected and unaffected hemispheres following stroke of all subtypes, dysfunctional autoregulation may have more serious consequences for cortical infarction, where oedema and haemorrhagic transformation are more likely to have influence on stroke evolution and where collateral blood flow is important to keeping surrounding neuronal tissue viable. Although a subgroup analysis according to cortical or sub-cortical stroke revealed no trend to adverse outcome in either group, a true difference could not be discounted due to lack of statistical power. Outcome according to stroke subtype should be successfully addressed by the COSSACS and CHHIPS trials, the latter recruiting dysphagic as well as non-dysphagic patients.

5.5 Summary

In summary, the oral ACE inhibitor Lisinopril at a dose of 5mg commenced within 24-hours of stroke onset is an effective hypotensive agent, leading to a prompt and predictable BP reduction within the first few hours. Hypotensive effect is sustained during the acute and sub-acute phase of stroke (first 14 days) with a once-daily formulation. Therapy for the first 14 days following stroke is associated with similar outcome measurements on day 14 and at 20-weeks follow up to those patients taking
placebo. The evidence base is increasing that BP reduction for hypertensive patients in the acute phase of stroke, particularly with drugs affecting the renin-angiotensin system, is not associated with adverse outcome in contrast to treatment with some other antihypertensive drug classes (9;21). ACE inhibitors may maintain CBF levels with concomitant antihypertensive effect following stroke and this has been shown in a number of studies (86;319). Despite the limited power of the present study, to the author's knowledge no previous work has studied ACE inhibition as early following stroke symptom-onset, in patients with a high level of neurological severity or to include patients with primary intracerebral haemorrhage. Lisinopril is a promising therapy to be explored further as treatment for hypertension in the acute stroke phase and the phase III studies are currently underway (260).

5.6. Conclusions

- Oral Lisinopril 5mg in a once-daily formulation results in prompt reduction of BP levels when administered immediately in the acute stroke phase (within 24 hours of stroke symptom-onset) and leads to sustained BP reduction during the acute and subacute stroke phases (first 14 days).

- Therapy appears to be well-tolerated and neutral in effect of patient outcome in this pilot study.
6. EFFECT OF ORAL LISINOPRIL ON
HAEMODYNAMIC STABILITY AND
CARDIOVASCULAR REFLEXES IN THE ACUTE AND
SUBACUTE PHASES OF STROKE
6.1 Background and aims

It has already been shown in this thesis that both beat-to-beat BPV levels and cardiac BRS are related to arterial stiffness and absolute BP levels in the acute stroke phase (i.e. at least for the first 14 days following ictus) (Chapters 3 and 4). It has also been shown that a single dose of oral Lisinopril 5mg within the first 24 hours of ictus decreases BP levels within the first few hours of administration and leads to sustained BP reduction in a once-daily regime during the acute stroke period (Chapter 5). This approach to the treatment of elevated BP levels immediately following stroke has been shown to be well-tolerated and does not appear to be associated with any short or medium-term adverse effect.

Pharmacological reduction of BP levels in the acute stroke phase might also be associated with changes in other related cardiovascular variables such as arterial stiffness, beat-to-beat BPV and cardiac BRS. Furthermore, treatment with ACEI might be associated with additional changes in these parameters due to effects over and above BP reduction. For example, ACEI have been shown to have BP-independent effects on cardiac BRS and arterial stiffness levels in hypertensive patients without cerebrovascular disease (125;187).

The hypothesis for the study was that oral Lisinopril administered within 24 hours of acute stroke and continued once-daily for 14 days would decrease central arterial stiffness and lead to a decrease in beat-to-beat BPV levels and an increase in cardiac BRS levels.
6.2 Methods

6.2.1 Protocol

Data from the patients participating in the CHIPS study were used for the analysis. Detailed description of the study is to be found in Chapter 5 but, in brief, this was a randomised, placebo-controlled, double-blind, parallel group study of patients with elevated casual brachial BP levels (SBP \( \geq 140 \) or DBP \( \geq 90 \) mmHg) in the acute phase of stroke (recruited within 24 hours of symptom-onset). The effect of oral Lisinopril therapy compared to placebo therapy commenced immediately and continued once-daily for the subsequent 14 days was evaluated. Where brachial SBP levels were \( \geq 140 \) or DBP \( \geq 90 \) mmHg on day 7 of the study, therapy was doubled for the subsequent 7 days (two Lisinopril 5mg [10mg] or two placebo capsules).

Data from the 20 patients undergoing successful 10-minute Finapres recordings on both day 0 (prior to randomisation) and on day 14 of the study (following the last dose) were analysed. Finapres recordings less than 10 minutes duration, with an ectopic beat rate \( >2\% \) or containing atrial fibrillation were rejected. Finapres recordings were analysed without any prior editing of ectopic beats to derive beat-to-beat BP and PI indices. Beat-to-beat BPV and PIV were calculated as the standard deviation of each parameter recorded over the 10-minute period. Cardiac BRS was calculated using a time domain (sequence analysis) method previously described in Chapter 4. Applanation tonometry was used to derive aortic PWV, aortic AIx, aortic Tr and aortic BP indices as previously described in Chapter 2. Aortic BP measurements were calibrated to casual brachial BP levels using a validated monitor (A&D UA-767). PP
amplification, the degree to which PP increases from central to peripheral arteries as a function of pulse wave reflection, was calculated by casual brachial PP divided by aortic PP.

6.2.2 Statistical methods

The Student's t test and the Mann-Whitney U test were used for the comparison of changes in cardiovascular variables according to the treatment group. Statistical significance was taken at the 5% level.

6.3 Results

6.3.1 Baseline data

20 patients (11 female) participated in the study. All participants took >90% of the prescribed study medication, and there were no adverse treatment-related effects during the course of the treatment period. There was no significant increase (doubling) in serum creatinine with treatment. Baseline demographic, cardiovascular data and the changes in cardiovascular variables according to allocated treatment group are displayed in tables 6.1, 6.2 and 6.3. Absolute BP levels, beat-to-beat BPV, PIV and aortic PWV levels tended to be higher in the Lisinopril-treated group at baseline compared to the placebo-treated group, although there was no statistically significant difference between the groups.
6.3.2 Day 14 data

The changes in cardiovascular parameters between treatment groups over the 14 day study period are shown in tables 6.2 and 6.3 and graphically represented in figures 6.1 and 6.2. On day 14, there was a significant reduction in SBP, MAP and PP levels \((P<0.05)\) in the Lisinopril-treated group compared to the placebo-treated group with casual brachial BP measurements and this observation was reflected by all the BP measurement methods (Finapres and derived aortic BP). There were no significant differences in the reduction of beat-to-beat BPV levels for all BP parameters between the Lisinopril-treated compared to the placebo-treated patients. There were also no significant differences between the changes in PI, beat-to-beat PIV, cardiac BRS, aortic PWV AIx or Tr between the Lisinopril-treated compared to the placebo-treated patients, although there was a trend to reduction in aortic PWV. Study sample size was inadequate to test if any changes were independent of BP reduction. Lisinopril therapy did not cause a preferential reduction in central PP over peripheral PP (increase in PP amplification) when compared to placebo therapy.
Table 6.1. Demographic data at baseline according to treatment group.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Day 0 (baseline)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lisinopril,</td>
<td>Placebo,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n=10</td>
<td>n=10</td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>70 ± 15</td>
<td>72 ± 10</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>3M :7F</td>
<td>6M :4F</td>
<td></td>
</tr>
<tr>
<td>Stroke type</td>
<td>9 infarct : 1 ICH</td>
<td>9 infarct : 1 ICH</td>
<td></td>
</tr>
<tr>
<td>Time between ictus and</td>
<td>19 ± 5</td>
<td>20 ± 5</td>
<td></td>
</tr>
<tr>
<td>randomisation (hrs)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke severity (NIHSS)</td>
<td>9 ± 5</td>
<td>8 ± 4</td>
<td></td>
</tr>
<tr>
<td>Dose increase (on day 7)</td>
<td>6/10</td>
<td>9/10</td>
<td></td>
</tr>
</tbody>
</table>

