THE BLOOD PRESSURE AND BARORECEPTOR CHANGES
FOLLOWING ACUTE STROKE

Doctor of Medicine Thesis
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<tr>
<td>AR</td>
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<td>BP</td>
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<td>BPV</td>
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<td>BR</td>
<td>baroreceptor</td>
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<td>CBF</td>
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<td>CI</td>
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<td>LF/HF</td>
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<td>PSA</td>
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<td>TACS</td>
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<tr>
<td>TIA</td>
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<td>VLF</td>
<td>very low frequency</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 the study was performed by myself with the help and advice of Professor John Potter, Professor of Medicine for the Elderly, University of Leicester.

The recruitment and study of all stroke patients was performed by myself. I also recruited and studied all of the control subjects, though I am grateful to my colleagues, Dr Martin James and Dr Jane Youde, for the eleven hypertensive control subjects' data reported in Chapter 4 of this thesis.

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

Dr Ronney Panerai, Senior Lecturer, Department 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. Dr Panerai also developed the software for the sequence and power spectral analysis techniques described in Chapter 4.

Ms Suzanne Ward-Close, Research Assistant, Department of Medicine for the Elderly, University of Leicester, constructed the database, and was responsible for the entry of analysed data.

Mr Nick Taub, Lecturer in Medical Statistics, and Mr Andy Waddington, MSc student, Department of Epidemiology and Public Health, University Of Leicester, assisted with the statistical analysis of the data reported in Chapter 2.
ETHICAL DECLARATION

For all studies reported in this thesis, informed consent was obtained from subjects or their carers (where appropriate) and approval was given by the Leicestershire Hospitals Ethics Committee.
I am indebted to my supervisor, Professor John Potter, for his advice, support and patience throughout this study.

I am grateful to the Stroke Association for their funding of the studies reported in this thesis.

I would also like to thank Dr Ronney Panerai, Dr Martin James, Dr Jane Youde, Mr Nick Taub, Mr Andy Waddington, and Ms Suzanne Ward-Close for their help and enthusiasm during the completion of this thesis.
ABSTRACT

This thesis examines aspects of blood pressure (BP) and its control in clinical studies during the acute and subacute phases of stroke with particular reference to the influence of baroreceptor function on these findings.

Casual and 24-hour BP levels fall spontaneously during the first week following acute stroke. Higher 24-hour systolic BP (SBP) levels within the first 24 hours of ictus are associated with an increased likelihood of poor short-term outcome, whether assessed by death, dependency in activities of daily living or neurological outcome.

Following acute stroke, not only are BP levels raised, but there is an increase in short-term SBP variability. This may reflect an impairment in cardiac baroreceptor sensitivity, as assessed by time and frequency domain analysis techniques. There is no evidence of increased sympathetic nervous system activity (SNSA) in acute stroke patients compared to control subjects as reflected by the ratio of low-to-high frequency pulse interval variability (a surrogate marker of SNSA), though this ratio was altered in favour of sympathetic predominance in right compared to left hemisphere strokes. Changes in autonomic control of BP variability are seen in the high frequency region following acute stroke, probably reflecting the mechanical effects of respiration.

However, an impairment in baroreceptor-mediated vasomotor control also appears to be present in the acute stroke period, as demonstrated by impaired forearm vascular resistance (FVR) responses to hypotensive lower body negative pressure. Furthermore, BP falls significantly in response to orthostatic, but not postprandial, stress in stroke patients, with no significant change in FVR.

Acute stroke is associated with increased BP levels which convey an adverse prognosis. This and the increased short-term BP variability after acute stroke may be related to changes in both cardiac baroreceptor sensitivity and control of vasomotor tone in the post-ictal period. The exact site responsible for these changes and the prognostic significance of these impaired mechanisms of BP
control requires further examination, in particular to permit an informed decision of the management of elevated BP in the acute stroke period.
Acute stroke is common and associated with significant morbidity and mortality. Over 100,000 first ever strokes are reported per annum in the United Kingdom, though incidence rates rise steeply with increasing age, such that the annual incidence rate for first ever stroke is 14 per 1000 of the population aged 75 to 84 years and 20 per 1000 in those 85 years and older [Bamford et al, 1988]. In the developed world, stroke is the third most common cause of death (after ischaemic heart disease and cancer), and accounts for 1 in 10 deaths per year [Bonita et al, 1993]. Between 17 and 34% of stroke patients are dead at one month post-ictus [Bonita, 1992], and of those that survive many have residual disability with up to 35% of survivors being still dependent at one year [Bamford et al, 1990]. Indeed, stroke is one of the most important causes of severe disability [Martin et al, 1988], and has major cost implications. In Scotland, stroke patients occupy 7% of all hospital-bed days, accounting for 6% of hospital costs and 4.6% of all National Health Service costs [Isard et al, 1992]. However, the bulk of the long-term care burden falls on the community services and carer(s) [Bonita et al, 1987], and it is the costs related to long-term care of disabled survivors which dominate the lifetime costs [Bergman et al, 1995]. It is therefore not surprising that a reduction in stroke incidence was an acknowledged aim of the Health of the Nation document [Secretary of State for Health, 1992].

1.1. Therapeutic Options in Acute Ischaemic Stroke

However, once a stroke has occurred, the major aim is to restore function, as well as to investigate the underlying cause(s) of the initial event, reduce potential risk factors and to prevent recurrence. This may be achieved by both specific and general treatments, which will be briefly reviewed though a detailed appraisal of all available treatments is beyond the scope of this review.

1.1.1. Specific Treatments

In acute ischaemic stroke, which accounts for 80% of all strokes, brain cells are deprived of oxygen and glucose. This results in the impairment of the normal neuronal energy metabolic processes with the prevention of oxidative phosphorylation and ATP production. This in turn leads to uncontrolled membrane
ion transport (particularly calcium), and impaired ATP-dependent reuptake of excitatory amino acids (such as glutamate and aspartate). Ultimately, this results in the activation of destructive lipases, proteases and endonucleases, and free radical generation with consequent contribution to ischaemic damage. Cerebral ischaemia not only causes loss of neuronal function but also cerebral oedema. Within minutes of onset of ischaemia, cytotoxic cerebral oedema occurs as a result of cell membrane damage allowing intracellular accumulation of water. However, after several days of ischaemia, breakdown of the blood-brain barrier leads to vasogenic cerebral oedema as plasma constituents enter the brain extracellular space. The effects of cerebral oedema are to further compromise cerebral blood flow (CBF) by increasing pressure in the extravascular space and causing vascular congestion and sometimes haemorrhagic transformation, and also to cause mass effect, brain shift and eventually brain herniation. These processes occur in an area of infarction which progresses from a central zone of lowest CBF in a circumferential fashion towards a maximum volume over an undetermined time in humans [Pulsinelli, 1992]. There is a rim of mild to moderate ischaemic tissue, the so-called penumbral zone [Astrup et al, 1981], between the normally perfused brain and the evolving infarct in which the aforementioned pathophysiological mechanisms are at their most dynamic, where cell death occurs last, and where a number of pharmacological interventions have been assessed.

Specific treatments have been directed at preventing neurotoxic ion fluxes (calcium antagonists, N-methyl D-aspartate receptor inhibitors), reducing cerebral oedema (glycerol, corticosteroids), improving cerebral haemodynamics (induced hypertension, avoidance of hypertension, cerebral vasodilators, prostacyclin), and improved cerebral oxygen delivery (haemodilution, hyperbaric oxygen) [Sandercock et al, 1992]. (Aspects of the medical treatment of acute stroke related to blood pressure (BP) management will be considered in more detail later.) Specific treatments have also been directed towards the restoration of arterial patency. There are significant risks associated with the use of thrombolytic agents, and the evidence of benefit of thrombolytic agents is conflicting [Wardlaw et al, 1992]. Recombinant tissue plasminogen activator was associated with an
improvement in neurological (assessed by the National Institutes of Health Stroke Scale) and functional outcome (Modified Rankin, Barthel Index and Glasgow outcome scales) at three months with no significant difference in mortality from the control group [NINDS rt-PA study group, 1995]. However, the European Cooperative Acute Stroke Study (ECASS) reported an increased rate of more serious parenchymal haemorrhages in the rt-PA group [Hacke et al, 1995], and the European trial of streptokinase in acute ischaemic stroke (MAST-E) was terminated prematurely because of an increased mortality in the study group, who also showed a symptomatic haemorrhage rate of 17.5% compared to a predicted of 4.5% [Hommel et al, 1994]. There remains a need to define patient characteristics further to minimise haemorrhage risk and maximise benefit before thrombolytic agents can be more widely used in the treatment of acute ischaemic stroke [del Zoppo, 1995]. However, to date there is no clear evidence from trials (and overviews) of a medical therapy that can be recommended for routine use in most patients with acute stroke [Sandercock et al, 1992].

1.1.2. General Measures
More general measures are also appropriate in the management of all stroke patients, and comprise supportive and symptomatic measures. These include the maintenance of airway, oxygenation and cardiopulmonary function, and the correction of fluid and electrolyte imbalance. Facilitation of rehabilitation and nursing care are also important aspects of stroke management, and the dedicated rehabilitation interventions offered by specialist stroke units may explain the improved functional outcome reported in patients admitted to such units [Langhorne et al, 1993].

The prevention of complications such as deep venous thrombosis, chest and urinary infections, seizures, pressure sores and contractures is also important. Whilst early deaths following acute stroke are mainly related to neurological factors, including transtentorial herniation, later deaths between two and four weeks post ictus are mainly caused by pneumonia, sepsis, and pulmonary emboli [Oppenheimer et al, 1992]. The recognition and appropriate acute medical management of such complications is one reason proposed to explain the 28 %
odds reduction in early mortality in patients admitted to specialist stroke units [Langhorne et al, 1993]. Despite theoretical benefits for routine early therapy with anticoagulants and antiplatelet drugs to prevent progressive cerebral artery occlusion and venous thromboembolism, these would be offset by a small increase in the risk of disabling or fatal haemorrhage. These risks are currently under investigation in a large multicentre trial - the International Stroke Trial [Sandercock et al, 1993].

Other aspects of the general management of patients with acute ischaemic stroke are also unclear, particularly with regard to appropriate acute BP management. Certainly, hypertension is associated with an increased risk of all major subtypes of stroke [MacMahon et al, 1990], and the role of antihypertensive therapy in the primary prevention of cerebrovascular disease is well established in subjects up to the age of 80 years [Collins et al, 1990]. In a recent overview of 17 randomised trials of antihypertensive therapy, MacMahon and colleagues reported a 38% decline (95% confidence intervals: 31 to 45%) in the risk of stroke over a mean follow-up period of 4.9 years with a mean reduction in BP of 10-12/ 5-6 mmHg. Indeed, the sizes of the reductions were similar in trials in mild, moderate and more severe hypertension, and in trials of older and younger patients [MacMahon et al, 1994]. It has been proposed that a reduction of systolic BP (SBP) by 2 to 3 mmHg in the general population by non-pharmacological measures would reduce stroke incidence by 10% [Ebrahim, 1990]. However, the management of hypertension in the post stroke period, both acutely and in secondary prevention is less clear, despite the well documented changes in casual BP levels.

1.2. Blood Pressure Changes Following Acute Stroke
BP levels are elevated within the first twenty-four hours following ictus, over 80% of patients having 'hypertensive' values by standard definitions [Oppenheimer et al, 1992]. Levels decrease spontaneously within 3 to 10 days in most patients (Table 1.1) [de Faire et al, 1978; Wallace et al, 1981; Britton et al, 1986; P Jansen et al, 1987; Harper et al, 1991]. Jansen and colleagues studied a group of 63 patients with transient ischaemic attack or cerebral infarction admitted an
undefined period after ictus. BP was significantly lower by day 5 compared to admission levels (183 (standard deviation (SD) 31)/104 (15) vs. 141 (18)/81 (8) mmHg), though changes in a control hospital population were not studied [P Jansen et al, 1987]. In a larger though still uncontrolled study, de Faire and colleagues measured BP at 6 hourly intervals for 3 days and thereafter at 12 hourly intervals following admission an undefined period after stroke. A significant reduction was observed during the first 3 days with 35% of patients having substantial BP elevations ≥ 195/110 mmHg at admission compared to only 10% at day 4, though levels remained relatively constant thereafter [de Faire et al, 1978]. Wallace and colleagues reported BP changes over the first 10 days of hospital admission in 312 stroke patients admitted within 24 hours of ictus. Levels fell after acute stroke from 181/100 mmHg on admission to 147/83 mmHg at day 10, though the fall reached statistical significance by day 4 in the largest diagnostic group, hemispheric thrombotic infarct. There was no significant BP change in a small control group of 28 men studied an undefined period after admission for routine surgical procedures [Wallace et al, 1981]. In the study of Britton and colleagues, a control group of 188 age- and sex-matched acute surgical admissions was recruited, and BP changes compared with 209 stroke patients, though the delay in hospital admission was unstated. Stroke patients had significantly higher admission BP levels, 69% had BP ≥ 170/100 mmHg compared to only 36% of controls (p<0.001). A significant spontaneous reduction was observed at 4 days after admission in both groups, with the largest falls being witnessed in those with the highest admission levels. However, stroke patients consistently had higher BP than their matched controls [Britton et al, 1986]. More recently, Broderick and colleagues have studied BP changes in 69 patients reviewed within a mean of 19 minutes of stroke and subsequently recruited into an acute treatment trial. They reported significant BP falls over the following 90 minutes of 29/10 mmHg [Broderick et al, 1993].

It is unclear whether the elevated BP on admission is present before stroke, or is a result of it, though two studies report an increase between prestroke and acute stroke BP levels [P Jansen et al, 1987; Kameyama et al, 1989]. Jansen and colleagues studied 63 patients with transient ischaemic attack or cerebral
<table>
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<th>Study</th>
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<th>Admission delay</th>
<th>Initial BP</th>
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<td>100</td>
<td>not stated</td>
<td>M: 174/94</td>
<td>M: 151/84 (day 4)</td>
<td>uncontrolled study</td>
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<td>F: 177/94</td>
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<td>Wallace et al 1981</td>
<td>312</td>
<td>&lt;24 hours</td>
<td>181/100</td>
<td>147/83 (day 10)</td>
<td>28 surgical control patients showed no BP change</td>
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<td>Britton et al 1986</td>
<td>209</td>
<td>not stated</td>
<td>ICH: 179/107</td>
<td>ICH: 158/91 (day 4)</td>
<td>188 surgical controls also showed BP fall, but absolute BP always less than strokes</td>
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<td>Cl: 181/95</td>
<td>Cl: 155/84 (day 4)</td>
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<tr>
<td>P Jansen et al 1987</td>
<td>63</td>
<td>not stated</td>
<td>183/104</td>
<td>141/81 (day 5)</td>
<td>uncontrolled</td>
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<td>Harper et al 1991</td>
<td>272</td>
<td>not stated</td>
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<td>20/10 fall (day 7)</td>
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**TABLE 1.1** Studies reporting casual blood pressure changes following acute stroke.

*BP: blood pressure; M: male; F: female; ICH: intracerebral haemorrhage; Cl: cerebral infarction.*
Introduction

infarction, and reported a rise in BP from 159(25)/92(10) pre to 183(31)/104(15) mmHg post-ictus, though the time intervals were not clearly stated [P Jansen et al, 1987]. Kameyama and colleagues reported changes in a group of 61 patients with recordings available during the week prior to stroke and subsequently taken within 12 hours of ictus. An increase in levels was recorded for both infarcts (149(29)/81(18) to 185(27)/93(15) mmHg) and haemorrhages (166(21)/89(13) to 212(28)/108(19) mmHg) [Kameyama et al, 1989].

The elevation in BP post-stroke may reflect the circumstances of measurement, particularly in relation to the place (hospital or clinic vs. home) and person (physician vs. nurse), the so-called ‘white coat’ effect [Pickering, 1990]. It has similarly been argued that mental stress related to hospital admission may play an important role in the high BP levels seen in stroke patients. In uncontrolled studies, Carlberg and colleagues reported no significant correlation between BP and latency from symptom onset to hospital admission, with no significant difference in admission BP in patients admitted within 1, 2, or 3 or more days of ictus [Carlberg et al, 1990; Carlberg et al, 1991a; Carlberg et al, 1991b].

BP measurement may also be affected by the random variability of BP and problems related to observer error (e.g. intra- and inter-observer variability, bias, etc.). Twenty-four-hour non-invasive BP monitoring (NIBPM) helps overcome some of these problems, as it reduces the pressor response to hospital admission [Antivalle et al, 1990; Fotherby et al, 1995]. The higher number of readings these devices record also reduce the measurement variability and observer bias when compared to casually recorded BP [Coats, 1990]. Harper and colleagues studied a group of 33 subjects admitted within 24 hours of stroke with 21 age- and sex-matched non-emergency medical admissions acting as controls. They observed a significant fall in casual BP in both groups during the first week of hospital admission, but 24-hour reductions were only recorded in the stroke group. They argued that though the ‘white coat’ effect plays a part in the high casual BP in acute stroke, this is unlikely to be the sole factor [Harper et al, 1994].
1.3. Pathophysiological Mechanisms Of Blood Pressure Change In Acute Stroke

Pathophysiological mechanisms responsible for the initial increase in BP may also be of importance in explaining changes in BP in the acute stroke period, particularly catecholamine and corticosteroid changes, and autonomic nervous system influences.

1.3.1. Catecholamine And Corticosteroid Changes

Elevated levels of plasma [Meyer et al, 1973a; Myers et al, 1981], cerebrospinal fluid [Meyer et al, 1973a], and 24-hour urinary [Feibel et al, 1981; Olsson, 1990] catecholamines and corticosteroids have been reported during the acute stages of cerebrovascular disease, as has increased serum dopamine-β-hydroxylase activity, an enzyme needed for the final step of norepinephrine synthesis [Kanda et al, 1979]. These changes probably reflect increased sympathetic nervous system (SNS) activity, and may explain the high prevalence of cardiac abnormalities including myocardial damage and cardiac arrhythmias that are well-documented in acute stroke [Natelson, 1985; Talman, 1985; Hachinski et al, 1986]. Indeed, the extent of increases in catecholamine levels and therefore the degree of SNS activation may be of prognostic significance. Feibel and colleagues studied 24-hour urinary catecholamine excretion in 65 acute stroke patients admitted within 72 hours of ictus. They identified a group of patients with increased urinary catecholamine excretion, who exhibited a significantly higher mortality rate at 57% compared to 8% in the group with normal levels of excretion [Feibel et al, 1977]. Correlations between elevated catecholamine levels and poor functional outcome have also been reported [Feibel et al, 1977; Olsson, 1990; O'Neill et al, 1991].

BP changes may be directly related to increased plasma catecholamine levels, and Feibel and colleagues have reported an association between increased 24-hour urinary catecholamine excretion and refractory hypertension in acute stroke patients [Feibel et al, 1981]. However, evidence from animal studies suggests a direct link between specific focal cerebral ischaemia and abnormalities of cardiovascular, including BP, regulation. Smith and colleagues observed
increases in plasma catecholamine levels in a cat middle cerebral artery (MCA) occlusion model only in those with insular cortex damage [Smith et al, 1986]. The insular cortex receives afferent information from autonomic nervous system receptors [Radna et al, 1981], and exerts an inhibitory influence on sympathetic cardioexcitatory brainstem structures [Saper et al, 1982; Shipley et al, 1982]. Electrical stimulation of brainstem structures on which the insular cortex has an inhibitory projection, particularly the central nucleus of the amygdala, the posteriolateral hypothalamus, and the parabrachial nucleus, leads to increases in BP and heart rate (HR) [Talman, 1985]. Therefore, removal of such inhibitory influences following insular cortical damage leads to manifestations of increased SNS activity, including increased BP. Cechetto and colleagues have also demonstrated increases in plasma catecholamines and BP in the rat MCA occlusion model in which insular cortical damage was consistently identified [Cechetto et al, 1989a]. Thus, direct damage to structures involved in cardiovascular system (CVS) regulation following stroke may also be responsible for acute BP changes. It is therefore appropriate to consider the regulation of BP by the autonomic nervous system in more detail, as well as the potential influences of stroke on this.

1.3.2. The Autonomic Nervous System

The baroreceptor (BR) reflex arc is the principal mechanism in the short-term regulation of the CVS, including BP changes (Figure 1.1). The main BR sites are in the carotid sinuses, the enlarged parts of the internal carotid arteries just above the bifurcation of the common carotid arteries, as well as the aortic arch and its proximal branches. Free and encapsulated BR nerve endings are embedded in the adventitial layer of the arterial wall. These tonically discharge via afferent fibres in the glossopharyngeal (carotid) and vagus (aortic) nerves to specialised nuclei within the brainstem, including the nucleus tractus solitarius, nucleus ambiguus, and the ventrolateral nuclei of the medulla oblongata. Afferent discharge is increased by stimulation of the BR nerve endings secondary to stretching of the arterial wall brought about by increased transmural pressure related to increased BP. Equally afferent discharge is decreased by reduced BP, reduced transmural pressure, and reduced stretch. Central fibres in the brainstem
nuclei may be influenced by the hypothalamus, cerebral cortex, and other higher brain centres. Efferent discharge via the parasympathetic (PNS) and SNS outflow tracts influences sinoatrial node, ventricular wall, arteriolar and capacitance vessel function in responses to the precipitating BP change.

Impairment in the BR reflex arc could occur anywhere with stroke, but is most likely to occur centrally. However, stroke patients have carotid atherosclerosis with consequent splinting, and therefore may not register BP changes as readily. Changes in BR function have been demonstrated in animal models of cerebral and brainstem lesions [Doba et al, 1974; Cechetto et al, 1989b]. Doba and colleagues demonstrated an increase in the BP fall to head-up tilt in anaesthetised cats following BR denervation, which was further impaired following the destruction of brainstem nuclei [Doba et al, 1974]. To date, clinical studies are limited and mainly confined to patients with chronic cerebrovascular disease using invasive arterial measurements. However, one recent study has assessed cardiovascular autonomic function in 40 stroke patients within 2 to 10 days of ictus. This study revealed a significant impairment in the HR responses to respiration, the Valsalva manoeuvre and passive 90° tilt, consistent with impaired PNS function, compared to age-and sex-matched control subjects. SNS function as assessed by BP responses to tilt and to handgrip were not significantly different. When reassessed at 2 and 6 months post stroke, improvements were seen with the exception of HR responses to tilting [Korpelainen et al, 1994].

However, the majority of studies are of subjects with chronic cerebrovascular disease, which have shown impaired BR and circulatory reflex responses to the Valsalva manoeuvre [Appenzeller et al, 1964; Gross, 1970a], though age was a more important factor than the presence of chronic cerebrovascular disease in producing the deterioration in one study [Gross, 1970a]. However, in a further study, Gross reported no difference in the latency of onset of circulatory reflex activity following an acute reduction in pulse pressure during the Valsalva manoeuvre in chronic cerebrovascular disease patients compared to normal subjects [Gross, 1970b]. Monga and colleagues assessed BP responses to isometric exercise and showed no significant differences between stroke and
FIGURE 1.1 Schematic diagram illustrating the main components of the baroreceptor reflex arc
control groups, though there was a delay of between 8 weeks and 15 years between stroke onset and testing [Monga et al, 1988].

More recently, Naver and colleagues have also reported no significant difference between the blood pressure response to handgrip in patients studied subacutely (between 8 and 48 days following stroke) compared to controls. However, there was some evidence of sympathetic dysfunction with a significant SBP fall to 5-minute 80° tilt. Assessment of the PNS revealed significant impairment in HR responses to tilt and to respiration, in particular there was evidence of significantly reduced respiratory HR variability (HRV) in right hemisphere strokes [Naver et al, 1996]. Similar laterality of impaired HR responses was observed by Yokoyama and colleagues in a study assessing HR changes to attention-demanding tasks [Yokoyama et al, 1987]. Evidence for lateralization of autonomic influences has recently been reviewed, and suggests that the sinoatrial node is predominantly under right-sided cortical control and therefore right-sided lesions are more likely to have greater influence on HR. Equally, the atrioventricular node and ventricles are predominantly under left-sided cortical control and lesions in this side are associated with a lower threshold for ventricular dysrhythmias [Natelson, 1985; Talman, 1985; Lane et al, 1992]. The prognostic significance of these observations has not been fully assessed, but this may be possible with the availability of newer non-invasive techniques of autonomic assessment, which will be discussed in the following section.

1.4. Assessment Of The Baroreceptor Reflex Arc
A number of experimental techniques can be used to assess BR sensitivity (BRS), and in particular the baroreceptor-heart rate reflex.

1.4.1. Pharmacological Methods
Smyth and colleagues first described the intravenous bolus injection of a pressor stimulus (angiotensin or phenylephrine) to assess cardiac BRS, by the continuous recording of intra-arterial BP and HR response [Smyth et al, 1969]. Typically, this method produces a slow onset (15 to 30 seconds), sustained ramp (15 to 20
beats duration) response. Pharmacological depressor agents (amyl nitrate, trinitroglycerin injection or sodium nitroprusside injection or infusion) have also been used to study cardiac BRS. The relationship between the evoked SBP change and the consequent alteration of PI (PI) is plotted, and the regression coefficient for the relation of BP to PI is taken as an index of BRS. Such artificial BP adjustments may produce different reflex responses to the smaller baroreflex-mediated adjustments operating under basal conditions. In addition, there are other objections to pharmacological methods of BRS assessment. Firstly, these methods assume a linear rather than sigmoidal relationship between BP and PI. If BP elevations occur in the threshold or saturation portions of the curve, then the calculated baroreflex slope will be less than if pressure elevations are confined to the linear portion [Eckberg, 1980]. Secondly, pressor agents may have direct effects on the arterial BR itself. In one experimental study on conscious dogs, phenylephrine was indeed shown to have a direct action on the smooth muscle of the carotid sinus [Bergel et al, 1979], though the potential role of this effect in humans is unknown. Finally, there are also clinical and experimental circumstances where pharmacological techniques cannot be used.

1.4.2. The Neck Chamber Method

The neck chamber has been used as an alternative method of assessing carotid BR reflexes [Eckberg et al, 1975; Eckberg, 1980]. Short-lasting external suction or pressure is applied to the region of the carotid sinus in the neck via an airtight chamber. External suction increases the transmural pressure in the carotid sinus, thereby activating the BR, whilst external pressure unloads the BR. Unlike the pharmacological methods, this technique has the advantage of allowing the measurement of BP responses to BR stimuli. However, there are a number of other problems. Firstly, the stimulus is only delivered to the carotid sinus, and other BR (principally aortic) will tend to mitigate the reflex responses [Eckberg, 1980]. Secondly, the pressure changes may be incompletely transmitted to the carotid sinus, with consequent variability in the induced alterations in carotid sinus transmural pressure [Ludbrook et al, 1977].
1.4.3. The Valsalva Manoeuvre

The Valsalva manoeuvre comprises an abrupt transient voluntary elevation of intrathoracic and intra-abdominal pressures provoked by straining, and is traditionally divided into four phases [Hamilton et al, 1936]. During the first few seconds of the Valsalva manoeuvre, there is an abrupt elevation of arterial pressure related to compression of the aorta and propulsion of blood into the peripheral arteries associated with increased intrathoracic and intra-abdominal pressures. There is an associated bradycardia mediated by increased efferent PNS activity (phase 1). Continued straining impedes venous return to the heart with consequent BP fall despite a tachycardia, though efferent SNS activity increases and the BP decline is arrested and begins to return to normal (phase 2). Immediately after expiratory pressure is released, BP falls transiently, probably as a result of mechanical factors (phase 3). Thereafter, there is a steep BP rise to peak at values above resting pressure provoking arterial BR stimulation and a reflex bradycardia (phase 4) [Eckberg, 1980]. The slope of the linear regression of PI on BP during phase 4 has been used as an index of cardiac BRS [Pickering et al, 1969].

Despite the attractions of the Valsalva manoeuvre in view of its safety, lack of need of sophisticated equipment, and reproducibility [Levin, 1966], there are a number of reservations regarding its use. These mainly relate to methodological considerations, especially the mouth pressure during straining, the duration of straining, and whether straining is initiated after maximal or normal inspiration [Eckberg, 1980]. The portion of phase 4 that is used in the calculation of BRS is also important. Pickering and Sleight used only the overshoot part of phase 4, where BP exceeds resting pressure, which amounts to only a few beats [Pickering et al, 1969]. Goldstein and colleagues included all beats from the lowest BP after the release of expiratory pressure at the beginning of phase 4 to the peak pressure at the end of phase 4, and correlated this with PI using one beat delay [Goldstein et al, 1982]. Horodyski similarly included all beats in phase 4 but imposed no delay [Horodyski et al, 1995]. This may result in significantly differing values for BRS with higher figures being obtained when earlier beats in phase 4 are excluded [Smith et al, 1987; Palmero et al, 1981; James et al, 1996a]. Other
groups have assessed BRS from the relationship of BP and PI changes in phase 2 [Goldstein et al, 1982; McAloney et al, 1987]. The concept of a delay between BP and PI has also been alluded to, with a variable delay often being required. For instance, two or three beats for calculations involving the whole of phase 4, and no or one beat delay when assessing the overshoot [Smith et al, 1987]. However, the Valsalva manoeuvre remains a complex global test of the mechanical status of the circulation, the integrity of arterial BR, cardiopulmonary receptor and chemoreceptor populations, complex central autonomic interactions, as well as efferent SNS and PNS mechanisms [Eckberg, 1980].

1.4.4. Time Domain Analysis

The increased availability of powerful microcomputers and appropriate analysis packages, as well as techniques of reliable non-invasive beat-to-beat BP recording, has made possible the calculation of BRS from the assessment of continuous BP and PI recordings taken at rest. BP and HR vary as a function of time. Analysis of beat-to-beat BP and PI recordings of at least 10 minutes taken at rest can be used to assess BRS. Recordings are analysed to document sequences of typically at least 3 beats associated with increasing BP and PI or decreasing BP and PI. These are associated with the BR-HR reflex, and account for at least 20% of beats in typical recordings [Bertinieri et al, 1988; Parlow et al, 1995]. Sequences associated with BP and PI changes in opposite directions are also noted though the cause of these are presently unclear. The slope of the linear regression of PI on BP gives a measure of BRS. Animal studies in the unanaesthetised cat demonstrate that these sequences are eliminated following sinoaortic denervation, and confirm that they result from BR modulation of the sinus node [Bertinieri et al, 1985; Bertinieri et al, 1988]. Appropriate changes in calculated BRS are also observed with SNS, PNS and combined pharmacological autonomic blockade in humans and further confirm the appropriateness of sequence analysis (SA) for the assessment of BRS [Parlow et al, 1995].

Parlow and colleagues assessed BRS in a group of healthy young volunteers with pharmacological (bolus phenylephrine, infused sodium nitroprusside) and sequence methods, and reported similar values for BRS assessed by SA
compared to values from the tangent between the pressor and depressor methods [Parlow et al, 1995]. Separate values for BRS may be quoted from up and down sequences [Bertinieri et al, 1988; Omboni et al, 1993], and these have been found by our group to compare with those derived from pressor and depressor pharmacological techniques in an elderly population [James et al, 1995]. Others have reported values for BRS from SA similar to those cited in the literature by standard pharmacological techniques [Fritsch et al, 1986; Parati et al, 1988; Steptoe et al, 1990].

However, there are some limitations to SA as it is restricted to resting points, and does not assess the overall reflex parameters, including the range of PI response, and the level of upper and lower plateaus of response. There are also a number of methodological discrepancies between studies that make direct comparisons difficult. Typically, a sequence length of 3 or more beats is used, though studies have shown that BRS is inversely related to sequence length [Bertinieri et al, 1988; James et al, 1995]. Short sequences may limit the accuracy of BRS calculations, but are more typical of the normal physiological state [Bertinieri et al, 1988]. The longer sequences associated with pharmacological methods may not therefore represent the true picture. Certainly, sequences of fewer than 3 beats are unlikely to represent the BR-HR reflex, Bertinieri and colleagues showed no reduction in the number of 1 beat sequences following sinoaortic denervation in cats [Bertinieri et al, 1988].

Some groups, though not all [Fritsch et al, 1986; Steptoe et al, 1990; Parlow et al, 1995], include criteria of BP change between beats in a sequence, typically 1 mmHg [Bertinieri et al, 1985; Bertinieri et al, 1988; Parati et al, 1988; Omboni et al, 1993]. Similarly, specific PI changes may be stated, varying between 4 msec [Bertinieri et al, 1985; Bertinieri et al, 1988] and 6 msec [Parati et al, 1988], though not universally [Steptoe et al, 1990; Parlow et al, 1995]. It has been stated that BP is only likely to influence the timing of the next heart beat at rates of 75 beats per minute (bpm) or less [Steptoe et al, 1990], and consequently the effect of a lag between BP and PI has been studied. Most studies found that a lag of one beat gave higher levels of BRS [Fritsch et al, 1986; Steptoe et al, 1990] and more
sequences on which BRS could be determined [Steptoe et al., 1990], though the lag used is not always stated [Parati et al., 1988; Parlow et al., 1995]. Finally, only lines of regression with a defined correlation coefficient can be selected to compute BRS, for example >0.80 [Steptoe et al., 1990] or >0.84 [Parati et al., 1988; Omboni et al., 1993].

Nonetheless, SA provides a method of measuring BRS over a period of time under normal physiological conditions, rather than in response to brief and extreme perturbations typically induced by the pharmacological methods. Furthermore, measurements may be taken at rest with minimal subject cooperation, which is not a feature of some other techniques of BRS estimation. The advent of reliable and reproducible methods of NIBPM has further enhanced the potential applications of such a technique, avoiding the potential discomfort and risk associated with invasive arterial methods.

The Finapres (FINger Arterial PRESsure) device measures beat-to-beat blood pressure in the digital arteries by the volume-clamp method of Penaz [Penaz, 1973]. An inflatable cuff is placed around the middle or index finger, occasionally the thumb, and the pressure in the cuff is maintained by a fast-acting servo-circuit so that the transmural pressure in the digital arteries remains constant, as judged by an infra-red photoplethysmograph. Cuff pressure thus equals intra-arterial pressure, and the output from the Finapres manometer represents beat-to-beat BP. The device contains a built-in system (physio-Cal) that briefly interrupts the BP recording automatically to keep the finger arteries fully unloaded and the transmural pressure equal to zero. Several studies have now compared NIBPM with the Finapres with that measured simultaneously in either the brachial or radial artery [Imholz et al., 1988; Parati et al., 1989; Imholz et al., 1990; Rongen et al., 1995]. These studies have examined the technique during a variety of cardiovascular laboratory tests, including the Valsalva manoeuvre, active and passive orthostasis, cold pressor test, isometric exercise, mental arithmetic, and pharmacological assessments of BRS by phenylephrine or nitroglycerin injection, and shown that the technique accurately tracks changes recorded in intra-arterial BP [Dorlas et al., 1985; Imholz et al., 1988; Parati et al., 1989; Christen et al., 1990;
Imholz et al, 1990; Imholz et al, 1992; Rongen et al, 1995. In a comparative study of intra-arterial and Finapres BP measurement during the Valsalva manoeuvre, Imholz and colleagues found that group mean values agreed to within 1 mmHg, though this concealed considerable interindividual variability of between +6 mmHg to -7 mmHg during the abrupt changes in peripheral blood flow and BP occurring during phase 4 of the manoeuvre [Imholz et al, 1988]. In the study conducted by Parati and colleagues, BRS indices derived from either Finapres or intra-brachial data to either a pressor (phenylephrine) or depressor (nitroglycerin) dynamic stimulus agreed very closely [Parati et al, 1989]. Rongen and colleagues found increased discrepancies between Finapres and intrabrachial pressures in older normotensive subjects during the Valsalva manoeuvre, but concluded that the advantages of NIBPM and ease of use of the Finapres outweigh the slight loss of precision [Rongen et al, 1995].

1.4.5. Frequency Domain Analysis

In addition to the cardiac cycle, the main rhythmic factors that affect the CVS include the long established PI and BP fluctuations associated with the respiratory cycle, and vasomotion [Malliani et al, 1991]. Slow oscillations in BP with a period of 10 seconds (0.1 Hz), termed Mayer waves, have only more recently been recognised [Penaz, 1978]. Associated rhythmic changes in SNS and vagal discharge in phase with respiration and vasomotor waves have been found, and the neural regulation of the CVS is ultimately effected through the interplay of these SNS and vagal outflows where activation of one is accompanied by inhibition of the other. The so-called sympathovagal balance reflects the result of the interactions of such peripheral excitatory and inhibitory reflex mechanisms, and central neural integration at rest [Malliani et al, 1991].

