CARDIOVASCULAR AND CEREBROVASCULAR FUNCTION IN SYNCOPAL & NON-SYNCOPAL PATIENTS

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Brian John Carey

MB, BCh, BAO, MRCPI

ProQuest LLC
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106-1346

To my wife, Emma, and daughters, Elisha and Anna.

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List of Abbreviations

ANOVA	analysis of variance
ARI	autoregulatory index
AVM	arteriovenous malformation
BP	blood pressure
BRS	cardiac baroreceptor sensitivity
CA	cerebral autoregulation
CBF(V)	cerebral blood flow (velocity)
CSM	carotid sinus massage
CO_2	carbon dioxide
CrCP	critical closing pressure
CCVR	classical cerebrovascular resistance
CT	computerised tomography
CVR	cerebrovascular resistance
DBP	diastolic blood pressure
ECG	electrocardiogram
EDCF	endothelial derived constricting factor
EDRF	endothelial derived relaxing factor
EEG	electroencephalogram
$ETCO_2$	end tidal carbon dioxide
FFT	fast Fourier transform
GPI	Gosling's pulsatility index
HR	heart rate
HUT	head-up tilt

ICP	intracranial pressure
LBNP	lower body negative pressure
MAP	mean arterial blood pressure
MCA	middle cerebral artery
MCADP	middle cerebral artery diastolic blood pressure
MCADV	middle cerebral artery diastolic blood flow velocity
MCAMP	middle cerebral artery mean blood pressure
MCAMV	middle cerebral artery mean blood flow velocity
MCASP	middle cerebral artery systolic blood pressure
MCASV	middle cerebral artery systolic blood flow velocity
MCAV	middle cerebral artery blood flow velocity
MRI	magnetic resonance imaging
NO(S)	nitrous oxide (synthetase)
OH	orthostatic hypotension
PI	pulse interval
PP	perfusion pressure
RAP	resistance-area product
RSD	spontaneous depressor blood pressure changes at rest
RSP	spontaneous pressor blood pressure changes at rest
SBP	systolic blood pressure
SD	standard deviation
SSNSA	systemic sympathetic nervous system activity
TCD	transcranial Doppler ultrasound
TCO_2	transcutaneous carbon dioxide
THC	thigh cuff

TPR	total peripheral resistance
VVS	vasovagal syncope

Study Declaration

As required by the University of Leicester, this declaration outlines the persons responsible for this thesis and the extent to which the work is my own.

The design, organisation and administration of the study was performed by myself with the help and advice of Professor John F. Potter, Professor of Medicine for the Elderly, University of Leicester, and Professor Ronney B. Panerai, Professor of Physiological Measurements, Department of Medical Physics, University of Leicester.

Patient recruitment, data handling and statistical analysis in this study were performed by myself. I am very grateful, however, for the considerable help of Dr. Penelope Eames and Dr. Melanie Blake with the recruitment and data analysis of young and older subjects reported in Chapter 3. In addition, I am very grateful to Mr. Bradley Manktelow and Miss Clare Gillies, Medical Statisticians, Department of Epidemiology, University of Leicester, who assisted with statistical analysis of data reported in Chapters 3, 5 and 6.

Professor Panerai developed the software for the recording, calibration and editing of raw data and the software used for frequency domain analysis and calculation of static and dynamic autoregulatory indices and cardiac baroreceptor sensitivity.

Ethical Declaration

In accordance with ethical requirements for medical research, all subjects gave written informed consent. All techniques and studies were approved by the Leicestershire Hospital Ethics Committee.

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

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CHAPTER ONE

Introduction

1.1. Vasovagal syncope

1.1.1. Historical aspects

Syncope is a transient loss of consciousness that is accompanied by loss of postural tone. The word 'syncope' is derived from the Greek word for 'cut short' and this concept of sudden cutting short of circulation and conscious awareness has been recognised as a clinical entity throughout the ages, with Maimonides (1135-1204 AD) stating:

"Only if one knows the causes of syncope will he be able to recognise its onset and combat the cause."

Crucifixion is the only method of execution in history which depended on the induction of recurrent syncope to cause death.

Gowers first coined the term "vaso-vagal" (hyphenated) in the early years of the last century [Gowers 1907]. This work addressed various clinical forms of epilepsy and the label was used to describe a symptom complex now more conventionally called anxiety/panic/hyperventilation attack syndrome. Some 25 years later, with due respect and acknowledgement, Sir Thomas Lewis redefined and appropriated Gowers' terminology [Lewis 1932]. In his analysis, Lewis provided crucial insights into the pathophysiology of 'vasovagal syncope' (no hyphen), particularly by pointing out the apparent dissociation between the vasodepressor and cardioinhibitory components (see section 1.1.3.):

"The proof that slowing is vagal is given by atropine..... Slowing....to 50 or 40, exceptionally to 30 beats per minute, is sufficient to induce unconsciousness..... Undoubtedly the main cause of the fall of blood pressure in these attacks, and the enfeeblement or loss of pulse, is independent of the vagus, and lies in the blood vessels. Atropine, while raising the pulse rate up to and beyond normal levels during

the attack, leaves the blood pressure below normal and the patient still pale and not fully conscious."

Lewis' paper proposed the carotid sinus baroreceptors as a possible site of origin of the depressor reflex and recognised that VVS could *"occur also in people in apparently robust health"*. Sharpey-Schafer's classic review [1956] contained most of what is clinically accepted today and proposed the mainstay of current management consisting of advice *"in avoiding the circumstances which cause the attack"*.