No statistically significant differences in baseline data between groups
Table 6.2. Baseline and day 14 BP levels according to treatment group.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Day 0 (baseline)</th>
<th>Day 14</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lisinopril, n=10</td>
<td>Placebo, n=10</td>
</tr>
<tr>
<td>Casual brachial SBP (mmHg)</td>
<td>178 ± 22</td>
<td>172 ± 24</td>
</tr>
<tr>
<td>MAP</td>
<td>119 ± 17</td>
<td>117 ± 10</td>
</tr>
<tr>
<td>DBP</td>
<td>89 ± 17</td>
<td>89 ± 9</td>
</tr>
<tr>
<td>PP</td>
<td>90 ± 16</td>
<td>83 ± 25</td>
</tr>
<tr>
<td>Finapres SBP (mmHg)</td>
<td>169 ± 26</td>
<td>166 ± 24</td>
</tr>
<tr>
<td>MAP</td>
<td>107 ± 18</td>
<td>105 ± 23</td>
</tr>
<tr>
<td>DBP</td>
<td>74 ± 26</td>
<td>74 ± 24</td>
</tr>
<tr>
<td>PP</td>
<td>95 ± 22</td>
<td>92 ± 21</td>
</tr>
<tr>
<td>Derived aortic SBP (mmHg)</td>
<td>167 ± 23</td>
<td>161 ± 24</td>
</tr>
<tr>
<td>MAP</td>
<td>116 ± 18</td>
<td>114 ± 10</td>
</tr>
<tr>
<td>DBP</td>
<td>91 ± 18</td>
<td>91 ± 9</td>
</tr>
<tr>
<td>PP</td>
<td>76 ± 15</td>
<td>70 ± 26</td>
</tr>
<tr>
<td>PP amplification</td>
<td>1.2 ± 0.1</td>
<td>1.2 ± 0.1</td>
</tr>
</tbody>
</table>

Drug effect†

-27 [-47, -7]*
-15 [-27, -2]*
-9 [-19, +2]
-18 [-33, -3]*
-22 [-48, +4]
-11 [-33, +10]
-6 [-28, +16]
-16 [-36, +4]
-23 [-43, -3]*
-14 [-27, -2]*
-10 [-21, +1]
-13 [-28, +3]
0.0 [-0.0, +0.1]

No statistically significant differences in baseline data between groups.
Data presented as mean ± standard deviation except † mean and 95% confidence intervals. *P<0.05
Table 6.3. Changes in cardiovascular parameters according to treatment group.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Day 0 (baseline)</th>
<th>Day 14</th>
<th>Difference between lisinopril and placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lisinopril, n=10</td>
<td>Placebo, n=10</td>
<td>Lisinopril, n=10</td>
</tr>
<tr>
<td>Pulse interval (ms)</td>
<td>867 ± 149</td>
<td>918 ± 128</td>
<td>922 ± 141</td>
</tr>
<tr>
<td>Pulse interval variability (ms)</td>
<td>59 ± 37</td>
<td>49 ± 45</td>
<td>40 ± 23</td>
</tr>
<tr>
<td>Finapres beat-to-beat SBPV (Variability) (mmHg)</td>
<td>10.7 ± 4.7</td>
<td>10.1 ± 3.3</td>
<td>9.2 ± 3.8</td>
</tr>
<tr>
<td>MAPV</td>
<td>7.5 ± 3.5</td>
<td>6.8 ± 1.9</td>
<td>6.0 ± 2.6</td>
</tr>
<tr>
<td>DBPV</td>
<td>5.7 ± 2.8</td>
<td>5.0 ± 1.5</td>
<td>4.3 ± 1.7</td>
</tr>
<tr>
<td>PWV carotid-femoral (m/s)</td>
<td>11.4 ± 2.0</td>
<td>13.1 ± 2.4</td>
<td>10.3 ± 1.8</td>
</tr>
<tr>
<td>AIx (%)</td>
<td>31 ± 6</td>
<td>28 ± 8</td>
<td>34 ± 5</td>
</tr>
<tr>
<td>Tr (ms)</td>
<td>132 ± 6</td>
<td>133 ± 6</td>
<td>130 ± 9</td>
</tr>
<tr>
<td>Cardiac BRS (ms/mmHg)</td>
<td>6.2 ± 2.4</td>
<td>5.2 ± 4.0</td>
<td>5.7 ± 3.7</td>
</tr>
</tbody>
</table>

Data presented as mean ± standard deviation except † mean and 95% confidence intervals.
No statistically significant differences between groups for baseline data or according to drug therapy.
AIx – aortic augmentation index, Tr – aortic time to reflected wave
Figure 6.1. Plots of beat-to-beat BPV, PIV and cardiac BRS across 14-day study period according to treatment group. (Mean ± S.E, individual data for cardiac BRS)
Cardiac baroreceptor sensitivity (ms/mmHg)

Placebo

Lisinopril

Day 0

Day 14

Sequence BRS
Figure 6.2. Plots of aortic PWV and AIx across 14-day study period according to treatment group. (Mean ± S.E.)
6.4 Discussion

This is the first study, to the author’s knowledge, to evaluate the effects of antihypertensive therapy on beat-to-beat BPV, PI and arterial stiffness indices during the acute phase of stroke.

6.4.1 BP levels

The effect of therapy on absolute BP levels has been discussed in Chapter 5, but briefly a 22/6 mmHg reduction in finapres BP levels is in keeping with other previous studies of ACEI therapy in acute stroke (86) and non-stroke subjects (65).

6.4.2 Beat to beat parameters and cardiac BRS

Although no reduction in beat-to-beat BPV levels for BP parameters was found in the Lisinopril-treated group in comparison to the placebo-treated group, this might have been expected considering the results from other studies conducted in hypertensive patients without cerebrovascular disease. Veerman et al. (310), in a study of the ACEI Spirapril utilising power spectral analysis to assess beat-to-beat SBPV found a significant reduction in relative power in the mid-frequency band (0.08 - 0.12 Hz) compared to placebo following only a single oral dose and this decrease was sustained following 8 weeks of treatment. The finding that there was no increase in beat-to-beat PIV and cardiac BRS with Lisinopril therapy in the presented work also run contrary to the findings of previous studies. Improvement in cardiac BRS has been observed with short periods of ACEI therapy in non-stroke patient groups. For example, a 7 day
course of oral Enalapril 5mg in elderly hypertensive patients has been shown to increase cardiac BRS (210) and a single dose of oral Captopril 50mg has been shown to improve cardiac BRS within one hour of administration following acute myocardial infarction (192). A 3-month duration of therapy with oral Quinapril has also been shown to lead to an increase in beat-to-beat PIV in patients with diabetic autonomic neuropathy (151). Reduction in BP levels in the acute stroke phase might have been expected to lead to differences in cardiac BRS as indicated in Chapter 4. The confidence intervals for the change in cardiac BRS were wide (table 6.3) suggesting lack of power in the study. Similarly, wide confidence intervals were found for the changes in beat-to-beat BPV and no account was taken for the effects of other potentially influencing variables such as respiratory activity.

6.4.3 Arterial stiffness

There was a trend to arterial stiffness reduction (as measured by aortic PWV and Tr) and no change in central AIX in the Lisinopril-treated group in comparison to the placebo-treated group. Reductions in aortic PWV, independently of BP reduction, have been found in hypertensive subjects without history of cerebrovascular disease following a single dose of oral quinapril (304), and following 8 weeks of oral Lisinopril therapy (282). ACEI have also been shown to reduce central AIX following short treatment durations, for example: oral captopril 100mg daily for 4 weeks (187), iv. captopril mean single dose 11mg and Fosinopril 10mg for 8 weeks in hypertensive subjects (300). Some studies suggest that ACEI may be more efficacious in lowering AIX than some other antihypertensive drugs, in particular beta-blockers (64;79). Perhaps reflecting the lack of change in indices of pulse wave reflection, there was no
preferential increase in PP amplification with Lisinopril therapy compared to placebo. A reduction in PP amplification has been shown to have important prognostic significance for patients with end-stage renal disease (270) and is thought to be associated with an increasing central AIx.