Thus, variability of BP and PI can be not only described as a function of time as has already been discussed, but also in the frequency domain by the sum of their oscillatory components defined in terms of frequency and amplitude (area or power). In brief, computer analysis of continuous beat-to-beat recordings of BP and PI stores consecutive values of BP and PI as a tachogram. Power spectral analysis (PSA) is subsequently used to detect underlying rhythmicity (Figure 1.2),
and various algorithms can be used to assess the number, frequency and amplitude of the oscillatory components [Kay et al, 1981].

Most studies rely on the autoregressive (AR) [Pagani et al, 1986] and fast Fourier (FFT) [Akselrod et al, 1981] algorithms. The AR method automatically determines the number and centre frequency of the oscillatory components, i.e. it derives the best-fitting model for the data and treats any signal components not fitting the model as noise and discards them. The selection of the best-fitting model relies on a posteriori formal statistical criteria, such as Akaike's criterion, to indicate the optimal model order fitting the data [Brovelli et al, 1983]. This method can therefore be used on short data segments, e.g. 200 cycles [Malliani et al, 1994], and has significant advantages over other algorithms as data is more likely to be stationary - an important prerequisite of PSA, but an uncommon occurrence in biological systems [Malliani et al, 1991].

The FFT is easier to implement but requires strict periodicity of the data and is frequently used with an a priori selection of the number and frequency range of oscillatory components. This method uses all the data in a prerecorded signal to derive the power spectrum, whether its frequency components appear as specific spectral peaks or nonpeaked broadband powers. It therefore requires longer recordings as the frequency resolution of the FFT spectrum is dependent on the length of the recording [Parati et al, 1995a]. Given the underlying requirement of PSA for stationarity of the data, this presents some limitations to the use of this model, particularly when sufficient segments are required to be analysed to control for bias and variance. It should be noted that the spectra derived by the AR and FFT techniques may approach one another when the AR model order approaches the number of data points and when the FFT is used with methodological manipulation such as smoothing [Parati et al, 1995a].
FIGURE 1.2 Example of simultaneous computer analysis of systolic blood pressure and pulse interval variabilities
These analysis techniques used to quantify variability in BP and PI usually focus on variability within frequencies of 0.025 to 0.5 Hz. based on evidence that the BP and PI spectra in these frequencies are at least in part modulated by neural autonomic influences [Akselrod et al, 1981; Malliani et al, 1991]. However, the precise interpretation of the resulting spectra is still a matter of debate despite the large number of studies completed.

**Interpretation Of Pulse Interval Spectra**

The evidence that the high frequency (HF) peak with a centre frequency of 0.25 Hz. is a reliable marker of vagal activity has recently been reviewed [Malliani et al, 1991; Malliani et al, 1994; Parati et al, 1995a]. In particular, the use of physiological measures recognised to increase vagal drive, such as controlled respiration, cold facial stimulation and rotational stimuli, result in an increase in the HF peak [Pomeranz et al, 1985; Pagani et al, 1986]. Conversely, the use of pharmacological vagal blockade with atropine practically abolishes PI variability in the HF band [Selman et al, 1982; Pomeranz et al, 1985]. However, not all PI fluctuations above 0.15 Hz. are entirely mediated by the PNS as when under conditions of combined pharmacological PNS and SNS blockade and after cardiac transplantation, some respiratory sinus arrhythmia persists [DeBoer et al, 1987; Peters et al, 1988a; Peters et al, 1988b; Bernardi et al, 1989; Saul et al, 1991]. Thus the HF peak is a satisfactory if incomplete measure of vagal cardiovascular control.

The low frequency (LF) peak may be significantly increased by measures which enhance SNS drive, including passive tilt or active standing [Brovelli et al, 1983; Pomeranz et al, 1985; Pagani et al, 1986; Lombardi et al, 1987] and mental stress induced by arithmetic calculation [Pagani et al, 1989; Pagani et al, 1991]. Pharmacological blockade with propranolol reduces LF power [Saul et al, 1989; Saul et al, 1991]. However, LF power is not entirely abolished by β-blockade, and atropine may also reduce LF power albeit under conditions of controlled respiration [Pomeranz et al, 1985], suggesting that LF power is not entirely a marker of the SNS.
Interpretation Of Blood Pressure Spectra

Vagally mediated changes in PI and cardiac output play a role in determining HF power in the BP spectrum [Saul et al, 1991]. However, the HF peak is not substantially altered in patients with denervated donor hearts [Peters et al, 1988a; Peters et al, 1988b; Bernardi et al, 1989]. Also, interventions that markedly reduce cardiac vagal drive, decreasing HF PI variability, only have a minor effect on HF BP variability [Di Rienzo et al, 1991]. Therefore, other factors may be of importance, including the mechanical effects of respiration on pressure gradients, size, and functions of the heart and large thoracic vessels [de Boer et al, 1987; Peters et al, 1988a; Peters et al, 1988b; Saul et al, 1991].

Factors involved in vasomotor tone and systemic vascular resistance including the renin-angiotensin system, endothelial factors, and local influences related to thermoregulation, and others are understood to influence the very low frequency (VLF) component (0.02 to 0.06 Hz.) of the power spectrum of BP variability (BPV) [Akselrod et al, 1985]. However, many of these factors are imprecise and speculative [Parati et al, 1995a]. LF power is increased by stimuli that increase SNS drive, such as head-up tilt and mental stress [Pagani et al, 1986; Pagani et al, 1989], and is reduced by stimuli that decrease SNS drive, such as sleep and α-blockade [Furlan et al, 1990]. Therefore, LF power represents a marker, albeit inconsistent, of SNS vasomotor tone [Parati et al, 1995a].

Spectral Powers As Measures Of Autonomic Cardiovascular Modulation

SNS and vagal influences are normally altered in opposite directions, so one can improve on the limited sensitivity of using LF and HF powers as surrogate markers of SNS and vagal drives, respectively, by using the ratio as an index of sympathovagal balance [Pagani et al, 1986]. Certainly, the LF/ HF ratio is significantly elevated in conditions of SNS predominance such as active or passive standing and mental stress, and reduced to levels below unity in association with increased vagal drive [Malliani et al, 1991].

Frequency domain methods have also been derived to assess BRS. Firstly, the LF peak in either PI or BP variability may be a marker of intact baroreflex control
itself. Studies of subjects with severe cardiac failure, in which high SNS tone is recognised, have shown reduced LF power [Saul et al, 1988]. This may be because there are a number of requirements for generation of the LF peak, including intact SNS efferents, a reactive vascular system, and importantly an intact baroreflex [de Boer et al, 1987]. Sleight and colleagues have studied 2 cardiac failure patients, one with preserved BRS as assessed by the phenylephrine method and one without. A LF peak was only generated in the patient with the intact baroreflex [Sleight et al, 1995]. Secondly, BRS may be estimated by the calculation of the square root of the ratio of the powers of PI to BP (the alpha index), which showed similar changes in values of BRS compared to simultaneous assessment by the phenylephrine method [Pagani et al, 1988; James et al, 1996b]. Finally, the modulus or gain of the transfer function between variations in BP and PI in the LF band can be used when the two signals show a significant coherence. The coherence between PI and BPV reflects the amount of linear coupling between the 2 spectra, and is therefore comparable to the correlation coefficient in regression analysis. Again, this gives an equivalent value of BRS to the phenylephrine method [Robbe et al, 1987].

There are several theoretical and methodological issues which remain unresolved [Parati et al, 1995a]. Both SA and PSA of course have a major difference in the underlying assumption about the physiology of the BR reflex. SA assumes that activation of the BR reflex is adaptive and intermittent, whilst PSA assumes that during stationary periods there is a permanent linear association between BP and PI, albeit limited to specific frequency bands. However, despite such a difference in their underlying assumptions, both methods have shown significant agreement for estimated values of BRS in a group of 8 volunteers [Hughson et al, 1993]. Panerai and colleagues also showed significant agreement between sequence estimates and the alpha index of spectral analysis in a group of 17 subjects, and concluded that the 2 methods share common elements and one should not be excluded to the detriment of the other except where non-stationarity precluded the use of PSA techniques [Panerai et al, 1995].
Therefore, these techniques show considerable promise in the assessment of neural cardiovascular control, and with the advent of reliable NIBPM allow this to be performed in a noninvasive and nonpharmacological fashion. These methods have also proved useful in pathological states with evidence from studies of patients with acute myocardial infarction [Schwartz et al, 1988; Osculati et al, 1990; Grassi et al, 1992; Odemuyiwa et al, 1993], and the results may be of prognostic significance [La Rovere et al, 1988; Farrell et al, 1992; Odemuyiwa et al, 1993]. However, studies of stroke patients are very limited. Barron and colleagues used PSA techniques to assess HRV in a group of 40 stroke patients studied within 4 to 11 days of ictus and compared their findings with 40 age- and sex-matched control subjects. They found reduced total spectral power, particularly in the HF band [Barron et al, 1994]. HF power was also significantly lower in right compared to left hemisphere strokes, which concords with previous findings of right sided dominance of control of the sinoatrial node with increased likelihood of HR influences [Natelson, 1985; Talman, 1985; Yokoyama et al, 1987; Lane et al, 1992].

1.5. Cerebral Autoregulation

The well-documented changes in BP following stroke, and the possible mechanisms and their assessment have been considered. The clinical relevance of such BP changes with particular regard to their effects on cerebral perfusion and the acute management of BP will now be considered. However, it is first necessary to review aspects of the control of cerebral perfusion.

Under normal conditions, cerebral perfusion pressure is maintained at a constant level despite perturbations in BP. Cerebral autoregulation, so called, typically operates over a range of mean arterial pressure of 60 to 150 mmHg [Strandgaard et al, 1990], though these levels are not fixed and may be modulated by a number of physiological factors. These include SNS activity, the renin-angiotensin system, and any factor that increases or decreases CBF (particularly arterial carbon dioxide, and to a lesser extent oxygen, tension) [Paulson et al, 1990]. CBF is
controlled by appropriate changes in the calibre of the cerebral resistance vessels, such that:

\[
\text{Cerebral blood flow} = \frac{\text{Cerebral perfusion pressure}}{\text{Cerebrovascular resistance}}
\]

For effective autoregulation, i.e. maintaining constant CBF, cerebrovascular resistance changes proportionally for changes in perfusion pressure. Therefore, at lower BP, the cerebral resistance vessels dilate to prevent brain ischaemia. However, below the lower limit of autoregulation, vasodilatation becomes inadequate and CBF falls. Initially, increased oxygen extraction maintains cerebral oxygen tensions. Also, CBF may be maintained by carbon dioxide inhalation [Harper et al, 1965; Haggendal et al, 1965] and vasodilator therapy [Barry et al, 1984], as maximum vasodilator capacity of the cerebral resistance vessels is below the lower limit of cerebral autoregulation [MacKenzie et al, 1979]. At the lowest BP, the resistance vessels collapse and there is a massive increase in cerebrovascular resistance. At the other end of the spectrum, the cerebral resistance vessels constrict as BP increases to prevent capillary damage and cerebral oedema. However, at the upper limit of cerebrovascular autoregulation, CBF increases as the resistance vessels give way to high pressure [Skinhoj et al, 1973; Strandgaard et al, 1974; Strandgaard et al, 1975; MacKenzie et al, 1976; Baumbach et al, 1985], resulting in forceful dilatation of the arterioles, blood-brain barrier damage [Rapoport, 1976], and cerebral oedema with a secondary decrease in CBF.

The exact mechanisms of cerebrovascular autoregulation are controversial [Paulson et al, 1990], but changes in resistance vessel calibre are probably mainly mediated by an interplay between myogenic and metabolic mechanisms. A myogenic mechanism was originally proposed by Folkow and stated that arteriolar constriction or dilatation was in response to an increase or decrease in the transmural pressure gradient [Folkow, 1964]. Certainly, the state of the actin and myosin filaments in smooth muscle cells are affected by changes in intravascular pressure. Changes in the metabolic microenvironment may also be responsible for
the vasomotor response, and also help explain highly localised and restricted changes in CBF. A variety of vasoactive molecules have been proposed as mediators of a coupling between neuronal activity and CBF [Kuschinsky et al, 1978]. Their exact roles remain to be established, though the most powerful stimulators are an increased carbon dioxide or reduced oxygen arterial tension. Other cerebrovascular autoregulatory mechanisms have also been proposed, including a role for the dense innervation of the large basal cerebral blood vessels by SNS and PNS fibres from the cranial ganglia as well as endothelial cell-related factors [Hossman, 1988; Paulson et al, 1990].

In conditions of ineffective cerebrovascular autoregulation, i.e. constant cerebrovascular resistance, CBF becomes pressure passive and follows perfusion pressure. Cerebral ischaemia (irrespective of aetiology) is associated with impaired or abolished cerebrovascular autoregulation [Dearden, 1985]. In acute ischaemic stroke, perfusion pressure may be below the lower limit of cerebrovascular autoregulation distal to the site of arterial occlusion, and reduced CBF may merely be a consequence of the changes in the pressure-flow relationship already discussed. However, CBF is further modified by the individual development of collateral circulation and the vascular reactivity of the surrounding tissue, as evidenced by experimental [Waltz, 1968; Symon et al, 1973; Symon et al, 1976; Shima et al, 1983; Avery et al, 1984; Dearden, 1985; Dirnagl et al, 1990] and clinical [Hoedt-Rasmussen et al, 1967; Agnoli et al, 1968; Fieschi et al, 1968; Paulson, 1970; Meyer et al, 1973b; Olsen et al, 1983a] studies of CBF responses to changes in perfusion pressure and arterial carbon dioxide tension. These studies measured CBF at a constant BP level and subsequently remeasured CBF after BP manipulation which is again allowed to reach steady state, i.e. static autoregulation. Such static measurements assess the overall efficiency of the vasoregulatory system, but do not provide a quantitative assessment of autoregulatory responses to rapid BP changes, i.e. dynamic autoregulation. Some of these studies will be considered in more detail.
1.5.1. Experimental Studies

Cerebral dysautoregulation has been reported in a number of animal models of stroke. In cats, Waltz reported the effects of induced hypertension (by phenylephrine) and hypotension (by sodium nitroprusside) on CBF assessed with $^{35}$ krypton following right MCA occlusion. CBF was proportional to BP at hypotensive and normotensive levels, though not at hypertensive levels. It was suggested that treatment in patients with cerebral ischaemia should include measures to maintain, but not increase, BP [Waltz, 1968]. Symon and colleagues also reported impaired autoregulation after stroke with more severe CBF alterations with decreasing rather than increasing BP [Symon et al, 1976]. However, at higher BP, there is a risk that the apparent increases in CBF will lead to an increase in local tissue pressure and oedema, thus precluding a substantial improvement in tissue perfusion pressure [Hossman, 1988]. Indeed, following severe temporary cerebral ischaemia in the gerbil, Avery and colleagues reported that the amount of hyperaemia on reperfusion and the amount of oedema was related to the severity of ischaemia [Avery et al, 1984].

The degree of ischaemia may also be relevant in determining the extent of cerebrovascular dysautoregulation. Dirnagl and colleagues reported a linear relationship between SBP and regional CBF in conditions of moderate to severe ischaemia (regional CBF <30% of baseline), consistent with cerebral dysautoregulation at all levels of SBP. Though even in conditions of mild ischaemia (regional CBF >30% of baseline), there was some evidence of impaired cerebrovascular autoregulation in the experimental model used, that of the spontaneously hypertensive rat with ischaemia induced by common carotid and MCA occlusions [Dirnagl et al, 1990]. Symon and colleagues similarly reported a correlation between the degree of ischaemia and the extent of impairment of cerebrovascular autoregulation in cats [Symon et al, 1973]. Metabolic regulation as assessed by the carbon dioxide reactivity of cerebral vessels is also impaired. Symon in an earlier study reported reduced arterial perfusion pressure in response to hypercapnia compared to normocapnia in baboons with MCA occlusion [Symon, 1970].
1.5.2. Clinical Studies

Cerebrovascular dysautoregulation is also well described in clinical studies. Hoedt Rasmussen and colleagues reported a focal loss of vasomotor regulation in response to induced hypertension in 6 patients studied within 4 days of ictus. They found increases in CBF measured by radiolabelled xenon in association with increased BP [Hoedt Rasmussen et al, 1967]. This acute loss of cerebrovascular autoregulation has been confirmed in further studies of 13 patients studied within 2 days of ictus [Agnoli et al, 1968], 21 patients within 4 days [ Fieschi et al, 1968] and 8 patients within 3 days [Olsen et al, 1983b], all using induced hypertension. Paulson has also reported reduced CBF in 10 patients studied within 3 days of angiographically confirmed MCA occlusion, with evidence of focal vasoparalysis to carbon dioxide, aminophylline, as well as induced hypertension [Paulson, 1970].

Meyer and colleagues observed the effects of induced hypotension following head up tilting in 30 stroke patients and reported a reduction in CBF with reduced mean arterial pressure (MAP) even in the autoregulatory range [Meyer et al, 1973b]. Though the magnitude of dysautoregulation reduced as the time interval from stroke increased, abnormalities were still demonstrable at 1 month post ictus [Meyer et al, 1973b]. This concurs with the findings of Mori and colleagues, who assessed 55 patients (16 haemorrhage) for a mean of 28 months and reported reduced CBF compared to age- and BP-matched controls as well as to the contralateral hemisphere [Mori et al, 1993]. Even following strokes with no residual MCA occlusion, evidence of vasomotor paralysis in response to induced hypertension, hypotension and arterial carbon dioxide changes was observed in patients studied several weeks after ictus [Paulson, 1970].

1.5.3. The Ischaemic Penumbra

A recognition of the pathophysiological changes in CBF accompanying cerebral ischaemia may have important implications for the understanding of BP management in the acute and chronic stroke patient. Experimental studies are able to provide a detailed description of such changes. Following arterial occlusion, a central zone of severe ischaemia is produced with a surrounding zone where flow is sufficient for cellular viability but insufficient for cellular function
and has been termed the ischaemic penumbra [Astrup et al, 1981]. Residual perfusion in the ischaemic penumbra is dependent on flow through collateral vessels and different flow states have been identified. Some areas show evidence of excess CBF, or normal or even reduced CBF with low oxygen extraction fraction, so called absolute or relative luxury perfusion [Lassen, 1966], where CBF is in excess of the metabolic requirements of the brain. This may reflect a temporary rise in CBF above resting level following a period of vascular arrest, may occur post vascular recanalisation, and has been demonstrated in both experimental [Meyer et al, 1954] and clinical studies [Lassen, 1966; Paulson, 1970]. It has been attributed to local vasomotor paralysis brought about by the effects of posthypoxic metabolic acidosis [Lassen, 1966; Shima et al, 1983; Harris et al, 1984]. Conversely, other areas show evidence of low CBF and high oxygen extraction fraction, where the needs of the tissue are not being met. Flow in these areas of ‘misery’ perfusion, where function is recoverable, may reach certain critical flow thresholds where there is evidence of cellular electrical (20 mls blood/100g brain/minute) followed by energy and ion pump failure (10 to 12 mls blood/100g brain/minute) [Astrup et al, 1981]. At flow rates between these two thresholds of transmitter and membrane failure, neurons do not function but are viable. It is these cells that constitute the ischaemic penumbra.

The extent and duration of the viability of the ischaemic penumbra is measured in hours in animals, but may be longer in human stroke which is a more complex and dynamic process where thrombus propagation and thrombolysis continue. Viability depends on a number of factors including severity and duration of ischaemia, age, temperature, glucose availability and the different ischaemic tolerances of different neuronal populations [Powers, 1993]. However, there is good reason to believe that there is a portion of viable brain surrounding the zone of severe central ischaemia that is dependent on the maintenance of cerebral perfusion pressure to preserve CBF. It further emphasises the clinical importance of BP management, particularly in the acute stroke period, and indeed some have advocated the therapeutic manipulation of BP, whether by induced hypertension or induced hypotension, in the acute stroke period, and this will now be considered.
1.6. Blood Pressure Management In The Acute Stroke Period

The management of BP in the acute stroke period is based mainly on anecdotal reports in the literature with little supporting evidence from large controlled trials.

1.6.1. Induced Hypertension

Initially, a rise in BP may be beneficial in increasing CBF to the ischaemic penumbra, and could be regarded as a physiological compensatory mechanism. Indeed, it has been stated that acute post-stroke hypotension should be sought and treated to avoid further hypoxic cerebral damage [O'Connell et al, 1994].

Hayashi and colleagues studied the theoretical benefits of induced hypertension in monkeys during a 4-hour period of MCA occlusion [Hayashi et al, 1984]. Increased CBF was seen in the ischaemic areas with associated improvement in neurological grading in the monkeys receiving phenylephrine compared to controls. This concords with findings from other experimental studies using different ischaemic models [Safar et al, 1976; Aspey et al, 1987], though Aspey and colleagues demonstrated a tendency towards a detrimental effect in one of the models studied [Aspey et al, 1987]. This probably reflected a sufficient duration of ischaemia to induce blood-brain barrier damage.

Clinical observations have been limited to sporadic anecdotal reports of an association between increasing BP and improving neurological status, at least in the short-term [Farhat et al, 1967; Wise et al, 1972; Vander Ark et al, 1973; van Dellen et al, 1977; Meyer et al, 1987]. However, even in the largest series, Wise and colleagues reported a temporary beneficial effect of vasopressor therapy commenced within 4 hours of ictus in only 5 of the 13 reported patients, and this effect was unsustained in two [Wise et al, 1972].

As well as increasing BP, other measures to increase CBF in the acute stroke period include surgical reperfusion and measures to lower cerebrovascular resistance including cerebral vasodilatation, arterial recanalisation by thrombolysis and lowering viscosity. By and large, the inconclusive nature of the results of such trials may be because of poor patient selection, delay in starting therapy, lack of
CBF effect in the vulnerable brain region, and variable return of CBF in such regions [Grotta, 1987]. For the case of induced hypertension, these difficulties are demonstrated by the study of Olsen of changes in regional CBF to induced angiotensin in 43 subjects studied within 72 hours of acute stroke [Olsen, 1983b]. A subgroup of 8 patients had critically low CBF with abnormal vascular reactivity in an intact uninfarcted area of brain surrounding an infarcted area, who would benefit from induced hypertension. However, Olsen also reported a further subgroup of 12 patients with a surrounding area of intact uninfarcted brain and moderate hyperaemia and normal or slightly impaired vascular reactivity, as well as infarcted areas of pronounced hyperaemia with abnormal vascular reactivity. It is argued that induced hypertension would have a detrimental effect in this group, producing increased cerebral oedema and risk of haemorrhage, though not all studies suggest an association between BP increase and further bleeding [Lavin, 1986]. These potential deleterious effects of induced hypertension have also been observed in controlled experimental studies whether sustained [Spatz et al, 1976; Michenfelder et al, 1977] or intermittent [Bleyaert et al, 1980; Kogure et al, 1981]. Induced hypertension may also have other detrimental systemic effects, such as cardiac failure [Dirnagl et al, 1990], and this was the cause of death in the study of Michenfelder and colleagues in experimental stroke in the three primates studied though a prolonged period of hypertension was used [Michenfelder et al, 1977]. Similar observations were reported with intermittent hypertension [Bleyaert et al, 1980].

1.6.2. Induced Hypotension
There are equally well-defined risks of overzealous BP reductions, which may expose patients to more harm than good [Yatsu et al, 1985], and have been elucidated in a number of case reports [Britton et al, 1980; Lavin, 1986]. Britton and colleagues reported 6 subjects with severe acute cerebrovascular disease, all but one being unconscious at the time of presentation [Britton et al, 1980]. BP was lowered below the normal lower limit of cerebral autoregulation and was associated with further neurological deterioration or death. Though the deterioration occurred in the context of BP reduction and one patient showed signs of improvement when BP was allowed to rise, it is difficult to establish the
relevance of this to final outcome given the poor prognosis of these patients, 4 of whom had autopsy evidence of intracerebral haemorrhage. Also, the hypotensive agent used was hydralazine, which causes cerebral vasodilatation and further cerebral dysautoregulation [Barry, 1989]. Similarly, Lavin reported 2 patients with worsening of neurological symptoms following the introduction of antihypertensive therapy, and improvement when BP was increased again [Lavin, 1986]. However, BP reductions in these patients were below the normal lower limit of cerebral autoregulation, which may partly explain the poor results. It has been argued that BP should only be reduced to the normal upper limit of cerebral autoregulation, whatever this may be, [Spence et al, 1985; Brott et al, 1989a], and certainly no more than 20% as this is enough to reduce cerebral oedema without the risk of borderzone ischaemia [Lavin, 1986].

Studies assessing the relative merits of hypotensive therapy have been largely uncontrolled. Gottstein and colleagues reported their observations on 194 hypertensive patients admitted to their unit and routinely treated with antihypertensive therapy (clonidine, methyldopa, thiouracil) and resulting in a fall in mean BP at admission of 220/110 to 150/90 mmHg over a 5-day period. This was tolerated well in 90% of patients, though this was uncontrolled and time of starting treatment after stroke was not stated [Gottstein et al, 1977]. There has been a small controlled study of 16 patients recruited within 72 hours of ictus to assess the effects of hypotensive therapy with nicardipine, captopril or clonidine for 3 days compared to placebo on neurological outcome [Lisk et al, 1993]. Patients with the greatest MAP falls and those with a fall greater than 16% of baseline, which tended to be those treated with nicardipine, showed the least increase and even a decrease in CBF to the affected area, though group size was too small to provide definite data.

However, hypotension is a predictable side effect of agents, the potential cerebroprotective effects of which have been studied in acute stroke. Nimodipine is a dihydropyridine calcium channel blocker, and by limiting post-ischaemic intracellular calcium flux may have a cerebroprotective effect. It is of proven benefit in reducing mortality and morbidity in aneurysmal subarachnoid
haemorrhage, though this is not related to any hypotensive effect. It may also be beneficial in acute stroke because of its preferential vasodilatory action on cerebral vessels and it increases CBF by 30% within the damaged hemisphere of stroke victims. Gelmers and colleagues reported improved neurological score and reduced mortality at 1 month in 186 patients, when treated within 24 hours [Gelmers et al, 1988], though this was not supported by 2 subsequent trials, albeit smaller [Bogousslovsky et al, 1990; Martinez-Vila et al, 1990]. More recently, the TRUST Study Group reported the results from a placebo-controlled study in 1215 patients treated with 40 mg tds of nimodipine within 48 hours of acute ischaemic stroke [TRUST Study Group, 1990]. They found a non-significant increase in mortality and delayed recovery, though there were no differences in SBP fall between the groups (16.4 vs. 13.5 mmHg). Similarly, the American Nimodipine Study Group reported no differences in 1 month mortality between placebo and 4 different nimodipine doses in 1064 patients treated for 21 days, though there were no significant differences in BP fall between groups over the first 4 days [American Nimodipine Study Group, 1992]. Also, Rosenbaum and colleagues studied 57 patients recruited within 12 hours of ischaemic stroke, and treated for 72 hours with intravenous nicardipine, though therapy was discontinued if MAP fell by greater than 10%. Thereafter patients received 30 days oral nicardipine. They reported improved neurological outcome at 3 months, particularly in those commencing therapy within 6 hours, though this study was uncontrolled [Rosenbaum et al, 1991].

β-blockers may also be of benefit by limiting catecholamine-induced cardiac and neurological damage, and reducing the metabolic demands of ischaemic brain. Barer and colleagues compared propranolol (lipophilic) and atenolol (hydrophilic) with good and poor cerebral penetration, respectively, in a placebo-controlled study in 302 patients within 48 hours of stroke [Barer et al, 1988]. Both β-blockers had a nonsignificant increase in mortality and decrease in neurological and functional outcome at 6 months compared to placebo, though functional differences were significant at 1 month. Significantly greater MAP falls were observed compared to placebo (9% (atenolol) vs. 6% (propranolol) vs. 2% (placebo)).
There are theoretical reasons for assuming that other hypotensive agents may have beneficial effects on CBF, including angiotensin converting enzyme inhibition which shifts the lower limit of autoregulation so improving regional CBF at low perfusion pressures [Waldemar et al, 1989], and carvediol, a vasodilator and β-adrenergic blocker with neuroprotective effects at the N-methyl-D-aspartate receptor [Lysko et al, 1992]. However, not all agents have been clinically assessed and the results to date have not demonstrated increases in regional CBF, but equally no detrimental effects have been observed [Waldemar et al, 1989].

1.6.3. Current Consensus
There are a number of accepted indications for the controlled reduction of BP in acute stroke, including hypertensive encephalopathy and the coexistence of other cardiac or vascular urgencies, such as aortic aneurysm, cardiac failure, or myocardial infarction [Spence et al, 1985; Hachinski, 1985; Reid, 1993, O’Connell et al, 1994]. It has been suggested that sustained BP levels, above 200/130 mmHg, should also be treated [Hachinski, 1985; Emergency Cardiac Care Committee and Subcommittee of The American Heart Association, 1992; Reid, 1993; O’Connell et al, 1994; Phillips, 1994], though there is no unanimity over which drug or route to use. In addition, there may be a need to widen the consensus view in the light of new therapies, such as the risk of haemorrhagic extension in patients with intracerebral haemorrhage, or in patients treated with thrombolytic drugs to reduce the risk of haemorrhagic transformation of the infarct [Reid, 1993].

1.7. Observational Prognostic Studies
Therefore, there is debate over the optimal management of BP in most acute stroke patients, and there remains a need for placebo-controlled studies of short-acting hypotensive agents with predictable and reversible BP effects in acute stroke [Yatsu et al, 1985; Reid, 1993]. However, some information regarding the prognostic significance of BP in acute stroke can be gained from observational studies, but the results of such studies to date are conflicting. Studies assessing

1.7.1. Negative Studies

Not all studies observed a significant relationship between BP and short-term outcome [Robinson et al, 1968; Miah et al, 1983; Britton et al, 1985; Dollberg et al, 1986; Carlberg et al, 1993; Fiorelli et al, 1995; M’Buyamba-Kabangu et al, 1995], and the details of these studies are shown in Table 1.2.

In one study of 945 patients with CT confirmation of diagnosis in all but 29 patients, high admission mean arterial BP was not related to thirty day mortality. However, in a subgroup of patients with impaired consciousness and MAP > 130 mmHg, there was a mortality rate of 42% compared to only 4% in those alert on admission but with similar BP levels. An odds change of 1.014 (p<0.0001) per 1 mmHg increase of BP was reported in ischaemic stroke patients with impaired consciousness on admission [Carlberg et al, 1993]. Though Miah and colleagues reported a significant association between in-hospital mortality and SBP and DBP on the first day of admission, with BP treated as a categorical variable, the significance values for these associations were not stated, and were no longer significant on multivariate analysis [Miah et al, 1983]. M’Buyamba-Kabangu and colleagues found no significant difference in BP between surviving and non-surviving blacks (171(41)/101(23) vs. 177(41)/104(26) mmHg, respectively) admitted a mean of 2 days after stroke. However, mortality rates were higher in the lowest (<160 mmHg) and highest (>200 mmHg) compared to the middle tertile of SBP (15.3 vs. 20.1 vs. 10.9 deaths per 100 patient days, respectively), though this J-shaped relationship was not repeated for DBP [M’Buyamba-Kabangu et al, 1995].
<table>
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<td>(no haemorrhagic)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miah et al 1983</td>
<td>Stroke Unit</td>
<td>283</td>
<td>Not stated</td>
<td>In-hospital mortality</td>
<td>Conscious level, Hemiplegia</td>
</tr>
<tr>
<td></td>
<td>(8% haemorrhagic)</td>
<td></td>
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<tr>
<td>Dollberg et al 1986</td>
<td>Multicentre (referred for CT)</td>
<td>77</td>
<td>Not stated</td>
<td>In-hospital mortality</td>
<td>Coma, Pupillary abnormalities, CT haemorrhage size, Intraventricular haemorrhage</td>
</tr>
<tr>
<td></td>
<td>(all haemorrhagic)</td>
<td></td>
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<tr>
<td>Carlberg et al 1993</td>
<td>Stroke Unit</td>
<td>945</td>
<td>&lt; 1 week</td>
<td>30-day mortality</td>
<td>Hemiplegia, MAP and impaired consciousness, Age, Diabetes, Cardiac failure</td>
</tr>
<tr>
<td></td>
<td>(85 haemorrhagic)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fiorelli et al 1995</td>
<td>Multicentre</td>
<td>300</td>
<td>&lt; 6 hours</td>
<td>4-month mortality and disablement</td>
<td>Low Canadian Neurological score on admission, Age &gt; 70 years</td>
</tr>
<tr>
<td></td>
<td>(no haemorrhagic)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M'Buyamba-Kabangu et al 1996</td>
<td>Retrospective</td>
<td>388</td>
<td>2+4 days</td>
<td>In-hospital mortality</td>
<td>Depressed consciousness, Tachycardia, Elevated blood urea, Alcohol abuse</td>
</tr>
</tbody>
</table>

**TABLE 1.2** Studies reporting no association between blood pressure and outcome.
1.7.2. Positive Studies

Those studies that have demonstrated an association between BP and short-term outcome variably report low [Allen, 1984; Jorgensen et al, 1994] and high [Harmsen et al, 1972; Hatano, 1976; Dunne et al, 1987; Tuhrim et al, 1988; Sacco et al, 1989; Britton et al, 1990; Davalos et al, 1990; Dandapani et al, 1995; Henon et al, 1995] BP on admission to be associated with a poor outcome. The details of these studies are shown in Tables 1.3 and 1.4, respectively.

Low Blood Pressure: Poor Outcome

Allen reported BP findings on 137 patients admitted within 2 weeks of stroke onset, and that were assessed a mean of 3.5 days post ictus. Poor outcome was defined as death (29 patients) or functional dependence (21 patients) at 2 months following acute stroke. Admission BP was lower in the poor outcome group at 147 (standard error of the mean (SEM) 4.8)/88 (3.0) mmHg compared to 162 (3.8)/94 (1.8) mmHg in the good outcome group, though this was only significant for SBP (p<0.05). Interestingly, there was a trend for patients with a poor outcome to have higher BP 24 hours after admission (152 (4.0)/89 (3.0) vs. 146 (3.0)/88 (1.8) mmHg) [Allen, 1984]. More recently, Jorgensen and colleagues studied factors associated with neurological deterioration as assessed by the Scandinavian Neurological Stroke Scale. In 433 patients admitted within 12 hours of ictus and neurologically deteriorating over the first 24 hours, admission SBP was significantly lower 156 (SD 30) compared to 170 (34) mmHg in those not deteriorating (p=0.0002). This explanatory variable remained significant in a logistic multiple regression analysis, the relative risk of early deterioration decreased by a factor of 0.66 (95% confidence intervals: 0.55 to 0.83) per 20 mmHg increase in SBP (p=0.0003). No significant association was demonstrated with DBP, neither was BP associated with patients with late stroke in progression (admitted >12 hours after ictus and progressing within the first week from admission) [Jorgensen et al, 1994].