1.1.2. Epidemiology

Syncope is common, comprising up to 3% of Accident & Emergency attendances [Day 1982], 1% to 6% of hospital admissions [Kapoor 1991], with up to 30% of the generally population experiencing a syncopal episode during their lifetime [Sutton 1996]. In addition, syncope can be dangerous [Manolis 1990], disabling [Linzer 1991, Silverstein 1982] and difficult to diagnose [Linzer 1997, Kapoor 1983]. Recurrent episodes of syncope, therefore, can have huge physical, psychological and social consequences similar to those resulting from chronic disabling illnesses such as rheumatoid arthritis [Linzer 1991]. The list of causes of syncope is extensive (table 1.1), encompassing neurogenic, cardiac, neurologic, iatrogenic and psychiatric aetiologies. A substantial proportion of cases, however, defy diagnosis [Kapoor 1983, Linzer 1997], though the advent of head-up tilt testing has greatly improved the diagnostic yield [Kenny 1986, Grubb 1991b, Strasburg 1989, Raviele 1989, Abi-Samra 1987].

Vasovagal syncope (VVS) is the commonest form of syncope presenting to medical practitioners [Sutton 1996] and is the focus of attention in this thesis. VVS occurs frequently in young adults but affects all age groups [Simon 2000] and is a significant

cause of morbidity in the elderly [Manolis 1990, Silverstein 1982, Grubb 1996a]. It comprises approximately 58% of all syncopal episodes presenting to emergency rooms [Sutton 1996] with an equal sex incidence [Simon 2000]. There is frequently a family history of the disorder (~37%), especially if the onset is below the age of 20 years [Mathias 1998]. The syndrome can be induced in everyone if a big enough stressor is applied [el-Bedawi 1994a], implying that lasting pathology need not necessarily be present for VVS to occur.

1.1.3. Pathophysiology

1.1.3.1. Normal physiological responses to adoption of upright posture

Adoption of the upright posture in humans causes a gravity-mediated increase of ~500-700ml of venous pooling in the lower limbs and results in a decrease in cardiac filling pressure, stroke volume and arterial BP [Hellebrandt 1943]. This is followed by a compensatory reflex increase in heart rate and total peripheral resistance (TPR) through sympathetic activation, withdrawal of parasympathetic tone and release of renin and vasopressin [Hellebrandt 1943, Abboud 1993]. The afferent limb of the reflex consists of arterial baroreceptors and cardiac mechanoreceptors embedded in the aortic arch, carotid sinus and cardiac chambers which are sensitive to mechanical deformation and chemical, paracrine and endocrine factors [Coleridge 1980, Abboud 1986]. A decrease in the stimulation of these sensory receptors leads to an decrease in the frequency of C fibre action potentials transmitted to the brainstem via the glossopharyngeal and vagal nerves. These signals are integrated in the nucleus tractus solitarius and rostral ventro-medial and ventro-lateral areas of the medulla resulting in altered efferent activity to vagal preganglionic nuclei in the medulla, sympathetic preganglionic nuclei in the spinal cord, other brainstem nuclei and higher central

nervous system centres. A subsequent increase in sympathetic nervous system activity and decrease in vagal activity results in reflex tachycardia and peripheral vasoconstriction which reverse the decline in blood pressure and maintain cerebral perfusion [Lagerhof 1951]. The heart has dual sensory and effector roles in this reflex. As a sensory organ, it relays a decrease in afferent activity to the brainstem and, as an effector organ, it uses an increased level of efferent sympathetic activity to increase heart rate and cardiac output. A simultaneous increase in sympathetic and neurohormonal stimulation of the peripheral vasculature also helps to maintain systemic BP through vasoconstriction. The normal physiological response to standing, therefore, consists of an increase in heart rate and diastolic pressure with an unchanged or slightly decreased systolic blood pressure.

1.1.3.2. Pathophysiological cardiovascular changes during pre-syncope

During pre-syncope, an initial gradual decrease in systemic BP and TPR is followed by a precipitous fall in BP, TPR with or without a fall in heart rate (HR) [Hainsworth 1991]. VVS has been classified, according to the BP and HR responses immediately prior to syncope, into three different types - cardioinhibitory, pure vasodepressor and mixed [Sutton 1992, Grubb 1996a]. A descriptive classifiation of any pathophysiology at such an early stage in its understanding is always fraught with difficulties. Nevertheless, the mixed form of VVS has been recognised as the commonest form and tailored treatment regimes have been proposed, with no subsequent validation, on the basis of this classification [Sutton 1992].

As hypotension and/or bradycardia become progressively more profound, CBF is compromised and, irrespective of the precipitant or type of cardiovascular changes,

syncope is ultimately thought to result from neuronal dysfunction due to cerebral hypoperfusion [Van Lieshout 1991, Sung 2000, Grubb 1991a,1998].

The pathophysiology and biochemistry underlying the above changes are a matter of some debate. Anomalies have been demonstrated in many different research areas which contribute to our understanding of the sequence of events but the precise sequence of events leading to VVS has not been fully elucidated. There is, however, general acceptance about events in the terminal stages of the pre-syncopal period. Excessive venous pooling leads to a gradual and then sudden fall in venous return to the heart [Streeten 1988]. The depleted ventricular volume causes excessively vigourous ventricular contraction with stimulation of a large number of mechanoreceptors (or C fibres) and a consequent surge in afferent neural traffic to nucleus tractus solitarius in the medulla oblongata [Samoil 1992, Mark 1983, Van Lieshout 1991]. Increased afferent neural output to the brainstem simulates hypertensive conditions and stimulates an anti-hypertensive homeostatic reflex resulting in a fall in peripheral vascular resistance and/or bradycardia - the so-called Bezold-Jarish reflex mechanism [Mark 1983, Van Lieshout 1991].