The pharmacological mechanisms by which ACE inhibitors might have effect on cardiovascular reflexes, beat-to-beat BPV and arterial stiffness are discussed in Chapter 1, but briefly, blockade of the central actions of angiotensin II on medullary receptors appears to shift autonomic balance in favour of parasympathetic activity, which may promote an increase in cardiac BRS and reduce beat-to-beat BPV (220). In addition to BP reduction, blockade of angiotensin II effects on the vascular endothelium may reduce local oxidative stress and improve the bioavailability of nitric oxide leading to a reduction in arterial stiffness (178).

6.4.4 Study limitations

The study was underpowered to detect any effect of treatment on the measured cardiovascular variables as indicated by the wide confidence intervals and any effect of therapy may also have been masked by the higher although non-significant baseline levels of absolute BP and beat-to-beat BPV at baseline in the Lisinopril-treated patients. Consequently the presented results should be considered exploratory and a larger body of work is now ongoing (260) to explore the effects of Lisinopril and other antihypertensive drugs on cardiovascular and cerebrovascular haemodynamics during the acute stroke phase.
The results presented previously in this thesis (Chapters 3 and 4) would suggest that pharmacological BP and arterial stiffness reduction during the acute stroke phase might be associated with favourable effects on other cardiovascular parameters. However, the mechanisms underlying some of the cardiovascular abnormalities may differ in acute stroke patients from hypertensive patients free of cerebrovascular disease and be less responsive to pharmacological intervention as a result. For example, increased beat-to-beat BPV may be associated with upper airway obstruction (306) as well as increased SNSA (22), BP and arterial stiffness levels. A 14-day treatment period with oral Lisinopril might be of insufficient duration to significantly influence these other cardiovascular variables in the acute stroke phase, and this point requires further evaluation.

6.5 Summary

In summary, once-daily oral Lisinopril therapy commenced within 24 hours of ictus and continued for 14 days is shown in this study not to result in significant changes in aortic stiffness, beat-to-beat BP variability or cardiac BRS levels despite significant reduction in absolute BP levels. Larger and sufficiently powered studies are currently ongoing to evaluate further the effects of ACEI therapy in the acute stroke phase.

6.6 Conclusions

- Oral lisinopril 5mg administered once-daily for 14 days and commenced within 24 hours of stroke-symptom onset did not result in significant changes in arterial stiffness, BP variability or cardiac BRS.
• The study may have been underpowered to detect such changes and larger, sufficiently powered studies are required.
7. CONCLUSIONS
In this thesis I undertook 2 different phases of study. Phase I looked at the relation of arterial stiffness to stroke type and its effect on cardiac baroreceptor sensitivity and beat-to-beat blood pressure variability and in phase II the effect of oral Lisinopril as treatment for hypertension immediately following stroke was evaluated.

7.1 Phase I: Arterial stiffness and stroke

7.1.1 Summary of study findings

In Chapter 2 I examined central and peripheral arterial stiffness utilising pulse wave velocity and analysis measurements derived by applanation tonometry in patients with acute ischaemic stroke and matched control subjects. Previous observational studies had reported increases of central arterial stiffness, assessed using a variety of methods, in patients with cerebrovascular disease (83;166;292) and at varying time intervals following the acute event (from a few days to several years) independently of differences in other cardiovascular risk factors including blood pressure. However, the association of cerebrovascular disease with pulse wave analysis or muscular arterial stiffness, or the effect of stroke subtype had not been previously evaluated. Although in the stroke group no overall difference was found in central arterial stiffness in comparison to control subjects, when considering the differences in other cardiovascular variables, differences were found in the subgroup analyses of stroke subtype. The results suggest that arterial stiffness may be selectively associated with stroke of arterial but not cardioembolic origin. No significant differences were found in the markers of pulse wave reflection or muscular arterial stiffness between the stroke and control groups suggesting the pathophysiology predisposing to stroke has predilection for the 'stiffening' of central elastic arteries. Acute stroke per se might not cause increased arterial stiffening, as arterial stiffness markers were not elevated in
patients with cardioembolic stroke, but due to the limited sample size caution should be exercised in making multiple inferences and larger studies are required to confirm the findings.

The study does however lend weight to other investigations showing that augmentation index may not be a useful surrogate marker of central arterial stiffness and may be of little value in predicting stroke risk (157), although this requires a more thorough evaluation in a prospective study.

The presented results are in keeping with the prospective study by Laurent et al. (163) showing aortic pulse wave velocity to be related to the risk of fatal stroke. The link between arterial stiffness and stroke may be due to the associated increase in pulse pressure, which has particularly adverse consequences for the extra and intra-cranial circulation. For example, it is recognised that carotid artery intima-media thickness, atherosclerotic plaque formation and plaque instability are more closely related to pulse pressure than any other blood pressure parameters (43;183;344). However other mechanisms might also be responsible and detailed discussion of these is to be found in Section 1.2.6.

Chapter 3 explored the relationship between impaired cardiac baroreceptor sensitivity levels in the acute phase of stroke and other cardiovascular variables including central arterial stiffness. For the first time in acute stroke patients, it is shown that impaired cardiac baroreceptor sensitivity is related to other cardiovascular factors including central arterial stiffness, age, previous vascular history and heart rate. The relationship with arterial stiffness persists for at least the first 14 days following stroke. The role of
any neurological factor is less clear in this study and the data suggest that cardiovascular factors sufficiently explain the cardiac baroreceptor sensitivity level with the presence of stroke appearing irrelevant. However, neurological effects on cardiac baroreceptor sensitivity cannot be discounted in the light of previous studies (22;115;120) and further work is required to assess the effects of stroke laterality and subtype on cardiac baroreceptor sensitivity.

Chapter 4 studied the dynamic relationships between cardiac baroreceptor sensitivity, beat-to-beat blood pressure variability, arterial stiffness and blood pressure values during the first 14 days following acute stroke. The principal findings were that the degree of beat-to-beat blood pressure variability was much more closely related to central arterial stiffness than cardiac baroreceptor sensitivity and both the changes in aortic pulse wave velocity and cardiac baroreceptor sensitivity were related to the blood pressure changes during the first 14 days following stroke. This implies that blood pressure reduction in the acute stroke phase may have pleotropic effects being associated with improvements in cardiac baroreceptor sensitivity and arterial stiffness, the latter being associated with a reduction in beat-to-beat blood pressure variability.

7.1.2 Implications and limitations of observational study findings

The first 3 chapters shed more light on the relevance of central arterial stiffness to increased stroke risk and on some of the pathological mechanisms that have prognostic relevance in the acute stroke phase. The current evidence suggests a measure of arterial stiffness in the clinical setting might be usefully included in stratifying individuals already at high risk of stroke. An elevated value might promote more detailed
investigation, for example, duplex ultrasound to evaluate carotid artery structure. Carotid plaques have been identified as being associated with aortic stiffness (345). From this study, and others (163), aortic pulse wave velocity might be the most sensitive non-invasive measure of arterial stiffness, but in larger populations a measure of the peripheral arterial waveform might be preferable as this is more convenient to measure. From the results of this work, the aortic time to reflected wave (aortic Tr) derived from the radial artery using a generalised transfer function appears to show potential and requires evaluation in a larger study. Alternative indices might also be evaluated, for example, the untransformed radial artery waveform which some authors have suggested may provide useful information on central arterial stiffness (200).