High Blood Pressure: Poor Outcome

A number of studies have demonstrated an association between high admission BP and poor outcome (Table 1.4), whether defined as neurological deterioration [Davalos et al, 1990], recurrent stroke [Sacco et al, 1989], residual functional
<table>
<thead>
<tr>
<th>Study</th>
<th>Site</th>
<th>Size</th>
<th>Admission delay</th>
<th>Outcome measures</th>
<th>Predictive factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allen 1984</td>
<td>Medical wards</td>
<td>137 (25 haemorrhagic)</td>
<td>&lt; 2 weeks</td>
<td>2-month mortality and functional dependence</td>
<td>Impaired consciousness</td>
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<td></td>
<td></td>
<td></td>
<td>Neurological progression</td>
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<tr>
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<td></td>
<td>Haemorrhage</td>
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<td></td>
<td></td>
<td>Gaze palsy</td>
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<td>Hemiplegia</td>
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<td>Age</td>
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<td></td>
<td></td>
<td></td>
<td>White cell count</td>
</tr>
<tr>
<td>Jorgensen et al 1994</td>
<td>Neurology wards</td>
<td>868 (46 haemorrhagic)</td>
<td>&lt; 1 week</td>
<td>Stroke in progression (within first week)</td>
<td>Diabetes</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Scandinavian Stroke Scale score</td>
</tr>
</tbody>
</table>

**TABLE 1.3**  Studies reporting an association between low blood pressure and poor outcome
<table>
<thead>
<tr>
<th>Study</th>
<th>Site</th>
<th>Size</th>
<th>Admission delay</th>
<th>Outcome measures</th>
<th>Other predictive factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harmsen et al 1972</td>
<td>All wards</td>
<td>97 (29 haemorrhagic)</td>
<td>&gt; 1 week (majority &lt; 1 day)</td>
<td>In-hospital mortality</td>
<td>-</td>
</tr>
<tr>
<td>Hatano 1976</td>
<td>Multicentre</td>
<td>6395 (23% haemorrhagic)</td>
<td>not stated</td>
<td>'Early' mortality</td>
<td>Age</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Unconsciousness</td>
</tr>
<tr>
<td>Dunne et al 1987</td>
<td>Medical wards</td>
<td>75 (all haemorrhagic)</td>
<td>not stated (majority &lt; 1 day)</td>
<td>In-hospital mortality</td>
<td>Gaze palsy</td>
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<td></td>
<td>Limb weakness</td>
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<td>Hydrocephalus</td>
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<td>Sacco et al 1989</td>
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<tr>
<td>Tuhrim et al 1988</td>
<td>Multicentre</td>
<td>82 (all haemorrhagic)</td>
<td>not stated</td>
<td>30-day mortality</td>
<td>Glasgow coma score</td>
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<td>Gaze palsies</td>
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<td></td>
<td></td>
<td></td>
<td>Weakness severity</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Haemorrhage size</td>
</tr>
<tr>
<td>Britton et al 1990</td>
<td>Stroke unit</td>
<td>388 (26 haemorrhagic)</td>
<td>&lt; 1 week (mean 17 hours)</td>
<td>In-hospital mortality</td>
<td>-</td>
</tr>
<tr>
<td>Davalos et al 1990</td>
<td>Neurology unit</td>
<td>98 (no haemorrhagic)</td>
<td>&lt; 8 hours</td>
<td>Stroke in progression (within first 48 hours)</td>
<td>Blood sugar</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Carotid territory</td>
</tr>
<tr>
<td>Dandapani et al 1995</td>
<td>Neurology unit</td>
<td>87 (all haemorrhagic)</td>
<td>&lt; 8 hours</td>
<td>30-day mortality and disability</td>
<td>-</td>
</tr>
<tr>
<td>Henon et al 1995</td>
<td>Neurology unit</td>
<td>152 (no haemorrhagic)</td>
<td>&lt; 24 hours</td>
<td>3-month mortality and disability</td>
<td>Orgogozo score</td>
</tr>
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<td></td>
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<td>Previous stroke</td>
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<td></td>
<td>Age</td>
</tr>
</tbody>
</table>

**TABLE 1.4** Studies reporting an association between high blood pressure and poor outcome

Increased mortality rates associated with high post-stroke BP have been reported at a number of cut-off points. Harmsen and colleagues found a 35% compared to a 24% in-hospital mortality rate with a cut-off point of 160/95 mmHg [Harmsen et al, 1972], and in a large multicentre trial of 6395 cases Hatano reported a level of >200/115 mmHg to be associated with increased early mortality [Hatano, 1976]. Britton and colleagues also found a significantly higher mortality rate in a subgroup of 27 acute stroke patients using an identical cut-off point compared to the rest of their 361 patient stroke population (30% vs. 14%, p<0.05). However, this group were more likely to have a history of hypertension, and also had a higher frequency of haemorrhagic stroke [Britton et al, 1990].

Indeed, stroke type may be important in drawing any conclusions from prognostic studies. Other groups have studied only subjects with intracerebral haemorrhage. Tuhrim and colleagues derived a logistic regression model to predict 30-day survival from information available on patient admission in 82 patients, 28 of whom died. SBP was an associated variable on univariate analysis, 41% of patients with values of ≥150 mmHg dying compared to 14% <150 mmHg, though only Glasgow coma score, haemorrhage size and pulse pressure remained significant explanatory variables in a multiple model [Tuhrim et al, 1988]. Dandapani and colleagues retrospectively reviewed 87 patients with a CT diagnosis of intracerebral haemorrhage, and reported 65% and 34% 30-day combined mortality and severe morbidity rates in those with an admission MAP above and below 145 mmHg, respectively (p<0.005). In addition, those patients with suboptimal BP control (defined as MAP >125 mmHg) during the first week post-ictus had a significantly higher combined 30-day mortality and severe morbidity rate (60% vs. 34%, p<0.005) [Dandapani et al, 1995]. In a highly selected population with cerebellar haemorrhage, Dunne and colleagues found SBP >200 mmHg in 66% of those deteriorating, but only 33% of those who did not [Dunne et al, 1987].
Studies of ischaemic strokes only have also been conducted, and similarly reported an association between high BP and poor outcome. Davalos and colleagues studied 98 patients admitted within 8 hours of CT scanned ischaemic stroke, of whom 40 showed signs of neurological deterioration within the first 48 hours as assessed by the Canadian Neurological Scale. Admission SBP was significantly higher in the deteriorating group (p=0.009), and in a multiple logistic regression analysis this factor, high blood glucose, and carotid territory involvement predicted 67% of deteriorating patients. The odds ratio for poor outcome associated with each 10 mmHg increase in admission SBP was 1.24 (95% confidence interval: 1.06 to 1.45) [Davalos et al, 1990]. In another study of 152 patients admitted within 24 hours of ischaemic stroke, Henon and colleagues found a significantly higher admission MAP in 53 patients dead or disabled as assessed by the Glasgow Outcome scale at 3 months (113 vs. 106 mmHg, p=0.0057). However, this factor was not predictive on multivariate analysis, and did not predict death at day 8, the other outcome assessed [Henon et al, 1995]. Sacco and colleagues also reported elevated admission DBP to be associated with increased risk of recurrent stroke within 30 days in 1273 patients with cerebral infarction. The reported risk was 5.23% for those patients with DBP >100 mmHg and 2.5% with lower values (p=0.02). However, rates were not significantly different for SBP with a 160 mmHg cut-off (3.86 vs. 2.64%), and were not significant on multivariate analysis [Sacco et al, 1989].

1.7.3. Explanations For The Discrepancies Between The Results Of Observational Prognostic Studies

The design and study population of the studies assessing the prognostic significance of BP in the acute stroke period were quite different, and may explain some of the conflicting findings.

Firstly, some studies were exclusively of patients with intracerebral haemorrhage [Dollberg et al, 1986; Dunne et al, 1987; Tuhrim et al, 1988; Dandapani et al, 1995], had a significantly higher number of haemorrhagic strokes in the high mortality group [Harmsen et al, 1972], or identified haemorrhage as a significant independent predictor on multivariate analysis [Allen, 1984]. This is relevant
because intracerebral haemorrhage, acting as a mass-producing lesion, can result in an increased intracranial pressure and augment any elevation of BP seen at acute stroke presentation. It has also been well-established that haemorrhagic strokes have poorer outcomes compared to other stroke types, independent of other factors [Hatano, 1976; Abu-Zeid et al, 1978b; Sacco et al, 1982]. Nonetheless, some studies identified an association between BP and outcome independent of haemorrhage [Dunne et al, 1987; Tuhrim et al, 1988; Dandapani et al, 1995], though not all [Dollberg et al, 1986]. Equally, studies exclusively of ischaemic stroke produced conflicting results [Davalo et al, 1990; Fiorelli et al, 1995; Henon et al, 1995].

Secondly, study populations were variably recruited from medical wards [Harmsen et al, 1972; Allen, 1984; Dunne et al, 1987], neurology centres [Davalo et al, 1990; Jorgensen et al, 1994; Dandapani et al, 1995; Henon et al, 1995], and stroke units [Miah et al, 1983; Britton et al, 1985; Britton et al, 1990; Carlberg et al, 1993]. This may have led to a selected study population, depending on the specific admission criteria operating on specialist neurology and stroke unit referrals, such that any conclusions are not necessarily applicable to a typical hospital stroke population.

Thirdly, admission BP were reported and entered into univariate and multivariate analyses. Some studies recruited patients up to 1 week [Sacco et al, 1989; Britton et al, 1990; Carlberg et al, 1993; Jorgensen et al, 1994], or even longer [Harmsen et al, 1972; Allen, 1984] after ictus, though admission delay is not clearly stated in all studies [Robinson et al, 1968; Hatano, 1976; Miah et al, 1983; Britton et al, 1985; Dollberg et al, 1986; Dunne et al, 1987; Tuhrim et al, 1988]. Such delays are pertinent if reliable conclusions are to be made regarding the prognostic significance and appropriate management of acute stroke BP, particularly in the light of reported falls in BP during the first few days post ictus [de Faire et al, 1978; Wallace et al, 1981; Britton et al, 1986; P Jansen et al, 1987; Harper et al, 1991]. However, even in those studies recruiting patients within 24 hours of ictus, there remains conflicting findings [Davalo et al, 1990; Dandapani et al, 1995; Fiorelli et al, 1995; Henon et al, 1995].
Fourthly, there are problems related to inter-observer error in the recording of BP. No study used one observer to record BP, though in some studies a limited number of specifically trained personnel were used [Britton et al, 1990]. Often BP values were taken from retrospective reviews of the medical notes [Robinson et al, 1968; Dollberg et al, 1986; Dunne et al, 1987; Dandapani et al, 1995]. As previously noted, 24-hour NIBPM may help overcome this problem, as with the higher number of readings these devices are able to record, it may reduce the variability and observer bias of casually recorded BP [Coats, 1990]. In a small study, higher admission 24-hour mean SBP was associated with a higher mortality over the 9 months of follow-up [Fotherby et al, 1993a].

Fifthly, antihypertensive treatment was continued or started in some studies [Dunne et al, 1987; Britton et al, 1990; Carlberg et al, 1993; Dandapani et al, 1995; Henon et al, 1995]. As previously discussed, there is a failure of cerebral autoregulation in the acute stroke period [Hoedt-Rasmussen et al, 1967; Agnoli et al, 1968; Fieschi et al, 1968; Paulson, 1970; Meyer et al, 1973b; Olsen et al, 1983a] such that CBF is dependent on BP levels. The introduction of antihypertensive therapy and the potential consequent BP reductions may have important prognostic implications. This could influence the conclusions of such studies, particularly as the BP changes were only considered in the subsequent analysis in 1 study [Dandapani et al, 1995].

Finally, though mortality was the main outcome measure used, some studies only used subtle changes in neurological scales [Britton et al, 1985; Davalos et al, 1990; Jorgensen et al, 1994], which may be prone to subjective bias.

1.8. Objectives
This review has outlined a number of issues related to BP in acute stroke that remain a matter of some debate. However, factors related to BP and its control are of utmost importance in the acute stroke period, as the failure of cerebrovascular autoregulation means that BP change is manifest in alterations of CBF with potential consequences for the viability of the ischaemic penumbra. This
has significant implications for the non-pharmacological and pharmacological manipulation of BP in the acute stroke period. The author therefore proposed to explore a number of factors related to BP and its control in a series of studies on acute stroke patients, and where indicated appropriately matched control subjects.

Firstly, in an attempt to resolve some of the controversy regarding the prognostic significance of BP in acute stroke, patients were assessed with 24-hour NIBPM, which reduces the observer bias and pressor effects of casual BP measurements.

Secondly, to clarify factors related to BPV, as well as its absolute level in the acute stroke period. It was proposed to assess medium term variability from aspects of the 24-hour NIBPM, and also short-term variability made possible with the advent of reliable methods of beat-to-beat NIBPM.

Thirdly, the BR reflex arc is an important mechanism in the short-term regulation of the CVS, and may be a pathophysiological factor in the cause and maintenance of BP change in acute stroke. It was proposed to assess the cardiac and vascular components of this arc in non-invasive studies of acute and subacute stroke patients.

Finally, to relate the potential significance of these haemodynamic changes in the day-to-day management of acute stroke patients, the cardiovascular responses to orthostasis and food were studied.

It is hoped that these studies will lead to a better understanding of the haemodynamic changes following acute stroke, and have implications in terms of BP management and its effect on prognosis in acute stroke.
CHAPTER TWO

THE PROGNOSTIC SIGNIFICANCE OF CASUAL AND 24-HOUR BLOOD PRESSURE CHANGES FOLLOWING ACUTE STROKE
2.1. Summary
The influence of casual BP levels following acute stroke on outcome is currently unclear. Whilst there are several studies reporting high BP levels are associated with an adverse outcome, others have found no relation between BP and outcome. These differences may in part reflect observer bias and the natural variability of casual recordings, which are reduced with 24-hour BP recordings. The author therefore proposed to assess the prognostic significance of 24-hour compared to casual BP in predicting 30-day mortality, dependency and neurological outcome following acute stroke. 136 consecutive patients were assessed within 24 hours of ictus by 1 observer with casual and 24-hour NIBPM. In addition, assessments of neurological function and dependency in activities of daily living were made using the NIHSS and the Modified Rankin scores, respectively. Repeat assessments of casual and 24-hour BP, and the NIHSS and Modified Rankin scores were made at 7 and 30 days.

Admission casual and 24-hour SBP and DBP levels were significantly higher in patients with poor outcome at 1 month following acute stroke, whether expressed in terms of mortality, dependency or neurological deterioration, on single variable logistic regression analysis. However, of these variables, only admission 24-hour (not casual) SBP remained a significant outcome predictor in a multiple model containing factors known to be associated with a poor prognosis post-stroke. The odds ratio for outcome of death or dependency associated with each 10 mmHg increase in 24-hour SBP at admission was 1.88 (95% confidence interval: 1.27 to 2.78). For an outcome of death or high dependency, the model had a specificity of 75% and sensitivity of 76% when tested by the jackknife technique.

Increasing 24-hour BP levels following acute stroke predict poor outcome. Whether BP should be reduced pharmacologically in the acute stroke period now warrants a suitable prospective, intervention trial.

2.2. Background
Changes in casual BP levels following acute stroke have now been well documented. BP levels are elevated within the first 24 hours following stroke with
over 80% of acute stroke patients having BP values >160/90 mmHg [Oppenheimer et al, 1992], though BP settles spontaneously within 4 to 10 days [de Faire et al, 1978; Wallace et al, 1981; Britton et al, 1986; P Jansen et al, 1987; Harper et al, 1991]. Such BP changes have important implications because of the well documented impairment of cerebrovascular autoregulation in acute stroke (Chapter 1.5), and the consequent dependence of CBF on systemic BP. Thus CBF is very sensitive to any acute BP changes. Initially, elevated BP may be beneficial in increasing blood flow to the ischaemic penumbra, and could be regarded as a physiological compensatory mechanism for impaired cerebral perfusion pressure. Indeed, it has been stated that acute post-stroke hypotension should be sought and treated to avoid further anoxic cerebral damage [O'Connell et al, 1994]. However, sustained increases in BP may be harmful by increasing cerebral oedema and the likelihood of haemorrhagic transformation of the infarct [Matakas et al, 1972; Hossman, 1988]. Therefore there is much debate about the optimal management of high BP in patients with acute stroke.

Data on the prognostic significance of BP levels following acute stroke, gained from observational studies, are conflicting, and have been previously reviewed (Chapter 1.7). The design of these studies assessing the prognostic significance of BP after acute stroke may explain some of the conflicting findings (Chapter 1.7.3). In particular, there may be problems related to observer bias and inter-observer error in BP recording, as no one study used a single trained observer to record BP, and often BP values were taken from retrospective reviews of the medical notes [Robinson et al, 1968; Dollberg et al, 1986; Dunne et al, 1987; Dandapani et al, 1995]. 24-hour NIBPM helps overcome some of these problems, as it reduces the pressor response to hospital admission [Antivalle et al, 1990; Fotherby et al, 1995]. The higher number of readings these devices record reduces the measurement variability and observer bias when compared to casually recorded BP [Coats, 1990], as well as providing additional information about day-night changes in BP. Previous work in our department from a small prospective study did suggest that a higher 24-hour BP and nocturnal increase in BP on admission were associated with a higher mortality rate over the 9 months of follow-up [Fotherby et al, 1993a].
2.3. Objectives

1. To assess the prognostic significance of 24-hour compared to casual BP levels in predicting short-term outcome factors to include death, dependency in activities of daily living, and neurological deterioration in a study population drawn from unselected medical emergency admissions to 3 District General Hospitals to ensure that the findings were relevant to everyday clinical practice.

2. To assess the significance of 24-hour and casual BP factors in predicting short-term outcome compared to other variables with an established association with poor outcome in a multiple logistic regression analysis model.

3. To validate the derived model in predicting outcome by use of the jackknife method.

2.4. Methods

2.4.1. Subjects

One hundred and thirty-six consecutive acute stroke patients (66 male) of mean age 71.6 years (range 39 to 91 years) presenting within 24 hours of symptom onset were studied. If patients awoke with symptoms then stroke onset was deemed to have occurred at the time of retiring to bed for the purposes of this study. Diagnosis was made according to the standard definition of the World Health Organisation (WHO) [WHO, 1978]. Patients were recruited from admissions to the medical wards of the three Leicester Teaching Hospitals following General Practitioner and Accident and Emergency referral. At the time of the study, one hospital (the Leicester Royal Infirmary) had an Acute Stroke Unit, which has a defined admissions policy. However, this would not have excluded patients other than those already precluded from entry by the design of the study.

The following patients were excluded: unconscious patients (National Institutes of Health Stroke Score (NIHSS) of 2 or 3 in loss of consciousness category) (7% of population screened for the study), those with atrial fibrillation (19%), a transient ischaemic attack (TIA) (2%), chronic illness preventing functional independence, or requiring treatment known to affect CVS or autonomic function. The
continuation of hypotensive medication on admission was left to the individual physician's choice, but only 1 in 5 treated hypertensives were excluded because of this (7%). Patients participating in other studies, including the International Stroke Trial, were also excluded. A total population of 206 patients was therefore screened to identify the 136 acute stroke patients recruited to the study.

2.4.2. Study Protocol
All patients were assessed within 24 hours of stroke onset by myself. Notification of stroke patients admitted to hospital was obtained by liason with a central Bed Bureau, admissions wards, and the Accident and Emergency department. A past medical history of ischaemic heart disease, non-disabling cerebrovascular disease, and hypertension was noted. Hypertension was defined if patients had a history of SBP $\geq$160mmHg and/ or DBP $\geq$90mmHg before stroke onset, or if they had received anti-hypertensive therapy, from patient and carer enquiry and by consultation with the patient's General Practitioner. The results of routine haematological and biochemical investigations were recorded. The presence of left ventricular hypertrophy was assessed on electrocardiographic criteria ($RV_t + SV_6 \geq 35\text{mm}$) in all patients [Kannel et al, 1970]. CT scans were not routinely performed on all stroke patients, but 90 patients did have CT scans which showed infarction in 70, haemorrhage in 11, and 9 were classified normal. A clinical scoring system was not used to exclude intracerebral haemorrhage in those patients not having a head CT scan.

Neurological And Dependency Assessments
A detailed neurological examination was performed, and the site of stroke (right or left hemisphere, or brainstem) was recorded. Stroke type was also recorded according to the Oxfordshire Community Stroke Project classification [Bamford et al, 1991]. Using this classification, patients are allocated to one of four groups according to presenting symptoms and signs: lacunar strokes (LACS), posterior circulation strokes (POCS), total anterior circulation strokes (TACS), or partial anterior circulation strokes (PACS) {Appendix 1}. For the purposes of subsequent statistical analysis, patients with a TACS or PACS were grouped together. This is because of significant interobserver differences in the classification of patients into these two categories [Lindley, 1993a; Dawson et al, unpublished data].
However, the classification as a whole has good interobserver reliability [Lindley et al, 1993b]. More recently, the classification by clinical subgroups has been compared to neuroradiological diagnoses. Patients with TACS were significantly more likely to have sustained a haemorrhage, and there was also a significant difference in volume of infarction assessed by CT and MRI scanning with TACS patients having the highest volume and LACS the least [Lindgren et al, 1994].

The NIHSS score was calculated (Appendix 2) [Brott et al, 1989b]. Assessment of handicap, in consultation with the carers and multidisciplinary staff was made by using a scale modified after Rankin [Rankin, 1957], the Modified Rankin Scale (Appendix 3) [Malgrem et al, 1989], and the presence/absence of urinary incontinence was documented. Patients were further reviewed at 1 month following acute stroke, and the NIHSS and Modified Rankin scores were repeated. Patients were then classed as dependent if exhibiting a moderate to severe handicap (Modified Rankin >3) or independent with no to mild handicap (Modified Rankin ≤2) [Censori et al, 1993], and neurologically deteriorated (NIHSS score increase >4), improved (NIHSS score decrease >4) or unchanged [Wityk et al, 1994]. Six patients died during the follow-up period, and were classed in the dependent and neurologically deteriorating groups for purposes of the prognostic analyses.

Blood Pressure Measurements
After making sure there was no between-arm difference in BP >10mmHg, casual supine BP was measured in the hemiparetic arm on 3 occasions using a standard mercury sphygmomanometer and cuff of appropriate size, and the mean value taken in the subsequent analysis. 24-hour NIBPM was performed immediately after casual BP measurements using a Spacelabs 90207 recorder (Spacelabs, Redmond, WA). BP measurement was taken a mean of 12.5 hours (SD 3.2) post ictus. The accuracy of this device has been established according to criteria proposed by the British Hypertension Society [O’Brien et al, 1991]. The recorder was programmed to record BP at 15-minute intervals during the day (07.00 to 22.00 hours) and at 30-minute intervals during the night (22.01 to 06.59 hours). BP recorded with the 24-hour NIBPM was calibrated against the casual BP at the beginning of the recording. Any patient in whom there was a discrepancy between
the two methods of >5mmHg in SBP and DBP was excluded. Data were
downloaded onto an IBM-compatible personal computer for further analysis, and
patients were excluded if there was less than 85% data capture. Data were
automatically edited to exclude unphysiological readings, i.e., where diastolic was
recorded higher than SBP, though no other editing was undertaken. The mean
24-hour, day and night SBP and DBP, and the difference between mean day and
night SBP and DBP were recorded. Repeat assessments of clinic and 24-hour BP
were made 1 week following acute stroke, and the changes in BP parameters
calculated.

2.4.3. Statistical Methods
Continuous data are presented as mean (SD). Normality of the data was
determined by construction of a normal probability plot using the Minitab statistical
package (Minitab 10 for Windows, Minitab Inc., PA, USA). If a p value of >0.05
was obtained using the Ryan-Joiner test, then the data were considered to be
Normally distributed. The Mann-Whitney and Kruskal-Wallis tests are used to
compare patients’ age, glucose levels and white cell count between groups
defined by patient outcome. BP related variables are approximately Normally
distributed and are compared using the unpaired Students’ t-test and one-way
analysis of variance. Sex, past medical history and symptoms are compared using
the $\chi^2$ test (without continuity correction) or the two-sided Fisher exact test, where
appropriate. Results with p value of ≤0.05 are considered statistically significant.

The GLIM statistical package was used to predict outcome at one month following
acute stroke using logistic regression. On the Modified Rankin scale, outcome
was a binary variable of independence (Modified Rankin ≤2), and dependence
(Modified Rankin ≥3) or death [Censori et al, 1993]. The ordinal logistic
regression program of the BMDP statistical package was also used to predict
neurological outcome at one month following acute stroke. On the NIHSS,
outcome was neurological improvement (score decrease ≥4), neurological
deterioration (score increase ≥4) or death, and no change [Wityk et al, 1994]. The
explanatory variables assessed were: age, history of hypertension, presence of
electrocardiographic left ventricular hypertrophy, stroke classification (TACS,
PACS, LACS, POCS), admission Modified Rankin score, presence of urinary
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incontinence, plasma glucose, white cell count, and admission 24-hour HR. In addition, the following BP variables were assessed: admission casual and 24-hour SBP and DBP, admission day-night change in SBP and DBP, and change over the first week following acute stroke in casual and 24-hour SBP and DBP. Age and HR were entered as continuous variables, as were clinic and 24-hour BP factors. This was considered appropriate to avoid the arbitrary division of continuous data into categories, and because these variables had a linear relationship with dependency on single variable analysis when analysed as 4 categories. Other data were either binary or categorical variables. To account for missing data, for instance if the patient died within the first week, a separate missing value group was included for categorical data. Missing BP data was entered as zero and linked with a binary variable describing the measurement as missing or present.

Single variable analysis was initially performed with each variable examined separately for association with outcome of dependence or death at 1 month for all patients. All variables were deemed candidates for inclusion in a multiple logistic regression model. Clinically important baseline characteristics previously recognised to be predictors of outcome [Sacco et al, 1982; Britton et al, 1985; Wade et al, 1985; Davalos et al, 1990; Bamford et al, 1991; Cazzato et al, 1991; Wolf et al, 1992; Czlonkowska et al, 1995], including age, stroke classification, stroke type (haemorrhage or infarction), presence of urinary incontinence, plasma glucose and white cell count, were forced into the model. Both clinic and 24-hour measures of SBP were then added to the model individually, and the variable with the most statistically significant effect was retained in the model. Due to the number of variables examined, statistical significance was taken at the 1% level. A similar technique was then used for measures of DBP. Finally, the remaining candidate variables were added, and only those variables with a statistically significant effect were retained.

The resulting logistic regression model with estimated coefficients provided estimated probabilities for patient outcome at one month as a function of the patient's recorded risk factors; values of >0.5 were taken to predict poor outcome. The prediction rule was then reassessed on the dataset using the jackknife
method in order to overcome the problem of circularity, where one uses the same
data to test the prediction rule as was used to derive the rule [Efron et al, 1983].
The jackknife method consists of removing one patient from the dataset,
recalculating the prediction rule using all other patients' data and then applying
the rule to predict the outcome of the one patient left out. This process is repeated
taking each patient in the dataset out one at a time. The jackknife method is
preferable to dividing the dataset into two groups: one used only for deriving the
prediction rule and one used only for testing. It makes more efficient use of the
data as it allows each patient to play both roles, and provides a statistically
rigorous method of overcoming the fact that the prediction rule was not tested on
an independent population.

2.5. Results
Baseline demographic data, past medical history and the results of certain
haematological, biochemical and cardiac investigations are shown in Table 2.1 for
all patients. There was no significant difference in the number of patients with
right and left hemisphere signs (47% vs. 51%, respectively), 2% of patients
having signs consistent with a brainstem cerebrovascular event. 65% of patients
were classified as having TACS or PACS, only 2% of patients had POCS, the rest
having neurological findings consistent with LACS [Bamford et al, 1991].

Concerning BP changes, mean admission casual BP was 164 (SD 26)/ 91 (16)
mmHg with a significant fall in SBP (17 mmHg; 95% confidence interval (CI): 13 to
22; p<0.001) and DBP (8 mmHg; 4 to 11; p<0.001) during the first week following
acute stroke in the 130 surviving patients. Mean 24-hour BP on admission was
148 (22) / 84 (13) mmHg, though 24-hour NIBPM did not satisfy the acceptance
criteria in 12 patients. Again, significant falls in SBP (7 mmHg; 4 to 10; p<0.001)
and DBP (3 mmHg; 1 to 5; p=0.006) were seen during the first week.

A total of 90 patients had a CT scan examination which confirmed the diagnosis in
81 patients (70 infarction, 11 haemorrhage), 9 patients having normal scans. In
those patients with a positive CT scan, admission BP levels were significantly
higher for haemorrhages than infarcts for both casual (SBP: 181 (27) vs. 162 (27)

55
### TABLE 2.1 Baseline data in all stroke patients.

Data expressed as mean (standard deviation) unless stated. LVH: left ventricular hypertrophy.

<table>
<thead>
<tr>
<th>n</th>
<th>136</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>71.6 (10.3)</td>
</tr>
<tr>
<td>Male sex</td>
<td>66 (49%)</td>
</tr>
</tbody>
</table>

**Past Medical History**

- Ischaemic Heart Disease | 31 (23%) |
- Cerebrovascular Disease | 31 (23%) |
- Hypertension | 59 (43%) |

**Investigations**

- Electrocardiographic LVH | 12 (10%) |
- Plasma Glucose (mmol/l) | 7.0 (2.3) |
- Blood White Cell Count (x10⁹/l) | 9.5 (3.1) |
BP and prognosis in acute stroke

mmHg, p=0.04; DBP: 103 (23) vs. 88 (16) mmHg, p=0.008) and 24-hour (SBP: 164 (28) vs. 144 (21) mmHg, p=0.007; DBP: 95 (16) vs. 81 (12) mmHg, p=0.001) BP values. There were greater BP falls over the first week in the haemorrhagic group in casual (25 (33)/14 (29) vs. 16 (26)/6 (18) mmHg) and 24-hour readings (13 (18)/8 (10) vs. 6 (13)/2 (9) mmHg), though these were not significantly different from the infarct group.

2.5.1. Dependency At One Month

Patients dependent or dead at one month following acute stroke had a significantly higher white cell count on admission, though there were no other significant differences in the baseline data (Table 2.2). In regard to stroke type, patients dead or dependent at one month were more likely to have had a TACS or PACS (88% vs. 45%, p<0.001). However, there were no significant differences in CT diagnosis with haemorrhages documented in 10% of the dependent or dead and 6% of the independent group. There were also no significant differences in CT scanning rates between the independent and dependent/dead groups (68% vs. 65%, respectively).

Admission casual and 24-hour BP were significantly higher in the dependent/dead than the independent group. There were also greater falls observed over the first week in casual and 24-hour BP in the dependent/dead group, though not all were statistically significantly different from the independent group at the 5% level (Table 2.3).

The association between the explanatory variables and death/dependency at 1 month on single variable analysis is shown in Table 2.4. Higher admission casual and 24-hour SBP and DBP values as well as a lack of day-night SBP and DBP fall were associated with an increased likelihood of dependency. For CT diagnosed infarcts alone, the results of single variable analysis were identical except that admission casual BP values were no longer significant explanatory variables.

Multiple logistic regression analysis showed admission 24-hour SBP levels (p<0.01) and increased dependency on admission (p=0.01) to be the only factors remaining significant outcome predictors in a forced model containing previously
TABLE 2.2 Baseline data in patients classed by Modified Rankin outcome at one month after stroke. Data expressed as mean (standard deviation) unless otherwise stated. IHD: ischaemic heart disease; CVD: non-disabling cerebrovascular disease; LVH: presence of left ventricular hypertrophy by electrocardiographic criteria; WCC: white cell count.
### TABLE 2.3 Clinic and 24-hour blood pressure data on admission and the changes over the first week in patients classed by dependency (Modified Rankin Scale) outcome at one month after acute stroke.

Data expressed as mean (standard deviation). SBP: systolic blood pressure (mmHg); DBP: diastolic blood pressure (mmHg).
<table>
<thead>
<tr>
<th>Factor</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>NS</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>NS</td>
</tr>
<tr>
<td>Presence of urinary incontinence</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Admission Modified Rankin score</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Electrocardiographic LVH</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma glucose</td>
<td>NS</td>
</tr>
<tr>
<td>Blood white cell count</td>
<td>NS</td>
</tr>
<tr>
<td>Stroke type (TAC/PAC/LAC)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CT (haemorrhage/infarct/normal)</td>
<td>NS</td>
</tr>
<tr>
<td>Casual admission SBP</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Casual admission DBP</td>
<td>0.03</td>
</tr>
<tr>
<td>Casual SBP change D0 to D7</td>
<td>NS</td>
</tr>
<tr>
<td>Casual DBP change D0 to D7</td>
<td>NS</td>
</tr>
<tr>
<td>24-hour admission SBP</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24-hour admission DBP</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Admission day-night SBP change</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Admission day-night DBP change</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24-hour SBP change D0 to D7</td>
<td>0.04</td>
</tr>
<tr>
<td>24-hour DBP change D0 to D7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Admission 24-hour heart rate</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

TABLE 2.4 Association between explanatory variables and 30-day outcome of death or dependency on single variable logistic regression analysis. LVH: left ventricular hypertrophy; TAC: total anterior circulation stroke; PAC: partial anterior circulation stroke; LAC: lacunar stroke; SBP: systolic blood pressure; DBP: diastolic blood pressure; D0: admission; D7: day 7; NS: not statistically significant.
FIGURE 2.1 Scattergram of predicted versus actual outcome of death or dependency at one month of final model assessed by the jackknife technique. With a predicted outcome cut-off point of 0.5 (as shown by dashed line):
Specificity = $B/(B+A) = 75.4\%$. Sensitivity = $D/(D+C) = 76.1\%$. Final model contained eight factors: admission 24-hour systolic blood pressure, admission Modified Rankin score, age, stroke type, CT result, presence of urinary incontinence, plasma glucose, blood white cell count.
recognised poor prognostic factors (age, stroke type, CT result, presence of urinary incontinence, plasma glucose, white cell count). The final model had eight terms: admission Modified Rankin score and admission 24-hour SBP, in addition to the forced factors. In this model, the odds ratio for poor outcome associated with each 10 mmHg increase in 24-hour SBP at admission was 1.88 (95% confidence interval: 1.27 to 2.78, p=0.01). When the model was tested against the data set by the jackknife technique, it gave a specificity of 75.4% and sensitivity of 76.1% with a predicted outcome cut-off point of 0.5 for the probability of dependency or death at one month (Figure 2.1).

As 24-hour NIBPM is not routinely used in clinical practice in all centres, the final multiple logistic regression model was also calculated with admission casual SBP being retained in the forced model in place of admission 24-hour SBP. This resulted in an odds ratio for poor outcome associated with each 10 mmHg increase in casual SBP at admission of 1.24 (95% confidence interval: 1.00 to 1.53). This confirms the improved predictive value of BP measured by 24-hour NIBPM, especially as casual BP in this study was recorded by only 1 observer under controlled conditions.

2.5.2. Neurological Deterioration At One Month
Baseline characteristics in patients classed by neurological outcome at 1 month as assessed with the NIHSS score are shown in Table 2.5. There was a significant difference in white cell count between groups with highest values observed in the group dead or with neurological deterioration at 1 month (Table 2.5). There were no significant differences in clinical or CT diagnosis of stroke type between groups. In the 10 patients dead or with neurological deterioration at 1 month, 8 were classed as TACS or PACS, and of the 4 patients scanned, 1 had a haemorrhage. In the 63 patients with neurological improvement at 1 month, 47 had had a TACS or PACS, and 10% had CT scan evidence of a haemorrhage.

Admission casual and 24-hour BP values were significantly higher in those patients neurologically deteriorating or dead at one month (Table 2.6). However, no significant differences in admission day-night BP change, or BP change over the first week were observed between the different outcome groups (Table 2.6).
TABLE 2.5 Baseline data in patients classed by National Institutes of Health Stroke Scale outcome at one month after stroke.

Data expressed as mean (standard deviation) unless stated. IHD: ischaemic heart disease; CVD: non-disabling cerebrovascular disease; LVH: presence of left ventricular hypertrophy by electrocardiographic criteria; WCC: white cell count.
### BP and prognosis in acute stroke

<table>
<thead>
<tr>
<th>Improved</th>
<th>Unchanged</th>
<th>Deteriorated/ dead</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td>158 (24)</td>
<td>170 (27)</td>
<td>172 (27)</td>
</tr>
<tr>
<td>DBP</td>
<td>88 (15)</td>
<td>91 (17)</td>
<td>102 (17)</td>
</tr>
</tbody>
</table>

#### Admission casual BP (mmHg)

<table>
<thead>
<tr>
<th>n</th>
<th>SBP</th>
<th>DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>63</td>
<td>158 (24)</td>
<td>88 (15)</td>
</tr>
<tr>
<td>62</td>
<td>170 (27)</td>
<td>91 (17)</td>
</tr>
<tr>
<td>10</td>
<td>172 (27)</td>
<td>102 (17)</td>
</tr>
</tbody>
</table>

#### Admission 24-hour BP (mmHg)

<table>
<thead>
<tr>
<th>n</th>
<th>24 SBP</th>
<th>24 DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>143 (22)</td>
<td>82 (13)</td>
</tr>
<tr>
<td>53</td>
<td>151 (21)</td>
<td>83 (12)</td>
</tr>
<tr>
<td>10</td>
<td>167 (21)</td>
<td>99 (13)</td>
</tr>
</tbody>
</table>

#### Casual BP change (mmHg)

<table>
<thead>
<tr>
<th>n</th>
<th>SBP</th>
<th>DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>63</td>
<td>14 (27)</td>
<td>6 (20)</td>
</tr>
<tr>
<td>61</td>
<td>19 (28)</td>
<td>9 (20)</td>
</tr>
<tr>
<td>6</td>
<td>30 (25)</td>
<td>10 (21)</td>
</tr>
</tbody>
</table>

#### 24-hour BP change (mmHg)

<table>
<thead>
<tr>
<th>n</th>
<th>24 SBP</th>
<th>24 DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>6 (13)</td>
<td>3 (8)</td>
</tr>
<tr>
<td>47</td>
<td>9 (18)</td>
<td>2 (11)</td>
</tr>
<tr>
<td>6</td>
<td>0 (30)</td>
<td>2 (18)</td>
</tr>
</tbody>
</table>

#### TABLE 2.6 Clinic and 24-hour blood pressure data on admission and the changes over the first week in patients classed by neurological outcome (National Institutes of Health Stroke Scale) at one month after stroke.