1.1.3.3. Venous Pooling & reduced intravascular volume

The physiological tendency to pooling of blood in the compliant veins of the lower limbs during orthostasis, with a consequent reduction in central circulatory volume, may be pathophysiologically increased in patients with recurrent VVS [Streeten 1988, Yamanouchi 1996, Hainsworth 1992], possibly due to a lack of variation in venous tone [Hargreaves 1992]. A highly significant correlation has been demonstrated between orthostatic tolerance and both plasma and blood volume [El-Sayed 1995] and salt loading has been shown to increase both plasma volume and tolerance to

orthostatic stress in certain subjects [El-Sayed 1996]. Similarly, a moderate exercise program has been shown to significantly increase plasma and blood volumes as well as improving symptoms and orthostatic tolerance [Mtinangi 1998,1999].

1.1.3.4. Ventricular volume and contraction

Increased venous pooling is hypothesised to result in a progressively smaller left ventricular volume, increased cardiac inotropy and consequent excitation of ventricular C fibre mechanoreceptors. In support of this hypothesis, the reduction of stroke index, ejection fraction, and the rate of reduction of end-diastolic volume indices during graded head-up tilt is larger in patients with VVS than normal subjects [Yamanouchi 1996]. In addition, a reduction in left ventricular volume assessed by echocardiography occurs at the onset of VVS [Fitzpatrick 1992, Mizumaki 1995, Shalev 1991]. Further support comes from reports that negative inotropic agents may attenuate the hypotension and bradycardia of VVS induced by head-up tilt [Rea 1989].

The hypothesis is challenged, however, by the fact that end-systolic left ventricular volume during central hypovolaemia does not surpass ~25%, suggesting that there is no progression to excessive cardiac emptying before the onset of syncope [Shalev 1991]. In addition, cardiac contractility as measured by fractional ventricular shortening does not increase during pre-syncope [Novak 1996]. Force imposed on the left ventricular wall and mechanoreceptors may be more accurately assessed, however, by left ventricular wall stress than by systolic fibre shortening. End systolic stress has recently been shown to be reduced during HUT in patients susceptible to VVS, suggesting that, if paradoxical ventricular mechanoreceptor activation occurs

during pre-syncope, it is not due to left ventricular hypercontractility or increased systolic wall stress [Liu 2000].

1.1.3.5. Central processing & neurotransmitters

Afferent cardiovascular baroreceptor and chemoreceptor C fibre nerve traffic arrives at the medulla via the vagus and glossopharyngeal nerves and is integrated in the nucleus tractus solitarius which also receives afferent impulses from other cranial nerves, hypothalamus, spinal cord and brainstem [Pelletier 1973, Donald 1978]. Signals from the nucleus tractus solitarius address the vagal preganglionic nuclei in the medulla, sympathetic preganglionic nuclei in the in the spinal cord, other brainstem nuclei and higher central nervous system centres. Two extreme haemodynamic reactions in response to afferent impulses to the nucleus tractus solitarius are recognised. The 'defence' or 'fight or flight' reaction is characterised by somatomotor and sympathetic neural activation while the alternative response, possibly mediated by activation of the cingulate gyrus by the nucleus tractus solitarius and/or somatic and visceral afferent signals, results in vagally mediated bradycardia, sympathetic withdrawal and diminished muscular tone [Benditt 1997]. The outcome may be of sufficient severity to elicit cerebral hypoperfusion and syncope and may be comparable to the 'playing dead' strategy of some animals. Electrical stimulation of the "defence area" in the hypothalamus of anaesthetised cats results in increases in heart rate and BP and vasodilatation in skeletal muscle [Eliasson 1951]. Emotional stress in humans can also result in tachycardia, hypertension and skeletal muscle vasodilatation [Barcroft 1960]. In view of these findings, and the fact that VVS may be precipitated by anxiety, physical pain, mental anguish, emotional distress and even the anticipation of physical pain or trauma, has led to the belief that the

pathophysiology of VVS may be, at least in part, centrally controlled [Hainsworth 1992].

Certain neurotransmitters may play a role in eliciting or facilitating the hypotension and bradycardia of VVS. Serotonin (5-hydroxytryptamine) may be involved in a sympathoinhibitory pathway in the central nervous system that results in hypotension and bradycardia during acute central hypovolaemia [Morgan 1988]. Depletion of serotonin stores attenuates the BP and HR decreases in response to acute blood loss in conscious mammals, a central hypovolaemic state similar to that prior to VVS [Elam 1985]. In addition, the serotonin receptor blocker, methylsergide, induces a marked pressor response during acute haemorrhage [Elam 1985]. Central intracerebroventricular serotonin has been shown to induce systemic hypotension, excitation of adrenal sympathetic nerve activity and inhibition of renal sympathetic nerve activity in rats [Morgan 1988, Abboud 1993]. The increase in adrenal sympathetic nerve activity can be abolished by the administration of para-chlorophenylalanine, an inhibitor of serotonin synthesis [Morgan 1988]. Activation of cerebral serotonin receptors has been shown to inhibit sympathetic nervous system activity and to facilitate a vasodepressor response [Kosinski 1994, Gonzalez-Heydrich 1990]. The hypothesis that serotonin plays a role in the pathophysiology of VVS is strengthened by the demonstration that the serotonin reuptake inhibitor, fluoxetine hydrochloride, may be effective in preventing both spontaneous and HUT-induced VVS [Grubb 1993a].