In the acute stroke phase, aortic stiffness is related to the prognostically relevant indices of beat-to-beat blood pressure variability and cardiac baroreceptor sensitivity. Given arterial stiffness is a risk factor for stroke, it is implied that cardiac baroreceptor sensitivity may have been impaired before stroke in these high risk individuals due to probable association with aortic stiffness in these patients prior to stroke. However, the pressor effect of acute stroke may have further splinted arterial baroreceptors coupling cardiac baroreceptor sensitivity and arterial stiffness more closely. Impairment of cardiac baroreceptor sensitivity has been shown to be a risk factor for cardiovascular disease (stroke and myocardial infarction) in hypertensive individuals free of cerebrovascular disease (159). The extent to which pulse wave velocity and cardiac baroreceptor sensitivity predict the risk of a primary stroke and the relative powers of each and their role in combination deserves further exploration.
Impaired cardiac baroreceptor sensitivity has long (months and years) but not short term (days and weeks) prognostic significance following stroke (258). Beat-to-beat blood pressure variability has short-term prognostic relevance (days and weeks) (77) and long-term significance has not been reported. Increased beat-to-beat blood pressure variability may influence short term outcome via increased oscillation in cerebral blood flow working in tandem with impaired dynamic cerebral autoregulation (75) thereby causing ischaemia, hyperaemia and reperfusion injury to the ischaemic penumbra. The lack of an association between cardiac baroreceptor sensitivity and beat-to-beat blood pressure variability in the acute stroke phase is a potential explanation for the observation that cardiac baroreceptor sensitivity abnormalities do not appear to convey short-term prognostic information post-stroke. In parallel with the situation before stroke, cardiac baroreceptor sensitivity may simply reflect the burden of risk factors such as age, arterial stiffness, previous cardiovascular history and heart rate indicating subsequent cardiovascular risk irrespective of the index event. Alternatively impaired cardiac baroreceptor sensitivity may arise as a consequence of stroke and have direct influence on outcome through increase in sympathetic nervous system activity, circulating catecholamines and activated platelets.

7.1.3 Prospects for further studies

It is yet to be established if a targeted reduction in arterial stiffness as well as other cardiovascular risk factors in high-risk patients is associated with a reduction in the primary incidence of cardiovascular disease including stroke. To date, evidence that this might be an effective strategy is very limited. A small trial of patients with end-stage renal disease showed that persistence of the reversibility of aortic stiffness in
response to blood pressure lowering had a beneficial and blood pressure-independent impact on long-term survival (months to years) (114).

Reductions in arterial stiffness with or without blood pressure reduction may, from the data presented, lead to improvements in beat-to-beat blood pressure variability and cardiac baroreceptor sensitivity in patients with acute stroke and this requires further evaluation. Blood pressure reduction per se, in the acute phase of stroke, may achieve reductions in arterial stiffness but this is not shown in the present study with a 5mg oral once-daily Lisinopril regime, despite a significant blood pressure reduction.

Antihypertensive medications influence arterial stiffness on a functional basis by reducing arterial wall distension but will often fall short of optimally reducing age-related increases in central arterial stiffness and pulse pressure (96). Some drugs appear to possess properties that specifically influence arterial stiffness. Over the longer term (months), reduced-sodium diets that are used to achieve a negative salt balance, with or without the use of diuretics, can reduce arterial stiffness independently of blood pressure (308). Medications that decrease sodium-associated arterial stiffness (eg. thiazide diuretics and spironolactone) may reduce collagen accumulation in arteries (29). It has been suggested that ACE inhibitors may reduce arterial stiffness independently of blood pressure reduction by effects on endothelial function and, in the longer term, via vascular remodelling. Long-term therapy with ACE inhibitors and angiotensin receptor blockers promotes arterial remodelling via inhibition of renin-angiotensin system-associated extracellular matrix deposition (11). Reductions in aortic pulse wave velocity with short-term ACE inhibitors therapy have been shown, for example oral quinapril 20mg single-dose in hypertensive subjects (304) but
controlling for the influence of blood pressure change has been problematic in studies to date.

Other drug classes may have direct influence over arterial stiffness. The non-lipid lowering effects of statins are of current interest. Statins may modify vascular endothelial function via upregulation of endothelial nitric oxide synthase and amelioration of oxidative stress. In patients with familial hypercholesterolaemia arterial stiffness was reduced after 2 years treatment with simvastatin, but not by 6 months of therapy indicating a prolonged time required to improve arterial stiffness in hypercholesterolaemic patients (103). A new class of drugs, advanced glycation end-product (AGE) cross-link breakers, have now reached evaluation in Phase II studies. Alagebrium (ALT-711) is a thiazolium derivative that breaks established AGE cross-links between collagen proteins implicated in arterial stiffening. In an animal study, alagebrium therapy reduced all indices of large artery stiffness (slowing pulse wave velocity and reducing carotid artery distensibility) (293). In a study of elderly patients with advanced arterial stiffening, 8-week therapy with oral alagebrium significantly decreased pulse pressure and increased arterial compliance in comparison with placebo with no significant change in mean arterial pressure (139). These preliminary studies highlight the potential of a specific drug to alter arterial function via changes in the extracellular matrix, with specific effects on arterial stiffness, pulse pressure and systolic blood pressure.
7.2 Phase II: ACE inhibition in acute stroke

7.2.1 Summary of study findings

Chapter 5 presented the results of a randomised placebo-controlled parallel group pilot study evaluating the effect of oral Lisinopril for the treatment of hypertension immediately following acute stroke. Administered orally within 24-hours of symptom onset, Lisinopril 5mg was an effective hypotensive agent, leading to a prompt but not rapid blood pressure reduction within the first few hours. Hypotensive effect was sustained during the acute and sub-acute phase of stroke (first 14 days) with a once-daily formulation. Therapy for the first 14 days following stroke was associated with similar outcome measurements on day 14 and at 20-weeks follow up to those patients taking placebo. No adverse effects were observed in relation to treatment, in particular no neurological worsening or rise in serum creatinine. This investigation and other similar work (86;277) confirms that the ACE inhibitors Lisinopril does not appear to lead to adverse patient outcome as treatment for hypertension during the acute phase of stroke and may, perhaps, provide benefit. In other studies, ACE inhibitors and angiotensin receptor blockers are shown to preserve cerebral blood flow in tandem with falls in blood pressure and cerebral perfusion pressure (86;215), and data on cerebral blood flow from a subgroup of patients in the CHIPS study is to be subsequently evaluated.

Chapter 6 presented the findings from a sub-group of patients participating in the pilot study evaluating the effect of therapy on these other haemodynamic indices, including beat-to-beat blood pressure variability and cardiac baroreceptor sensitivity. Despite
significant reduction in blood pressure levels in the subgroup, improvements in arterial stiffness, cardiac baroreceptor sensitivity or beat-to-beat blood pressure variability were not shown in relation to the study drug although the wide confidence intervals for mean differences suggest this study was underpowered to detect such differences.

7.2.2 Implications and limitations of study findings

How might immediate blood pressure reduction bring about benefit to the hypertensive acute stroke patient? It is well-recognised that an elevated blood pressure level correlates with an increased risk of adverse short term outcome (170;254) although the mechanisms are unclear and may be related to an increased risk of cerebral oedema or haemorrhagic transformation of infarct. To date, most trials of blood pressure lowering have reported neutral or trends to negative outcomes. The ACCESS study reported a positive outcome in relation to angiotensin receptor blocker therapy (277) but did not, surprisingly, show any blood pressure reduction with the active therapy (Candesartan) compared with placebo during the treatment phase. Work from this thesis has gained some insight into where additional cardiovascular benefits may lie. Firstly, it has been shown that central arterial stiffness and cardiac baroreceptor sensitivity are related to the blood pressure level in the acute stroke phase and, secondly, beat-to-beat blood pressure variability is dependent upon central arterial stiffness, which in turn is related to the blood pressure level. Although caution is to be exercised in interpreting these multiple inter-relationships with a relatively small study, blood pressure reduction may appear to improve several prognostically-important parameters.
The CHIPS pilot study provides sufficient evidence that therapy with ACE inhibitors in the acute phase of stroke should be evaluated in a larger (phase III) trial powered to evaluate patient outcome. However, despite broader inclusion criteria than some other trials of antihypertensive therapy in acute stroke (for example, recruiting patients with milder elevations in blood pressure (277)) one limitation to the pilot study was that only patients who were conscious and able to swallow were included. 18% of the screened patients were found to be dysphagic (see Appendix 1). Partly as a result, there may have been an excess of strokes of milder severity and with lacunar pathology compared to unselected stroke admissions (Chapter 5.4.4). Patients with systolic blood pressure levels ≥140 mmHg (15% of CHIPS participants had baseline systolic blood pressure levels between 140 and 149 mmHg – Appendix 1) were recruited, although the IST data (170) (published after the set up of the trial) suggested optimum short and medium-term survival with admission systolic blood pressure levels between 140 and 179 mmHg with a nadir at 150 mmHg. The study was underpowered to evaluate outcome and to provide information on the effect of baseline blood pressure and achieved blood pressure.