Data expressed as mean (standard deviation). SBP: systolic blood pressure (mmHg); DBP: diastolic blood pressure (mmHg).
# BP and prognosis in acute stroke

<table>
<thead>
<tr>
<th>Factor</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>NS</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>NS</td>
</tr>
<tr>
<td>Presence of urinary incontinence</td>
<td>NS</td>
</tr>
<tr>
<td>Admission Modified Rankin score</td>
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</tr>
<tr>
<td>Electrocardiographic LVH</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma glucose</td>
<td>NS</td>
</tr>
<tr>
<td>Blood white cell count</td>
<td>0.02</td>
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<tr>
<td>Stroke type (TAC/PAC/LAC)</td>
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<td>CT (haemorrhage/infarct/normal)</td>
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<td>Casual admission SBP</td>
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</tr>
<tr>
<td>Casual admission DBP</td>
<td>0.02</td>
</tr>
<tr>
<td>Casual SBP change D0 to D7</td>
<td>NS</td>
</tr>
<tr>
<td>Casual DBP change D0 to D7</td>
<td>NS</td>
</tr>
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<td>24-hour admission DBP</td>
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<td>Admission day-night SBP change</td>
<td>NS</td>
</tr>
<tr>
<td>Admission day-night DBP change</td>
<td>NS</td>
</tr>
<tr>
<td>24-hour SBP change D0 to D7</td>
<td>NS</td>
</tr>
<tr>
<td>24-hour DBP change D0 to D7</td>
<td>NS</td>
</tr>
<tr>
<td>Admission 24-hour heart rate</td>
<td>NS</td>
</tr>
</tbody>
</table>

**TABLE 2.7** Association between explanatory variables and 30-day outcome of death or neurological deterioration on single variable logistic regression analysis. *LVH: left ventricular hypertrophy; TAC: total anterior circulation stroke; PAC: partial anterior circulation stroke; LAC: lacunar stroke; SBP: systolic blood pressure; DBP: diastolic blood pressure; D0: admission; D7: day 7; NS: not statistically significant.*
The association between the explanatory variables and neurological outcome at 1 month on single variable analysis is shown in Table 2.7. Admission casual and 24-hour SBP and DBP levels were useful in predicting neurological outcome at 1 month. Only admission 24-hour SBP (P=0.007) remained a significant predictor on multiple logistic regression analysis in a forced model containing previously recognised poor prognostic factors.

2.6. Discussion

The prognostic significance and therefore the management of acute post-stroke BP remains a matter of considerable debate though little consensus [Spence et al, 1985; Yatsu et al, 1985], which has been fuelled by the conflicting results of previous studies. The present study found that although increasing casual and 24-hour BP were associated with an increased risk of poor outcome (whether assessed by death, dependency or neurological deterioration) following acute stroke on single variable logistic regression analysis; in the multiple model, which included well recognised predictors of poor outcome, only admission 24-hour SBP remained a significant explanatory variable. The relation between 24-hour BP and outcome was almost linear over the levels studied with no evidence of a U- or J-shaped relation, with lower BP not associated with an increase in mortality, dependency or neurological deterioration. This relation was found even if CT diagnosed cerebral infarcts alone were taken.

A number of mechanisms have been proposed to explain the BP changes following acute stroke. These have already been reviewed in Chapter 1.3, but briefly comprise SNS stimulation as reflected by increased plasma and urinary catecholamine levels [Meyer et al, 1973a; Feibel et al, 1981; Myers et al, 1981; Olsson, 1990] and altered baroreceptor function, though this has to date only been demonstrated in animal studies [Doba et al, 1974; Cechetto et al, 1989b] and in chronic stroke patients [Appenzeller et al, 1964; Gross, 1970a]. Stress, related to acute illness and hospital admission - the 'white coat' effect, may also be relevant [Carlberg et al, 1990; Carlberg et al, 1991a; Carlberg et al, 1991b]. This could in part explain the conflicting results from previous studies assessing the prognostic significance of BP in acute stroke [Robinson et al, 1968; Harmsen

To overcome these problems, in this study all patients were assessed prospectively within 24 hours of stroke onset and all casual BP measurements were recorded by 1 observer. In addition, we also performed 24-hour NIBPM, which helps to reduce the variability and observer bias of casual BP measurements [Coats, 1990]. Furthermore, reproducibility of NIBPM is greater than casual readings with reported coefficients of variation of 4 and 10%, respectively [Fotherby et al, 1993b]. Admission casual and 24-hour BP were strongly associated with poor outcome on single variable analysis, as was the lack of the normal nocturnal fall in BP, an abnormality which has previously been observed in stroke patients (Table 2.8) [Fotherby et al, 1991; Lin et al, 1992; Fotherby et al, 1993a; Sander et al, 1994; Prattichizzo et al, 1994a]. The lack of nocturnal fall in BP may be of prognostic significance, as seen in the present study. Fotherby and colleagues studied a group of 33 acute stroke patients, and reported a nocturnal rise in BP within 24 hours of ictus of 4/3 mmHg and at 1 week of 14/10 mmHg in those not surviving to 6 months [Fotherby et al, 1993a]. However, Nakamura and colleagues studied 76 patients surviving more than 1 month, and found the highest 3-year stroke recurrence rate in treated hypertensive patients exhibiting a nocturnal fall in MAP of >10 mmHg [Nakamura et al, 1995].
<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Time after stroke</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fotherby et al 1991</td>
<td>49 strokes</td>
<td>Not stated</td>
<td>Mean nocturnal BP change reduced in strokes</td>
</tr>
<tr>
<td></td>
<td>71 hypertensive controls</td>
<td>(acute and chronic stages)</td>
<td>(1/5 vs. 9/10 mmHg)</td>
</tr>
<tr>
<td>Lin et al 1992</td>
<td>19 strokes</td>
<td>(i) &lt; 3 days</td>
<td>No difference between day and night average on first</td>
</tr>
<tr>
<td></td>
<td>(8 haemorrhagic, 11 infarct)</td>
<td>(ii) 10 to 20 days (n=9)</td>
<td>(145/93 vs. 139/89 mmHg, p&gt;0.5) or second</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(143/95 vs. 135/96 mmHg, p&gt;0.05) readings</td>
</tr>
<tr>
<td>Fotherby et al 1993</td>
<td>33 strokes</td>
<td>(i) &lt; 24 hours</td>
<td>Diurnal changes stated at 6 ± 2 days only. Fall in controls</td>
</tr>
<tr>
<td></td>
<td>17 controls</td>
<td>(ii) 6 ± 2 days</td>
<td>(5.4/6.5 mmHg, p&lt;0.05), but not strokes (-1.9/2.1 mmHg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(iii) 6 ± 3 months</td>
<td></td>
</tr>
<tr>
<td>Prattichizzo et al 1994</td>
<td>18 strokes (all infarcts)</td>
<td>Not stated</td>
<td>Two groups were identified: 6 dippers (&gt;10% SBP and/ or DBP nocturnal fall) and 12 non-dippers</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(11.2/14.5 vs. -1.1/1.2%, p&lt;0.001)</td>
</tr>
<tr>
<td>Sander et al 1994</td>
<td>10 haemodynamic infarct (HI)</td>
<td>(i) &lt; 1 week (HI)</td>
<td>HI increased variation compared to controls at 1 week</td>
</tr>
<tr>
<td></td>
<td>35 thromboembolic infarct (TI)</td>
<td>(ii) 6 months (HI)</td>
<td>(18.9/25.2%, P&lt;0.005) and at follow-up.</td>
</tr>
<tr>
<td></td>
<td>56 controls</td>
<td>(iii) &lt; 48 hours (TI)</td>
<td>TI reduced fall compared to controls at &lt; 48 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(iv) 7 to 10 days (TI)</td>
<td>(-4.2/-5.2%, p&lt;0.001). Variation increased compared to initial values at 7 to 10 days (-8.5%, p&lt;0.05). No further changes at 21 days.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(v) 21 days (TI)</td>
<td></td>
</tr>
</tbody>
</table>

TABLE 2.8  Studies of diurnal blood pressure variability following acute stroke
The prognostic significance of BP factors was further assessed in a multiple model containing previously recognised poor prognostic factors [Sacco et al, 1982; Britton et al, 1985; Wade et al, 1985; Davalos et al, 1990; Bamford et al, 1991; Cazzato et al, 1991; Wolf et al, 1992; Czlonkowska et al, 1995]. However, only admission 24-hour SBP remained a significant predictor of poor outcome, the odds ratio for a 10 mmHg increase was 1.88 for outcome of death or dependency.

It is unlikely that the higher BP values in the poor outcome group represented a group of patients with marked cerebral oedema and raised intracranial pressure, Cushing's response, because higher 24-hour HR values were strongly associated with poor outcome [Cushing, 1902; Vann Jones, 1989]. Equally, elevated BP and HR may reflect increased SNS activity which is well recognised following acute stroke [Natelson, 1985; Talman, 1985], and may be associated with myocardial damage and cardiac arrhythmias [Norris et al, 1978; Natelson, 1985; Talman, 1985; Hachinski et al, 1986].

The mortality rate in the present study was low at 4.4%, and probably reflects the exclusion of unconscious patients who are well-known to have a poor outcome [Barer et al, 1989]. These patients were intentionally excluded, because the main purpose of the study was to establish the importance of elevated BP in patients with other factors that were remediable to treatment. However, the study was also designed to assess poor outcome by measures other than mortality. It is possible to use any one of a number of measures in stroke outcome research, which assess impairment, disability and handicap [Wade, 1992]. These concepts were defined by the WHO in the International Classification of Impairments, Disabilities, and Handicaps [WHO, 1980]. Briefly, impairments are defined as organic dysfunctions, disabilities as a patient's difficulty with tasks, and handicap as the social disadvantage for a given individual resulting from an impairment or a disability that limits or prevents the fulfillment of a role that is normal for that individual. This latter concept is obviously of major importance for a patient's overall quality of life, and is of particular relevance in stroke care. However, its assessment may be influenced by cultural expectations, the patient's environment, and observer bias [Wade, 1992], and therefore the evaluation of medical therapy in stroke should concentrate on more tangible manifestation of disease in terms of disability [de Haan et al, 1995].
The Rankin scale was originally defined as a 6-point rating scale that graded patients on their overall level of independence with reference to previous activities [Rankin, 1957]. It has subsequently been modified to introduce the concept of modification of lifestyle and to remove reference to ambulation [Malgrem et al, 1989]. It remains a matter of debate as to whether it is a pure assessment of handicap or measures disability. De Haan and colleagues have recently studied a group of 438 stroke patients, and found a high correlation between disabilities in daily living and the Modified Rankin score, concluding that the Modified Rankin scale should be viewed as a global functional health index with a strong accent on physical disability [de Haan et al, 1995]. In addition, this scale has proven reliability in terms of interobserver agreement, and reproducibility has been assessed with satisfactory results [van Swieten et al, 1988; Wolfe et al, 1991]. It is therefore of use as a simple and time-efficient assessment of functional outcome in stroke, particularly when used as a dichotomous variable by dividing the scores into two frequently used scoring categories: grades 0 to 2, and grades 3 to 5 [Censori et al, 1993]. Also to avoid bias, scoring was based on the observations of both multidisciplinary hospital carers as well as family members.

Outcome was also assessed by the NIHSS [Brott et al, 1989b]. This is a simple and short scale, which summarises neurological impairments in a number of domains, and consequently has some of the disadvantages of summary measures [Wade, 1992]. However, it is of proven validity and reliability [Brott et al, 1989b; Goldstein et al, 1989; Wade, 1992], and can be used in the serial assessment of neurological recovery or deterioration [Wityk et al, 1994]. The use of this measure of neurological outcome confirmed the importance of admission 24-hour SBP in predicting poor outcome in a multiple logistic regression model, as was found using the Modified Rankin scale.

The question remains as to whether the treatment of elevated BP in the acute stroke period would improve outcome, particularly in view of the reported association between high admission 24-hour SBP and poor outcome in the present study. To date, no randomised controlled trials of acute antihypertensive treatment in stroke have been reported. However, hypotension is a predictable side-effect of agents such as β-blockers and nimodipine, the potential
cerebroprotective effects of which have been studied in acute stroke, but these agents have shown no beneficial effect on morbidity or mortality [Barer et al, 1988; TRUST Study Group, 1990]. There have also been many documented cases in the literature of the hazards of anti-hypertensive therapy in acute stroke [Britton et al, 1980; Lavin, 1986]. The appropriate management of elevated BP in acute stroke needs to be determined by a prospective intervention study, and such studies are now progressing [O'Connell et al, 1994; PROGRESS Management Committee, 1995; Potter, unpublished data]. NIBPM may be the most appropriate method of BP measurement in such studies.

2.7. Conclusions

1. There was significant reduction in casual and 24-hour BP over the first week following acute stroke, in keeping with previous reports. This observation was confirmed in those patients with confirmed CT diagnosis of cerebral infarction.

2. Patients with CT-diagnosed cerebral haemorrhage had significantly higher admission casual and 24-hour BP, with greater falls in BP over the first week though this did not reach statistical significance.

3. Those patients with an outcome at 1 month of death or dependency (as assessed by the Modified Rankin score) had significantly higher casual and 24-hour BP on hospital admission, within 24 hours of acute stroke. They also had a significantly higher blood white cell count, and were more likely to have sustained a TACS or PACS than LACS. However, there were no differences in CT scan diagnosis from the independent group of patients.

4. On single variable logistic regression analysis, higher admission casual and 24-hour BP as well as a lack of day-night BP fall were associated with an increased likelihood of death or dependency at 1 month.

5. Multiple logistic regression analysis showed admission 24-hour SBP and increased dependency on admission to be the only remaining significant outcome
predictors in a forced model containing previously recognised poor prognostic factors, namely age, stroke type, CT result, presence of urinary incontinence, plasma glucose, and blood white cell count.

6. The odds ratio for an outcome of death or dependency at 1 month associated with each 10 mmHg increase in 24-hour SBP at admission was 1.88.

7. The validity of the model was tested against the dataset using the jackknife technique, and had a specificity of 75.4% and sensitivity of 76.1% with a predicted outcome cut-off point of 0.5.

8. Using an outcome measure of death or neurological deterioration (as assessed by the NIHSS), 24-hour SBP on admission remained the only significant outcome predictor on multiple logistic regression analysis.

9. Whether BP should be reduced pharmacologically in the acute stroke period now warrants a suitable prospective, intervention trial.
CHAPTER THREE

SHORT- AND MEDIUM-TERM BLOOD PRESSURE VARIABILITY IN ACUTE AND SUBACUTE STROKE
3.1. Summary
Cerebrovascular dysautoregulation is well recognised following acute stroke, and thus systemic BP changes may have important effects on CBF. Whilst absolute BP levels have been shown to influence outcome (Chapter 2), the importance of BPV has not been addressed. The present study therefore assessed short-term (beat-to-beat Finapres recordings) and medium-term (15 minute NIBPM recordings) BPV and PI variability non-invasively in 32 patients with CT-diagnosed acute cerebral infarction compared to a control group matched with respect to age and sex.

Short-term SBPV (taken as either the SD or the root mean square of successive differences (RMSSD)) was significantly greater in acute stroke patients (studied within 72 hours of ictus) than controls. Medium-term SBPV was also significantly greater following acute stroke, as expressed by the SD of 15-minute recordings. However, there was no significant difference in short-term PI variability or medium-term pulse rate variability (PRV), whether expressed by the SD or RMSSD between the 2 groups. There were no significant changes in short- or medium-term SBPV between stroke patients studied acutely and subacutely (studied within 10 to 14 days of ictus), whether assessed by SD or RMSSD.

Significantly increased short-term BPV, independent of mean BP levels, was observed following acute stroke, which persisted in the subacute period. This difference may be due to impaired cardiac BRS in acute stroke patients or related to alterations in vasomotor tone mediated by centrally induced changes in SNS. This increased variability of short- and medium-term BP levels may have clinical implications with regard to BP control post-stroke. Further work is needed to define its prognostic implications.

3.2. Background
Under normal conditions, cerebral perfusion pressure is maintained even in the face of large BP changes, typically over a range of MAP of 60 to 150 mmHg [Strandgaard et al, 1990]. However, cerebral ischaemia (irrespective of aetiology)
is associated with impaired or abolished cerebrovascular autoregulation [Dearden, 1985]. In acute ischaemic stroke, perfusion pressure may be below the lower limit of cerebrovascular autoregulation distal to the site of arterial occlusion, and reduced CBF may merely be a consequence of changes in the pressure-flow relationship. However, cerebral blood vessels have also been demonstrated to react abnormally to stimuli such as a change in perfusion pressure and carbon dioxide in both experimental models of acute ischaemic stroke, as well as in clinical studies, as has previously been discussed (Chapter 1.5). Such abnormalities may persist for weeks [Paulson, 1970; Meyer et al, 1973b] or even months post stroke [Mori et al, 1993].

CBF is therefore to a major degree dependent on systemic BP levels in acute stroke, so any changes in perfusion pressure may have important effects on CBF and therefore have important prognostic implications. Certainly, an association between BP levels and short-term outcome has already been clearly demonstrated (Chapter 2). As well as the absolute BP level, BPV by influencing CBF may also be important in predicting outcome. Certainly, increased BPV is not a benign phenomenon. It is known to be associated with an increased risk of target organ damage in hypertensive subjects [Pickering, 1991; Palatini et al, 1992], and may be the earliest marker of cardiovascular autonomic dysfunction in diabetics [McKinlay et al, 1994]. To date, the assessment of BPV in stroke is very limited, though Prattichizzo and Galetta reported increased BPV in an uncontrolled study of 13 thromboembolic compared to 8 haemorrhagic stroke patients. BPV was assessed from the ratio of the SD of 10 to 15 minute BP measurements to the 24-hour BP mean [Prattichizzo et al, 1994b]. However, the advent of well-validated techniques of beat-to-beat NIBPM using the Finapres device, as has previously been described (Chapter 1.4.4), allows a simple method of assessing short-term BPV. In addition, the SD of BP measurements taken at least 15-minute intervals differs by only 10% from that obtained from beat-to-beat analysis of intraarterial recordings, and therefore provides a measure of medium-term BPV [Mancia et al, 1985].
3.3. Objectives

1. To assess short-term BPV by the SD and RMSSD from beat-to-beat NIBPM in acute stroke patients within 72 hours of ictus compared to a group of control subjects matched with respect to age and sex.

2. To assess medium-term BPV by the SD and RMSSD of daytime (0700 to 2200 hours) 15-minute NIBPM readings in acute stroke patients within 24 hours of ictus compared to appropriately matched control subjects.

3. To compare short- and medium-term BPV in stroke patients in the acute and subacute periods.

3.4. Methods

3.4.1. Subjects

Thirty-two consecutive acute stroke patients (14 male) of mean age 66.6 years (range 39 to 85 years) presenting within 24 hours of symptom onset to the medical wards of the 3 Leicester Teaching Hospitals were studied. On admission, median Barthel score was 43 (range 0 to 100) {Appendix 4}, and median NIHSS was 8 (range 1 to 19) {Appendix 2}. Diagnosis of acute cerebral infarction was confirmed in all patients by head CT scan. Fourteen patients had a history of hypertension defined as SBP $\geq$160 mmHg and/ or DBP $\geq$90 mmHg before stroke onset, or if they had received antihypertensive therapy. However, those patients requiring the continuation of any treatment known to affect cardiovascular autonomic function, or with a history of atrial fibrillation, TIA, diabetes mellitus, chronic illness preventing functional independence, and those patients unconscious were excluded.

In addition, 32 control subjects matched with respect to age and sex (14 male; mean age 65.5 years; age range 39 to 82 years) were recruited from among respondents to a local newspaper advertisement, as well as elective orthopaedic admissions prior to joint replacement surgery. Control subjects with known diagnoses of ischaemic heart disease, diabetes mellitus, atrial fibrillation, cerebrovascular disease, or conditions associated with autonomic dysfunction
were excluded. No subject received antihypertensive therapy or medication known to affect cardiovascular or autonomic responses.

3.4.2. Study Protocol

All stroke patients were assessed within 24 hours of stroke onset by myself. Casual BP and 24-hour NIBPM was measured as previously described (Chapter 2.4.2). 24-hour NIBPM was repeated in all stroke patients at 10 to 14 days post-ictus. Control subjects were also assessed with casual and 24-hour NIBPM as defined above for stroke patients. BP was recorded in the non-dominant arm, assuming that there was no significant between-arm BP difference (>10 mmHg). Elective orthopaedic admissions were assessed on the day of admission, which was at least 24 hours prior to major joint replacement surgery. Other control subjects were visited on 3 separate occasions, and casual BP taken as the mean of the 3 visits recordings. 24-hour NIBPM was performed on the final visit.

3.4.3. Laboratory Assessments

Stroke patients were assessed on 2 occasions - within 72 hours of ictus and again at 10 to 14 days post-ictus to allow the acute BP changes following stroke to stabilise [de Faire et al, 1978; Wallace et al, 1981; Britton et al, 1986; P Jansen et al, 1987; Harper et al, 1991]. At the time of study, all stroke patients were haemodynamically stable, did not require intravenous or subcutaneous fluid administration, and were not biochemically dehydrated. Control subjects were assessed on 1 occasion - either on the day prior to surgery for elective orthopaedic admissions or within 2 weeks of the last assessment visit at which 24-hour NIBPM had been performed for all other control subjects.

All subjects attended the cardiovascular laboratory at least 2 hours following a light meal, and having abstained from smoking, alcohol, and all caffeinated products for at least 12 hours. The investigations took place in a quiet room (ambient temperature 20°C to 24°C), and the subjects were asked to micturate before the study. The subject was fitted with chest leads for continuous electrocardiogram (ECG) recording (model CR7, Cardiac Recorders Limited, London, UK), and the appropriately sized cuff of the Finapres 2300 NIBPM (Ohmeda, Englewood, Colorado, USA). This is a fully automated instrument that
allows continuous beat-to-beat measurement of finger BP, and has already been described in detail (Chapter 1.4.4). The cuff was fitted to the middle finger or thumb of the hemiparetic hand in strokes and the non-dominant hand in controls and was maintained at heart level by resting on an adjustable support throughout. The analogue outputs from the Finapres and simultaneous ECG recording were downloaded to a dedicated personal computer fitted with an analogue-to-digital converter sampling at 200 Hz per channel. Specially written software allowed the recording, calibration and editing of the digitised signal, and the derivation of beat-to-beat data for SBP, DBP, and MAP, as well as PI.

After 15 minutes of supine rest, subjects underwent 2 periods of 30 minutes simultaneous beat-to-beat BP and ECG recording. Subjects were asked to maintain a respiratory rate of >15 breaths/minute by breathing in time to a metronome, and were not allowed to sleep though environmental stimulation was kept to a minimum. The Finapres device has a built-in system (Physio-Cal) that briefly interrupts the BP recording automatically to keep the finger arteries fully unloaded and the transmural pressure equal to zero (usually for 2 to 3 beats every 70 beats). This was switched off, but applied at 10 minute intervals throughout the monitoring period.

3.4.4. Statistical Methods

Data are presented as mean (SD). Casual BP was taken as the mean of the 3 supine readings. In addition, the mean day SBP and DBP were recorded, from the 24-hour NIBPM. Short-term and medium-term BPV was thereafter assessed from the beat-to-beat and daytime BP recordings, respectively.

Regarding the beat-to-beat BP recording, BP and PI variability were assessed in 2 ways. Firstly, the pooled SD was calculated from the individual SD of each 30 minute recording period balanced for the number of BP or PI readings made for each subject. Secondly, the RMSSD were obtained for the first and last 5 minutes of each 30 minute monitoring period using a specially constructed macro in the Excel 5.0 package. The advantage of this technique is that it removes the portion of variability related to the underlying BP level [Schachinger et al, 1989].
Regarding the medium-term BPV assessed from 15 minute recordings taken during daytime (0700 to 2200 hours) by the Spacelabs model 90207 recorder (Spacelabs, Redmond, Washington, USA). Mancia and colleagues have demonstrated that the SD derived from NIBPM at 5, 10 or 15 minute intervals differs by only 10% from that obtained from beat-to-beat analysis of intraarterial recordings, though non-invasive measurements at 30 and 60 minute intervals may show strikingly large differences from intraarterial values in some subjects [Mancia et al, 1985]. Therefore, the SD of BP measurements taken at 15 minute intervals was used as a measure of medium-term BPV. In addition, the RMSSD were obtained.

Statistical comparisons between paired and unpaired Normally distributed data were made by Student’s paired and unpaired t tests, respectively. Significance was taken at the 5% level. Pearson’s linear correlation and stepwise logistic regression analysis (using the proc logistic programme of the SAS for Windows statistical package) techniques were also used where indicated.

3.5. Results
Mean casual SBP was significantly higher in stroke patients than age- and sex-matched control subjects (Table 3.1).

3.5.1. Short-term Blood Pressure Variability
Short-term SBPV, expressed as the pooled SD of 2 successive 30-minute beat-to-beat BP recordings, was significantly higher in acute stroke patients (Table 3.2). SBPV correlated with increasing SBP levels in both control (r=0.64, p<0.001) and stroke subjects (r=0.50, p=0.004). Mean SBP, as assessed by the Finapres device, was significantly higher in acute stroke patients, even when taking this into account using the RMSSD method, SBPV was still greater in the acute stroke patients (Table 3.2).

Mean beat-to-beat PI was lower in acute stroke patients compared to controls (Table 3.2), though there was no significant difference in PI variability whether
TABLE 3.1 Baseline data in control and acute stroke subjects (within 72 hours of ictus).

Data presented as mean (standard deviation). SBP: systolic blood pressure; DBP: diastolic blood pressure; bpm: beats per minute.

<table>
<thead>
<tr>
<th></th>
<th>CONTROLS (n=32)</th>
<th>STROKES (n=32)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65.5 (10.2)</td>
<td>66.6 (11.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (male: female)</td>
<td>14:18</td>
<td>14:18</td>
<td>NS</td>
</tr>
<tr>
<td>Casual SBP (mmHg)</td>
<td>147 (19)</td>
<td>167 (27)</td>
<td>0.002</td>
</tr>
<tr>
<td>Casual DBP (mmHg)</td>
<td>84 (12)</td>
<td>89 (18)</td>
<td>NS</td>
</tr>
<tr>
<td>Pulse rate (bpm)</td>
<td>67 (10)</td>
<td>71 (12)</td>
<td>NS</td>
</tr>
</tbody>
</table>
### TABLE 3.2 Systolic blood pressure (mmHg) and pulse interval (ms) variability from beat-to-beat measurement with the Finapres device in acute and subacute stroke patients and age- and sex-matched control subjects. Values as mean (standard deviation). **p<0.01, *p<0.05 stroke patients compared to control subjects. None of the comparisons between acute and subacute stroke patients reached statistical significance. BP: systolic blood pressure; DBP: diastolic blood pressure; SD: standard deviation; RMS: root mean square.

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=32)</th>
<th>Acute Stroke (n=32)</th>
<th>Subacute Stroke (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td>126 (14)</td>
<td>136 (20)*</td>
<td>136 (22)*</td>
</tr>
<tr>
<td>SBP Variability (SD)</td>
<td>10.3 (4.0)</td>
<td>13.0 (4.6)*</td>
<td>11.6 (4.0)</td>
</tr>
<tr>
<td>SBP Variability (RMS)</td>
<td>4.0 (1.4)</td>
<td>5.8 (3.0)**</td>
<td>5.4 (2.2)**</td>
</tr>
<tr>
<td>Pulse Interval</td>
<td>918 (140)</td>
<td>856 (133)</td>
<td>838 (137)</td>
</tr>
<tr>
<td>Pulse Interval</td>
<td>37 (16)</td>
<td>41 (17)</td>
<td>37 (15)</td>
</tr>
<tr>
<td>Variability (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulse Interval</td>
<td>32 (17)</td>
<td>35 (16)</td>
<td>29 (18)</td>
</tr>
<tr>
<td>Variability (RMS)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
expressed by the SD or the RMSSD (Table 3.2). There was a significant negative correlation with increasing age \( r=-0.42, p=0.004 \).

A logistic regression model was constructed to determine whether BP and PI variability predicted the presence or absence of stroke in the whole study population. The following explanatory variables were significant predictors on single variable logistic regression analysis: casual SBP \( p=0.005 \) and SBPV as assessed by the RMSSD \( p=0.02 \). Other variables tested were not significant (age, sex, casual DBP, HR, SBPV assessed by the SD, and PI variability assessed by RMSSD and SD). To determine those variables most important in acute stroke, a stepwise logistic regression model was constructed. Only SBPV assessed by the RMSSD \( p<0.001 \) and casual SBP \( p=0.002 \) were significant.

Changes in BP and PI variability were reassessed in all stroke patients 10 to 14 days post ictus. There was a significant improvement in stroke patients in the Barthel score of 6 \( 95\% \) CI: 1 to 11, \( p<0.03 \) during this time. Stroke patients showed a significant reduction in casual SBP (19 mmHg, 95% CI: 9 to 29 mmHg, \( p<0.001 \)) and DBP (8 mmHg, 95% CI: 1 to 15 mmHg, \( p<0.03 \)) during the acute and subacute periods. However, no significant changes in Finapres BP levels were seen between acute and subacute assessments (Table 3.2).

There was no significant changes in SBPV, assessed by the SD or the RMSSD, between acute and subacute study periods (Table 3.2). Similarly, there was no significant change in PI variability in the subacute period (Table 3.2).

### 3.5.2. Medium-term Blood Pressure Variability

Medium-term SBPV, expressed as the SD of NIBPM measurements taken at 15 minute intervals during the day (0700 to 2200 hours), was significantly greater in acute stroke patients compared to control subjects (Table 3.3). Day SBPV correlated with increasing age \( r=0.53, p<0.001 \) and increasing day SBP levels \( r=0.53, p<0.001 \) in all subjects. Day SBPV was also correlated with increasing age \( r=0.54, p=0.001 \) and increasing day SBP levels \( r=0.62, p<0.001 \) in the
<table>
<thead>
<tr>
<th></th>
<th>CONTROLS (n=32)</th>
<th>ACUTE STROKES (n=32)</th>
<th>SUBACUTE STROKES (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day SBP (mmHg)</td>
<td>133 (18)</td>
<td>148 (22) *</td>
<td>140 (22)</td>
</tr>
<tr>
<td>Day SBP Variability (SD)</td>
<td>10.6 (3.7)</td>
<td>13.6 (5.3) *</td>
<td>13.1 (6.0)</td>
</tr>
<tr>
<td>Day SBP Variability (RMS)</td>
<td>9.7 (1.8)</td>
<td>11.6 (3.7)</td>
<td>10.5 (4.2)</td>
</tr>
<tr>
<td>Day PR (bpm)</td>
<td>73 (10)</td>
<td>76 (14)</td>
<td>77 (14)</td>
</tr>
<tr>
<td>Day PR Variability (SD)</td>
<td>8.7 (4.3)</td>
<td>8.2 (3.8)</td>
<td>7.8 (2.9)</td>
</tr>
<tr>
<td>Day PR Variability (RMS)</td>
<td>6.3 (1.6)</td>
<td>5.9 (1.7)</td>
<td>5.0 (1.7)</td>
</tr>
</tbody>
</table>

TABLE 3.3 Medium-term blood pressure and pulse rate variability in control subjects and patients with cerebral infarction. Values as mean (standard deviation). *p<0.01 acute stroke patients compared to control subjects. None of the comparisons between subacute stroke patients and either control subjects or acute stroke patients reached statistical significance. SBP: systolic blood pressure; DBP: diastolic blood pressure; PR: pulse rate; bpm: beats per minute; SD: standard deviation; RMS: root mean square.
stroke population alone. Mean day SBP was significantly higher in acute stroke patients compared to control subjects (Table 3.3). When taking this into account using the RMSSD, day SBPV was not significantly greater in acute stroke patients (Table 3.3).

Mean day PR was not significantly different between acute stroke patients and control subjects. There was also no significant difference in day PRV whether expressed as the SD or RMSSD between acute stroke patients and control subjects (Table 3.3).

Changes in daytime SBP and PRV were reassessed in all stroke patients 10 to 14 days post ictus. There was a non-significant reduction in mean day SBP, though no significant changes in day SBPV whether expressed by the SD or RMSSD between the acute and subacute periods in stroke patients (Table 3.3). Similarly, there were no significant changes in absolute day PR or PRV expressed by the SD and RMSSD between the acute and subacute phases (Table 3.3).

3.6. Discussion

In the present study, short-term SBPV as expressed by the pooled SD of 2 successive 30 minute beat-to-beat BP recordings was significantly greater in stroke patients with CT-diagnosed acute cerebral infarction studied within 72 hours of ictus than a group of control subjects matched with respect to age and sex. SBPV was significantly positively correlated with baseline BP, and remained significantly greater in acute stroke patients when assessed by the RMSSD, which removed the portion of variability related to underlying BP. No further changes were seen in SBPV at follow-up 10 to 14 days post-ictus compared to the acute stroke period, when calculated by either the SD or the RMSSD.

The level of SBPV reported in our control group was in keeping with that of 7 ± 2 mmHg observed in the study of Veerman and colleagues using similar methodology [Veerman et al, 1994]. The findings of increased systolic BPV with increasing BP levels and reduced PI variability with increasing age reported in this study have also been shown in others using both short-term Finapres
Blood pressure variability

[Veerman et al, 1994; Siche et al, 1995] and 24-hour intra-arterial BP recordings [Watson et al, 1980; Parati et al, 1995b]. However, the assessment of BPV in stroke is very limited.

To the author's knowledge, the present study is the first to report a higher beat-to-beat SBPV in acute stroke compared to a control group. Prattichizzo and Galetta have previously reported an increase in medium-term BPV in thromboembolic compared to haemorrhagic stroke patients. However, their study was uncontrolled, and assessed BPV by the variability coefficient (SD/ 24-hour mean) taken from 10 to 15 minute BP recordings made by 24-hour NIBPM devices [Prattichizzo et al, 1994b]. The present study also assessed SBPV from the SD, as well as the RMSSD, of daytime 15 minute NIBPM recordings, and found a significantly greater variability following acute stroke compared to control subjects, though when corrected for mean BP levels no difference between strokes and controls was found.

3.6.1. Mechanisms Of Increased Blood Pressure Variability

The increase in short-term BPV found following acute stroke may be related to impaired BRS, as short-term BPV is inversely related to BRS [Mancia et al, 1980; Mancia et al, 1986; Floras et al, 1988]. There is certainly good reason to suppose abnormalities of baroreceptor function following stroke, as has previously been discussed {Chapter 1.3.2}, though clinical studies of cardiac baroreflex responses in stroke are to date limited to patients with chronic disease [Appenzeller et al, 1964; Gross, 1970a; Monga et al, 1988], and have methodological problems related to the use of intra-arterial cannulation and pharmacological agents. Only the study of Appenzeller and colleagues of cardiac BR and circulatory responses to the Valsalva manoeuvre demonstrated these to be clearly impaired in acute stroke [Appenzeller et al, 1964]. Other studies showed a closer relationship with age [Gross, 1970a], or no difference from controls [Monga et al, 1988].