The discovery of an increase in plasma β endorphin levels in humans during syncope [Perna 1990] has raised questions about the role of endogenous opiates in VVS. Endogenous opoids have a tonic inhibitory effect on sympathetic tone [van Lieshout 1997]. Naloxone, an opiate receptor antagonist, enhances the cardiopulmonary

baroreflex excitation of sympathetic activity [Schobel 1992] while opiate receptor agonists inhibit renal sympathetic nerve activity during hypotensive haemorrhage in conscious rabbits [Morita 1988]. In addition, in an experimental haemorrhagic model in rabbits, intracisternal administration of naloxone was more effective than intravenous administration of the drug in preventing hypotension [Evans 1989]. However, parenteral naloxone, even in very high doses, has failed to prevent induction of VVS during lower body negative pressure studies in humans [Smith 1993].

Increased levels of a number of other centrally released vasoactive agents have been associated with VVS. Pancreatic polypeptide is closely associated with, and is often considered a marker of, parasympathetic neural activity and has been found to be elevated during pre-syncope [Sander-Jensen 1985, 1986]. Vasopressin levels are also increased in the pre-syncopal period, a finding attributable to neural connections from the nucleus tractus solitarius [Fitzpatrick 1990]. The role of nitric oxide (NO) is discussed in section 1.1.3.11.

1.1.3.6. Autonomic function

Bradycardia during VVS is thought to be due to an increase in parasympathetic nerve activity as heart rate can be maintained by the administration of atropine [Lewis 1932]. In addition, failure to decrease parasympathetic tone during upright tilt may be a feature of patients with recurrent VVS [Lippman 1995]. The presumption of an increase in parasympathetic tone during the pre-syncopal period [Abboud 1993] has been challenged, however, with a number of investigators failing to find an increase in high frequency power that would support this view [Kouakam 1999, Morillo 1994, Sneddon 1993, Prinz-Zaiss 1995].

Vasodilatation and the subsequent decline in peripheral resistance and systemic BP are thought to be primarily the result of diminished sympathetic vasoconstrictor tone. Microneurographic recordings have illustrated sudden sympathetic withdrawal from skeletal muscle prior to VVS [Wallin 1982, Van Lieshout 1991, Chosy 1965, Bie 1986], a finding supported by the disappearance of muscle sympathetic nerve activity (MSNA) assessed using spectral analysis [Mosqueda-Garcia 1997, Morillo 1997]. Patients with recurrent VVS display blunted increases in MSNA at low levels of head-up tilt [Mosqueda-Garcia 1997] and a subtle though significant decline MSNA has been demonstrated even before the development of pre-syncopal symptoms [Morillo 1997]. Studies of forearm muscle blood flow in fainting humans has demonstrated vasodilatation to be confined to muscle [Roddie 1977, Barcroft 1944,1945].
Spectral analysis of heart rate variability during HUT in normal subjects has demonstrated an increase in low frequency power that has been interpreted as mainly indicating an increase in sympathetic tone [Pagani 1986, Vybiral 1989, Hayono 1991, Montano 1994]. Similar testing in patients prone to VVS has yielded conflicting results with both normal increases and abnormal decreases in LF power being reported [Theodorakis 1992, Pruvot 1994, Morillo 1994, Lippman 1995, Prinz-Zaiss 1995, Boulos 1996, Kochiadakis 1997]. Most of these studies have examined responses during late pre-syncope, but similar methods have also demonstrated inadequate sympathovagal balance immediately after head-up tilt in subjects who subsequently develop VVS [Morillo 1994, Kochiadakis 1997, Kouakam 1999]. A decrease in pulse interval low frequency to high frequency ratio (LF:HF) after five minutes of head-up tilt has a 92% positive and 86% negative predictive value for the occurrence of VVS [Kouakam1999]. A recent review, however, suggested that the

use of pulse interval LF:HF ratio as a measure of sympathovagal balance may have limitations [Eckberg 1997].

Evidence for passive vasodilatation has also been found in disproportionately low plasma noradrenaline levels in pre-syncopal humans with severe hypotension [Eckberg 1986]. Little evidence exists for an active vasodilator mechanism during pre-syncope in humans [Van Lieshout 1997].

More recently, Furlan et al [1998] used spectral analysis of heart rate variability to propose two different sympathetic patterns prior to HUT-induced VVS in normal subjects. One syncopal group demonstrated continued sympathetic activation immediately prior to syncope while a second group exhibited a slow inversion of the cardiac sympathovagal balance with progressive sympathetic inhibition. BP variability was not assessed in Furlan's study, however, and the findings may not be similar in patients with recurrent VVS.

Release of acetylcholine by the parasympathetic nervous system is known to exert a feedback inhibitory effect on noradrenaline release from nearby sympathetic nerve endings [Muscholl 1980, Levy 1984, Benditt 1997]. Conversely, release of noradrenaline and neuropeptide-Y from sympathetic nerve endings inhibits synaptic acetylcholine release [Potter 1985, 1987]. The temporal sequence, therefore, as well as the magnitude of sympathetic and parasympathetic activation may have important consequences in terms of the severity of vasodilation or the degree of bradycardia associated with pre-syncope.