7.2.3 Prospects for further studies

We have come a long way from the rather nihilistic approach to the management of acute stroke that existed only a few years ago. As a result of an ever-expanding evidence-base more stroke patients are admitted to hospital and more (although not yet all) are receiving early active therapy in a dedicated stroke unit. In the next few years we may also be moving away from the current approach of leaving elevated blood pressure levels untreated unless associated with another medical emergency, as is the
current recommendation (265). While the evidence base for other antihypertensive
drug classes including assessments of cerebral blood flow and patient outcome is not
uniformly favourable, all the published data to date on the use of ACE inhibitors or
angiotensin receptor blockers are encouraging, although caution should be exercised
until the larger trials have reported. The major ongoing trials evaluating blood pressure
reduction in the acute phase of stroke are detailed below.

7.2.3.1 CHHIPS trial

On the basis of the data from the CHIPS study presented herein, a large multicentre
phase III study is now ongoing. Control of Hypertension and Hypotension
Immediately Post-Stroke (CHHIPS) is a randomised, double-blind, placebo-controlled,
step-therapy trial evaluating 5mg Lisinopril in oral or sublingual formulation, with the
advantage that dysphagic patients can also be recruited (comprising approximately
one-third of unselected acute stroke admissions). Subgroups of this study are
evaluating the effects on cardiovascular variables such as arterial stiffness, cerebral
blood flow and cerebral autoregulation, cardiac baroreceptor sensitivity and beat-to-
beat blood pressure variability in the acute stroke phase and the study should be
sufficiently powered to establish the effects on short and medium term outcome. This
trial is also evaluating Labetalol in an oral and intravenous formulation for the
treatment of hypertension in the acute phase of stroke. Labetalol has been shown in a
small trial to have no adverse effect when given following cerebral haemorrhage and
may ameliorate excess SNSA (260). The primary outcome measure of CHHIPS is
death and disability at 2 weeks post-stroke, and secondary neurological status,
disability and health-related quality of life outcomes are evaluated at 2 weeks and 6 months.

7.2.3.2 COSSACS trial

Up to 40% of acute stroke patients are already taking antihypertensive therapy on hospital admission (97) and it remains uncertain if pre-existing therapy should be continued or stopped. The Continue Or Stop post-Stroke Antihypertensives Collaborative Study will establish the efficacy and safety of blood pressure manipulation in the acute stroke period by the continuation or stopping of pre-existing therapy. Primary outcome is death or dependency at 2 weeks and secondary outcomes include neurological status and disability and quality of life outcomes at 2 weeks and 6 months, as well as 6-month mortality.

7.2.3.3 ENOS trial

The Efficacy of Nitric Oxide in Stroke trial is a prospective, multicentre, randomised, parallel-group, double-blind, placebo-controlled trial designed to test the safety and efficacy of nitric oxide, given as transdermal glyceryl trinitrate within 48 hours of stroke onset. The primary outcome measure is death and dependency at 3 months and effects on stroke recurrence, blood pressure changes, cerebral blood flow and the arterial pulse wave are early secondary outcome measures. Late secondary outcome measures include quality of life indicators, cognition and neurological status and disability.
7.3 Summary

Within the next decade further advances may occur in the identification of cardiovascular event risk in high risk individuals in routine clinical practice utilising an assessment of arterial stiffness. Specific drug therapy targeted at arterial stiffness reduction, together with control of other cardiovascular risk factors is likely to be evaluated in phase III trials. Treatment of hypertension in the acute phase of stroke is to be further evaluated in ongoing trials with the results of these trials hopefully providing some answers to the common questions about the clinical management of acute stroke for which no firm evidence currently exists: should previous blood pressure lowering therapy be stopped following stroke, at what blood pressure level should intervention with antihypertensive therapy take place and to what blood pressure target, and which drug should be used. Further analysis of the results may provide information according to stroke subtype including haemorrhage, baseline and target blood pressure levels and, from CHHIPS, whether elevation of blood pressure for relative hypotension is of benefit. Subgroups of these studies will further evaluate changes in other relevant cardiovascular variables and should possess sufficient statistical power to inform which changes are particularly relevant to improving outcome: arterial stiffness, cardiac baroreceptor sensitivity, cerebral autoregulation, beat-to-beat blood pressure variability or other cardiovascular parameter.
Appendix 1: CHIPS recruitment data

During the period of recruitment for the CHIPS pilot study (March 2002 to October 2003) 47 patients were recruited (Chapter 5). In all, 130 patients with a clinical diagnosis of acute stroke and presenting to hospital within 24 hours of symptom-onset were reviewed. 36% of patients met all the suitability criteria for the study (Table 8.1). 35 (27%) of screened patients had blood pressure levels below the levels required for participation. This figure is consistent with the IST data where 32% of unselected ischaemic stroke admissions had a SBP level below 150 mmHg within 48 hours of ictus (170). The reasons for non-participation and respective frequencies are displayed in table 8.2.
Entry criteria for the CHIPS pilot study.

- Stroke symptom-onset within previous 24 hours
- Mean casual brachial SBP ≥140 or DBP ≥90 mmHg over 30 minutes
- Non-dysphagic
- Pre-morbid modified Rankin score < 3
- Provision of informed consent (patient) or assent (relative)
- Serum creatinine < 200 umol/l
- No known contraindication to ACEI therapy
- No requirement to continue therapy with antihypertensive effect (eg. angina)
- No concomitant medical emergency eg. myocardial infarction, aortic dissection
- No uncontrolled congestive cardiac failure
- No features of severe aortic stenosis (>50mmHg)
- No established significant carotid stenosis (>70%)
- No signs of dehydration
Frequencies of non-participation in the CHIPS trial in patients presenting with symptoms of acute stroke within 24 hours of onset (more than one contraindication present in some patients).

<table>
<thead>
<tr>
<th>Reason for non-participation</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP &lt;140 and DBP &lt;90 mmHg</td>
<td>35</td>
<td>27%</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>24</td>
<td>18%</td>
</tr>
<tr>
<td>Pre-morbid modified rankin score &gt; 2</td>
<td>8</td>
<td>6%</td>
</tr>
<tr>
<td>Transient ischaemic attack</td>
<td>8</td>
<td>6%</td>
</tr>
<tr>
<td>Non-provision of consent/assent</td>
<td>4</td>
<td>3%</td>
</tr>
<tr>
<td>Requirement to continue antihypertensive therapy</td>
<td>4</td>
<td>3%</td>
</tr>
<tr>
<td>Serum creatinine &gt; 200 umol/l</td>
<td>4</td>
<td>3%</td>
</tr>
<tr>
<td>Uncontrolled congestive cardiac failure</td>
<td>3</td>
<td>2%</td>
</tr>
<tr>
<td>Antihypertensive therapy already taken following stroke</td>
<td>3</td>
<td>2%</td>
</tr>
<tr>
<td>Severe aortic stenosis</td>
<td>1</td>
<td>1%</td>
</tr>
<tr>
<td>Concomitant vascular emergency</td>
<td>1</td>
<td>1%</td>
</tr>
</tbody>
</table>
Some patients were referred, particularly out-of-hours (6 p.m to 9 a.m weekdays and at weekends), by attending medical staff. Some bias in the above data may therefore have arisen, as to a variable extent medical staff performed some preliminary screening prior to telephone referral. The data cannot therefore be interpreted as necessarily indicative of the characteristics of consecutive unselected acute stroke admissions to the acute hospitals in Leicester.