BR-derived responses to BPV are mediated by appropriate changes in HR and vasomotor tone. However, we found no significant differences in PI variability between acute stroke patients and age- and sex-matched control subjects, which may be against a significant role for cardiac BR impairment to account for the
change in BPV observed. Therefore, it may be conjectured that the increased BPV may be mediated by an impairment of vasomotor tone. This was not assessed in the present study, but changes following acute stroke in forearm vascular resistance (FVR) (used as a reflection of vasomotor tone) in response to a fall in BP induced by lower body negative pressure (LBNP) and orthostatic change will be considered in subsequent studies (Chapters 5 and 6, respectively).

Another factor which may be relevant is SNS activity, which has been shown to be important in the mediation of increased BPV [Alper et al, 1987], and is increased following acute stroke [Natelson, 1985; Talman, 1985]. PI was significantly lower in acute stroke patients in the present study consistent with SNS hyperactivity, though quantitative measurements of cardiac output or SNS activity were not made to support or refute this hypothesis. Again, this is to be the subject of further study with the use of PSA techniques of beat-to-beat BP and PI assessment to derive measures of BRS and sympathovagal balance following acute stroke (Chapter 4).

3.6.2. Implications Of Increased Blood Pressure Variability

Increased BPV may not be a benign phenomenon, as evidenced by work in hypertensive and diabetic subjects [Pickering, 1991; Palatini et al, 1992; McKinlay et al, 1994]. Palatini and colleagues assessed BPV by the SD of BP readings taken at 15 minute intervals during the day. They divided the 728 subjects studied into 5 bands of BP, and found an increased risk of hypertensive cardiovascular complications with increased day SBPV at all levels of BP [Palatini et al, 1992]. In a group of 20 non-insulin dependent diabetics, McKinlay and colleagues found that increased day SBPV predated changes in the diurnal BP profile. It was proposed that increased BPV may be the earliest marker of cardiovascular autonomic dysfunction [McKinlay et al, 1994].

Increased BPV may also have important implications in patients following acute stroke. Cerebrovascular dysautoregulation is well-documented in acute stroke (Chapter 1.5), such that CBF is pressure passive. Therefore, increased BPV may have important effects on CBF, and the potential viability of the ischaemic penumbra. There may also be implications for the management of BP in acute
stroke, which is already a matter of considerable debate [Yatsu et al, 1985; Spence et al, 1985; O'Connell et al, 1994], as has previously been reviewed (Chapter 1.6). Though the absolute level of BP is reduced by antihypertensive therapy, there is little evidence to support a reduction of BPV with most agents [Pickering, 1990]. However, there is some evidence that centrally acting adrenergic blocking drugs reduce BPV as well as the absolute BP level [Prattichizzo et al, 1994a], and may be the agents of choice in acute stroke, though there are well-documented risks of acute BP reduction in stroke [Britton et al, 1980; Yatsu et al, 1985; Lavin, 1986].

3.6.3. Summary
In summary, the present study has demonstrated a significant increase in short- and medium-term SBPV within the first 72 hours of acute stroke, which remains increased on further assessment at 10 to 14 days post ictus. This increased BPV may reflect impairment of BRS which has previously been documented in chronic stroke, or abnormalities of peripheral vasomotor tone. These issues will be addressed in the following sections, which will consider BRS following acute and subacute stroke (Chapter 4), and vasomotor responses to BP changes induced by LBNP (Chapter 5) and orthostatic change (Chapter 6).

3.7. Conclusions
1. Short-term SBPV is significantly increased following acute stroke compared to a group of control subjects matched with respect to age and sex.

2. Increased short-term SBPV is independent of the higher mean BP levels observed following acute stroke, when assessed using the RMSSD to remove the portion of variability related to BP level.

3. The increases in short-term SBPV compared to control subjects persist in the subacute period despite resolution of the acute casual BP changes.
4. Daytime (medium-term) SBPV, assessed by the SD of 15 minute recordings, is also significantly greater following acute stroke compared to control subjects, but there is no difference when corrected for the underlying BP level.

5. These differences in BPV are unlikely to be totally due to impaired cardiac BRS in stroke patients, as no differences were observed in PI variability compared to controls. Increased BPV may be related to alterations in vasomotor tone mediated by centrally induced changes in SNS activity, and these hypotheses will be considered in subsequent chapters.
CHAPTER FOUR

THE NON-INVASIVE ASSESSMENT OF CARDIAC BARORECEPTOR SENSITIVITY IN ACUTE AND SUBACUTE STROKE
4.1. Summary

The BP changes and increased BPV following acute stroke have been previously described in this thesis. The underlying pathophysiological mechanisms producing these findings are unclear, but may include abnormalities of cardiac BRS. To date, evidence of impaired cardiac BRS following stroke is limited to patients with chronic disease only using invasive methodology. Therefore, it was proposed to assess cardiac BRS using novel non-invasive techniques following acute stroke.

Thirty-seven consecutive acute stroke patients were studied within 72 hours of ictus, and again at 10 to 14 days. Subjects underwent 3 consecutive periods of 10 minutes simultaneous surface ECG and beat-to-beat BP recording using the non-invasive Finapres device. Cardiac BRS was assessed by SA and PSA (using FFT and AR algorithms) techniques, as well as phase IV of the Valsalva manoeuvre. Responses were compared with an age-, sex-, casual and 24-hour BP-matched group of control subjects.

Cardiac BRS was significantly lower in stroke patients both acutely and subacutely compared to control subjects, as assessed by the combined pressor/depressor sequences and by the combined α index. The absolute and normalised HF power of SBPV was significantly greater in acute and subacute stroke patients, probably reflecting the mechanical effects of respiration. No significant differences were observed in the power spectrum of PI variability between stroke patients and control subjects. Right hemisphere strokes had a significant reduction in HF PI power compared to left hemisphere strokes, which was associated with a change in sympathovagal balance in favour of increased SNS tone.

Cardiac BRS is impaired following stroke. This may be important in explaining the increased BPV following stroke, though the finding of increased HF power of BPV related to the mechanical effects of respiration may also be important. Right hemisphere strokes had a significant alteration in the sympathovagal balance of PI variability in favour of SNS predominance compared to left hemisphere strokes,
which may be important in the development of cardiac arrhythmias following stroke. The prognostic implications of these findings needs to be further explored.

4.2. Background

The author has already confirmed the well-recognised BP changes following acute stroke, and has shown that BP levels within the first 24 hours of ictus are important predictors of outcome {Chapter 2}. The underlying pathophysiological mechanisms for such changes are debated, and the evidence has previously been reviewed {Chapter 1.3}. In particular, the BR reflex arc, which includes peripheral afferent (aortic and carotid BR) and efferent (vagal and SNS tone) as well as central mechanisms (brainstem and higher cerebral centres), plays an important role in the short-term regulation of the cardiovascular system (Figure 1.1).

In the previous section {Chapter 3}, the author has demonstrated an increase in short-term SBPV independent of the underlying BP level in acute stroke patients compared to control subjects. This may reflect impaired cardiac BRS, may be related to alterations in the vascular-BR reflex mediated by centrally induced changes in SNS activity, or related to mechanical effects on the vasculature. To date, evidence of impaired cardiac BRS in stroke is limited to animal models [Doba et al, 1974; Cechetto et al, 1989b] and to patients with chronic disease using invasive methodology [Appenzeller et al, 1964; Gross, 1970a]. However, the advent of newer reliable non-invasive techniques of beat-to-beat BP measurement together with the increased availability of powerful microcomputers and appropriate analysis techniques has made possible the calculation of cardiac BRS from the assessment of continuous BP and PI recordings taken at rest. These techniques have already been discussed in detail in Chapter 1.4. The technique of PSA may also be useful in identifying abnormalities of autonomic cardiovascular control following acute stroke.
4.3. Objectives

1. To assess cardiac BRS in acute stroke patients compared to an age-, sex- and casual- and 24-hour BP-matched control population.

2. To assess indirectly the potential integrity of underlying PNS and SNS neural cardiovascular control by PSA techniques.

3. To observe the changes in cardiac BRS and autonomic cardiovascular control between the acute and subacute stroke periods.

4. To observe the differences in cardiac BRS and autonomic cardiovascular control between right and left hemisphere strokes.

4.4. Methods

4.4.1. Subjects

Thirty-seven consecutive acute stroke patients (17 male) of mean age 69.4 years (range 45 to 89 years) admitted to the medical wards of the Leicester Teaching Hospitals within 24 hours of ictus were studied. Head CT scanning was performed in 29 patients (24 infarctions, 5 haemorrhages). In addition, patients were classified by reference to the site of the neurological lesion (18 right hemisphere, 17 left hemisphere, and 2 cerebellar/brainstem) and according to the Oxfordshire Community Stroke Project classification (25 TACS or PACS, 10 LACS, and 2 POCS) [Appendix 1] [Bamford et al, 1991].

Of the 37 subjects, 14 had a history of hypertension defined as a past medical history of SBP >160 mmHg and/ or DBP >90 mmHg before stroke onset, or if they had received antihypertensive therapy. However, those patients requiring the continuation of antihypertensive therapy, or any treatment with effects on cardiovascular or autonomic function were excluded. Unconscious patients, those with atrial fibrillation, or neurological signs lasting < 24 hours were also excluded, as were patients with a past medical history or evidence at the time of study of
diabetes mellitus, impaired renal function (creatinine >200 μmol/l), or other conditions associated with autonomic dysfunction.

Thirty-seven age- and sex-matched control subjects (18 male) of mean age 67.5 years (range 45 to 82 years) were also studied. These subjects were recruited from among respondents to a local newspaper advertisement, as well as elective orthopaedic admissions prior to major joint replacement surgery. However, to ensure that the study groups would also be matched for BP, a proportion of untreated hypertensive control subjects (n=11) were recruited from among outpatient attenders at two of the Leicester Teaching Hospitals and through liaison with several large local general practices. Control subjects with known diagnoses of ischaemic heart disease, cerebrovascular disease, atrial fibrillation, diabetes mellitus, impaired renal function (creatinine >200 μmol/l), or other conditions associated with autonomic dysfunction were excluded. No subject received antihypertensive therapy or medication known to affect cardiovascular or autonomic responses.

4.4.2. Study Protocol
All stroke patients were assessed within 24 hours of stroke onset by myself. Height (or armspan), weight and body mass index (weight (kg) divided by height (m)squared) were recorded. Casual and 24-hour NIBPM was performed as previously described (Chapter 2.4.2). Control subjects were also assessed with casual and 24-hour NIBPM as defined above for stroke subjects. BP were recorded in the non-dominant arm, assuming that there was no significant between-arm BP difference (>10 mmHg). Elective orthopaedic admissions were assessed on the day of admission, which was at least 24 hours prior to major joint replacement surgery. Other control subjects were visited on 3 separate occasions, and casual BP taken as the mean of the 3 visits recordings. 24-hour NIBPM was performed on the final visit.

4.4.3. Laboratory Assessments
Non-invasive assessments of the cardiac-BR reflex arc were thereafter performed in the cardiovascular laboratory. Stroke patients were assessed on two occasions - within 72 hours of ictus and again at 10 to 14 days post-ictus to allow the acute
BP changes following stroke to stabilise [de Faire et al, 1978; Wallace et al, 1981; Britton et al, 1986; P Jansen et al, 1987; Harper et al, 1991]. At the time of study, all stroke patients were haemodynamically stable, did not require intravenous or subcutaneous fluid administration, and were not clinically or biochemically dehydrated. Control subjects were assessed on one occasion - either on the day prior to surgery for elective orthopaedic admissions or within two weeks of the last assessment visit at which 24-hour NIBPM had been performed for all other control subjects.

All subjects attended the cardiovascular laboratory at least 2 hours following a light meal, and having abstained from smoking, alcohol, and all caffeinated products for at least 12 hours. The investigations took place in a quiet room (ambient temperature 20°C to 24°C), and the subjects were asked to micturate before the study. The subject was fitted with chest leads for continuous ECG recording (model CR7, Cardiac Recorders Limited, London, UK), and the appropriately sized cuff of the 2300 Finapres NIBPM monitor (Ohmeda, Englewood, Colorado, USA), as previously described (Chapter 3.4.3). After a period of at least 15 minutes rest and following achievement of a satisfactory BP signal from the Finapres and the stabilisation of BP at the same level (mean 2 minute BP levels not varying by more than 10 mmHg over at least 10 minutes), recordings were performed for 3 sequential periods of 10 minutes each. The Finapres device has a built-in system (Physio-Cal) that briefly interrupts the BP recording automatically to keep the finger arteries fully unloaded and the transmural pressure equal to zero (usually for 2 to 3 beats every 70 beats). This was switched off during the recording period, but applied at 10 minute intervals during the monitoring period. Subjects were asked to maintain a respiratory rate > 15 breaths/minute, and were not allowed to sleep.

An estimation of cardiac BRS was also made from the PI and SBP responses during phase 4 of the Valsalva manoeuvre. To this end, all subjects were then asked to perform the Valsalva manoeuvre in the seated position. After several practices, subjects blew into a pressure transducer to maintain a pressure of 40 mmHg for a period of 15 seconds. The system contained a small air leak to ensure that subjects maintained a constant respiratory effort. This was repeated
on 3 occasions with a period of at least 2 minutes rest between recordings, and the mean value from the 3 manoeuvres used in the subsequent analysis. This could only be performed by 16 acute stroke patients, because either the extent of the facial palsy prohibited maintenance of an adequate seal between the mouth and air-piece of the pressure transducer, or there was sufficient receptive impairment that the patient was unable to understand the instructions for the procedure.

4.4.4. Data Analysis

Software specially written by Leicester University Division of Medical Physics, and which is in routine use in the department at which these studies were undertaken [James et al, 1995; Panerai et al, 1995; James et al, 1996b], was used in the off-line analysis of the beat-to-beat BP and PI recordings. Initially, the beginning and end of each cardiac cycle was marked on both the ECG and the BP signals. This allowed the extraction of the PI time series from both of these signals and the beat-to-beat SBP series from the foot of the BP signal. Comparison of the PI signals extracted form the ECG and BP signals showed identical patterns with the latter being less susceptible to drift and noise. For this reason the BP derived PI series was used in subsequent analysis.

The derived PI and SBP series were thereafter analysed by a number of techniques to evaluate cardiac BRS. These methods have already been considered elsewhere [Chapter 1.4], and will now be considered only briefly:

Sequence Analysis

Sequences of spontaneously rising or falling SBP in association with increasing and decreasing PI, respectively, were automatically detected, and a linear regression was performed of PI as a function of SBP. SBP change was correlated with PI change for the immediately succeeding beat (a 'lag' of one) [Fritsch et al, 1986; Steptoe et al, 1990]. Three conditions were imposed to accept any sequences as significant. Firstly, a noninterrupted rise or fall of SBP over 3 or more beats. Secondly, an absolute rate of change of SBP of at least 0.5 mmHg/beat. Thirdly, a p value significant at the 5% level for the linear regression of PI as a function of SBP. No further stipulations were made regarding the response in
order not to bias the analysis in favour of higher values of cardiac BRS. Using these criteria, we have shown a good correlation between values for cardiac BRS obtained by this method and by using standard pharmacological pressor (phenylephrine) and depressor (sodium nitroprusside) stimuli [James et al, 1995].

It should be noted that specific criteria for PI change between beats were not imposed in keeping with other groups [Steptoe et al, 1990; Parlow et al, 1995]. To create a minimum criteria for the PI response (usually 4 ms [Bertinieri et al, 1988; Siche et al, 1995]) risks biasing the analysis in favour of higher cardiac BRS values, thereby skewing the results. Also, the exclusion of lines of regression below a defined correlation coefficient was not imposed, unlike others [Parati et al, 1988; Steptoe et al, 1990; Omboni et al, 1993], which again protects against the exclusion of sequences of low cardiac BRS.

Estimates of cardiac BRS were obtained as the mean slope of all significant sequences for pressor, depressor, and combined pressor/ depressor responses. In addition, data were obtained on the percentage of the entire recording represented by baroreflex sequences and the absolute number of sequences of each type.

**Power Spectral Analysis**

PSA was also performed using the FFT with 512 samples. The beat-to-beat series of PI and SBP were interpolated with a third order polynomial and resampled with an interval of 0.5 seconds to produce signals with a uniform time axis. The power spectra were obtained as the average of 3 recordings for each patient and 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.

Recordings with an ectopy rate greater than 2% were rejected. Spikes on the resampled tracings of the PI and SBP recordings were manually removed, though resampled tracings with more than 4 spikes were excluded from subsequent analysis to avoid bias.
Power spectra for the resampled PI and SBP series were also calculated using an AR model with 512 samples. This method derives the best-fitting model for the data and treats any signal components not fitting the model as noise and discarding them, and is therefore able to operate on shorter data segments [Malliani et al, 1994]. The best-fitting model was assessed on the basis of Akaike's criterion, and a model order of 15 was selected.

PSA estimates of cardiac BRS were obtained by calculation of the $\alpha$ index (square root of the ratio of the powers of PI to BP) for the LF band (0.05 to 0.15 Hz.), for the HF band (0.20 to 0.35 Hz.), and for the combined $\alpha$ index ($0.5 \times (\text{LF cardiac BRS} + \text{HF cardiac BRS})$). The $\alpha$ index has been shown to correlate well with the combined pressor/ depressor value for cardiac BRS obtained by SA [Panerai et al, 1995], and by the phenylephrine method [Pagani et al, 1988; James et al, 1996b].

In addition, the power of the LF and HF spectra for PI and for SBP were calculated in normalised units:

$$\text{Power (normalised units)} = \frac{\text{absolute power of given component} \times 100}{\text{total variance} - \text{VLF power}}$$

The origins of SBP and PI variability in the LF and HF bands has been considered previously {Chapter 1.4.5}.

**Valsalva Manoeuvre**

Finally, the slope of the linear regression of PI on SBP during phase 4 of the Valsalva manoeuvre was used as a measure of cardiac BRS. Two measures were derived. Firstly, all beats from the lowest SBP after the release of expiratory pressure at the beginning of phase 4 to the peak pressure at the end of phase 4 were included. Secondly, using only the overshoot part of phase 4, where the SBP exceeded its resting level. The relative merits of each of these methods has been discussed elsewhere {Chapter 1.4.3}. 
4.4.5. Statistical Methods

Normality of the data was determined by construction of a normal probability plot, as previously described (Chapter 2.4.3). For Normally distributed data the results are presented as mean (SD), and statistical comparisons between stroke and control groups were made using the Student’s unpaired t test, and between acute and subacute stroke with the paired Student t test. For non-Normally distributed data, results are presented as median (range), and statistical comparisons between stroke and control groups were made with the Mann Whitney test, and between acute and subacute stroke with the Wilcoxon test. Significance was taken at the 5% level.

4.5. Results

Stroke patients and control subjects were age-and sex-matched. There were also no significant differences between SBP and DBP, whether assessed on casual or 24-hour levels (Table 4.1). However, baseline PI was significantly lower in the acute stroke patients (Table 4.1).

4.5.1. Estimations Of Cardiac Baroreceptor Sensitivity

Cardiac BRS was assessed by a number of techniques, and the results are shown in Table 4.2.

Power Spectral Analysis

Cardiac BRS was estimated by PSA using the FFT method. The α index (the square root of the ratio of powers of PI to BP) was calculated for the low (0.05 to 0.15 Hz.) and high (0.20 to 0.35 Hz.) frequency bands, as well as a combined α index. Cardiac BRS was significantly lower by all methods in acute stroke patients compared to age-, sex-, and BP-matched control subjects as assessed in the HF band and by the combined α index (Table 4.2). The gain or transfer function between variations in SBP and PI over the frequency range 0 to 0.5 Hz was also calculated at 0.0039 Hz intervals (Figure 4.1).
The amount of linear coupling between SBP and PI in the frequency domain can be expressed in terms of coherence, and is comparable to the regression coefficient in regression analysis. The mean coherence between the SBP and PI spectra was 0.47 and 0.47 at the low and 0.52 and 0.45 at the HF bands for control subjects and for acute stroke patients (Figure 4.2). These figures confirm that coherence was highest over the LF and HF bands. The phase difference between PI and SBPV was approximately 0° at HF (Figure 4.2). However, at LF, there was an approximately linear relationship between phase and frequency. The phase was negative, implying that the SBP was leading the PI variability, and therefore consistent with a BR-derived response (Figure 4.2).

From PSA, cardiac BRS as defined by the combined α index was significantly correlated with the combined pressor/ depressor value derived using SA for both acute stroke patients (r=0.67, p<0.001) and control subjects (r=0.93, p<0.001) (Figure 4.3).

In control subjects, there was a negative correlation with increasing casual (r=-0.40, p<0.02) and 24-hour (r=-0.45, p=0.006) SBP and cardiac BRS as assessed by the combined α index, though the negative relationship with age was not significant (r=-0.27, p=0.11). The negative correlations between these factors were not significant in acute stroke subjects (age: r=-0.25, p=0.19; casual SBP: r=-0.13, p=0.51; 24-hour SBP: r=-0.16, p=0.44).

Finally, cardiac BRS was calculated from PSA techniques using an AR algorithm with model order 15. Values are again quoted for the LF, HF and combined α indices, and were lower in acute stroke patients compared to control subjects, though the LF α index values were not statistically significantly different (Table 4.2).
<table>
<thead>
<tr>
<th></th>
<th>CONTROLS (n=37)</th>
<th>STROKES (n=37)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>67.5 (8.3)</td>
<td>69.4 (10.8)</td>
<td>0.41</td>
</tr>
<tr>
<td>Sex (male: female)</td>
<td>18: 19</td>
<td>17: 20</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>BMI (kg/ m²)</td>
<td>27.0 (3.3)</td>
<td>29.3 (5.1)</td>
<td>0.44</td>
</tr>
<tr>
<td>Casual SBP (mmHg)</td>
<td>163 (19)</td>
<td>171 (27)</td>
<td>0.16</td>
</tr>
<tr>
<td>Casual DBP (mmHg)</td>
<td>86 (10)</td>
<td>92 (20)</td>
<td>0.11</td>
</tr>
<tr>
<td>Pulse Interval (ms)</td>
<td>936 (122)</td>
<td>827 (146)</td>
<td>0.002</td>
</tr>
<tr>
<td>24-hour SBP (mmHg)</td>
<td>145 (16)</td>
<td>154 (25)</td>
<td>0.10</td>
</tr>
<tr>
<td>24-hour DBP (mmHg)</td>
<td>81 (10)</td>
<td>85 (12)</td>
<td>0.17</td>
</tr>
</tbody>
</table>

**TABLE 4.1**  Baseline characteristics of stroke patients and control subjects. 
*BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure.*
<table>
<thead>
<tr>
<th></th>
<th>CONTROLS</th>
<th>STROKES</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spectral Analysis (FFT)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Frequency</td>
<td>5.08</td>
<td>3.93</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>(1.56-20.67)</td>
<td>(1.43-12.00)</td>
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</tr>
<tr>
<td>High Frequency</td>
<td>6.50</td>
<td>4.89</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>(2.31-21.49)</td>
<td>(1.83-14.62)</td>
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</tr>
<tr>
<td>Combined α Index</td>
<td>5.46</td>
<td>4.65</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>(2.82-16.83)</td>
<td>(1.86-13.31)</td>
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</tr>
<tr>
<td><strong>Spectral Analysis (AR)</strong></td>
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<tr>
<td>Low Frequency</td>
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<td>NS</td>
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<tr>
<td></td>
<td>(1.54-22.86)</td>
<td>(1.53-12.93)</td>
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<tr>
<td>High Frequency</td>
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<tr>
<td>Combined α Index</td>
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<td>4.61</td>
<td>0.01</td>
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<td></td>
<td>(3.03-16.67)</td>
<td>(1.92-13.94)</td>
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<td><strong>Sequence Analysis</strong></td>
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<td>Depressor</td>
<td>6.92</td>
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<td>0.01</td>
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<td>(2.47-14.44)</td>
<td>(1.98-16.74)</td>
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<td><strong>Valsalva Manoeuvre</strong></td>
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<td></td>
</tr>
<tr>
<td>V1</td>
<td>2.51</td>
<td>3.41</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>(0.70-8.96)</td>
<td>(0.44-6.62)</td>
<td></td>
</tr>
<tr>
<td>V2</td>
<td>5.31</td>
<td>5.67</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>(1.63-15.70)</td>
<td>(1.67-13.84)</td>
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</table>

**TABLE 4.2** Values of cardiac baroreceptor sensitivity (ms/ mmHg) in acute stroke patients and control subjects assessed by the Valsalva manoeuvre, and sequence and spectral analysis techniques.

*Values presented as median (range). FFT: Fast Fourier Transform; AR: autoregressive.*
FIGURE 4.1 Mean gain over frequency range 0 to 0.5 Hz. in acute stroke patients and control subjects
FIGURE 4.2 Coherence (thick line) and phase responses in radians (thin line) over frequency range 0 to 0.5 Hz. in control subjects and acute stroke patients
Cardiac BRS was also assessed by SA from the mean slope of all significant sequences of at least 3 beats of rising SBP and PI (pressor), of falling SBP and PI (depressor), and combined pressor/ depressor sequences. Only 28 acute stroke patients fulfilled the requirements of sequence length, SBP change between beats, and p value for the linear regression of PI as a function of SBP to allow an estimation of cardiac BRS by this technique. Cardiac BRS was significantly lower by all methods in the acute stroke patients compared to the control subjects (Table 4.2).

In acute stroke patients, the median number of sequences based on pressor change was 24 (range 3 to 112) and on depressor change was 24 (3 to 83) (p=0.97). Similarly, there was no significant difference between the number of pressor compared to depressor sequences in control subjects (33 (10 to 79) vs. 34 (1 to 77), respectively, p=0.77). However, the median number of beats per sequence was higher in control subjects compared to acute stroke subjects for pressor sequences (4.0 (3.0 to 5.6) vs. 3.5 (3.0 to 5.4), p<0.02), depressor sequences (4.0 (3.0 to 6.1) vs. 3.8 (3.0 to 6.8), p=0.35), and combined pressor/ depressor sequences (4.3 (3.0 to 6.3) vs. 3.9 (3.0 to 6.5), p=0.31).

There was no significant differences between acute stroke patients and control subjects in the mean proportion of the entire recording that was represented by baroreflex sequences (22.5 (11.0)% vs. 24.4 (10.1)%, respectively, p=0.48). The range of baroreflex sequences in acute stroke patients was 4.3 to 47.2%, and 3.9 to 54.6% in control subjects.

Cardiac BRS assessed by the combined pressor/ depressor sequences showed a significant negative correlation with age (r=-0.35, p<0.04), and SBP, whether assessed on casual (r=-0.38, p=0.02) or 24-hour (r=-0.42, p=0.01) BP recordings. Again, a negative correlation was observed between combined pressor/ depressor sequence cardiac BRS and age in acute stroke patients, though this did not reach the level of statistical significance (r=-0.34, p<0.08). However, no correlation was observed between cardiac BRS and casual or 24-hour SBP (r=0.02, p=0.90; r=-0.15, p=0.49, respectively).
Cardiac BRS was assessed from phase 4 of the Valsalva manoeuvre by two methods. Firstly (V1), from the slope of the linear regression of PI on SBP using all the beats from the lowest SBP after the release of expiratory pressure at the beginning of phase 4 to the peak pressure at the end of phase 4 [Goldstein et al, 1982; Horodyski et al, 1995]. Secondly (V2), using only the overshoot part of phase 4, where the SBP exceeded its resting level [Pickering et al, 1969]. There was no significant difference in cardiac BRS between acute stroke patients and control subjects by either method (Table 4.2). However, the values for cardiac BRS derived by using the overshoot method (V2) compared to the all beat method (V1) were significantly higher for both acute stroke patients (3.07 ms/ mmHg, 95% CI: 1.31 to 4.84 ms/ mmHg, p<0.004) and control subjects (3.14 ms/ mmHg, 95% CI: 2.19 to 4.08 ms/ mmHg, p<0.001).

In control subjects, cardiac BRS using the Valsalva method (V1) was significantly negatively correlated with age (r=-0.44, p=0.006) and SBP, whether from casual (r=-0.39, p<0.02) or 24-hour (r=-0.33, p=0.05) measurements. Similarly, acute stroke patients demonstrated a negative correlation between cardiac BRS (V1) and age (r=-0.66, p=0.006), casual (r=-0.61, p=0.01) and 24-hour (r=-0.64, p<0.03) SBP.

The analyses of cardiac BRS were repeated to compare the 24 acute stroke patients with a CT diagnosis of cerebral infarction with the control subjects. The acute stroke patients and control subjects were again matched for age (66.7 (standard deviation 9.9) vs. 67.5 (8.3) years, respectively, p=0.74) and sex (11 vs. 18 male, p>0.2). There were also no significant differences in casual SBP (169 (27) vs. 163 (19) mmHg, p=0.36) and DBP (89 (19) vs. 86 (10) mmHg, p=0.56), or 24-hour SBP (148 (26) vs. 145 (16) mmHg, p=0.12) and DBP (81 (12) vs. 81 (10) mmHg, p=0.92). The values obtained for cardiac BRS by the different techniques are reported in Table 4.3. These largely confirm the findings of the acute stroke group as a whole, with a tendency towards lower cardiac BRS in the patient group. Values for cardiac BRS are significantly lower when calculated by PSA in the HF band and by the combined α index (Table 4.3).
FIGURE 4.3 Scattergram of values of baroreceptor sensitivity calculated by sequence analysis (combined depressor/pressor sequences) and power spectral analysis using the Fast Fourier Transform (combined $\alpha$ index) in acute stroke patients and control subjects.

BRS: baroreceptor sensitivity; FFT: Fast Fourier Transform
### TABLE 4.3

Values of cardiac baroreceptor sensitivity (ms/ mmHg) in CT diagnosed cerebral infarct patients and control subjects assessed by spectral analysis techniques.

*Values presented as median (range). FFT: Fast Fourier Transform; AR: autoregressive.*

<table>
<thead>
<tr>
<th></th>
<th>CONTROLS</th>
<th>STROKES</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spectral Analysis (FFT)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Frequency</td>
<td>5.08 (1.56-20.67)</td>
<td>4.51 (1.43-12.00)</td>
<td>NS</td>
</tr>
<tr>
<td>High Frequency</td>
<td>6.50 (2.31-21.49)</td>
<td>4.75 (2.00-14.62)</td>
<td>0.03</td>
</tr>
<tr>
<td>Combined $\alpha$ Index</td>
<td>5.46 (2.82-16.83)</td>
<td>4.75 (1.86-13.31)</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Spectral Analysis (AR)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Frequency</td>
<td>5.18 (1.54-22.86)</td>
<td>4.69 (1.53-12.93)</td>
<td>NS</td>
</tr>
<tr>
<td>High Frequency</td>
<td>7.03 (2.32-20.99)</td>
<td>5.00 (2.31-14.94)</td>
<td>0.04</td>
</tr>
<tr>
<td>Combined $\alpha$ Index</td>
<td>5.54 (3.03-16.67)</td>
<td>4.87 (1.92-13.94)</td>
<td>NS</td>
</tr>
</tbody>
</table>
4.5.2. Spectral Powers

The power of the LF and HF components of the decomposed PI variability and SBPV spectra can be compared. This allows an assessment of the integrity of the underlying autonomic control of the CVS. Given the often large variations in total power between subjects as well as between groups, this is best achieved by a comparison of normalised powers (by correcting for the VLF component of total variance), or by the LF/ HF ratio, as has previously been discussed (Chapter 4.4.4).

The absolute and normalised values of the LF and HF components of the PI variability and SBPV spectra derived by the FFT and AR methods of PSA, as well as the absolute and normalised LF/ HF ratios are quoted in Tables 4.4 (PI) and 4.5 (SBP). No significant differences were observed in the LF component of either PI or SBPV between acute stroke patients and control subjects (Tables 4.4 and 4.5). However, the HF component of absolute SBPV, assessed by the FFT and AR techniques, was significantly higher in strokes compared to controls (Table 4.5). This resulted in a significantly lower LF/ HF ratio (Table 4.5). In addition, the normalised PSA power of the HF component of SBPV was significantly greater in acute stroke patients, with a similar significant reduction in the normalised LF/ HF ratio (Table 4.5). The power spectra for PI (Figure 4.4) and SBPV (Figure 4.5) are shown.

Finally, the LF and HF components of PI and SBPV were compared in the 18 right and 17 left hemisphere stroke patients, the 2 patients with signs of cerebellar/ brainstem stroke were excluded. Right hemisphere stroke patients showed a significant reduction in the normalised HF component of PI variability, with an associated increase in the LF/ HF ratio when assessed by the FFT method (Table 4.6).
<table>
<thead>
<tr>
<th></th>
<th>FAST FOURIER</th>
<th>AUTOREGRESSIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CONTROLS</td>
<td>STROKES</td>
</tr>
<tr>
<td>Total Variance (ms²)</td>
<td>889 (183-4904)</td>
<td>1140 (183-3467)</td>
</tr>
<tr>
<td>VLF (ms²)</td>
<td>261 (32-1238)</td>
<td>236 (17-1034)</td>
</tr>
<tr>
<td>LF (ms²)</td>
<td>190 (25-1942)</td>
<td>241 (17-1260)</td>
</tr>
<tr>
<td>HF (ms²)</td>
<td>83 (8-1064)</td>
<td>79 (9-985)</td>
</tr>
<tr>
<td>LF/ HF Ratio (ms²)</td>
<td>2.44 (0.36-15.75)</td>
<td>1.90 (0.32-11.40)</td>
</tr>
<tr>
<td>LF (nu)</td>
<td>32 (11-60)</td>
<td>32 (8-60)</td>
</tr>
<tr>
<td>HF (nu)</td>
<td>13 (3-46)</td>
<td>13 (4-46)</td>
</tr>
<tr>
<td>LF/ HR Ratio (nu)</td>
<td>2.44 (0.36-15.75)</td>
<td>1.94 (0.31-10.40)</td>
</tr>
</tbody>
</table>

**TABLE 4.4** Comparison of pulse interval variability in acute stroke patients compared to control subjects. Values presented as median (range). *nu*: normalised units; *VLF*: very low frequency (0.02 to 0.06 Hz); *LF*: low frequency (0.05 to 0.15 Hz); *HF*: high frequency (0.20 to 0.35 Hz).
<table>
<thead>
<tr>
<th></th>
<th>FAST FOURIER</th>
<th>AUTOREGRESSIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CONTROLS</td>
<td>STROKES</td>
</tr>
<tr>
<td>Total Variance (mmHg^2)</td>
<td>46 (12-228)</td>
<td>51 (17-188)</td>
</tr>
<tr>
<td>VLF (mmHg^2)</td>
<td>16 (2-102)</td>
<td>16 (3-65)</td>
</tr>
<tr>
<td>LF (mmHg^2)</td>
<td>9 (2-90)</td>
<td>13 (3-78)</td>
</tr>
<tr>
<td>HF (mmHg^2)</td>
<td>1.9 (0.3-7.0)</td>
<td>3.5 (1.1-24.1)***</td>
</tr>
<tr>
<td>LF/ HF Ratio (mmHg^2)</td>
<td>5.0 (0.4-43.3)</td>
<td>3.2 (0.4-16.5)*</td>
</tr>
<tr>
<td>LF (nu)</td>
<td>33 (14-71)</td>
<td>38 (11-72)</td>
</tr>
<tr>
<td>HF (nu)</td>
<td>6.7 (0.7-56.0)</td>
<td>11.0 (3.0-35.0)***</td>
</tr>
<tr>
<td>LF/ HR Ratio (nu)</td>
<td>5.0 (0.4-43.3)</td>
<td>3.3 (0.3-15.5)*</td>
</tr>
</tbody>
</table>

TABLE 4.5  Comparison of systolic blood pressure variability in acute stroke patients compared to control subjects. Values presented as median (range). ***p<0.001, **p<0.01, *p<0.05 acute stroke compared to control groups. nu: normalised units; VLF: very low frequency (0.02 to 0.06 Hz.); LF: low frequency (0.05 to 0.15 Hz.); HF: high frequency (0.20 to 0.35 Hz.).
FIGURE 4.4 Power spectrum using the Fast Fourier Transform for pulse interval variability (ms$^2$) over frequency range 0 to 0.5 Hz. in acute stroke patients and control subjects.
FIGURE 4.5 Power spectrum using the Fast Fourier Transform for systolic blood pressure variability (mmHg²) over frequency range 0 to 0.5 Hz. in acute stroke patients and control subjects. Inset shows the differences between acute stroke patients and control subjects in the power spectrum for systolic blood pressure variability in the high frequency range (0.20 to 0.35 Hz.)
TABLE 4.6  Values of baroreceptor sensitivity (ms/ mmHg) and normalised spectral powers of pulse interval and systolic blood pressure variability derived by the Fast Fourier method in right compared to left hemisphere stroke patients. 
*Values presented as median (range). BRS: baroreceptor sensitivity; PI: pulse interval; SBP: systolic blood pressure; LF: low frequency; HF: high frequency; nu: normalised units.*
4.5.3. Subacute Stroke Patients
Thirty-five stroke patients were further assessed at 10 to 14 days post ictus, 2 patients died. Between the acute and subacute periods of the study, there were significant reductions in casual SBP (21 mmHg, 95% CI: 10 to 32 mmHg, p<0.001) and DBP (8 mmHg, 95% CI: 0 to 16 mmHg, p=0.05). Reductions were also observed in 24-hour SBP (8 mmHg, 95% CI: 2 to 15 mmHg, p<0.02) and DBP (2 mmHg, 95% CI: -2 to 6 mmHg, p=0.4). PI was not significantly reduced (14 ms, 95% CI: -38 to 65 ms, p=0.6).