1.1.3.7. Baroreceptor sensitivity

As early as 1932, Lewis proposed abnormalities in cardiopulmonary baroreceptor sensitivity (BRS) as a possible explanation for recurrent VVS. Cardiac BRS

decreases in normal subjects during head-up tilt [Cooke 1999], but a number of investigators have found significantly lower cardiac BRS during head-up tilt and after pharmacological testing in patients with recurrent VVS [Mosqueda- Garcia 1997, Haruhiko 1996, Morillo 1994]. Thomson et al [1997] displayed impaired forearm vasoconstriction and paradoxical vasodilation during the application of subhypotensive lower body negative pressure (LBNP) in patients with tilt-table-positive VVS compared with age-matched normal control subjects, suggesting possible reduced activation of cardiopulmonary baroreceptors. Morillo [1997] found no differences in vagal baroreflex responses between normal subjects and patients with VVS during supine rest but found impaired responses to pharmacologically induced arterial pressure changes below resting levels. Other studies have shown abnormal forearm resistance vessel vasodilator responses and impaired splenic vasoconstriction during dynamic leg exercise in patients with VVS, which may be the result of exaggerated cardiopulmonary mechanoreceptor activation on exercise [Thomson 1995, 1996, Sneddon 1994]. Overall these observations suggest that patients with VVS may have abnormal cardiac baroreflex responses during both central volume unloading and exercise. Nevertheless, patients in these studies tended to be young and no data are currently available on cardiac BRS in older patients with VVS.

1.1.3.8. Plasma catecholamines

A number of investigators have demonstrated a marked increase in plasma adrenaline levels prior to both spontaneous and induced VVS [Sra 1994, Sander-Jensen 1986, Abi-Samra 1988, Chosy 1965, Hackel 1991, Fitzpatrick 1992] with the increase antedating evident changes in BP and heart rate [Benditt 1997]. Changes in plasma

noradrenaline levels during pre-syncope are less clear with increases [Vingerhoets 1984, Chosy 1965] and no increases [Sander-Jensen 1986, Abi-Samra 1988] being reported. Adrenaline produces β_2-adrenergic dilatation in both skeletal muscle and splanchnic resistance vessels at concentrations measured in humans under stress [Rowell 1989, Shepherd 1979]. Several studies have used intravenous administration of the non-selective β adrenergic agonist isoproterenol to enhance susceptibility to VVS [Grubb 1991b, Kapoor 1994], while propranolol is known to reduce the firing of cardiac mechanoreceptors with vagal afferents [Thames 1980]. These findings suggest that both endogenous and exogenous increases in catecholamines may exacerbate a tendency to VVS through both arterial vasodilatation and the Bezold-Jarish reflex mechanism [Mark 1983]. This is the rationale behind the widespread therapeutic use of β adrenergic blockers in patients with recurrent VVS [Abboud 1993, Almquist 1989], with some evidence that beneficial effects may be mediated by β_1 rather that β_2 adrenergic receptors [Waxman 1994].

1.1.3.9. Cerebral autoregulation

The advent of transcranial Doppler ultrasonography (TCD) has led to an explosion of interest in cerebral haemodynamics prior to VVS. Irrespective of the pathophysiology involved in VVS, it is thought that the loss of consciousness during syncope is caused by cerebral hypoperfusion [Van Lieshout 1991, Yonehara 1994, Mattle 1995]. Reductions in mean and diastolic cerebral blood flow velocity (CBFV), a surrogate for cerebral blood flow (see section 2.1.5.), with relative preservation of systolic CBFV have been consistently reported during pre-syncope [Schondorf 1997, Sung 2000, Grubb 1991a, 1998, Janosik 1992]. These findings led to the hypotheses that an

impairment of cerebral autoregulation (CA) may be contributing to the symptoms of VVS and that impaired CA may, in fact, be the primary problem in patients with recurrent VVS. A number of investigators have added weight to this hypothesis by using TCD with either head-up tilt or incremental lower body negative pressure to apparently show paradoxical cerebral vasoconstriction prior to syncope [Janosik 1992, Bondar 1995, Sung 2000, Grubb 1991a, 1998, Levine 1994, Giller 1992]. Indeed, a number of authors have described a form of 'cerebral syncope' whereby syncope, occasionally confirmed by electroencephalography, has occurred in the presence of apparent cerebral vasoconstriction but in the absence of systemic hypotension or bradycardia [Gomez 1999, Njemanze 1993, Daffertshafer 1995, Grubb 1998, Fredman 1995]. Most of these studies have, in the main, used Gosling's pulsatility index (GPI) as a marker for rises in cerebrovascular resistance (CVR) (see section 2.1.5.4.). As arterial BP is not taken into account in its calculation, GPI may, however, be poorly applicable to the cerebral circulation [Czosnyka 1996b, Schondorf 1997, Aaslid 1992]. More recently, others have used Poiseuille's Law to suggest that classical CVR (CCVR) falls prior to syncope and that CA is, therefore, preserved in VVS [Schondorf 1997]. Neither GPI nor CCVR, however, take into account the critical closing pressure (CrCP) of the cerebral circulation, i.e. the pressure below which flow in a blood vessel ceases, which can have a profound effect on cerebral blood flow [Dewey 1974, Panerai 1995, Dawson 1999a]. Resistance area product (RAP) is an index of CVR that takes CrCP into account (see section 2.1.5.4.) and may, therefore, be more appropriate for use when analysing the cerebral circulation [Panerai 1993, Evans 1988, Carey 2000].