**Blood pressure**

The distribution of SBP levels on admission to hospital with acute stroke among those participating in the CHIPS trial is presented in the figure. The median [IQR] level for SBP was 170 [157, 188] mmHg and for DBP 90 [79, 96] mmHg. 15% of subjects had a SBP level below 150 mmHg (170). The data are in keeping with the admission SBP frequencies in the IST (170).

**Dysphagia**

Swallowing ability was assessed according to a standard nurse dysphagia protocol, the author having attended a course and attained certification. Some patients were assessed by a speech and language therapist within the first 24 hours where swallowing ability was in doubt. In the case of patients being deemed appropriate for thickened fluids only, drug capsules were administered in a thickened base.

**Consent and assent**

Relative assent was witnessed where the patient was unable to provide informed consent, for example due to dysphasia. It was often the experience that relatives felt understandably obliged to consult other members of the family before granting
assent. However, this was not always possible to arrange within the short recruitment
time-window (within 24 hours of stroke), although in practice this was rarely a
barrier to participation. A debate is ongoing about the recruitment of patients lacking
capacity in hyperacute stroke studies, particularly with relevance to the thrombolysis
trials (24).
Distribution of baseline, pre-randomisation SBP levels for CHIPS participants.
Appendix 2: Stroke severity and functional assessment tools.

1. National Institutes of Health Stroke Severity Scale

Level of consciousness:

0 = Alert, keenly responsive
1 = Drowsy, but rousable by minor stimulation to obey, answer, or respond
2 = Stuporous, require repeated stimulation to attend, lethargic or obtunded, requiring strong or painful stimulation to make movements
3 = Coma, respond only with reflex motor or autonomic effects, or unresponsive.

Level of consciousness questions:

Ask patient the month and his/her age. Score for the first answer.

0 = Answers both correctly
1 = Answers one correctly
2 = Both incorrect.

Level of consciousness commands:

Ask patient to open/close hand and eyes. Score if he/she makes unequivocal attempt.

0 = Obeys both correctly
1 = Obeys one correctly
2 = Incorrect.

Pupillary response:

0 = Both reactive
1 = One reactive
2 = Neither reactive.

Best gaze:

0 = Normal
1 = Partial gaze palsy; abnormal but not forced deviation
2 = Forced deviation/total gaze paresis.

Best visual:

Confrontation testing using finger movements, including double simultaneous stimulation. Use visual threat if consciousness or comprehension limit testing, Scoring '1' for any asymmetry demonstrated.

0 = No visual loss
1 = Partial hemianopia
2 = Complete hemianopia, to within 5 degrees of fixation.

Facial palsy:

0 = Normal
1 = Minor
2 = Partial
3 = Complete.

Best motor - arm:

Arms held for 10 seconds at 90 degrees if sitting, 45 degrees if lying. Grade weaker arm. Place arms in position if comprehension reduced.

0 = No drift after 10 seconds
1 = Drift after brief hold
2 = Can not resist gravity, but some effort made
3 = No effort against gravity.

Best motor - leg:

While lying, patient to hold weaker leg raised at 30 degrees for 5 seconds. Place leg in position if comprehension reduced.

0 = No drift after 5 seconds
1 = Drift within 5 seconds
2 = Can not resist gravity, falling to bed but some effort made
3 = No effort against gravity.

Plantar reflex:

0 = Normal
1 = Equivocal
2 = One extensor
3 = Bilateral extensor

Limb ataxia:

Finger-nose and heel-to-shin tests performed; ataxia is only scored if out of proportion to weakness. If total paralysis score as absent.

0 = Absent
1 = Present in leg or arm
2 = Present in leg and arm.

Sensory:

Tested with pin; only hemisensory loss scored. If comprehension or consciousness reduced, only score if obvious evidence.

0 = Normal
1 = Partial loss, subjectively different but still felt
2 = Dense loss, unaware of being touched

Neglect:
0 = No neglect
1 = Partial neglect, visual, tactile, or auditory
2 = Complete neglect, affecting more than one modality.

*Dysarthria:*

0 = Normal articulation
1 = Mild to moderate dysarthria, slurring some words
2 = Near unintelligible or worse.

*Best language:*

Assessed from responses during evaluation.

0 = No aphasia
1 = Mild to moderate aphasia; nominal errors, paraphasias, etc.
2 = Mute.
2. **Modified Rankin Scale.**

0  No symptoms at all
1  No significant disability, despite symptoms; able to carry out all usual duties and activities.
2  Slight disability; unable to carry out all previous activities but able to look after own affairs without assistance.
3  Moderate disability; requiring some help, but able to walk without assistance.
4  Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance.
5  Severe disability; bedridden, incontinent and requiring constant nursing care and attention.
### 3. Barthel Index.

<table>
<thead>
<tr>
<th>TASK</th>
<th>DESCRIPTION</th>
<th>SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeding</td>
<td>Independent</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Food needs to be cut</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Dependent</td>
<td>0</td>
</tr>
<tr>
<td>Moving bed to chair including sitting up</td>
<td>Independent</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>With minimal help</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Able to sit but maximum assistance to transfer</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Unable</td>
<td>0</td>
</tr>
<tr>
<td>Personal toilet: wash face, comb hair, shave, clean teeth</td>
<td>Independent</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Needs help</td>
<td>0</td>
</tr>
<tr>
<td>Getting on and off toilet, handling wipe, flush.</td>
<td>Independent</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Needs help</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Unable</td>
<td>0</td>
</tr>
<tr>
<td>Bathing self</td>
<td>Independent</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Needs Help</td>
<td>0</td>
</tr>
<tr>
<td>Walking on a level surface (or propel wheelchair if unable to walk).</td>
<td>Independent for 50 yards</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>With help for 50 yards</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Wheelchair for 50 yards</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Unable</td>
<td>0</td>
</tr>
<tr>
<td>Ascend and descend stairs</td>
<td>Independent</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>With help</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Unable</td>
<td>0</td>
</tr>
<tr>
<td>Dressing: including tying shoes, fastening buttons</td>
<td>Independent</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>With help</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Dependent</td>
<td>0</td>
</tr>
<tr>
<td>Controlling bowels</td>
<td>No accidents</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Occasional accidents</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Incontinent</td>
<td>0</td>
</tr>
<tr>
<td>Controlling bladder</td>
<td>No accidents</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Occasional accidents</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Incontinent</td>
<td>0</td>
</tr>
</tbody>
</table>
Appendix 3: Patient information leaflets and consent forms

1) CHIPS Study

PATIENT INFORMATION LEAFLET

Patient number: ...........

Control of Hypertension Immediately Post-Stroke (CHIPS) Trial

Principal Investigator – Professor J F Potter
Study investigator – Dr David Eveson. Telephone no. (0116) 256 3365

We would like to invite you to participate in this research study.

1. What is the purpose of the study?
Stoke is a common condition, newly affecting approximately 100,000 people per year in the United Kingdom. Hypertension (high blood pressure) is common immediately following stroke, affecting up to three-quarters of patients. In a few emergency situations, it is accepted clinical practice to treat high blood pressure in the first few days following stroke. However, in the majority of patients, it is not clear whether treatment should be started or not. This is because increased blood pressure following acute stroke may be a protective mechanism to increase blood flow to the brain, and also blood pressure commonly slowly falls over the first two weeks following acute stroke. However, persistent very high blood pressure may increase the risk of swelling and bleeding into the brain, which could be damaging. This study will compare the effects of starting with not starting antihypertensive treatment immediately following stroke (within the first 24 hours) and its effect on brain, heart and blood vessel function (part of which can be measured with a blood test) following stroke.