Cardiac BRS, assessed by SA and PSA (using the FFT) techniques, remained significantly impaired in stroke patients in the subacute period compared to control subjects (Table 4.7). However, there were no significant changes in values for cardiac BRS between the acute and subacute periods (Table 4.7). Coherence was again highest in the LF and HF bands in the subacute study, with mean values of 0.47 and 0.54, respectively.

No significant differences in the PI power spectrum were observed between subacute stroke patients and control subjects (Table 4.8, Figure 4.6). However, as in acute stroke, patients studied during the subacute period had increased HF power in the SBP spectrum compared to control subjects (Table 4.8, Figure 4.7). This was associated with a significant reduction in the LF/ HF ratio (Table 4.8). No significant changes were observed in the PSA powers of PI or SBPV between the acute and subacute stroke periods (Table 4.8).
<table>
<thead>
<tr>
<th></th>
<th>CONTROLS</th>
<th>ACUTE STROKES</th>
<th>SUBACUTE STROKES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sequence Analysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressor BRS</td>
<td>6.92 (2.53-15.53)</td>
<td>5.03 (1.06-17.99) **</td>
<td>4.56 (0.96-21.26) **</td>
</tr>
<tr>
<td>Pressor BRS</td>
<td>6.52 (2.39-16.60)</td>
<td>5.35 (1.53-19.11) *</td>
<td>3.83 (1.03-13.60) ***</td>
</tr>
<tr>
<td>Combined pressor/ depressor BRS</td>
<td>6.49 (2.47-14.44)</td>
<td>5.05 (1.98-16.74) *</td>
<td>4.29 (1.00-13.11) **</td>
</tr>
<tr>
<td><strong>Spectral Analysis (FFT)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Frequency</td>
<td>5.08 (1.56-20.67)</td>
<td>3.93 (1.43-12.00)</td>
<td>4.14 (0.31-19.14)</td>
</tr>
<tr>
<td>High Frequency</td>
<td>6.50 (2.31-21.49)</td>
<td>4.89 (1.83-14.62) **</td>
<td>4.19 (0.73-15.61) ***</td>
</tr>
<tr>
<td>Combined α index</td>
<td>5.46 (2.82-16.83)</td>
<td>4.65 (1.86-13.31) *</td>
<td>4.09 (0.52-17.38) **</td>
</tr>
</tbody>
</table>

TABLE 4.7  Values of baroreceptor sensitivity (ms/ mmHg) in acute and subacute stroke patients and control subjects assessed by sequence analysis and spectral analysis (using the Fast Fourier Transform).

*Data are presented as median (range).***p<0.001, **p<0.01, *p<0.05 stroke patients versus control subjects.

BRS: baroreceptor sensitivity; FFT: Fast Fourier Transform.
<table>
<thead>
<tr>
<th></th>
<th>CONTROLS</th>
<th>ACUTE STROKES</th>
<th>SUBACUTE STROKES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pulse Interval Spectrum</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Frequency</td>
<td>32 (11-60)</td>
<td>32 (8-60)</td>
<td>28 (5-69)</td>
</tr>
<tr>
<td>High Frequency</td>
<td>13 (3-46)</td>
<td>13 (4-46)</td>
<td>14 (4-54)</td>
</tr>
<tr>
<td>Low-to-high Frequency Ratio</td>
<td>2.4 (0.4-15.8)</td>
<td>1.9 (0.3-10.4)</td>
<td>1.5 (0.4-15.1)</td>
</tr>
<tr>
<td><strong>SBP Spectrum</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Frequency</td>
<td>33 (14-71)</td>
<td>38 (11-72)</td>
<td>28 (7-62)</td>
</tr>
<tr>
<td>High Frequency</td>
<td>7 (1-56)</td>
<td>11 (3-35) **</td>
<td>13 (3-40) **</td>
</tr>
<tr>
<td>Low-to-high Frequency Ratio</td>
<td>5.0 (0.4-43.3)</td>
<td>3.3 (0.3-15.5) *</td>
<td>2.9 (0.2-14.0) **</td>
</tr>
</tbody>
</table>

**TABLE 4.8** Values of normalised low (0.05 to 0.15 Hertz) and high frequency (0.20 to 0.35 Hertz) powers and the normalised low-to-high frequency ratios of the pulse interval and systolic blood pressure spectra using the Fast Fourier Transform method in acute and subacute stroke patients and control subjects. Data are presented as median (range). **p<0.001, *p<0.05 stroke patients compared to control subjects. SBP: systolic blood pressure.
FIGURE 4.6 Power spectrum using the Fast Fourier Transform for pulse interval variability (ms²) over frequency range 0 to 0.5 Hz. in subacute stroke patients and control subjects.
FIGURE 4.7 Power spectrum using the Fast Fourier Transform for systolic blood pressure variability (mmHg²) over frequency range 0 to 0.5 Hz. in subacute stroke patients and control subjects. Inset shows the differences between subacute stroke patients and control subjects in the power spectrum for systolic blood pressure variability in the high frequency range (0.20 to 0.35 Hz.)
4.6. Discussion

Cardiac BRS has been assessed using novel non-invasive techniques in stroke patients studied within 72 hours and again at 10 to 14 days of ictus and age-, sex-, casual and 24-hour BP-matched control subjects. The present study has demonstrated a significant reduction in cardiac BRS following acute stroke by SA and PSA techniques, which persists in the subacute period. The findings of reduced cardiac BRS using PSA techniques are confirmed when only patients with CT-diagnosed cerebral infarction are included in the analysis. The integrity of SNS and PNS autonomic control of the cardiac BR reflex was also assessed from the powers of the LF and HF components of the decomposed PI and SBPV spectra. The HF component of SBPV was significantly increased in the acute and subacute stroke patients, probably reflecting the mechanical effects of respiration though formal measurements of respiratory rate or tidal volume were not made in the present study.

4.6.1. Cardiac Baroreceptor Sensitivity Following Acute Stroke

The traditional pharmacological vasopressor (using angiotensin or phenylephrine) and vasodepressor (using nitroglycerin or sodium nitroprusside) stimuli are usually considered the 'gold standard' techniques of cardiac BRS estimation. These techniques and potential problems associated with their use have already been addressed (Chapter 1.4.1). The recent availability of reliable non-invasive methods of beat-to-beat BP measurement, such as the Finapres device [Imholz et al., 1988; Parati et al, 1989; Imholz et al, 1990; Rongen et al, 1995], has lead to the development of alternative analyses for the assessment of cardiac BRS, including SA and PSA techniques (Chapters 1.4.4 and 1.4.5, respectively). These techniques obviate the need for drug-induced BP disturbances and were utilised in the present study.

Using these alternative non-invasive methods of cardiac BRS estimation, the present study has demonstrated a significant reduction in cardiac BRS in patients studied within 72 hours of acute stroke which persists in the subacute period (10 to 14 days of ictus in the present study). To date, observations of the effects of stroke on the BR reflex arc have largely been limited to patients with chronic stroke using invasive methodology [Appenzeller et al, 1964; Gross, 1970a].
Appenzeller and Descarries assessed beat-to-beat HR and intra-arterial BP responses to the Valsalva manoeuvre in 123 patients an undefined period after stroke (18 were said to be studied in the acute phase as defined by no neurological improvement) compared to 39 control subjects. There was markedly reduced BR function in all ‘acute’ and 32 chronic patients, though some were also known to be diabetic [Appenzeller et al, 1964]. Gross also studied intra-arterial circulatory responses to the Valsalva manoeuvre in 62 subjects with chronic cerebrovascular disease compared to 18 controls. Cardiac BRS was significantly impaired in strokes, but this was predominantly a reflection of their greater age. In addition, no significant differences were reported in cardiac BRS in those with clinical evidence of carotid compared to vertebrobasilar ischaemia [Gross, 1970a].

Using the technique of SA, cardiac BRS was indeed observed to be significantly lower in acute and subacute stroke patients, whether assessed from depressor, pressor, or combined pressor/ depressor sequences. There was no significant difference in the number of sequences, or the proportion of the recording comprising baroreflex sequences between strokes and controls. There was a tendency for a higher number of beats per sequence in control subjects, though this was only significant for pressor sequences. However, this would tend to reduce the value for cardiac BRS as James and colleagues have demonstrated a tendency towards lower regression coefficients with longer sequences [James et al, 1995].

Cardiac BRS was also assessed by PSA techniques, using the FFT and AR algorithms (Chapter 1.4.5). The gain of the neural feedback from BP to PI, assessed from the simultaneous variabilities of BP and PI, was lower in acute stroke patients compared to control subjects above 0.05 Hz (Figure 4.1). In keeping with other groups, the mean coherence was highest in the low (0.05 to 0.15 Hz) and HF (0.20 to 0.35 Hz) bands (Figure 4.2) [Robbe et al, 1987; Pagani et al, 1988; Lucini et al, 1994], and approximated to the arbitrary threshold of 0.50 used by most investigators to assume a significant linear dependence in the cross-spectrum between BP and PI [de Boer et al, 1985; Baselli et al, 1986]. The phase difference between BP and PI changes in the LF band was negative with an approximately linear relationship, in accordance with other groups [Pagani et
al, 1986]. Thus BP changes led PI changes by approximately 1 beat in both acute stroke patients and control subjects (the phase corresponding to the LF band was about 20°). In the HF band, BP and PI changes occurred in phase, as reported by others [Pagani et al, 1986].

Cardiac BRS was therefore assessed by the squared root of the ratio of the power spectra of PI to BP (the α index) in the LF and HF bands [Pagani et al, 1988], where mean coherences were highest. The α index in the HF band and the combined α index was significantly lower for both the FFT and AR methods in acute stroke patients compared to control subjects. These results are in keeping with the results of SA, the combined α index having good agreement with the combined pressor/ depressor value (r=0.93, p<0.001, Figure 4.3). Panerai and colleagues in a study of 17 elderly normotensive and hypertensive subjects also reported the closest agreement between these 2 measures of cardiac BRS (r=0.86) [Panerai et al, 1995]. They have subsequently confirmed this high level of agreement between SA and PSA-derived measures of cardiac BRS in a larger study, reporting a close linear relationship (β=0.97, 95% CI 0.80 to 1.14), with no systematic bias (mean difference=0.42 + 0.28 ms/ mmHg, p=0.15) [James et al, 1996b]. The identification of an intrinsic relationship between SA and PSA is reassuring, as it allows the use of SA in conditions where non-stationarity would preclude the use of PSA techniques.

4.6.2. Implications of Impaired Cardiac Baroreceptor Sensitivity

Impaired cardiac BRS may not be a benign phenomenon. Impaired cardiac BRS is now well-recognised following acute myocardial infarction [Schwartz et al, 1988; Osculati et al, 1990; Grassi et al, 1992; Odemuyiwa et al, 1993]. In particular, Odenuyiwa and colleagues observed that early markedly depressed cardiac BRS (< 3 ms/ mmHg) predicted markedly depressed cardiac BRS at three months [Odenuyiwa et al, 1993]. This may explain the observation that impaired cardiac BRS post acute myocardial infarction identifies a group of patients at high risk of serious ventricular arrhythmias and sudden death not only acutely but for several months post myocardial infarction [La Rovere et al, 1988; Farrell et al, 1992]. Indeed the importance of impaired cardiac BRS in the risk assessment of
patients following acute myocardial infarction is currently being assessed in an ongoing multicentre trial, Autonomic Tone and Reflexes After Myocardial Infarction [Maggioni et al, 1994]. The numbers in the present study are too small to assess the prognostic significance of impaired cardiac BRS post stroke, but this is to be the subject of further study.


As previously stated, the powers of the LF and HF components of the decomposed BP and PI variability spectra can be compared. This allows an assessment of the integrity of the underlying autonomic control of the cardiovascular system.

In the present study, the total power of SBPV was increased in acute stroke patients compared to control subjects, though the difference was not statistically significant (Table 4.5). This concords with the findings reported in Chapter 3, namely of increased SBPV as measured by the SD or RMSSD of 15 minute readings taken during the daytime or of beat-to-beat recordings taken over a 1 hour period. The possible explanations for these findings can now be considered in more detail.

Increased BPV may be related to BR dysfunction. Cardiac BRS is inversely related to short-term BPV [Mancia et al, 1980; Mancia et al, 1986; Floras et al, 1988], i.e. the greater the BPV, the less sensitive the BR. The author has clearly demonstrated an impairment of BR function in acute stroke patients compared to age-, sex-, and casual and 24-hour BP-matched control subjects by SA and PSA techniques. BR-derived responses to BPV are mediated by changes in PI or vasomotor tone. However, no significant difference in PI variability in stroke patients compared to control subjects was observed, as reported in Chapter 3. Also, no significant differences were observed in the power spectra of PI variability between the 2 groups, as will be discussed later. Issues related to the control of vasomotor tone may therefore be implicated to account for these differences.
Factors involved in vasomotor tone and systemic vascular resistance including the renin-angiotensin system, endothelial factors, local influences related to thermoregulation, and others are understood to influence the very LF (VLF) component (0.02 to 0.06 Hz) of the power spectrum of BPV [Akselrod et al, 1985]. However, no significant difference was observed between VLF power in strokes and controls, though the influence of many of the factors on VLF power is imprecise and speculative [Parati et al, 1995a]. Given these limitations, it is proposed to study vasomotor responses to hypotension induced by LBNP and orthostatic change in more detail in the following sections (Chapters 5 and 6, respectively).

In addition to impaired cardiac BRS, increased short-term BPV following acute stroke may be related to increased SNS tone. Certainly, elevated plasma and urinary catecholamine and corticosteroid levels reflecting increased SNS nervous system and adrenocortical activity have been reported during the acute stages of cerebrovascular disease, as previously reviewed in Chapter 1.3.1. PI was significantly lower in acute stroke patients compared to control subjects in the present study consistent with SNS hyperactivity. LF power is a marker of SNS activity, as has been previously reviewed (Chapter 1.4.5). However, no significant differences were observed in absolute or normalised LF power between the 2 groups, which one might have expected.

Factors influencing HF power have also been discussed (Chapter 1.4.5), and in the present study significant differences in SBPV were observed in HF powers (0.20 to 0.35 Hz). Subjects were asked to breathe at a rate of more than 15 breaths/minute (0.25 Hz), and an appropriate peak is seen in the HF band in control subjects (Figure 4.5, inset). Two comments can be made regarding the comparative HF band in acute stroke patients (Figure 4.5, inset). Firstly, HF power is significantly increased (Table 4.5). Secondly, there appears to be two HF peaks, below and above 0.30 Hz (Figure 4.5, inset). This could be explained by greater variability in respiration in stroke patients. However, Cheyne-Stokes type respiration would produce an increase in VLF power, and unconscious or drowsy patients were deliberately excluded from the study. Alternatively, this may reflect 2 groups of stroke patients: one group who maintain the required rate with a peak at
approximately the same peak as the control subjects, and one group with greater respiratory variability and possibly a poorer prognosis.

The increased HF power is associated with relative PNS predominance of control of BPV as reflected by an increased LF/ HF ratio. Certainly, there is some evidence that altered vagal tone may be implicated in myocardial damage, though this is unsettled [Talman, 1985]. Manning and colleagues demonstrated that electrical stimulation of the vagal nerve caused myocardial damage that could be prevented by pre-treatment with atropine [Manning et al, 1937]. However, more commonly, one might have expected there to be SNS predominance following acute stroke, given the indirect evidence of significantly reduced PI in the present study and the well recognised increases in plasma and urinary catecholamine levels [Meyer et al, 1973a; Feibel et al, 1981; Myers et al, 1981; Olsson, 1990]. However, as previously discussed, LF power may not invariably be a consistent marker of SNS nervous system activity [Parati et al, 1995a]. Also, the PSA of SBPV is most suited to demonstrate increased SNS drive under conditions of mild levels of physical activity [Pagani et al, 1988; Furlan et al, 1990]. However, the subjects in the present study were studied at rest. Therefore, the differences in HF power between the 2 groups may reflect the mechanical effects of respiration rather than increased PNS activity, and the possible explanations for respiratory changes in patients following stroke have been discussed. Certainly, in a study of 40 patients assessed within a median of 7 days (range 2 to 10 days) of cerebral infarction, Korpelainen and colleagues reported evidence of PNS hypofunction, albeit by impaired HR responses to normal respiration, deep breathing, the Valsalva manoeuvre, and tilting [Korpelainen et al, 1994]. However, to the author's knowledge, the present study is the first to use the technique of PSA in the study of BPV following acute stroke, though others have assessed PI variability [Barron et al, 1994].

4.6.4. Sympathovagal Balance Following Acute Stroke: Pulse Interval Variability

The interpretation of the power spectrum of PI variability is more clear-cut than that for BPV, and has previously been discussed {Chapter 1.4.5}, and the changes in PI variability following acute stroke will now be considered.
The present study found no significant difference in the power spectra for PI variability during supine rest between acute stroke patients compared to control subjects (Figure 4.4). In addition, there were no significant differences between normalised powers (to take account of any differences in total variance) or the LF/HF ratio (Table 4.4). Barron and colleagues have recently reported the results of the PSA of PI variability in 40 patients studied 4 to 11 days after ictus compared to age- and sex-matched control subjects [Barron et al, 1994]. In contrast to the present study, they found a significant reduction in respiratory-related activity (frequency range not stated) in stroke patients. However, the results are expressed in absolute units despite a significant reduction in total power in the stroke patients. Also, it is not stated if there were any BP differences between the 2 groups. This is relevant with the reported reduction in HF power of PI variability in hypertensive subjects studied at rest [Guzzetti et al, 1988], given that one would expect the stroke patients to have increased BP levels in view of the well-recognised pressor responses post-stroke [de Faire et al, 1978; Wallace et al 1981; Britton et al, 1986; P Jansen et al, 1987; Harper et al, 1991]. More importantly, the respiratory pattern of both groups is not clearly stated, despite the differing effects of spontaneous respiration and respiration controlled at different rates on the HF peak [Sanderson et al, 1996]. The clear HF peak at 0.23 Hz in the example control subject suggests a rate of 14 breaths/minute. It is stated that all stroke patients had a clinically normal respiratory pattern and a rate of 19 breaths per minute, though the presence of numerous small peaks between 0.15 and 0.45 Hz (9 to 27 breaths/minute) suggests considerable variability.

Barron and colleagues also reported further differences in the PI variability power spectra between the 20 right and 20 left hemisphere strokes [Barron et al, 1994]. Respiratory-related activity was further reduced in right compared to left hemisphere, though once again normalised units were not used and total power was also significantly lower in the right hemisphere group. Naver and colleagues also assessed PI changes, expressed by the ratio of maximum to minimum PI during a 1 minute cycle of 6 breaths/minute, and found evidence of selective PNS dysfunction in right hemisphere stroke [Naver et al, 1996]. The present study identified a significant reduction in normalised HF power of PI in the 18 right hemisphere compared to the 17 left hemisphere patients. This resulted in a
change in the sympathovagal balance, as evidenced by a significant increase in the normalised LF/HF ratio in right hemisphere strokes, favouring increased SNS activity. Such an increase in SNS tone may be important in explaining the increased risk of abnormalities of HR control after stroke [Natelson, 1985; Talman, 1985]. Certainly, right cortical influences appear to dominate the sinoatrial node [Rosen et al., 1982; Lane et al., 1988; Zamrini et al., 1990; Lane et al., 1991]. Lane and colleagues observed a significant increase in supraventricular arrhythmias following right hemisphere stroke, and suggested that this may be related to an alteration in PNS/SNS tone [Lane et al., 1992], a hypothesis supported by the findings of the present study. The number of patients in each group is too small to allow meaningful analysis according to localisation within the hemisphere. However, this may warrant further investigation to establish if infarct localisation within the right hemisphere is relevant, if this is of prognostic significance, and therefore if the prophylactic treatment of a subgroup of patients with antiarrhythmic agents is justified.

4.6.5. Summary

In summary, the present study has confirmed the increase in SBPV following acute stroke reported in the previous chapter (Chapter 3). This was not associated with an alteration in HRV, which you might expect with an isolated impairment of cardiac BRS. This suggests an abnormality of control of vasomotor tone, as well as cardiac BRS impairment. Certainly, impaired cardiac BRS was found in the present study using novel non-invasive techniques as an alternative to traditional pharmacological vasopressor methods. Cardiac BRS, as assessed by the combined pressor/depessor sequences in time domain analysis and the combined \( \alpha \) index derived by the FFT and AR methods of frequency domain analysis which are well correlated with values obtained for cardiac BRS obtained by the phenylephrine method, was significantly reduced in acute stroke patients compared to age-, sex-, and casual and 24-hour BP-matched control subjects. The prognostic significance of this finding needs to be further explored.

Potential changes in vasomotor responses may also be responsible, and these are to be explored in the following chapters. Also, increased BPV appears to be due partly to an increased HF power, possibly reflecting the mechanical effects of
respiration on BP. In particular, there appeared to be 2 peaks in the HF band of BPV, one equivalent to that seen in control subjects. This may suggest a group of stroke patients with abnormalities of respiratory centre control, associated with increased BPV, and a poorer prognosis, though this hypothesis requires further exploration.

Finally, in keeping with one previous study, right hemisphere stroke patients exhibited evidence of reduced vagally-mediated PI variability with an associated change in the sympathovagal balance in favour of SNS predominance. This may increase the risk of arrhythmogenesis and its associated prognostic implications, which requires further study.

4.7. Conclusions
1. Cardiac BRS was significantly impaired in acute stroke patients compared to age-, sex-, and casual and 24-hour BP-matched control subjects, as assessed by combined pressor/ depressor sequences (time domain) and the combined α index (frequency domain using FFT and AR algorithms).

2. The degree of linear coupling (or coherence) between SBP and PI was highest in the low (0.05 to 0.15 Hz) and high (0.20 to 0.35 Hz) frequency bands. In the HF band, SBP and PI changes occurred in phase, though SBP changes led those in PI in the LF band.

3. In control subjects, cardiac BRS was significantly correlated with age, and casual and 24-hour SBP. However, in acute stroke patients, cardiac BRS was impaired regardless of underlying SBP level, though a negative correlation with age was still observed.

4. Impaired cardiac BRS, as assessed by SA and PSA (using FFT), persisted in the subacute stroke period, when patients were restudied at 10 to 14 days of ictus.
5. The power spectrum of SBPV at HF was significantly greater following acute stroke, reflecting the mechanical effects of respiration. It is hypothesised that some stroke patients may have greater variability in respiration compared to control subjects, and this could be used to identify a group of patients with poorer prognosis.

6. PI variability was not significantly different in the stroke group as a whole compared to control subjects. However, right hemisphere stroke patients had a significant reduction in HF power compared to left hemisphere stroke patients, resulting in a significant change in the LF/HF ratio. This change in sympathovagal balance in favour of a relative increase in SNS tone may favour the development of myocardial damage and arrhythmias.
CHAPTER FIVE

ASSESSMENT OF CARDIOPULMONARY AND ARTERIAL BARORECEPTOR FUNCTION USING LOWER BODY NEGATIVE PRESSURE TECHNIQUES FOLLOWING ACUTE AND SUBACUTE STROKE
5.1. Summary
In Chapter 3, an increase in short-term SBPV following acute stroke was reported. This may in part be related to impaired cardiac BRS, as has been demonstrated, but could also reflect abnormalities in BR-mediated control of vasomotor tone. LBNP can be used to assess the integrity of 'low pressure' cardiopulmonary (CP) and 'high pressure' arterial BR derived responses, by inducing cardiovascular changes comparable to orthostasis. The present study therefore assessed the cardiovascular responses to non-hypotensive and hypotensive LBNP in 19 stroke patients during the acute and subacute periods compared to control subjects matched with respect to age and sex.

At a LBNP of -10 mmHg, a significant increase in forearm vascular resistance (FVR) was observed in control subjects, but not acute stroke patients, BP being unchanged in either group. LBNP at -40 mmHg reduced SBP in acute stroke patients and control subjects, and was associated with a significant increase in HR in both groups, though cardiac BRS (assessed from the ratio of HR increase to MAP fall during LBNP) was significantly impaired in acute stroke patients. A significant increase in FVR was only observed in control subjects.

This study has identified abnormal vasomotor responses to LBNP following acute stroke, which may partly explain the increased short-term BPV previously reported. Increased BPV may also be related to impaired cardiac BRS, which was again demonstrated using different techniques than those in the previous chapter. Abnormalities of autonomic control of the CVS may have implications for management of BP changes following acute stroke, as well as for the day-to-day management of stroke patients.

5.2. Background
The author has previously described an increase in both short- and medium-term BPV following acute stroke (Chapter 3). Arterial BRS is important in short-term BP regulation, and impairment of cardiac BRS following acute stroke (using the techniques of SA and PSA) has already been described (Chapter 4). However, reflex control of the circulation also depends on the CP receptors. Reductions in
Lower body negative pressure

CVP, right atrial and right ventricular pressures are detected by mechanoreceptors sited in the atria and ventricles, as well as the lungs - the low pressure CP receptors. Unencapsulated nerve endings subserved by myelinated vagal afferent nerves and nerve nets subserved by unmyelinated vagal and spinal cord afferent nerves tonically discharge to specialized nuclei within the brainstem, including the nucleus tractus solitarius. Reduced CVP and right heart pressures results in decreased afferent fibre activity. Increased efferent discharge via the SNS outflow tract produces constriction of splanchnic, renal, and muscle resistance vessels [Shepherd et al, 1988]. These receptors are also of primary importance in regulating renin release from the kidney [Mancia et al, 1976]. Therefore, increased BPV may also be related to alterations in vasomotor tone mediated by centrally induced changes in SNS activity.

The CP receptors can be tested by activation (using passive leg raising) or deactivation (using LBNP). LBNP typically involves the application of reduced atmospheric pressure to supine resting subjects from the iliac crests caudally. This results in pooling of blood in the lower body, which is proportional to the degree of stress applied, and a consequent reduction in central blood volume which in turn initiates a compensatory series of complex neurocirculatory and humoral reflexes [Brown et al, 1966; Wolthuis et al, 1974].

At low levels of LBNP (-5 to -10 mmHg), falls in central venous pressure (CVP) are observed with no significant changes in BP or HR, though reduced FBF and consequent increased FVR are seen. This might suggest that the ‘low pressure’ CP receptors are selectively affected without significant unloading of the ‘high pressure’ arterial BR [Johnson et al, 1973; Wolthuis et al, 1974; Victor et al, 1987; Zanchetti et al, 1991]. However, animal studies suggest that the arterial BR may be involved in the initiation of reflex responses to low level LBNP. Cornish and colleagues have shown that these reflex responses were reduced following sinoaortic denervation in conscious monkeys [Cornish et al, 1988]. Also, Hakumaki and colleagues have demonstrated a reduction in aortic BR activity following gradual haemorrhage in intact anaesthetised dogs in the absence of BP changes [Hakumaki et al, 1985]. Human studies have reported HR increases to low level LBNP, consistent with changes in high pressure arterial BR activity.
Lower body negative pressure

[Walker et al, 1980; Baily et al, 1990]. Therefore, it is possible that decreases in venous return and stroke volume produced by low levels of LBNP may initiate high pressure arterial BR responses [Hainsworth, 1990; Eckberg et al, 1992], as well as stimulating the low pressure group.

At higher levels of LBNP (greater than -40 mmHg), reductions in SBP associated with increases in HR are seen, reflecting arterial BR stimulation [Wolthuis et al, 1974; Abboud et al, 1979; Mark et al, 1983]. Increased vascular resistance is again reported in muscle [Baily et al, 1990], splanchnic [Abboud et al, 1979], and coronary [Trimarco et al, 1988] vascular beds. This is associated with proportional increases in muscle SNS activity [Baily et al, 1990] and plasma noradrenaline levels [Grassi et al, 1985]. The ratio of HR to MAP changes during LBNP at -40 mmHg has been used as an index of cardiac BRS [Grassi et al, 1988; Smith et al, 1988; Zanchetti et al, 1991], and has identified similar differences in cardiac BRS between groups of endurance-trained and untrained subjects to phenylephrine infusion methods of cardiac BRS estimation [Smith et al, 1988].

Therefore, LBNP studies provide a method of assessing the overall integrity of the autonomic control of the CVS. This technique initiates physiological changes comparable to those observed during orthostasis or head-up tilt [Wolthuis et al, 1974], though forearm vasoconstrictor responses may be attenuated with LBNP compared to orthostatic stress in an elderly population [Taylor et al, 1992]. However, the experimental method of LBNP has distinct advantages over orthostatic techniques. The subject is supine throughout the procedure, which allows the monitoring of a number of physiological variables, including FVR by mercury-in-silastic strain gauge plethysmography, without concerns regarding the effects of gravity, movement artifact, or constant position with respect to the right atrium. To date, the majority of studies have been of young healthy male volunteers to assess physiological responses to central hypovolaemia as occurs with orthostasis or acute haemorrhage. Also, it allows the assessment of presyncopal changes that occur in patients with primary or secondary autonomic dysfunction, as well as in selected healthy individuals, such as endurance athletes, astronauts returning from spaceflight, and after prolonged bed rest.
[Levine et al, 1994]. The present study proposed to assess the cardiovascular reflex responses to LBNP following acute stroke.

5.3. Objectives

1. To assess the cardiovascular responses, including BP, HR, FBF and FVR changes, to LBNP at -10 and -40 mmHg in acute stroke patients compared to control subjects.

2. To assess cardiac BRS using the ratio of HR to MAP changes during sustained LBNP of -40 mmHg.

3. To observe the changes in cardiovascular responses to LBNP and cardiac BRS between the acute and subacute stroke periods.

5.4. Methods

5.4.1. Subjects

Nineteen consecutive acute stroke patients (10 male) of mean age 65.4 years (range 45 to 86 years) were recruited following admission to the medical wards of the Leicester Teaching Hospitals within 24 hours of first-time acute stroke (8 TACS or PACS, 11 LACS; 6 dominant hemisphere). If patients awoke with symptoms the stroke onset was deemed to have occurred at the time of retiring to bed for the purposes of this study. Diagnosis was confirmed by head CT scanning in 14 patients (all cerebral infarctions). Subjects were haemodynamically stable, did not require intravenous fluid administration, and were not biochemically dehydrated. The following patients were excluded: unconscious or impaired conscious level, atrial fibrillation, subsequent diagnosis of TIA, conditions associated with autonomic dysfunction, continuation of medication with effects on the cardiovascular or autonomic nervous systems.

Nineteen age- and sex-matched control subjects (10 male) of mean age 65.5 years (range 45 to 75 years) were also studied. These subjects were recruited from among respondents to a local newspaper advertisement. Control subjects
with known diagnoses of ischaemic heart disease, cerebrovascular disease, atrial fibrillation, diabetes mellitus, impaired renal function (creatinine >200 μmol/l) or other conditions associated with autonomic dysfunction were excluded. No subject received antihypertensive therapy or medication known to affect cardiovascular or autonomic responses.

5.4.2. Study Protocol
All studies were performed in the morning after an overnight fast, including abstaining from smoking, alcohol, and all caffeinated products. The investigations took place in a quiet room (ambient temperature 20 to 24°C) and the subjects were asked to micturate prior to the study commencing. Casual BP measurements were recorded as previously described (Chapter 2.4.2).

Subjects were then familiarised with the protocol, including the LBNP procedure. The LBNP device was a aluminium box in which the subject rested supine on a well-padded seat. The subject wore a Kayak skirt that was used to make an airtight seal between the subject and the box at the level of the iliac crest. Suction was produced by a commercial vacuum cleaner with a variable speed motor and an adjustable air-leak on the suction hosepipe, and box pressure (mmHg) was monitored continuously. Equipment for the beat-to-beat monitoring of BP and HR, as well as monitoring equipment for the assessment of FBF was then applied. (The details of this equipment are considered later in this Chapter).

Following a period of 15 minutes rest, the subject underwent 4 consecutive periods of 10 minutes study. Baseline recordings of HR, BP, FBF, and FVR were made over a 2 minute period. This was followed by 3 minutes of LBNP. Following release of the LBNP, there was a 5 minute rest period. This process was repeated on 4 occasions - on 2 occasions at -10 mmHg and on 2 further occasions at -40 mmHg.

Blood Pressure And Heart Rate Measurements
The subject was fitted with chest leads for continuous electrocardiogram recording (model CR7, Cardiac Recorders Limited, London, UK), and the appropriately
sized cuff of the 2300 Finapres non-invasive BP monitor (Ohmeda, Englewood, Colorado, USA), as previously described {Chapter 3.4.3}.

**Forearm Blood Flow Measurements**

FBF and FVR were measured with a mercury-in-silastic strain gauge plethysmograph (QMC Medical Physics, Nottingham, UK). This measures FBF by the venous occlusion method originally described by Whitney [Whitney, 1953]. The circumference of the forearm was assessed using a tape measure at a point 5 cm distal to the olecranon process. An appropriately sized mercury-in-silastic strain gauge, determined by the double circumference of the forearm plus 5 cm, was attached to a Wheatstone bridge, and looped around the forearm. This was then connected to a chart recorder (WR7400, Graphtec Corp., Japan), where the slope of the trace recorded was proportional to the volume change in the forearm over time. In addition, 2 cuffs were applied to the upper limb. One was placed around the upper arm, and used to occlude venous return by inflation to a subdiastolic pressure of 40 mmHg for 8 seconds at a rate of 4 cycles/minute. The other cuff was placed at the wrist, and used to simultaneously occlude arterial circulation to the hand by inflation to 40 mmHg above SBP. FBF was assessed in the non-hemiparetic arm of stroke patients, because of the potential for vasomotor changes in the hemiparetic arm, and in the dominant arm in control subjects.

5.4.3. **Data Analysis**

FBF was calculated according to the following equation:

\[
\text{FBF} = \frac{200 \cdot p \cdot S \cdot \tan \theta}{C \cdot a}
\]

where,

- C is the circumference of the forearm (in cms.),
- \(p/a\) is the ratio produced by the calibration of the strain gauge off the forearm on a wooden former where a stretch equivalent to a change in limb circumference of \(p\) produces a pen deflection of \(a\),
- S is the chart recorder speed (set to 120 mm/minute), and
θ is the slope of the chart recorder trace.

FBF is expressed as mls/ minute/ 100mls of forearm, and resting FVR was derived by dividing the MAP by the FBF. This well-established method is acceptable to subjects and correlates well with Doppler flowmetry [Lipsitz et al, 1991].

Cardiac BRS was estimated from the ratio of increase in HR to decrease in MAP during the 3 minutes of LBNP at -40 mmHg [Grassi et al, 1988; Smith et al, 1988; Zanchetti et al, 1991].

5.4.4. Statistical Methods
Data are presented as mean (SD). Baseline values of SBP, DBP, MAP and HR prior to LBNP were taken as the mean of the 1 minute of beat-to-beat ECG and NIBP recordings immediately prior to the application of LBNP. Baseline values of FBF were taken as the mean of the 4 cycles immediately prior to the application of LBNP. Mean values of these variables were calculated during the 3 minutes of LBNP at -10 and -40 mmHg, and the changes with LBNP expressed as the absolute difference between mean baseline and mean during LBNP values.