1.1.3.10. Respiration

Respiratory patterns prior to VVS have been a matter of some debate. Lipsitz [1998] recently described rather convincingly an increase in respiratory amplitude during pre-syncope with no change in respiratory rate. Schondorf [1997] similarly reported no change in respiratory rate during pre-syncope but tidal volume was not measured. An increase in respiratory amplitude during pre-syncope is unsurprising, as an increase in respiratory depth is a well-known mechanism that results in an increase in BP through venoconstriction and a mechanical increase in preload [Shepherd 1981]. Gilliat [1948] has also reported a spinal vasoconstrictor reflex activated by deep inspiration which may lead to increases in systemic BP. Respiratory changes during pre-syncope may, therefore, be secondary to an established pathophysiological process but it is possible that they may also play a primary role in the process. In spite of the reported increase in respiratory amplitude and probable subsequent hyperventilation, carbon dioxide levels have not yet been assessed during pre-syncope. This is surprising considering the known marked effects of carbon dioxide on CBF (see section 1.3.3.1) which could account for the proposed cerebral vasoconstriction prior to syncope.

1.1.3.11. Endothelial factors

The role of endothelial factors in the pathphysiology of VVS is attracting increasing attention. Nitric oxide (NO) acts not only as an endothelial mediator of vascular smooth muscle relaxation, but it is now well established that NO is also a modulator of sympathetic and parasympathetic nervous system activity in animals [Chowdhary 1999]. Histochemical staining techniques have identified neuronal populations that contain NO synthetase within medullary cardio-regulatory sites and their peripheral autonomic pathways [Zanzinger 1997, Dun 1994, Tanaka 1994, Klimaschewski 1992,

Anderson 1993, Chowdhary 1999]. NO has both pre- and post-ganglionic sympathetic nerve activity and may attenuate cardiovascular end-organ response to sympathetic stimulation [Chowdhary 1999]. Central attenuation of sympathetic outflow and baroreflex-mediated vagal control by NO has also been described [Chowdhary 1999, Sakuma 1992].

There is a scarcity, however, of information regarding the role of NO in the regulation of human cardiovascular autonomic control. Two groups of investigators used NO synthetase inhibitors to suggest that, in agreement with animal studies, NO significantly modulates sympathetic nerve activity in humans [Lepori 1998, Owlya 1997]. In addition, a NO synthetase inhibitor significantly potentiated the cardiac contractile response to dobutamine in patients with heart failure, but not in patients with normal cardiac function [Hare 1998].

There is even less information regarding possible endothelial dysfunction during VVS in humans. Kaufmann et al [1993] demonstrated a rise in NO activity during neurally mediated syncope which has the potential to explain the withdrawal of sympathetic activity prior to VVS discussed earlier. Others previously showed that HUT induces the release of endothelin-1 into plasma, probably from the neurohypophysis, and hypothesised that impaired endothelin-1 release could account for failure to maintain vascular tone during orthostasis [Matzen 1992, Kaufmann 1991].

In summary, the pathophysiology of VVS is complex and unclear and may involve autonomic, central, neurohormonal, humeral, venous, endothelial, plasma volume, respiratory and cerebrovascular mechanisms.

1.1.4. Clinical characteristics

VVS most commonly occurs in the upright position but may also occur when sitting [Thilenius 1992] and when supine [Verrill 1970]. Patients often report situations or events likely to trigger an event such as standing for long periods, warm environments, anxiety, physical pain, mental anguish, emotional distress and even the anticipation of physical pain or trauma. In most patients, the occurrence of VVS is usually preceded by a prodrome which is highly variable in duration, lasting anywhere from several seconds to several minutes [Lewis 1932, Wayne 1961]. Typical symptoms include dizziness, vertigo, diaphoresis, nausea, disturbances of vision, fatigue, weakness, headache, paraesthesiae, abdominal discomfort and visual and auditory hallucinations [Lewis 1932, Van Lieshout 1991]. Observers often report patients as becoming pale and diaphoretic with cold skin and dilated pupils [Wayne 1961].

Symptoms during this pre-syncopal period are often recognised by patients and offer the opportunity to take evasive action to prevent loss of consciousness ensuing. If evasive action is not taken, however, a variable period of loss of consciousness intervenes with diffuse loss of muscle tone and collapse. Urinary and faecal incontinence are not unknown and tonic-clonic movements due to transient cerebral hypoxia may lead to confusion with epilepsy. The post-syncopal period is often characterised by dizziness, nausea, headache and a general malaise and, once again, varies substantially in duration [Wayne 1961]. Many patients with recurrent VVS report a relapsing and remitting course [Grubb 1996a].

Many elderly patients have little or no prodrome prior to VVS leading to an increased risk of morbidity due to failure to take evasive action [Fitzpatrick 1991a, Grubb 1996a, Manolis 1990, Linzer 1991, Silverstein 1982]. Older patients may often display atypical features during VVS that pose diagnostic dilemmas. Confusion and

disorientation may occur during both the prodromal and recovery periods and may be particularly prolonged after the event [Grubb 1996a]. Focal neurological deficits, such as dysarthria, may lead to an incorrect diagnosis of a transient ischaemic attack, especially if hypotension and bradycardia are not sufficiently profound to induce loss of consciousness [Grubb 1993b]. Post-prandial VVS is not uncommon in the elderly, probably exacerbated by sequestration of blood by the mesenteric circulation [Lipsitz 1986]. This situation may be compounded by the consumption of alcohol with a meal due to an increase in venous pooling secondary to the vasodilatory effects of alcohol [Lipsitz 1986]. In addition, comorbidity and polypharmacy may complicate the diagnosis and treatment of an older patient [Linzer 1997].