2. What will be involved if I take part in the study?
If you agree to participate in this study, you will have a study assessment now (visit 1), at 24 hours to 48 hours (visit 2), at 7 days (visit 3), at 14 days (visit 4) in 4 weeks time (visit 5) and in 3-4 months time from now (visit 6).

When you are discharged during the initial study period, arrangements can be made to bring you to the Glenfield Hospital for the remaining measurements.
Now, as visit 1, you will have a blood test (the equivalent of approximately 8 tea-spoonfuls in quantity) and your blood pressure checked with an arm cuff approximately 10 times over a 30 minute period. If your blood pressure is high, you will be assigned at random (like the tossing of a coin) to receive antihypertensive treatment or placebo ('dummy') treatment. The treatment will be a tablet to swallow. Neither you nor your doctor will be aware of which treatment you are taking, though your doctor can find out in an emergency if he/she needs to.

Following this, your blood pressure will be taken every 30 to 60 minutes for 24 hours to monitor the immediate effects of the tablet. You will be asked some questions and examined to see how the stroke has affected you, if the doctors have not already done this.

At visit 2 (24 to 48 hours time) you will have your blood pressure taken again, and the results of blood tests reviewed. You will have your blood pressure recorded with a normal blood pressure cuff, and with a small cuff attached to one of your fingers to automatically measure your blood pressure whilst you are lying in bed for a period of 10 minutes. A 10 minute recording will also be made of the pulse of the artery in the neck, groin, arm or wrist using a pressure sensor shaped like a pencil which is held lightly against the skin. Separate measurements of the pulses will then be made. Once the correct position has been found a 10-15 second recording is all that is required. The period of measurement should take no longer than 1 hour and 20 minutes.

There may also be an additional recording of brain blood flow performed at visit 2. This involves an ultrasound recording of the blood flow to the brain using a probe held lightly against the skin of the scalp by a frame. Small changes in your blood pressure are brought about by inflating and deflating cuffs placed around your thighs and the change in blood flow to the brain measured. Some people find the thigh-cuff inflations a little uncomfortable. If you find this to be the case, please let the investigator know and this part of the study will not be repeated. This recording takes about 45 minutes. All recordings will be conducted at the bedside or in the research laboratory in the case of patients at the Glenfield Hospital. Your dignity will be preserved at all times.

At visit 3 (day 7), you will have a second 24 hour blood pressure recording.

At visit 4 (day 14), the recordings made at visit 2 will be repeated to see what effect the drug and/or the passage of time has had on your circulation. A further assessment will be made of how the stroke has affected you as regards standing up, walking, washing and dressing, and going to the toilet. These assessments are performed to assess your progress in recovering from the stroke. There will also be a further blood test at this time and a 24 hour blood pressure recording.
At visit 5 (4 weeks), the recordings made at visit 2 will be repeated to see if the benefits of any treatment have persisted. You will have a more detailed assessment of how the stroke has affected you, a blood test and a final 24 hour blood pressure recording. This can be done in hospital if you are still an inpatient, or transport can be arranged to bring you to the Glenfield Hospital.

At visit 6 (3 months), you will have another more detailed assessment of how the stroke has affected you, and a final blood test. This can be done in hospital if you are still an inpatient, at your place of discharge or transport can be arranged to bring you to the Glenfield Hospital.

Many aspects of the study are already routinely carried out on patients admitted to hospital with suspected stroke. These include: a history to collect details about you and your risk factors for stroke; an examination to find out how the stroke has affected you; and investigations to confirm the diagnosis and to identify modifiable risk factors to prevent future stroke including blood tests, a heart tracing and a brain scan.

At the completion of the study, after analysis, all blood samples will be destroyed and will not be used for further research.

3. What treatments will be used?
A blood pressure treatment will be used in the study, which is commonly used in the treatment of hypertension in the United Kingdom.

Lisinopril is an angiotensin-converting enzyme inhibitor, and will be taken as a tablet to swallow. It may rarely affect the blood test of your kidney, and for this reason a blood test will be taken before you start the study and after one week. If there are any changes in the results of this test, then your doctor will withdraw you from the study. Lisinopril may also lower the blood pressure excessively when first started, and for this reason your blood pressure will be monitored every 30 minutes for 24 hours after the first tablet. The dose of lisinopril will be doubled at 7 days following your stroke if your blood pressure remains high.

4. Will information obtained in the study be confidential?
The information collected during the study will be recorded in your hospital notes and treated with the usual degree of confidentiality under the data protection act. Some information will also be recorded on data forms, which will be sent to a data processing office for computer entry and analysis. The data forms will not identify you by name. Only your doctor will know that the information is related to you.

Authorised persons will look at your medical records, without violating confidentiality, to check that the study has been properly performed.
This can only be done with your permission, and it is understood that by signing this consent form you are granting this permission.

Your identity will not be revealed in any publication or presentation of the results from this study.

5. **What if I am harmed in the study?**
Medical research is covered for mishaps in the same way as for patients undergoing treatment in the National Health Service, i.e. compensation is only available if negligence occurs.

If you have private medical insurance you should let the insurers know that you intend to take part in a research project. They will be able to tell you if this will affect your medical insurance.

6. **Will I receive out of pocket expenses for taking part in the study?**
You may be reimbursed for any extra travel costs incurred during your participation in this study.

7. **What happens if I do not wish to participate in this study or wish to withdraw from the study?**
Your participation in this study is entirely voluntary. If you do not wish to participate or if you wish to withdraw from the study you may do so without justifying your decision and your future treatment will not be affected. Your doctor may, at any time, decide that you should stop the study if he/she believes that it is in your best interests to do so.

*In the case of study-related injury, or whenever you have questions about the study or your treatment, please contact:*

**Dr David Eveson**

**Telephone number (0116) 256 3365**
CONSENT FORM

Patient number: ...........

Control of Hypertension Immediately Post-Stroke (CHIPS) Trial

This form should be read in conjunction with the Patient Information Leaflet.

I agree to take part in the above study as described in the Patient Information Leaflet, Final Protocol dated 08/01/02.

I understand that I may withdraw from the study at any time without justifying my decision and without affecting my normal care and medical management.

I understand that members of the research team may wish to view relevant sections of my medical records, but that all the information will be treated as confidential.

At the termination of this trial, I understand that there is no guarantee that the drug treatment received during this trial will continue.

I understand medical research is covered for mishaps in the same way as for patients undergoing treatment in the NHS, i.e. compensation is only available if negligence occurs.

I have read the Patient Information Leaflet on the above study and have had the opportunity to discuss the details with ............... and ask any questions.

The nature and the purpose of the tests to be undertaken have been explained to me and I understand what will be required if I take part in the study.

Signature of patient ........................................

(Name in BLOCK LETTERS) ........................................

Date ........................................

I confirm I have explained the nature of the trial, as detailed in the Patient Information Leaflet, in terms, which in my judgment are suited to the understanding of the patient.

Signature of investigator ........................................

(Name in BLOCK LETTERS) ........................................

Date ........................................
2) Arterial compliance and stroke subtype study

PATIENT INFORMATION SHEET

‘Arterial Compliance and Blood Pressure following Stroke’

Principal Investigator: Professor JF Potter – Professor of Medicine for the Elderly

If you have any questions about the study please feel free to contact Dr. David Eveson (Research Fellow to Professor Potter) by telephone on (0116) 256 3643.

What is the purpose of study?

High blood pressure is the biggest treatable risk factor for preventing stroke and is very common in the days to weeks following stroke but as yet we do not know how best to treat these raised blood pressure levels or even if they should be reduced. Increasing blood pressure levels are associated with a decrease in the natural elasticity of the large blood vessels and this reduction can predict the development of heart disease and stroke. What happens to blood vessel elasticity after stroke is unknown and whether a measure of this elasticity of the blood vessel can be used to predict outcome is also unclear. There may also be a difference in elasticity of the main blood vessels serving the brain and this may predict the type of stroke that can potentially develop. It is now possible to quickly and simply measure the elasticity of large blood vessels including those to the brain using new non-invasive methods that do not involve needles or any discomfort to the patient.