Statistical comparisons between paired and unpaired Normally distributed data were made by the Student's paired and unpaired t tests, respectively. Bonferonni's correction was applied for multiple comparisons where appropriate [Bland et al, 1995], and significance was taken at the 5% level.

5.5. Results
Stroke patients and control subjects were matched with respect to age and sex (Table 5.1). There was no significant difference between stroke patients and control subjects in Finapres BP measurements (Tables 5.2 and 5.3), though casual SBP and DBP values were higher in stroke patients compared to control subjects (Table 5.1).
5.5.1. Cardiovascular Responses To -10 mmHg Lower Body Pressure

No significant differences were seen prior to LBNP at -10 mmHg in SBP, DBP, MAP, HR, FBF, or FVR between control subjects and acute stroke patients (Table 5.2). There was no significant mean change in SBP, DBP, MAP in either control subjects or acute stroke patients during LBNP at -10 mmHg (Figure 5.1). However, there was a significant fall in FBF in both control subjects (0.48 mls/ min/ 100 mls forearm, 95% CI: 0.32 to 0.64 mls/ minute/ 100mls forearm, p<0.001) and acute stroke patients (0.64 mls/ minute/ 100 mls forearm, 95% CI: 0.04 to 1.24 mls/ min/ 100mls forearm, p<0.05), though this was associated with a significant increase in FVR in the control group only (controls: 9 mmHg mls$^{-1}$ minute$^{-1}$ 100mls forearm$^{-1}$, 95% CI: 1 to 17 mmHg mls$^{-1}$ minute$^{-1}$ 100mls forearm$^{-1}$, p<0.05; acute strokes: -2 mmHg mls$^{-1}$ minute$^{-1}$ 100mls forearm$^{-1}$, 95% CI: -28 to 23 mmHg mls$^{-1}$ minute$^{-1}$ 100mls forearm$^{-1}$, p=0.82) (Figure 5.1). There was no HR change in acute stroke patients (1 bpm, 95% CI: -3 to 4 bpm, p=0.63), though a significant increase was seen in the control group (2 bpm, 95% CI: 1 to 4 bpm, p<0.01) (Figure 5.1). Any differences in response between the control and acute stroke groups were not significantly different (Figure 5.1).

5.5.2. Cardiovascular Responses To -40 mmHg Lower Body Pressure

No significant differences were seen prior to LBNP at -40 mmHg in SBP, DBP, MAP, HR, FBF, or FVR between control subjects and acute stroke patients (Table 5.3). A significant reduction was observed in SBP in both groups to LBNP at -40 mmHg (controls: 8 mmHg, 95% CI: 3 to 14 mmHg, p<0.01; acute strokes: 9mmHg, 95% CI: 2 to 16 mmHg, p<0.01), though no significant changes were observed in DBP (controls: 0 mmHg, 95% CI: -2 to 2 mmHg, p=0.89; acute strokes: 0 mmHg, 95% CI: -3 to 3 mmHg, p=0.89) (Figure 5.1). FBF also fell significantly in both groups (controls: 0.70 mls/ minute/ 100mls forearm, 95% CI: 0.51 to 0.89 mls/ minute/ 100mls forearm, p<0.001; acute strokes: 0.44 mls/ minute/ 100mls forearm, 95% CI: 0.10 to 0.78 mls/ minute/ 100mls forearm, p<0.05) (Figure 5.1). This was associated with a significant rise in HR in both groups (controls: 7 bpm, 5 to 9 bpm, p<0.001; acute strokes: 5 bpm, 2 to 8 bpm, p<0.01)(Figure 5.1). FVR increased significantly from baseline in the control group only (controls: 23 mmHg mls$^{-1}$ minute$^{-1}$ 100mls forearm$^{-1}$, 95% CI: 14 to 33 mmHg mls$^{-1}$ minute$^{-1}$ 100mls forearm$^{-1}$, p<0.01; acute strokes: -10 mmHg mls$^{-1}$ minute$^{-1}$ 100mls forearm$^{-1}$, 95% CI: -29 to 21 mmHg mls$^{-1}$ minute$^{-1}$ 100mls forearm$^{-1}$, p=0.82) (Figure 5.1).
forearm$^{-1}$, $p<0.001$; acute strokes: 4 mmHg mls$^{-1}$ minute$^{-1}$ 100mls forearm$^{-1}$, 95% Cl: -8 to 16 mmHg mls$^{-1}$ minute$^{-1}$ 100mls forearm$^{-1}$, $p=0.53$) (Figure 5.1).

5.5.3. Subacute Stroke Patients

A significant reduction in casual SBP (13 mmHg, 95% Cl: 1 to 26 mmHg, $p<0.05$), but a non-significant reduction in casual DBP (7 mmHg, 95% Cl: -4 to 19 mmHg, $p=0.20$), was seen between the acute and subacute study periods. Falls were also observed in beat-to-beat SBP and DBP compared to the acute stroke period, though the differences were not significant, prior to LBNP at -10 mmHg (Table 5.2) and -40 mmHg (Table 5.3).

Similar changes in haemodynamic responses to -10 and -40 mmHg LBNP were also seen in the subacute and acute stroke periods (Figure 5.1). A significant rise in HR (acute strokes: 5 bpm, 95% Cl: 2 to 8 bpm, $p<0.01$; subacute strokes: 7 bpm, 95% Cl: 3 to 11 bpm, $p<0.01$), but only a non-significant rise in FVR was seen in the subacute stroke period (acute strokes: 4 mmHg mls$^{-1}$ minute$^{-1}$ 100mls forearm$^{-1}$, 95% Cl: -8 to 16 mmHg mls$^{-1}$ minute$^{-1}$ 100mls forearm$^{-1}$, $p=0.53$; subacute strokes: 22 mmHg mls$^{-1}$ minute$^{-1}$ 100mls forearm$^{-1}$, 95% Cl: -2 to 46 mmHg mls$^{-1}$ minute$^{-1}$ 100mls forearm$^{-1}$, $p=0.07$) despite the evidence of hypotensive stress induced by the LBNP (Figure 5.1).

5.5.4. Arterial Cardiac Baroreceptor Sensitivity

Cardiac BRS may be estimated from the ratio of increase in HR to fall in LBNP during the period of -40 mmHg LBNP, as previously described [Grassi et al, 1988; Smith et al, 1988; Zanchetti et al, 1991]. Values for cardiac BRS were significantly higher in control subjects compared to acute stroke patients matched with respect to age and sex (2.6 vs. 0.6 bpm/ mmHg, 95% CI of the difference: 0.6 to 3.4 bpm/ mmHg, $p<0.01$) (Figure 5.2). There was a non-significant increase in cardiac BRS in the subacute compared to the acute stroke period (0.6 bpm/ mmHg, 95% CI: -0.9 to 2.0 bpm/ mmHg, $p=0.41$) (Figure 5.2).
### TABLE 5.1 Baseline data in stroke patients and control subjects.

*Data presented as mean (standard deviation). SBP: systolic blood pressure; DBP: diastolic blood pressure; bpm: beats per minute.*

<table>
<thead>
<tr>
<th></th>
<th>CONTROLS (n=19)</th>
<th>STROKES (n=19)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65.5 (6.7)</td>
<td>65.4 (12.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (male: female)</td>
<td>10: 9</td>
<td>10: 9</td>
<td>NS</td>
</tr>
<tr>
<td>Casual SBP (mmHg)</td>
<td>131 (18)</td>
<td>156 (28)</td>
<td>0.003</td>
</tr>
<tr>
<td>Casual DBP (mmHg)</td>
<td>74 (12)</td>
<td>86 (18)</td>
<td>0.02</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>69 (8)</td>
<td>69 (13)</td>
<td>NS</td>
</tr>
</tbody>
</table>
### TABLE 5.2 Baseline cardiovascular data prior to the application of lower body negative pressure at -10 mmHg in acute and subacute stroke patients and control subjects.

Data presented as mean (standard deviation). None of the between group differences reached statistical significance. SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; HR: heart rate; bpm: beats per minute; FBF: forearm blood flow; FVR: forearm vascular resistance.

<table>
<thead>
<tr>
<th></th>
<th>CONTROLS</th>
<th>ACUTE STROKES</th>
<th>SUBACUTE STROKES</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mmHg)</td>
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<td>154 (40)</td>
<td>147 (28)</td>
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<td>DBP (mmHg)</td>
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<td>69 (24)</td>
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<td>MAP (mmHg)</td>
<td>98 (18)</td>
<td>105 (25)</td>
<td>95 (23)</td>
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<tr>
<td>HR (bpm)</td>
<td>61 (7)</td>
<td>65 (10)</td>
<td>69 (9)</td>
</tr>
<tr>
<td>FBF</td>
<td>2.40 (0.75)</td>
<td>2.98 (1.28)</td>
<td>2.87 (1.55)</td>
</tr>
<tr>
<td>FVR (units)</td>
<td>49 (29)</td>
<td>61 (81)</td>
<td>50 (40)</td>
</tr>
</tbody>
</table>
TABLE 5.3 Baseline cardiovascular data prior to the application of lower body negative pressure at -40 mmHg in acute and subacute stroke patients and control subjects.

Data presented as mean (standard deviation). None of the between group differences reached statistical significance. SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; HR: heart rate; bpm: beats per minute; FBF: forearm blood flow; FVR: forearm vascular resistance.
Lower body negative pressure

(A)

ΔSBP (mmHg)

-15 -10 -5 0 5

ΔMAP (mmHg)

-10 -5 0 5

ΔDBP (mmHg)

-10 -5 0 5 10

ΔHR (bpm)

0 5 10

CON Acute Subacute CVA CVA

*** **

CON Acute Subacute CVA CVA

**
FIGURE 5.1 Bar graphs showing the haemodynamic changes accompanying -10 (□) and -40 (■) mmHg lower body negative pressure for three minutes in control subjects (CON) and acute (acute CVA) and subacute (subacute CVA) stroke patients. Values expressed as mean (standard error of the mean) increases (+) or decreases (-) from baseline. ***p<0.001, **p<0.01, *p<0.05 for changes compared to baseline. SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; HR: heart rate; bpm: beats per minute; FBF: forearm blood flow; FVR: forearm vascular resistance.
FIGURE 5.2 Scatterplots showing ratios of increases in heart rate (HR) over decreases in mean arterial pressure (MAP) observed during the application of lower body negative pressure of -40 mmHg for three minutes. Individual data (symbols) and means (horizontal lines) from control subjects and acute and subacute stroke patients are shown.
5.6. Discussion

In the present study, in response to -10 mmHg LBNP, control subjects, matched with respect to age and sex, demonstrated a significant increase in FVR, though no such change was seen in acute stroke patients. No other significant differences in the haemodynamic responses assessed were observed between control subjects and acute stroke patients. At SBP hypotensive levels of LBNP, again a significant increase in FVR was observed in control subjects, which was significantly greater than in the acute stroke group, in whom no significant changes from baseline were seen. HR increased in both control subjects and acute stroke patients. However, when stroke patients were further studied during the subacute period, rises in FVR were observed with LBNP at both -10 and -40 mmHg though these were not significantly different from baseline. Cardiac BRS, as assessed by the ratio of HR increase to MAP fall during LBNP at -40 mmHg, was significantly reduced in acute stroke patients compared to control subjects.

5.6.1. Haemodynamic Changes To LBNP In Control Subjects

As previously discussed, LBNP causes cardiovascular changes comparable to those observed during active standing and passive tilt [Wolthuis et al, 1974], and allows an assessment of the integrity of these physiological responses to haemodynamic stress. At negative pressures of less than -20 mmHg, approximately 500 to 1000 mls of blood pools in the lower body, though the exact amount depends on the population studied, the techniques used and the degree of stress applied [Wolthuis et al, 1974]. This reduces central venous return with consequent reduction in CVP, and right ventricular filling and output. There are no associated BP changes [Johnson et al, 1973; Wolthuis et al, 1974; Victor et al, 1987; Grassi et al, 1988], as was also found in the present study for control subjects, and therefore potentially no stimulation of the high pressure arterial BR. However, it is possible that decreases in venous return and stroke volume produced by low levels of LBNP may stimulate the high pressure arterial BR [Hainsworth, 1990; Eckberg et al, 1992]. Certainly, a significant rise in HR was seen in the present study, in keeping with others [Walker et al, 1980; Baily et al, 1990], and consistent with stimulation of the efferent limb of the arterial baroreflex. However, some groups have reported no HR change to LBNP at -10 mmHg [Johnson et al, 1973; Victor et al, 1987; Grassi et al, 1988], or a non-significant
HR rise [Taylor et al, 1992]. Equally, HR changes may also reflect physiological overlay, though subjects were trained in the LBNP procedure as part of the study to avoid this effect.

Changes in FBF were assessed in the present study, and showed a significant reduction of 0.5 mls/minute/100 mls forearm in blood flow in control subjects in response to LBNP at -10 mmHg. This was in keeping with a fall of 0.5 mls/minute/100 mls forearm reported in a study group of healthy elderly subjects of similar age to the present study [Taylor et al, 1992]. Other studies have reported larger absolute falls in FBF of the order of 1 ml/minute/100 mls forearm, albeit in a younger population [Grassi et al, 1988; Taylor et al, 1992], or have quoted percentage falls of the order of 35% [Johnson et al, 1973]. Changes in FBF were associated with a significant rise in FVR of 9 mmHg mls⁻¹ minute⁻¹ 100 mls forearm⁻¹, calculated from the ratio of MAP to FBF, in the present study. Again, this is in keeping with previously reported changes in both young and elderly healthy subjects [Grassi et al, 1988; Taylor et al, 1992]. Such a rise in FVR without an increase in BP suggests that there is an initial BP reduction which is compensated for by an increase in FVR, a further argument favouring involvement of the high pressure arterial BR in the reflex responses to lower levels of LBNP [Eckberg et al, 1992].

At a LBNP of -40 mmHg, a significant hypotensive MAP response of 4 mmHg was seen in control subjects in the present study, in keeping with other studies [Grassi et al, 1988; Fortnay et al, 1992]. A significant fall in SBP of 8 mmHg was also seen, though Taylor and colleagues reported no significant change in SBP in the healthy elderly subjects studied [Taylor et al, 1992]. It is well established that the hypotensive responses produced by high levels of LBNP trigger reflex changes mediated by the arterial BR as well as CP receptors [Eckberg et al, 1992]. These reflex changes include:

Firstly, SNS-mediated adjustments in vasomotor activity to increase systemic vascular resistance. These effects are predominantly mediated via skeletal muscle and splanchnic, though other regional vascular beds are also involved. The present study only assessed changes in the forearm vascular bed, and
reported significant increases in FVR of the order of 23 mmHg ml\(^{-1}\) minute\(^{-1}\) 100 mls forearm\(^{-1}\) in control subjects in the present study, similar to those found in other studies [Grassi et al, 1988; Taylor et al, 1992].

Secondly, there is an increase in SNS outflow to the sinoatrial node, which is slower in onset than the systemic vascular resistance changes. An associated increase in HR of 7 beats/minute was seen in keeping with that previously reported in healthy elderly subjects [Fortnay et al, 1992; Taylor et al, 1992], though lower than that reported in younger subjects where absolute increases of 20 beats/minute [Grassi et al, 1988; Taylor et al, 1992] and percentage increases of 8 to 29% [see Wolthuis et al, 1974] have been reported.

5.6.2. Haemodynamic Responses To LBNP Following Stroke

Acute stroke patients showed no BP changes with LBNP at -10 mmHg, but similar hypotensive responses to control subjects were witnessed at -40 mmHg. There was no significant difference in HR response between groups. However, differences might have been expected given the impairment of cardiac BRS following acute stroke reported in this and the previous chapters. With LBNP at both -10 and -40 mmHg, no significant changes were seen in FVR in acute stroke patients. These differences in FVR to hypotensive stimuli will be further explored in Chapter 6.

It will be recalled that the author has previously reported an increase in short-term beat-to-beat SBPV in acute stroke patients compared to control subjects (Chapter 3). This may partly be explained by impaired cardiac BRS, though no significant differences were observed in HRV between acute stroke patients and control subjects. Therefore, it was hypothesized that alterations in the control of vasomotor tone, mediated possibly by centrally induced changes in SNS activity, may also be partly responsible (Chapter 4). Interestingly, in the present study, the changes in FVR were significantly different between control subjects and acute stroke patients during LBNP at -40 mmHg. There are a number of possible explanations:
Firstly, the absence of a significant increase in FVR to LBNP may reflect abnormalities of cardiovascular reflex control following acute stroke. Impairment of the low and high pressure reflex arcs may occur following stroke, the exact site(s) are not clear but are most likely to occur centrally. To the author's knowledge, changes in CP receptor reflexes have not been previously assessed following acute stroke. However, impaired baroreflex and circulatory reflexes to the Valsalva manoeuvre are well documented in patients with chronic cerebrovascular disease [Appenzeller et al, 1964; Gross, 1970a]. Furthermore, the author has reported significantly impaired cardiac BRS using the techniques of SA and PSA in patients studied within 72 hours of acute stroke compared to control subjects matched with respect to age, sex and BP (Chapter 4). In the present study, cardiac BRS was assessed from the ratio of HR increase to MAP decrease during 3 minutes of LBNP at -40 mmHg [Grassi et al, 1988; Smith et al, 1988; Zanchetti et al, 1991], and was also found to be significantly impaired compared to control subjects.

Secondly, though vascular responses were studied in the non-hemiparetic forearm in the present study, vasomotor changes have been previously described in hemiplegic limbs [Herbault et al, 1990; Wanklyn et al, 1994; Wanklyn et al, 1995], and some information can be derived from these studies. Wanklyn and colleagues reported a significant reduction in hand blood flow in a group of chronic stroke patients with symptomatic coldness of the hemiplegic limb [Wanklyn et al, 1994]. This may simply reflect muscle disuse, but may also be related to alterations in vasomotor tone and reactivity. A spinally mediated vasoconstriction response to deep inspiration or coughing is increased in tetraplegic patients, indicating the loss of a descending inhibitory influence [Cole et al, 1985]. Equally, a descending inhibitory response may be interrupted following stroke, thus resulting in abnormal persistent vasoconstriction secondary to a spinal reflex, with consequent reduced blood flow and absence of further vasoconstriction [Wanklyn et al, 1994].

Stroke patients were further studied during the subacute period following the resolution of any BP changes associated with acute stroke. Similar haemodynamic responses were observed in response to LBNP at -10 and -40
mmHg between acute and subacute periods. However, increases in FVR were found in the subacute period, though these remained not significantly different from baseline. This concords with previous studies, which have demonstrated impaired vasomotor responses in chronic stroke patients [Herbault et al, 1990; Wanklyn et al, 1994; Wanklyn et al, 1995]. Also, cardiac BRS was not significantly different from the acute period, in keeping with the findings reported earlier in this thesis using different techniques to estimate cardiac BRS (Chapter 4).

5.6.3. Summary
In summary, the present study has further demonstrated abnormalities of autonomic control of the CVS following acute stroke. Impaired cardiac BRS has been confirmed, as assessed by HR and MAP responses to LBNP at -40 mmHg, in keeping with the results presented in Chapter 4. As hypothesized in Chapter 3, abnormalities of vasomotor tone in response to stimulation of both low pressure CP receptors and high pressure arterial BR, assessed by LBNP at -10 and -40 mmHg respectively, have been identified. This may be related to stroke-related damage to the central connections of the cardiovascular reflex arcs, or to the loss of inhibitory control of spinal reflexes and consequent persistent vasoconstriction. This would prevent further vasomotor changes in response to CVP reductions or hypotension. Vasomotor changes in response to orthostatic and postprandial hypotensive stimuli following acute stroke are to be further studied in Chapter 6.

5.7. Conclusions
1. Significant increases were induced in FVR by non-hypotensive LBNP at -10 mmHg in control subjects, but not acute stroke patients.
2. Significant increases were also induced in FVR to hypotensive stimulation using LBNP at -40 mmHg in control subjects, but not acute stroke patients.
3. Hypotensive stimulation induced significant increases in HR in the control and acute stroke groups.
4. FVR showed a non-significant increase in response to both LBNP at -10 and -40 mmHg when stroke patients were further studied during the subacute period.

5. Cardiac BRS, as assessed by the ratio of HR to MAP changes during LBNP at -40 mmHg, was significantly impaired following acute stroke.

6. These findings suggest abnormal low (CP) and high pressure (arterial) baroreceptor control of cardiovascular responses following acute stroke. The exact mechanisms underlying these changes have still to be elucidated.
CHAPTER SIX

ORTHOSTATIC AND POSTPRANDIAL CARDIOVASCULAR RESPONSES FOLLOWING ACUTE STROKE
6.1. Summary

Rapid falls in BP may be particularly deleterious post-stroke, and any day-to-day measures that produce such changes may have an adverse prognostic effect. It is known that large decreases in BP to postprandial and orthostatic stresses occur in some fit and frail elderly subjects. In the previous work in this thesis, it has been shown that there are impairments of the cardiovascular responses to hypotensive LBNP following acute stroke (Chapter 5). Therefore, postprandial and orthostatic haemodynamic responses were examined in 9 acute stroke patients and 8 age-, sex- and BP-matched controls after an oral energy load. All subjects were studied on 2 occasions in a randomised, double-blind, cross-over trial following either oral glucose (1g/kg body weight) or equivalent isovolumic, isoosmotic xylose (0.83g/kg). Measurements of BP, PR and FBF were recorded for 30 minutes pre and 90 minutes postprandially. Haemodynamic responses to 60° tilt, along with plasma glucose and insulin changes were measured at baseline and at 30 minute intervals for 90 minutes postprandially.

Supine MAP and DBP fell significantly following glucose but not xylose in controls (p<0.03), but not stroke subjects, whereas supine PR increased in stroke subjects only (p<0.04). No significant changes in FVR were recorded in either control or stroke subjects. Following tilt, stroke subjects showed a fall in MAP compared to controls preprandially (p=0.03), and at 30 (p<0.005) and 90 (p<0.03) minutes postprandially, though no differences were observed between the xylose and glucose phases. Orthostatic tolerance was maintained in controls throughout both phases of the study. PR increased significantly to tilt at all time intervals in both groups, though there were no significant changes in FVR in either group.

Acute stroke subjects are not at significantly greater risk of BP falls in response to an oral energy load than age, sex and BP-matched controls. Unlike controls, the stroke group increased PR postprandially, which could result in a compensatory rise in cardiac output as a result of increased SNS activity in the post-stroke period. Orthostatic BP control is however impaired after acute stroke, although these changes are unaffected by meals.
6.2. Background

As well as the potential adverse effects of post-stroke BP changes on outcome and the controversies regarding the most appropriate management of these, BP changes due to normal physiological stresses of orthostasis and postprandially may also be important in other aspects of the clinical management of acute stroke patients. Falls in BP after meals have now been convincingly demonstrated in even fit normotensive as well as hypertensive elderly subjects [Westenend et al, 1985; Lipsitz et al, 1986a; R Jansen et al, 1987], and the institutionalised elderly [Lipsitz et al, 1983], though no such BP changes have been demonstrated in healthy young subjects using similar protocols [Westenend et al, 1985; R Jansen et al, 1987; Potter, 1996]. Postprandial hypotension probably results from age-related alterations in cardiovascular homeostatic mechanisms, including impairment of BRS [Gribbin et al, 1971] and a decrease in insulin-induced SNS activation [Minaker et al, 1982], though the exact mechanisms are unknown [Potter, 1996]. Carbohydrate type and content of the meal also appear to be important contributing factors [Potter et al, 1989; Heseltine et al, 1991], as do higher BP levels [R Jansen et al, 1987; Haigh et al, 1991; Sidery et al, 1993] and coexisting autonomic failure [Robertson et al, 1981; Robinson et al, 1985].

Postprandial BP changes have already been implicated in the increased prevalence of syncopal episodes in elderly institutionalised subjects [Lipsitz et al, 1983], as well as the reduced postprandial exercise tolerance in those with angina pectoris [Cowley et al, 1991]. As has been previously discussed, cerebrovascular dysautoregulation is well-documented following stroke {Chapter 1.5}, so BP changes, such as could occur postprandially or orthostatically, may result in altered CBF and in progression of the stroke after the acute event. Certainly, previous studies reported in this thesis have demonstrated impairments in the cardiovascular homeostatic responses that would be initiated in response to any BP changes {Chapters 4 and 5}. Kamata and colleagues recently described a patient with evidence of severe MCA disease and impaired cerebral vasodilatory responses to acetazolamide, who had repetitive, stereotyped TIAs after food ingestion [Kamata et al, 1994]. Also, Krajewski and colleagues have reported an increase in calculated cerebrovascular resistance postprandially, which may be an important factor in stroke progression when associated with reduced CBF.
To date, studies of the diurnal variability in stroke occurrence have found an increased incidence associated with lower BP levels [Marshall, 1977; Tsementzis et al, 1985], but a specific postprandial effect has not been assessed.

Cerebral infarction has been reported to be associated with an impairment of orthostatic BP control, which Appenzeller and colleagues attributed to a blunting of BRS after stroke [Appenzeller et al, 1964]. In another study of chronic stroke subjects, they demonstrated that baroreceptor function was further impaired by the oral administration of 75g glucose [Appenzeller et al, 1970]. Johnson and colleagues have also reported a series of patients with evidence of chronic cerebrovascular disease who demonstrated marked orthostatic hypotension and evidence of impaired BP responses to the Valsalva manoeuvre [Johnson et al, 1965]. Thus orthostatic changes, particularly in a postprandial context, may also be of clinical relevance.

6.3. Objectives

1. To study the BP responses to an oral energy load and orthostasis in acute stroke patients.

2. To assess if acute stroke patients have a greater risk of BP fall in response to food and/or postural change than matched controls.

3. To study the possible cardiovascular and metabolic mechanisms responsible for any BP change.

6.4. Methods

6.4.1. Subjects

Nine subjects (6 male) of mean age 67.2 years (range 54 to 74 years) were recruited following admission to the medical wards of the Leicester Teaching Hospitals for first-time acute TACS or PACS (3 dominant hemisphere). All subjects had neurological signs lasting >24 hours, and were neurologically stable...
Orthostatic and postprandial BP responses

at the time of the study. All subjects had cerebral infarction diagnosed by head CT scan (5 cortical (1 with haemorrhagic transformation), 2 subcortical, and 2 lacunar). None had significant clinical carotid artery stenosis though carotid duplex ultrasound scanning on all subjects was not performed. Subjects were haemodynamically stable, did not require intravenous fluid administration, were not biochemically dehydrated, and had a safe swallow reflex. They were dependent in activities of daily living (as assessed by a Modified Rankin score ≥3) as a result of their stroke, had no history of ischaemic heart disease, diabetes mellitus, atrial fibrillation, or conditions associated with autonomic dysfunction, and were not receiving antihypertensive therapy or medication known to affect cardiovascular or autonomic responses.

Eight control subjects (4 male) of mean age 66.1 years (range 60 to 74 years) were also recruited from among respondents to a local newspaper advertisement. Control subjects with known diagnoses of ischaemic heart disease, diabetes mellitus, atrial fibrillation, cerebrovascular disease, or conditions associated with autonomic dysfunction were excluded. No subject received antihypertensive therapy or medication known to affect cardiovascular or autonomic responses.

All subjects were within 15% of ideal body weight with a mean weight of 70.5 kg (range 49.7 to 85.7 kg), and body mass index of 24.4 kg/m².

6.4.2. Study Protocol

All subjects were studied on 2 occasions at least 3 days apart, in a randomised, double-blind, cross-over trial. Randomisation was performed independently by the hospital pharmacy department. Stroke subjects were studied between 7 and 21 days after stroke onset to allow the acute BP changes following acute stroke to stabilise [de Faire et al, 1978; Wallace et al, 1981; Britton et al, 1986; P Jansen et al, 1987; Harper et al, 1991].

All studies were performed in the morning after an overnight fast, including abstaining from smoking, alcohol, and all caffeinated products. The investigations took place in a quiet room (ambient temperature 20 - 24°C) and the subjects were asked to micturate prior to the study commencing. On arrival, height and weight
were recorded, and supine BP measured on 3 occasions in both arms with a standard mercury sphygmomanometer (Diastolic phase V). There were no significant interarm differences in BP (>10 mmHg) in control or stroke subjects. All subjects were then familiarised with the protocol, including the tilt procedure. An intravenous cannula was inserted into an antecubital fossa vein, patency being maintained with a heparinised saline flush (Pump-Hep, Leo Laboratories Ltd, Princes Risborough, UK). Equipment for the beat-to-beat measurement of BP and PR, as well as monitoring equipment for the assessment of FBF was applied. (The details of this equipment have been considered previously {Chapter 5.4.2}).

After 30 minutes supine rest on a tilt table, a blood sample was drawn for the measurement of preprandial blood glucose and plasma insulin. Over the next thirty minutes, continuous measurements of BP and PR were recorded. In addition, tilt studies were performed on 2 occasions during this period. Measurements of BP and PR were recorded for 2 minutes before and for 3 minutes during 60° tilt using a foot-plate and restraining support straps (Akron Medical Products, Ipswich, UK), as well as FBF. During tilt both arms were kept at heart level by specially designed supports fitted to the tilt table to avoid hydrostatic artefacts.

The subjects then consumed either a control xylose drink (0.83g/kg body weight) or a glucose drink (1g/kg body weight) at room temperatures over a period of 5 minutes while semi-recumbent. Xylose was chosen as an isoosmotic, isovolumic monosaccharide drink, which is non-absorbed and non-metabolised compared to glucose. Subjects then returned to the supine position and continuous measurements of BP and PR were recorded for the next 90 minutes. Recording of BP, PR, and FBF were taken at 30, 60 and 90 minutes during tilt as previously described. Further blood samples for the measurement of blood glucose and plasma insulin were drawn immediately prior to tilt on each occasion.

**Blood Glucose And Plasma Insulin Measurements**

Blood glucose was measured by the glucose oxidase method (Astra Reagent Kit, Beckman Instruments Inc., Galway, Ireland). Plasma insulin was assayed using a radioimmunoassay kit (Coat-A-Count Insulin, Diagnostic Products Corporation,
Los Angeles, CA 90045, USA). Sensitivity for this assay was 1.2 μIU/ml with an interassay coefficient of 7.3%.

**6.4.3. Statistical Methods**

Data are presented as mean ± SEM. Statistical comparisons between baseline paired and unpaired Normally distributed data were made by Student’s paired and unpaired t-tests respectively. To reduce the overall probability of a Type I error, Bonferroni’s correction factor was used as indicated in the text for multiple comparisons.

BP and PR readings were analysed from the printed Finapres output to provide 5 minute supine and 15 second tilt mean values. Mean BP and PR values for the last 5 minutes of every 15 minutes for supine readings and the last 15 seconds of every minute for tilt readings were used for subsequent analysis. Comparison of differences in the changes in BP, PR and FVR over time following xylose and glucose between control and stroke groups was made using repeated measures analysis of variance with the GLM programme of the SAS statistical package. Group, time, treatment, and interaction terms were studied, and a p value of ≤0.05 was considered statistically significant.

**6.5. Results**

All subjects consumed the entire drink on both occasions and none reported any symptoms during the study period. The control and stroke groups were matched for age, sex, body mass index, and casual SBP, DBP and MAP (Table 6.1).

**6.5.1. Supine Haemodynamic Responses**

There were no significant differences in preprandial supine Finapres BP and FVR between the 2 phases for control or stroke groups, though supine PR tended to be higher in the stroke group this difference did not reach statistical significance (Table 6.2). The changes in SBP (Figure 6.1a), DBP (Figure 6.1b), MAP (Figure 6.2a), and PR (Figure 6.2b) over the 90 minutes following xylose and glucose are shown for both groups.
In control subjects, there was a greater fall in supine DBP (Figure 6.1b) and MAP (Figure 6.2a) following glucose compared to xylose, which was reflected by a significant treatment-time interaction (df 6, 42, F=2.23, p=0.05, and df 6, 42, F=3.14, p<0.02, respectively, p value corrected for multiple comparisons), though the difference for supine SBP changes did not reach statistical significance (df 6, 42, F=0.88, p=0.52). However, there were no significant differences in BP responses between xylose and glucose phases in stroke subjects.

Comparing the BP responses, there was a greater fall in supine DBP (Figure 6.1b) and MAP (Figure 6.2a) following glucose in control than stroke subjects, which was reflected by significant group-time interactions (df 6, 90, F=2.91, p<0.02, and df 6, 90, F=2.56, p<0.03, respectively), though there was no significant group difference for supine SBP changes (df 6, 90, F=0.96, p=0.46).

There was no associated significant change in PR in controls. However, PR increased in the stroke group which was reflected by a significant time effect (df 6, 90, F=2.51, p<0.04, Figure 6.2b), but no treatment effect was observed. A maximum rise of 7 beats per minute was observed 30 minutes post-glucose loading. There were no associated significant changes in FVR in either stroke or control groups (Figure 6.3).
Orthostatic and postprandial BP responses

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control subjects (n=8)</th>
<th>Stroke patients (n=9)</th>
<th>p value</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>66.1 (1.9)</td>
<td>67.2 (2.1)</td>
<td>NS</td>
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<tr>
<td>Sex (male: female)</td>
<td>4:4</td>
<td>6:3</td>
<td>NS</td>
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<tr>
<td>Casual SBP (mmHg)</td>
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<td>154 (10)</td>
<td>NS</td>
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<tr>
<td>Casual DBP (mmHg)</td>
<td>79 (5)</td>
<td>88 (5)</td>
<td>NS</td>
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<tr>
<td>Weight (kg)</td>
<td>67.2 (3.7)</td>
<td>73.5 (3.6)</td>
<td>NS</td>
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<tr>
<td>Body mass index (kg/ m²)</td>
<td>24.6 (1.4)</td>
<td>24.2 (0.6)</td>
<td>NS</td>
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</table>

TABLE 6.1 Clinical characteristics of the study subjects. Values presented as mean (standard error of the mean). SBP: systolic blood pressure; DBP: diastolic blood pressure.
<table>
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<tr>
<th></th>
<th>CONTROLS</th>
<th>Xylose</th>
<th>MAP (mmHg)</th>
<th>84 (5)</th>
<th>91 (6)</th>
<th>104 (6)</th>
<th>93 (6)</th>
<th>Pulse rate (bpm)</th>
<th>65 (5)</th>
<th>62 (3)</th>
<th>74 (5)</th>
<th>69 (5)</th>
<th>FVR</th>
<th>66 (14)</th>
<th>42 (6)</th>
<th>70 (16)</th>
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<td>SBP (mmHg)</td>
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<td>MAP (mmHg)</td>
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<td>Pulse rate (bpm)</td>
<td></td>
<td>73 (4) *</td>
<td>80 (5) †</td>
<td>75 (3) †</td>
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<tr>
<td>FVR</td>
<td></td>
<td>81 (17)</td>
<td>92 (27)</td>
<td>74 (18)</td>
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TABLE 6.2 Preprandial haemodynamic parameters supine and during three minutes of 60° tilt in control (n=8) and stroke (n=9) subjects prior to xylose and glucose loading.

Data presented as mean (standard error of the mean). *p<0.01, †p<0.05 (compared to supine pulse rates). SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial blood pressure; bpm: beats per minute; FVR: forearm vascular resistance (measured in mmHg mls⁻¹ minute⁻¹ 100mls of forearm).
FIGURE 6.1 Changes from preprandially in (a) supine systolic blood pressure (SBP) (mmHg) and (b) supine diastolic blood pressure (DBP) (mmHg) over the 90 minutes following oral xylose (○) or glucose (●) in control and stroke (□, ■ respectively) subjects.

Values are expressed as mean ± standard error of the mean. Occasional standard error bars are omitted for clarity. *p < 0.05 (control glucose compared to control xylose and stroke glucose phases).
FIGURE 6.2 Changes from preprandially in (a) supine mean arterial (MAP) blood pressure (mmHg) and (b) supine pulse rate (PR) (beats/minute) over the 90 minutes following oral xylose (○) or glucose (●) in control and stroke (□, ■ respectively) subjects.