1.1.5. Investigations

Investigators in the 1980's demonstrated that the cause of syncope could not be established in up to 45% of cases [Mathias 2001, Kapoor 1991]. It was hypothesised that a large proportion of these patients had VVS, but no confirmatory test existed. In the past, therefore, VVS was a diagnosis of exclusion with other causes of syncope (Table 1.1) excluded using a variety of investigations (Table 1.2). These investigations have a low diagnostic yield, but, in combination with careful history taking and physical examination, form the mainstay of diagnostic testing in patients presenting with syncope [Mathias 2001, Linzer 1997].

Head-up tilt (HUT) table testing has been used as an investigative tool in the pathophysiology of orthostatic stress for over fifty years [Hellebrandt 1943] before the initial demonstration of its utility in the diagnosis of unexplained syncope [Kenny 1986]. Since then, a number of investigators have confirmed its usefulness as a method of unmasking susceptibility to VVS and related disorders [Fitzpatrick 1989,

Grubb 1991b, Strasberg 1989, Raviele 1989, Abi-Samra 1988]. BP, HR and catecholamine changes and prodromal symptoms experienced prior to VVS induced by HUT are virtually identical to those experienced prior to spontaneous episodes [Grubb 1996a]. HUT was initially validated in younger patients but has recently been validated as a useful diagnostic test in patients ≥ 65 years [Bloomfield 1999]. The usefulness of the HUT test in clinical practice and as a research tool has been limited, however, by a lack of standard methodology [Kenny 2000, Kapoor 1994].

1.1.5.1. Normal cardiovascular, respiratory & cerebrovascular responses to HUT

Right atrial pressure falls immediately after HUT from 4-6 mmHg to 0-2 mmHg [Bridgden 1950] but a reduction in left ventricular stroke volume (SV) does not take place until after about six beats, possibly due to the reservoir of blood available in the lungs and heart [Wieling 1993]. A temporary small decline occurs in arterial BP, with a minimum pressure at around 7 seconds [Borst 1984, Wieling 1993], which may be greater after a long period of supine rest prior to HUT and is possibly attributable to an increase in the unstretched volume of the veins [Borst 1984]. An increase in systemic vascular resistance does not occur until about 6 seconds after HUT, but a subsequent increase of about 40% results in a net rise in mean arterial BP of approximately 10mmHg after 30 seconds. SV falls to a stable level of about 70% of supine after 30 seconds, by which time heart rate has increased by approximately 10 beats. A fast (1.5 seconds) speed of tilting evokes similar haemodynamic effects as the most commonly used speed of tilting (3 seconds) [Ten Harkel 1990] but much slower speeds of tilting may attenuate these responses [Smith 1994].

After about 5 minutes of HUT, increases have occurred in DBP (~10mmHg), MAP (5-10%), heart rate (~20-30%) and systemic vascular resistance (~30-40%) while

decreases have occurred in intrathoracic blood volume (~20-30%), SV (~30-45%) and cardiac output (~15-20%) [Wieling 1993]. In contrast, SBP changes very little. The decrease in intrathoracic blood volume is mostly accounted for by the accumulation of 500-1000ml of blood in the leg veins during orthostasis.

CBFV has been shown to fall significantly during orthostatic stress with HUT and lower body negative pressure (LBNP) in normal subjects [Bondar 1995, Giller 1992, Levine 1994, Schondorf 1997, Stoll 1999, Cencetti 1997]. Arterial, end-tidal and transcutaneous carbon dioxide (CO_2) levels have also been shown to fall significantly in normal subjects after HUT [Cencetti 1997, Serrador 1998, Anthonisen 1965, Bjurstedt 1962, Yoshizaki 1998] and this is probably due to an increase in tidal volume without any change in respiratory frequency [Cencetti 1997, Yoshizaki 1998]. Changes in CO_2 are well known to affect CBFV [Garnham 1999, Panerai 1999b] and Cencetti et al [1997] have shown a significant link between the declines in CBFV and CO_2 after HUT.

1.1.5.2. Indications, contraindications and risks of HUT testing

Any patient with recurrent syncope unexplained by history, physical examination and the neurological and cardiovascular investigations outlined above should be considered for HUT testing [Kenny 2000, Grubb 1996a]. Tilt table testing may also be useful for investigating elderly patients with recurrent unexplained falls or transient ischaemic attack-like symptoms [Grubb 1996a, Grubb 1993b]. A role for testing has also been proposed in the investigation of patients with recurrent, treatment-resistant unexplained seizures [Grubb 1996a, Zaidi 1998], recurrent vertigo [Grubb 1992c] and high risk patients with a single unexplained syncopal episode [Kenny 2000].

Caution should be exercised when subjecting patients with severe left ventricular outflow obstruction, mitral stenosis, coronary artery disease and carotid stenosis to HUT [Kenny 2000]. In spite of the marked BP and HR changes induced during HUT, very few adverse events and no fatalities have been attributed to the test in the literature [Kapoor 1994, Gatzoulis 1995] although many centres undoubtedly have anecdotal reports of same [Kenny 2000].

1.1.5.3. Equipment

Tilt tables should be of the foot-plate support type as physiological responses may differ with the use of saddle tables [Kenny 2000, 1996]. They are generally padded and calibrated to allow accurate placement at a chosen angle. Both manually operated and electrically automated tables are available but each should allow rapid changes of posture to both the tilted and supine positions. HR is monitored, usually continuously, with standard three-lead electrocardiography. It is recommended that BP is monitored on a beat-to-beat basis as sphygmomanometry is insufficient to assess rapid changes in arterial BP [Kenny 2000]. Non-invasive devices such as the Finapres (see section 2.2) and Portapres are ideal and obviate the need for invasive intra-arterial monitoring. Future classifications and treatments of VVS may be based on continuous BP assessment and sphygmomanometry must now be considered inadequate for use during HUT [Kenny 2000]. Intravenous cannulation may affect the specificity of the test [McIntosh 1994] and is, therefore, not routinely recommended, but advanced cardiac life support equipment should be on constant standby [Kenny 2000].