We would like to invite you to take part in this study to find out what happens to the elasticity of the large blood vessels following a stroke and to see if there are differences between patients who have suffered a stroke and those that have not. This work will help us understand why patients develop strokes and potentially what treatments can be used, particularly with regards to the treatment of blood pressure.

What will be involved if I take part?

If you decide to take part you will be assessed on three separate occasions:

- Immediately after admission to hospital with a stroke
- 10 to 14 days later or just before discharge home, whichever is earlier
- After 30 days or at the routine outpatient appointment that is usually 4 to 6 weeks after your stroke.

At the first meeting information will be collected from your medical notes regarding your medical history and results of your scans, x-rays and blood tests.

On each of the three meetings the recordings made will be exactly the same and include:

- A ten-minute recording of your blood pressure made while you are lying down using a small cuff around one finger and also a cuff around your arm.
- A ten-minute recording made of the pulse of the artery in the neck, groin, arm or wrist using a small button-like pressure sensor held lightly against the skin.
— A measurement of the elasticity of the large blood vessels made using a pressure sensor, shaped like a narrow pencil, which is placed over the pulse in the wrist and the neck. Once the correct position has been found a 10-15 second recording is all that is required.

The period of measurement should take no longer than 1 hour and 45 minutes on each occasion.

No needles are used, no drugs are given and the recordings are entirely painless. Your dignity will be preserved at all times.

You will then be offered a blood pressure recording, where you wear a cuff for 24 hours so that your blood pressure can be recorded every half hour or so. Arrangements will be made to collect the cuff once the recording has finished.

**Will information on the study be confidential?**

All information collected will be kept confidential. Your general practitioner will be informed of your entry to the study.

**What if I am harmed by the study?**

Medical research is covered for mishaps in the same way as for patients undergoing treatment in the NHS i.e. compensation is only available if negligence occurs.

**Will I receive out of pocket expenses for taking part in the study?**

Travelling expenses will be provided for all participants or taxis will be provided as necessary.

What happens if I do not wish to take part in this study or wish to withdraw from the study?

If you do not wish to take part in this study or wish to withdraw from the study you may do so without justifying your decision and your future treatment will not be affected.

**Will these studies affect the treatment of my stroke?**

These studies will have no effect or alter any of the treatments, medical or rehabilitation, that you receive following your stroke.
PATIENT CONSENT FORM

‘Arterial Compliance and Blood Pressure following Stroke’

Principal Investigator: Professor JF Potter – Professor of Medicine for the Elderly

This form should be read in conjunction with the patient information leaflet, Version 2.01.

I agree to take part in the above study as described in the patient information sheet.

I understand that I may withdraw from the study at any time without justifying my decision and without affecting my normal care and medical management.

I understand that members of the research team may wish to view relevant sections of my medical records, but that all the information will be treated as confidential.

I understand that medical research is covered for mishaps in the same way as for patients undergoing treatment in the NHS i.e. compensation is only available if negligence occurs.

I have read the patient information leaflet on the above study and have had the opportunity to discuss the details with ................. and ask any questions. The nature and the purpose of the tests to be undertaken have been explained to me and I understand what will be required if I take part in the study.

Signature of patient ..........................................Date ........................................

Name in capitals: ......................................................................

I confirm I have explained the nature of the Trial, as detailed in the Patient Information Sheet, in terms that, in my judgement, are suited to the understanding of the patient.

Signature of Investigator......................................................Date..............................

Name in capitals: ......................................................................
Appendix 4: Ethical committee approval

University Hospitals of Leicester
NHS Trust

DIRECTORATE OF RESEARCH AND DEVELOPMENT
Leicester General Hospital
Gwendolen Road
Leicester
LE5 4PW

Direct Dial: (0116) 258 4109
Fax No: (0116) 258 4226
e-mail: aimee.gefrey@uhl-tr.nhs.uk

11 March 2002

Dr Tom Robinson
Consultant Physician
LGH

Dear Dr Robinson

RE: Project Number: 6206  [Please quote this number in all correspondence]
Control of Hypertension Immediately Post-Stroke (CHIPS) Trial

We have now been notified by the Ethical Committee that the proposed amendments to this project have been given ethical approval (please see the attached letter from the Ethical Committee).

I can therefore now re-confirm the full approval of this project on behalf of the University Hospitals of Leicester NHS Trust.

This approval means that you are fully authorised to proceed with the project, using all the resources which you have declared in your original notification form (and subsequent amendments).

The project continues to be covered by Trust Indemnity, except for those aspects already covered by external indemnity (e.g. ABPI in the case of most drug studies).

We will be requesting annual and final reports on the progress of this project, both on behalf of the Trust and on behalf of the Ethical Committee.

In the meantime, in order to keep our records up to date, could you please notify the Research Office if there are any significant changes to the start or end dates, protocol, funding or costs of the project.

I look forward to the opportunity of reading the published results of your study in due course.

Yours sincerely

Dr Nichola Seare
Research and Development Business Manager

cc  Prof Potter
    David Eveson

Trust Headquarters, Glenfield Hospital, Groby Road, Leicester, LE3 9QP
Website: www.uhl-tr.nhs.uk
Chairman Mr Philip Hammersley CBE Chief Executive Dr Peter Reading
1 October 2001

Professor J Potter
Professor Medicine for Elderly
Dept of Medicine for the Elderly
Glenfield Hospital

Dear Professor Potter

RE: Project Number: 7060 [Please quote this number in all correspondence]
Arterial compliance and stroke subtype

Since all aspects of your UHL R&D notification are complete, I now have pleasure in confirming full approval of the project on behalf of the University Hospitals of Leicester NHS Trust.

This approval means that you are fully authorised to proceed with the project, using all the resources which you have declared in your notification form.

The project is also now covered by Trust Indemnity, except for those aspects already covered by external indemnity (e.g. ABPI in the case of most drug studies).

We will be requesting annual and final reports on the progress of this project, both on behalf of the Trust and on behalf of the Ethical Committee.

In the meantime, in order to keep our records up to date, could you please notify the Research Office if there are any significant changes to the start or end dates, protocol, funding or costs of the project.

I look forward to the opportunity of reading the published results of your study in due course.

Yours sincerely

Dr Nichola Seare
Research and Development Business Manager
Appendix 5: Publications arising from this thesis

Paper


Abstracts

Eveson, D J; Eames, P J; Robinson, T G; Potter, J F Central arterial stiffness is increased in acute ischaemic stroke and is related to stroke aetiology. Journal of Human Hypertension. 18(12):929-930, December 2004.


Eveson, D J; Robinson, T G; Panerai, R B; Potter, J F Abnormalities in cardiac baroreceptor sensitivity in acute ischaemic stroke patients are related to central arterial stiffness. Journal of Human Hypertension. 17(10):732, October 2003.
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(4) Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. Lancet 2001; 358(9287):1033-1041.


Davies JI, Band MM, Pringle S, Ogston S, Struthers AD. Peripheral blood pressure measurement is as good as applanation tonometry at predicting ascending aortic blood pressure. J Hypertens 2003; 21(3):571-576.


(89) Egan BM, Fleissner MJ, Stepniakowski K, Neahring JM, Sagar KB, Ebert TJ. Improved baroreflex sensitivity in elderly hypertensives on lisinopril is not


(96) Franklin SS. Systolic blood pressure: it's time to take control. Am J Hypertens 2004; 17(12 Pt 2):49S-54S.


Ref Type: Abstract


Ref Type: Abstract


Ref Type: Report


(298) Targonski PV, Bonetti PO, Pumper GM, Higano ST, Holmes DR, Jr., Lerman A. Coronary endothelial dysfunction is associated with an increased risk of cerebrovascular events. Circulation 2003; 107(22):2805-2809.


(300) Ting CT, Chen CH, Chang MS, Yin FC. Short- and long-term effects of antihypertensive drugs on arterial reflections, compliance, and impedance. Hypertension 1995; 26(3):524-530.