Values are expressed as mean ± standard error of the mean. Occasional standard error bars are omitted for clarity. *p<0.02 (control glucose compared to control xylose and stroke glucose phases); **p<0.04 (time-effect in stroke group only).
FIGURE 6.3 Changes from preprandially in supine forearm vascular resistance (FVR) (mmHg mls⁻¹ minute⁻¹ 100 mls forearm⁻¹) over the 90 minutes following oral xylose (○) or glucose (●) in control and stroke (□, ■ respectively) subjects. Values are expressed as mean ± standard error of the mean. Occasional standard error bars are omitted for clarity.
6.5.2. Haemodynamic Responses To Tilt

Preprandial haemodynamic variables between the 2 phases for control or stroke groups were similar, although preprandial tilt PR was significantly higher in both groups (Table 6.2). The changes in MAP, PR and FVR over the 3 minutes following 60° tilt are shown in Figures 6.4, 6.5 and 6.6, respectively, with changes from supine values expressed at 1 minute intervals up to 3 minutes post-tilt preprandially, and at 30, 60 and 90 minutes postprandially.

In control subjects, there were no significant changes in MAP following tilt in both phases. However, comparing the MAP responses to tilt between groups, there was a significant fall in stroke compared to control subjects following xylose (Figure 6.4), reflected by significant group-time effects (preprandial: df 3, 45, F=3.20, p=0.03, and T=30: df 3, 45, F=5.07, p<0.005), and following glucose (preprandial: df 3, 45, F=3.83, p<0.02, T=30: df 3, 45, F=5.80, p=0.002, T=90: df 3, 45, F=3.27, p<0.03). No treatment effect was observed in the stroke group.

PR increased significantly following tilt at all time intervals in controls and strokes, though there were no significant treatment-time or group-time interactions (Figure 6.5). There were no significant changes in FVR in either stroke or control groups (Figure 6.6).
FIGURE 6.4 Changes from supine in mean arterial blood pressure (MAP) (mmHg) at 1, 2 and 3 minutes after 60° tilt preprandially and at 30 minute intervals for 90 minutes postprandially following oral xylose (○) and glucose (●) in control and stroke (□,■ respectively) subjects.

Values are expressed as mean ± standard error of the mean. Occasional standard error bars are omitted for clarity. *p<0.03, **p<0.005 (between control and stroke groups).
FIGURE 6.5 Changes from supine in pulse rate (PR) (beats/minute) at 1, 2 and 3 minutes after 60° tilt preprandially and at 30 minute intervals for 90 minutes postprandially following oral xylose (○) and glucose (●) in control and stroke (□, ■ respectively) subjects.

Values are expressed as mean ± standard error of the mean. Occasional standard error bars are omitted for clarity.
FIGURE 6.6 Changes from supine in forearm vascular resistance (FVR) (mmHg mls⁻¹ minute⁻¹ 100mls forearm⁻¹) at 1, 2 and 3 minutes after 60° tilt preprandially and at 30 minute intervals for 90 minutes postprandially following oral xylose (○) and glucose (●) in control and stroke (□,■ respectively) subjects. 

*Values are expressed as mean ± standard error of the mean. Occasional standard error bars are omitted for clarity.*
6.5.3. Changes In Plasma Insulin And Blood Glucose Levels

Plasma insulin levels between the 2 phases for both control and stroke subjects were not significantly different preprandially (Figure 6.7). The rise in plasma insulin following glucose ingestion was greater when compared to xylose for control and stroke subjects (p=0.0001). Peak plasma insulin levels occurred 60 minutes post-glucose ingestion with a mean increase of 60.6 μIU/ml (95% CI of the increase, +31.2 to +90.0 μIU/ml).

Preprandial blood glucose levels were 4.4 (0.1) and 5.7 (0.5) mmol/l in control and stroke subjects, respectively, and were not significantly different (Figure 6.8). As expected, the increase in plasma glucose levels after glucose loading was greater than after xylose loading in both controls and strokes (p=0.0001), but there was no significant overall difference in the changes between the 2 groups. Peak blood glucose levels occurred 60 minutes post-glucose ingestion, and were not significantly different with a mean increase of 2.5 mmol/l (95% CI of the increase, +2.0 to +4.8 mmol/l) in the control group and 4.3 mmol/l (95 % CI of the increase, +1.6 to +7.1 mmol/l) in the stroke group.
FIGURE 6.7 Changes in plasma insulin levels (μU/ml) following oral xylose (○) and glucose (●) in control and stroke (□, ■ respectively) subjects. Values are expressed as mean ± standard error of the mean. *p=0.0001 (between xylose and glucose) for both control and stroke subjects.
FIGURE 6.8 Changes in blood glucose (mmol/l) following oral xylose (○) and glucose (●) in control and stroke (□, ■ respectively) subjects.

Values are expressed as mean ± standard error of the mean. *p≤0.0003 (between xylose and glucose) for control and stroke subjects.
6.6. Discussion

It has been suggested that following stroke, glucose ingestion may significantly impair BRS [Appenzeller et al, 1964; Appenzeller et al, 1970]. This could result in large postprandial BP falls, and such rapid BP reductions in the acute stroke period are probably best avoided. A recent case report has highlighted the possible relation between postprandial hypotension and stroke [Kamata et al, 1994].

The present study therefore set out to address if postprandial BP changes occur after acute ischaemic stroke and to compare these changes with a matched control group. Perhaps surprisingly, the study failed to show that oral glucose resulted in a decrease in BP in the acute stroke period, although a significant postprandial fall in BP was demonstrated in the control group. No postprandial BP changes were seen after xylose in either group. The findings in the control group are in keeping with the results of other studies using a similar number of subjects and glucose load [R Jansen et al, 1987; Jansen et al, 1988; Jansen et al, 1989]. However, the acute stroke group did show impairment of orthostatic tolerance compared to controls with a reduction in MAP on tilting pre- and postprandially, though no difference was observed between the xylose and glucose phases. These changes occurred despite an increase in PR, though there was no change in peripheral vascular resistance as measured by FBF, in keeping with the lack of increase in FVR in responses to hypotensive LBNP reported previously {Chapter 5.5.2}.

6.6.1. Cardiovascular Responses In The Control Group

'Meal' ingestion (both oral glucose drinks and mixed meals) is associated with increased splanchnic blood flow, possibly due to the effects of locally released adenosine [Granger et al, 1978] or vasoactive gut peptides [Thulin et al, 1978], which in the young is compensated for by increased PR and cardiac output [Sidery et al, 1991]. In the elderly, there is failure to adequately compensate for such haemodynamic changes which results in postprandial hypotension. The present study demonstrated significant reductions in MAP and DBP in healthy elderly control subjects following oral glucose compared to xylose, maximum changes occurring at 45 to 60 minutes postprandially. These results are in
Orthostatic and postprandial BP responses

keeping with previous work in elderly normal subjects using a 75g glucose load, where mean reductions of 5/6/6 (SBP/ MAP/ DBP) mmHg [R Jansen et al, 1987], 5/7/9 mmHg [Jansen et al, 1988], and 1/8/7 mmHg [Jansen et al, 1989] have been reported. However, Lipsitz and colleagues observed no significant BP effects with a similar energy load as the present study [Lipsitz et al, 1986b].

Despite the fall in BP following glucose in control subjects, there was no significant rise in PR, a finding in keeping with that of others [Lipsitz et al, 1986a; Potter et al, 1989; Heseltine et al, 1991], though not all [R Jansen et al, 1987]. This may reflect blunted baroreceptor responses secondary to increasing age as has been previously reported [Gribbin et al, 1971], or elevated blood glucose or insulin levels [Miles et al, 1968; Appenzeller et al, 1970]. The failure to increase PR may also be due to the insulin-mediated antagonism of the noradrenaline-induced positive chronotropic effect [Jacobsen et al, 1979]. However, it seems unlikely that glucose and insulin are primarily responsible for these changes as there were similar responses in both control and stroke groups, and other investigators have reported that insulin and glucose have no effect on BRS [Jansen et al, 1989]. It is also unlikely that there was marked baroreceptor impairment in controls in the present study, because there were significant increases in PR and BP following tilt, findings similar to that in other postprandial BP studies in the elderly [Potter et al, 1989].

There was also no compensatory increase in FVR (as assessed by changes in FBF) in controls which may have contributed to the BP fall. Sidery and colleagues similarly reported a lack of peripheral vasoconstriction, though in the calf, in healthy elderly subjects following a 2.5 MJ high carbohydrate meal [Sidery et al, 1993]. However, Lipsitz and colleagues have demonstrated intact forearm vasoconstrictor responses in healthy elderly subjects in response to a 1.6MJ meal [Lipsitz et al, 1993].

Insulin may also produce postprandial hypotension independent to its effects on baroreceptor function, by direct vasodilatation [Liang et al, 1982; Creager et al, 1985], by impaired vasoconstrictor responses to catecholamines [Yagi et al, 1988], or by antagonism of noradrenaline-induced chronotropic effects [Jacobsen
et al, 1979]. However, there were no differences in insulin responses to glucose between control and stroke groups. Increasing age may also impair myocardial chronotropic and inotropic responses to catecholamines [Lakatta et al, 1975], and cardiac and peripheral vascular responsiveness to β-adrenergic stimulation [van Brummelen et al, 1981]. The role of other proposed mechanisms such as vasoactive gut peptides [Thulin et al, 1978], adenosine [Granger et al, 1978], and possible changes in plasma volume were not investigated in the present study.

6.6.2. Cardiovascular Responses In The Acute Stroke Group
A link between postprandial hypotension and stroke has been suggested [Appenzeller et al, 1964; Appenzeller et al, 1970], and supported by limited clinical evidence [Kamata et al, 1994]. However, no significant postprandial BP changes were observed in the acute stroke group in the present study, despite changes that might have been expected in view of the reported impairment of BRS following acute (Chapter 4) and chronic stroke [Appenzeller et al, 1964], the further reduction in BRS in stroke subjects by glucose loading [Appenzeller et al, 1970], and the greater preprandial BP falls to tilt. Our results concord with the results of a previous study of elderly “chronic” ambulant stroke patients, which reported no differences in postprandial BP control after a 2.6MJ (50% carbohydrate) compared to a sham meal (water only) [Farnsworth et al, 1994]. Such findings may have important clinical implications in as much as postprandial hypotension is unlikely to have significant clinical importance in the management of stroke subjects.

The increase in SNS activity following acute stroke [Natelson, 1985; Talman, 1985] may compensate for any tendency to a postprandial BP fall, by resulting in an increase in PR and cardiac output. Certainly, baseline PR was higher in strokes than controls, though this difference did not reach formal statistical significance, and there was a significant postprandial increase in PR not seen in control subjects. However, we did not make quantitative measurements of cardiac output or SNS activity to support or refute this hypothesis, and PSA was not performed in this study.
Orthostatic and postprandial BP responses

Orthostatic BP control in the acute stroke subjects was impaired with significant falls in MAP compared to controls pre- and postprandially, though no difference in effect was observed between the xylose and glucose phases. In the previous chapter, MAP falls of similar magnitude were also reported in response to LBNP at -40 mmHg. This has important implications in the clinical management of stroke patients, as such orthostatic BP changes may be a risk factor for stroke extension in the acute period when CBF is sensitive to sudden alterations in systemic BP. Previous studies reporting abnormalities of orthostatic BP control have been of "chronic" stroke patients, Farnsworth and Heseltine reported a significant mean reduction in SBP of 11 mmHg following postural change [Farnsworth et al, 1994], as have others [Johnson et al, 1965]. More recently, Naver and colleagues have also compared the BP and HR responses to 80° tilt in 23 stroke patients studied between 8 and 48 days following acute ictus compared to a group of age-, sex- and BP-matched control subjects. They found an approximate fall of 9 mmHg in systolic BP in stroke patients, maximal at 2.5 minutes after tilting, this decrease being significantly greater than in the control group. There was no associated change in DBP on tilting, though this was not significantly different from controls, changes for MAP were not reported. Unlike the present study, the associated increase in PR was significantly greater in strokes than controls [Naver et al, 1996].

Impaired orthostatic control in stroke subjects may reflect blunting of the baroreflex arc [Appenzeller et al, 1964], though an appropriate compensatory increase in PR was observed which was not significantly different from controls. Equally, despite the orthostatic fall in BP, there was no significant change in FVR. Therefore, these results suggest an abnormality of centrally mediated SNS vasomotor activity, as do the results reported in response to LBNP (Chapter 5) and those of Naver and colleagues [Naver et al, 1996].

However, other factors may also be relevant in explaining the impaired orthostatic control in stroke subjects. Firstly, age may be an important factor in determining cardiovascular responses to orthostatic stress in stroke subjects. Korpelainen and colleagues studied subjects within 10 days of stroke and found no differences in orthostatic BP responses from controls. However, their subjects had a mean age
of only 51.4 years (compared to 67.2 years in the present study) and the oldest subject studied was 67 years [Korpelainen et al, 1994]. Gross reported impaired circulatory reflex function to the Valsalva manoeuvre in a group of subjects with "chronic" cerebrovascular disease, and found that age was a more important factor than cerebrovascular disease in producing the deterioration [Gross, 1970a].

Secondly, cerebrovascular disease has been implicated in the deterioration of cardiovascular reflexes by producing ischaemic brainstem changes which interfere with the baroreceptor reflex arc [Appenzeller et al, 1964; Johnson et al, 1965], though the subjects in the present study had no clinical or radiological evidence of brainstem ischaemic damage. However, abnormalities of circulatory reflex function are not significantly different between stroke subjects with carotid or vertebrobasilar disease [Gross, 1970a], though the precise mechanism underlying autonomic dysfunction following cerebral hemisphere stroke is unclear.

6.6.3. Summary
In summary, no evidence of a postprandial fall in BP in acute stroke subjects was found, though only the stroke group increased PR postprandially. This compensatory effect may result from increased SNS activity post-stroke, and lead to a greater postprandial increase in cardiac output than controls. However, orthostatic BP control is impaired after acute stroke but is unaffected by glucose or xylose loading. The exact mechanisms underlying these haemodynamic changes after acute cerebral hemisphere stroke remain unclear, though a failure of SNS-mediated vasomotor activity or impaired BR function may be implicated. Orthostatic, though not postprandial, BP changes may be a risk factor for stroke extension in the acute period, and therefore important considerations in the clinical management of patients.

6.7. Conclusions
1. Control subjects showed evidence of a postprandial fall in DBP and SBP following a glucose load, in keeping with the results of previous studies.
2. Acute stroke patients showed no evidence of a postprandial BP fall, though had significantly greater increases in PR than age-, sex-, and BP-matched control subjects. This may reflect increased SNS activity, well-documented following acute stroke, and leading to compensatory postprandial increases in cardiac output, though this remains unproved.

3. Orthostatic BP responses were impaired in acute stroke patients, with significant falls preprandially and postprandially to 60° tilt compared to control subjects.

4. Significant increases in PR were seen in response to tilt in both stroke and control groups. Despite the orthostatic fall in BP, stroke patients did not demonstrate any significant change in FVR, suggesting an impairment of vasomotor control.

5. Orthostatic, though not postprandial, BP changes may be a risk factor for stroke extension in the acute period, and therefore an important consideration in the clinical management of such patients.
CHAPTER SEVEN

CONCLUSIONS OF THE THESIS
The work described in this thesis sought to examine the BP changes following stroke, the relation of these changes to outcome and the potential pathophysiological mechanisms that may account for these changes.

7.1. Summary Of Study Findings

Chapter 2 examined the BP changes and the prognostic significance of these changes following stroke. The results of previous studies assessing the prognostic significance of casual BP levels following acute stroke have been conflicting, some showing no influence on outcome [Robinson et al, 1968; Miah et al, 1983; Britton et al, 1985; Dollberg et al, 1986; Carlberg et al, 1993; Fiorelli et al, 1995; M'Buyamba-Kabangu et al, 1995], others that high values have a good [Allen, 1984; Jorgensen et al, 1994] or adverse effect [Harmsen et al, 1972; Hatano, 1976; Dunne et al, 1987; Tuhrim et al, 1988; Sacco et al, 1989; Britton et al, 1990; Davalos et al, 1990; Dandapani et al, 1995; Henon et al, 1995]. These differences may in part reflect observer bias and the natural variability of casual BP recordings. The work conducted in Chapter 2 was intended therefore to resolve some of these issues in a prospective study, using one observer and multiple BP recordings employing 24-hour BP monitoring (which overcomes some of the difficulties associated with casual recordings [Antivalle et al, 1990; Coats, 1990; Fotherby et al, 1995]). The study confirmed the results of previous work, namely that casual [de Faire et al, 1978; Wallace et al, 1981; Britton et al, 1986; P Jansen et al, 1987; Harper et al, 1991] and 24-hour BP levels [Harper et al, 1994] fall spontaneously over the first week in the majority of patients after acute stroke. In addition, the study demonstrated that admission casual and 24-hour SBP and DBP were significantly higher in patients with poor outcome at one month following stroke, whether expressed in terms of mortality, dependency in activities of daily living, or neurological deterioration. However, multiple logistic regression analysis revealed only admission 24-hour SBP, of the BP measurements assessed, was a significant predictor of poor outcome at one month following ictus in a model containing factors known to be associated with a poor prognosis.

The importance of such changes in absolute BP levels following acute stroke cannot be underestimated, because systemic BP changes may have important
effects on CBF in the presence of post-stroke cerebrovascular dysautoregulation [Dearden, 1985]. BPV will therefore become an increasingly important cause of variability in CBF. To date there has only been one small uncontrolled study testing medium-term (i.e. BP recorded at 15 minute intervals) BPV [Prattichizzo et al, 1994b]. Therefore, in Chapter 3, BPV was assessed from the SD and RMSSD of beat-to-beat Finapres (short-term) and 15-minute NIBPM recordings (medium-term) in a group of stroke patients with CT-diagnosed cerebral infarction compared to a control group matched with respect to age and sex. Short-term SBPV was significantly greater in acute stroke patients (studied within 72 hours of ictus). Medium-term SBPV, assessed by the SD, was also significantly greater following acute stroke, though the difference was not significant when the underlying BP level was accounted for using RMSSD. There were no significant changes in short- or medium-term SBPV between stroke patients studied acutely and subacutely (studied within 10 to 14 days of ictus).

The pathophysiological mechanisms accounting for the aforementioned BP changes following acute stroke are a matter of debate. One possible mechanism is impaired autonomic BP control and in particular abnormalities of cardiac BRS. To date abnormalities of cardiac BRS have only been reported in studies of chronic stroke patients using invasive methodology [Appenzeller et al, 1964; Gross, 1970a]. BPV has been shown to be inversely related to cardiac BRS [Mancia et al, 1980; Mancia et al, 1986; Floras et al, 1988], and the findings of increased short- and medium-term SBPV reported in Chapter 3 would support a hypothesis of impaired cardiac BRS in acute stroke. In Chapter 4 this issue was examined in greater detail in acute and subacute stroke patients using reliable non-invasive techniques of beat-to-beat BP and PI measurements with subsequent analysis using SA and PSA (using FFT and AR algorithms) techniques to derive values for cardiac BRS. In addition, there is evidence that BP and PI variabilities in specific frequency bands derived by PSA may act as markers of the integrity of autonomic cardiovascular control [Malliani et al, 1991; Malliani et al, 1994; Parati et al, 1995]. Cardiac BRS was significantly lower in both acute and subacute stroke patients compared to control subjects matched with respect to age, sex and BP, as assessed by the combined pressor/ depressor sequences (SA) and by the combined $\alpha$ index (PSA). The normalised HF power of
SBPV was significantly greater in acute and subacute stroke patients compared to control subjects, possibly reflecting differences in the mechanical effects of respiration on the vasculature between strokes and controls. No significant differences were observed in the power spectrum of PI variability between stroke patients and control subjects. However, right hemisphere strokes had a significant reduction in the normalised HF PI power compared to left hemisphere strokes, which may reflect differences in sympathovagal balance in favour of increased SNS tone in this group, as has been proposed by other workers [Natelson, 1985; Talman, 1985].

Chapters 5 and 6 describe further studies assessing the BR reflex, in particular BR-mediated control of vasomotor tone. In Chapter 5, LBNP was used to assess the integrity of CP and arterial BR-derived cardiovascular responses to non-hypotensive (-10 mmHg) and hypotensive (-40 mmHg) stresses. Abnormal vasomotor responses to LBNP were observed following acute stroke. At non-hypotensive levels of LBNP, a significant increase in FVR was observed in control subjects, but not acute stroke patients. At hypotensive levels of LBNP, a significant increase in FVR was again only observed in control subjects. Cardiac BRS, assessed from the ratio of HR increase to MAP fall during hypotensive LBNP, was again significantly impaired in acute stroke patients. Chapter 6 describes a further study of cardiovascular responses to orthostatic and postprandial stresses. Postprandial BP responses were studied because it has been suggested that glucose ingestion may significantly impair BRS following stroke [Appenzeller et al, 1964; Appenzeller et al, 1970]. This may result in large postprandial falls in BP, and a recent case report has highlighted a possible relationship between postprandial hypotension and stroke [Kamata et al, 1994]. However, following 60° tilt, stroke patients showed a fall in MAP compared to controls pre- and postprandially, though no differences were observed between the xylose and glucose phases. Orthostatic tolerance was maintained in controls throughout both phases of the study. PR increase significantly to tilt at all time intervals in both groups. However, no significant change was seen in FVR in stroke patients despite the hypotensive response, providing further evidence of impaired vasomotor control following acute stroke.
7.2. Implications And Limitations Of Study Findings
The results of these studies have important clinical implications. The management of BP in the acute stroke period is a matter of considerable debate, though consensus does exist for a minority of indications [Spence et al, 1985; Hachinski et al, 1995; Reid, 1993; O'Connell et al, 1994]. This may be due to a number of reasons. Firstly, spontaneous reductions are observed in BP over the first week following stroke [de Faire et al, 1978; Wallace et al, 1981; Britton et al, 1986; P Jansen et al, 1987; Harper et al, 1991], which have been further confirmed by the data presented in this thesis. Secondly, the hazards of overzealous BP reduction with the risks of neurological deterioration are well reported [Britton et al, 1980; Yatsu et al, 1985; Lavin, 1986]. Thirdly, to date, the prognostic significance of elevated BP in the acute stroke period has been a matter of considerable controversy [Robinson et al, 1968; Harmsen et al, 1972; Hatano, 1976; Miah et al, 1983; Allen, 1984; Britton et al, 1985; Dollberg et al, 1986; Dunne et al, 1987; Tuhrim et al, 1988; Sacco et al, 1989; Britton et al, 1990; Davalos et al, 1990; Carlberg et al, 1993; Jorgensen et al, 1994; Dandapani et al, 1995; Fiorelli et al, 1995; Henon et al, 1995; M'Buyamba-Kabangu et al, 1995]. Data presented in this thesis report an association between increasing 24-hour BP levels following acute stroke and poor outcome. The methodology used in the collection of these data overcome many of the concerns expressed about previous studies, particularly with regard to delay between stroke and admission BP recording, observer issues, and outcome measures. However, there remain a number of unresolved issues before the therapeutic manipulation of BP in the acute stroke period can be subjected to the rigors of a suitable prospective, randomised, intervention trial, and these issues highlight some of the limitations of the studies.

The data provide no information regarding the level at which treatment should be initiated. The data were intentionally handled in a continuous fashion to avoid the arbitrary division into categories, and because of the linear association between BP and outcome observed. Nonetheless, protocols for intervention demand levels for intervention. An ongoing trial of secondary prevention of stroke by BP reduction in patients within 5 years of stroke is recruiting both non-hypertensive and hypertensive patients [PROGRESS Management Committee, 1995], though the Treatment of Post Stroke Hypertension Trial (TOPS) will be recruiting patients
using conventional definitions of hypertension [Potter, unpublished data]. There was also no evidence of a U- or J-shaped curve, though preliminary data from the first 16,000 patients recruited into the International Stroke Trial suggest a non-linear association between SBP and an outcome of death or dependency at 6 months [Slattery et al, 1996], i.e. there may be a lower BP limit below which patients would benefit from measures to increase BP. However, the International Stroke Trial recruited patients that were excluded in the present studies, e.g. atrial fibrillation, impaired conscious level.

The results of other studies reported in this thesis highlight other areas in which BP and its control may be of importance in acute stroke. These include increased BPV and an impairment of the normal homeostatic mechanisms, i.e. impaired cardiac BRS and vasomotor control. Thus reducing systemic BP levels in acute stroke may be even more hazardous, resulting in decreased CBF. However, the observations on cardiac BRS are preliminary and on a limited number of patients, so that the prognostic relevance of impaired cardiac BRS cannot be addressed. Certainly, increased BPV is associated with an increased likelihood of target organ damage in both hypertensive [Pickering, 1991; Palatini et al, 1992] and diabetic populations [McKinlay et al, 1994]. The presence of increased BPV following acute stroke may also be important in the selection of antihypertensive therapy. Indeed, the use of centrally acting adrenergic blocking drugs has been advocated in hypertensive stroke patients as it addresses both issues of absolute BP level as well as BPV [Prattichizzo et al, 1994a]. Impaired cardiac BRS is however recognised as an indicator of poor prognosis following acute myocardial infarction [La Rovere et al, 1988; Schwartz et al, 1988; Osculati et al, 1990; Farrell et al, 1992; Grassi et al, 1992; Odemuyiwa et al, 1993]. This may also have implications for the selection of antihypertensive agents, as angiotensin enzyme inhibitors have been shown to cause a greater improvement in BRS than calcium antagonists for the same reduction in BP [Egan et al, 1993].

In addition, impairment in BR-mediated cardiovascular responses to orthostatic stress as well as non-hypotensive and hypotensive LBNP stresses may have implications for the day-to-day clinical management of stroke patients. These
findings may be pertinent in the aetiology of stroke, but may also be a possible mechanism in progression of stroke in the post-ictal period.

7.3. Prospects For Further Studies

The findings from the studies presented in this thesis suggest many possible further lines of investigation. The issues related to the prognostic significance of the interrelated variables studies, namely BP, BPV, cardiac BRS and vasomotor control, need to be further explored in a larger study before more informed decisions regarding BP management in the acute stroke period can be made. Preliminary data from the PSA of BP and PI variabilities pose interesting questions. Data from this study identified a significant difference in sympathovagal balance with a relative sympathetic predominance of PI variability in right compared to left hemisphere strokes, though there was no direct evidence of increased sympathetic activity from the surrogate measures studied, which requires further investigation. Increased sympathetic tone may precipitate abnormalities of HR control, and is in keeping with previous work reporting right cortical dominance of the sinoatrial node [Rosen et al, 1982; Lane et al, 1988; Zamrini et al, 1990; Lane et al, 1991] and increased risk of supraventricular arrhythmias following right hemisphere stroke [Lane et al, 1992]. However, these preliminary data require further study, in particular to ascertain the prognostic significance of these findings.

7.4. Conclusion

These studies have identified abnormalities of the baroreflex arc following acute stroke, which may be important in the aetiology of the BP changes post-ictus. These abnormalities may be in the afferent arm (e.g. age- or hypertension-related damage to the arterial baroreceptor), in the efferent arm (as reported in this thesis), or most likely by direct damage as a result of acute stroke to the central integration of the afferent and efferent limbs of the BR reflex. It remains to be established if impaired BRS is an independent prognostic indicator following acute stroke, as it is following acute myocardial infarction.
Conclusions

Stroke is a significant cause of morbidity and mortality in the United Kingdom, and comprises a significant proportion of National Health Service spending. Acute treatment trials are now in progress to identify therapies that will reduce post-stroke morbidity and mortality, and include identifying modifiable factors that influence the viability of the ischaemic penumbra. In the presence of cerebrovascular dysautoregulation, CBF is related to BP following stroke, and is clearly amenable to therapeutic manipulation. Certainly, elevated BP levels in acute stroke are a poor prognostic predictor. However, the interrelationship of the BP aspects reported in this thesis (namely, absolute BP level, BPV and BRS) with prognosis must be further addressed before embarking on randomised control trials of BP treatment in acute stroke.
APPENDIX I

THE OXFORDSHIRE COMMUNITY STROKE PROJECT CLASSIFICATION

Using this classification, patients are allocated to one of four groups according to presenting symptoms and signs:

1. **Total Anterior Circulation Stroke**
   
   All of:
   - (a) new higher cerebral dysfunction (e.g. dysphasia, dyscalculia, visuospatial disorder)
   - (b) homonymous field defect contralateral to the lesion
   - (c) contralateral motor and/or sensory deficit of at least two of face, arm and leg

2. **Partial Anterior Circulation Stroke**
   
   Two of:
   - (a) new higher cerebral dysfunction (e.g. dysphasia, dyscalculia, visuospatial disorder)
   - (b) homonymous field defect contralateral to the lesion
   - (c) contralateral motor and/or sensory deficit of at least two of face, arm and leg

3. **Posterior Circulation Stroke**
   
   Any of:
   - (a) ipsilateral cranial nerve palsy with contralateral motor and/or sensory deficit
   - (b) bilateral motor and/or sensory deficit
   - (c) disorder of conjugate eye movement
   - (d) cerebellar dysfunction without ipsilateral long-tract deficit
   - (e) isolated hemianopia or cortical blindness

4. **Lacunar Stroke**
   
   e.g.
   - (a) pure motor stroke
   - (b) pure sensory stroke
   - (c) sensori-motor stroke
   - (d) ataxic hemiparesis
## APPENDIX II

### THE NATIONAL INSTITUTES OF HEALTH STROKE SCALE

<table>
<thead>
<tr>
<th>Deficit tested</th>
<th>Categories</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOC</td>
<td>0 alert&lt;br&gt;1 drowsy&lt;br&gt;2 stuporous&lt;br&gt;3 coma</td>
</tr>
<tr>
<td>LOC questions</td>
<td>0 answers both correctly&lt;br&gt;1 answers one correctly&lt;br&gt;2 incorrect</td>
</tr>
<tr>
<td>LOC commands</td>
<td>0 obeys both correctly&lt;br&gt;1 obeys one correctly&lt;br&gt;2 incorrect</td>
</tr>
<tr>
<td>Gaze abnormality</td>
<td>0 normal&lt;br&gt;1 partial gaze palsy&lt;br&gt;2 forced deviation/total gaze palsy</td>
</tr>
<tr>
<td>Visual loss</td>
<td>0 normal&lt;br&gt;1 partial hemianopia&lt;br&gt;2 complete hemianopia</td>
</tr>
<tr>
<td>Facial palsy</td>
<td>0 normal&lt;br&gt;1 minor&lt;br&gt;2 partial&lt;br&gt;3 complete</td>
</tr>
<tr>
<td>Motor arm</td>
<td>0 no drift&lt;br&gt;1 drift&lt;br&gt;2 cannot resist gravity&lt;br&gt;3 no effort against gravity</td>
</tr>
<tr>
<td>Motor leg</td>
<td>0 no drift&lt;br&gt;1 drift&lt;br&gt;2 cannot resist gravity&lt;br&gt;3 no effort against gravity</td>
</tr>
<tr>
<td>Limb ataxia</td>
<td>0 absent&lt;br&gt;1 present in arm or leg&lt;br&gt;2 present in arm and leg</td>
</tr>
<tr>
<td>Sensory</td>
<td>0 normal&lt;br&gt;1 partial loss&lt;br&gt;2 dense loss</td>
</tr>
<tr>
<td>Language</td>
<td>0 normal&lt;br&gt;1 mild to moderate aphasia&lt;br&gt;2 severe aphasia&lt;br&gt;3 complete aphasia</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>0 normal&lt;br&gt;1 mild to moderate dysarthria&lt;br&gt;2 unintelligible or worse</td>
</tr>
<tr>
<td>Inattention</td>
<td>0 no neglect&lt;br&gt;1 partial neglect (visual, tactile or auditory)&lt;br&gt;2 complete neglect (more than 1 modality)</td>
</tr>
<tr>
<td>Distal motor function</td>
<td>0 normal&lt;br&gt;1 some extension after 5 seconds&lt;br&gt;2 no extension</td>
</tr>
</tbody>
</table>
### THE MODIFIED RANKIN SCORE

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Independent</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>No symptoms</td>
</tr>
</tbody>
</table>
| 1 | Minor symptoms  
*Symptoms that do not interfere with lifestyle* |
| 2 | Minor handicap  
*Symptoms that do lead to some restriction in lifestyle, but do not interfere with patients' capacity to look after themselves* |
| **Dependent** | |
| 3 | Moderate handicap  
*Symptoms that appreciably restrict the patients' lifestyle, or prevent totally independent existence, or both* |
| 4 | Moderately severe handicap  
*Symptoms that clearly prevent independent existence, though patient does not need constant attention* |
| 5 | Severe handicap  
*Totally dependent, patient requiring constant attention day and night* |
<table>
<thead>
<tr>
<th>Function</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bowels</td>
<td>0 incontinent</td>
</tr>
<tr>
<td></td>
<td>5 occasional accident</td>
</tr>
<tr>
<td></td>
<td>10 continent</td>
</tr>
<tr>
<td>Bladder</td>
<td>0 incontinent/ catheterised</td>
</tr>
<tr>
<td></td>
<td>5 occasional accident</td>
</tr>
<tr>
<td></td>
<td>10 continent</td>
</tr>
<tr>
<td>Grooming</td>
<td>0 needs help with personal care</td>
</tr>
<tr>
<td></td>
<td>5 independent</td>
</tr>
<tr>
<td>Toilet use</td>
<td>0 dependent</td>
</tr>
<tr>
<td></td>
<td>5 needs some help</td>
</tr>
<tr>
<td></td>
<td>10 independent</td>
</tr>
<tr>
<td>Feeding</td>
<td>0 unable</td>
</tr>
<tr>
<td></td>
<td>5 needs help</td>
</tr>
<tr>
<td></td>
<td>10 independent</td>
</tr>
<tr>
<td>Transfer</td>
<td>0 unable, no sitting balance</td>
</tr>
<tr>
<td></td>
<td>5 major help (physical, 1 or 2 people)</td>
</tr>
<tr>
<td></td>
<td>10 minor help (verbal or physical)</td>
</tr>
<tr>
<td></td>
<td>15 independent</td>
</tr>
<tr>
<td>Mobility</td>
<td>0 immobile</td>
</tr>
<tr>
<td></td>
<td>5 wheelchair independent</td>
</tr>
<tr>
<td></td>
<td>10 walks with help of 1 person</td>
</tr>
<tr>
<td></td>
<td>15 independent</td>
</tr>
<tr>
<td>Dressing</td>
<td>0 dependent</td>
</tr>
<tr>
<td></td>
<td>5 needs help</td>
</tr>
<tr>
<td></td>
<td>10 independent</td>
</tr>
<tr>
<td>Stairs</td>
<td>0 unable</td>
</tr>
<tr>
<td></td>
<td>5 needs help (verbal, physical, carrying aid)</td>
</tr>
<tr>
<td></td>
<td>10 independent up and down</td>
</tr>
<tr>
<td>Bathing</td>
<td>0 dependent</td>
</tr>
<tr>
<td></td>
<td>5 independent (including bath/ shower transfers)</td>
</tr>
</tbody>
</table>
APPENDIX V

PUBLICATIONS ARISING FROM THIS THESIS

24-hour, but not casual, blood pressure predicts outcome following acute stroke.

Robinson T, Ward-Close S, Potter J.
A comparison of beat-to-beat blood pressure variability in acute and subacute stroke patients with cerebral infarction.

Robinson T, James M, Youde J, Panerai R, Potter J.
Cardiac baroreceptor sensitivity is impaired after acute stroke.

Robinson T, Potter J.
Cardiopulmonary and arterial baroreflex-mediated control of forearm vasomotor tone is impaired following acute stroke.
Stroke 1997; (in press).

Robinson T, Potter J.
Postprandial and orthostatic cardiovascular changes following acute stroke.


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Dawson S, Ardon M. Can stroke be reliably classified? (Unpublished data).


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Hachinski V. Hypertension in acute ischemic strokes. Archives of Neurology 1985; 1002.


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Levin A. A simple test of cardiac function based upon the heart rate changes induced by the Valsalva maneuver. American Journal of Cardiology 1966; 18: 90-99.
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McKinlay S, Foster C, Clark A, Clark S, Kemp F, Denver E, Coats A. Increased blood pressure variability during 24h blood pressure monitoring as an early sign...


Palmero H, Caeiro T, Iosa D, Bas J. Baroreceptor reflex sensitivity index derived from phase 4 of the Valsalva maneuver. Hypertension 1981; 3(suppl II): II-134-II-137.


Potter J. Treatment of Post Stroke (TOPS) Hypertension Study. (Unpublished data).


Vann Jones J. Differentiation and investigation of primary versus secondary hypertension (Cushing reflex). American Journal of Cardiology 1989; 63: 10C-13C.