1.1.5.4. Prior instructions & environment

HUT was often initially performed in the fasting state, though this was inconsistently included as part of the protocol [Kapoor 1994]. It is now recognised that, in order to avoid dehydration and consequent hypotension, especially in older subjects, affecting the test result, patients should be fasted for no more than two hours before the procedure [Benditt 1996, Victor 1996, Kenny 2000]. Drugs affecting the cardiovascular and autonomic systems or that may affect intravascular volume are generally discontinued a minimum of five half-lives before HUT [Victor 1996], unless implicated in symptomatology, when testing is usually performed on medications [Kenny 2000]. A quiet, dimly lit, temperature controlled environment (20-23°C) is required to minimise autonomic stimulation. The test is usually supervised by a physician and nurse or cardiovascular technician familiar with the test protocol and complications [Kenny 2000]. After explanation of the protocol and an instruction to minimise lower limb movement to maximise venous pooling during tilt [Benditt 1996, Victor 1996], a period of supine rest of between 20-45 minutes is normally allowed prior to HUT [Kapoor 1994, Fitzpatrick 1991].

1.1.5.5. Tilt angle and duration

The angle and duration of HUT are the two primary determinants of the number of positive tests yielded by a particular protocol [Benditt 1996, Kapoor 1992, Mansourati 1996]. Angles of between 40° and 90° have been used, but the commonest angle employed is 60° [Kapoor 1994]. Angles < 60° produce significantly less haemodynamic effects than steeper angles, but increasing the tilt angle beyond 60° produces no apparent additional effect on cardiac output or sympathetic tone [Zaidi 2000]. Despite these findings, there have been suggestions that higher tilt angles may increase the yield of positive tests [Mansourati 1996, Kapoor 1994].

The duration of passive HUT, where pharmacological provocative agents are not used, varies widely from centre to centre ranging from 10 to 60 minutes [Kapoor 1994, Grubb 1996a, Fitzpatrick 1991, Kenny 2000]. The optimum duration of passive HUT is in doubt, but there may be a relationship between duration and the number of positive results [Kapoor 1994], probably due to a reduction in the number of false negative results [Kapoor 1994, Fitzpatrick 1991, Kenny 2000]. One study reported a mean time to syncope of 24 minutes [Fitzpatrick 1991], and if a normal distribution and 2 standard deviations are assumed, a HUT duration of between 30-45 minutes seems reasonable [Kenny 2000].

1.1.5.6. Provocation during HUT testing

A number of centres introduced provocative agents during HUT in an attempt to increase the sensitivity and shorten the duration of the test.

1.1.5.6.1. Isoproterenol

The most commonly used provocative agent is the non-selective β adrenergic agonist isoproterenol which is administered intravenously either by continuous or bolus infusion [Graham 2001, Almquist 1989, Waxman 1989, Grubb 1991b, Fitzpatrick 1996, Carlioz 1997, Kapoor 1992, Chen 1992]. Again, no standard protocol exists and the drug is widely administered at differing doses and at different times after HUT [Kapoor 1994, Kenny 2000]. It is thought that isproterenol shortens the time to syncope by augmenting the Bezold-Jarish reflex by stimulating cardiac β_1 adrenergic receptors but a central mechanism cannot be fully discounted [Mark 1983, Waxman 1994]. A comprehensive literature review of tilt table tests up to 1994 found that the

use of intravenous isoproterenol increased the yield of positive results by a factor of approximately 33% over passive HUT [Kapoor 1994]. The increase in positive results may have been attributable to higher tilt angles or intravenous cannulation rather than the drug itself, as studies performed at 60° demonstrated identical percentages of positive responses whether isoproterenol was used or not [Kapoor 1994]. Neither could any relationship be shown between the maximal dose of isoproterenol and the percentage of positive responses, but higher doses of isoproterenol are not recommended due to concerns about adverse effects on specificity [Kapoor 1992, Carlioz 1997, Fitzpatrick 1996, Kenny 2000]. Surprisingly, a literature review found no evidence for the generally accepted assumption that isoproterenol shortens the time to a positive response [Kapoor 1994]. Contraindications to the use of isoproterenol include ischaemic heart disease and left ventricular outflow obstruction, while known dysrhythmias are a relative contraindication. Side effects necessitating discontinuation are commoner in the elderly and include arrhythmias, chest pain, severe tremulousness and vomiting.

1.1.5.6.2. Sublingual nitroglycerin

More recently, sublingual nitroglycerin has emerged as a possibly more user-friendly provocative agent for use with HUT [Del Rosso 1999, Raviele 1995, Kurbaan 1999, Natale 1998]. It has been found to be as effective as intravenous infusions of isoproterenol for provoking VVS, but has a lower incidence of adverse events [Graham 2001]. Nitroglycerin is thought to act as a provocative agent by causing vasodilation of capacitance vessels [Mason 1971] thereby significantly increasing venous pooling [Raviele 1995]. Due to ease of administration, sublingual administration superceded earlier attempts to devise protocols using intravenous

methods [Raviele 1994]. A variety of doses have been used but, due to variable absorption and linear pharmacokinetics, metered doses of between 400-800 μg are currently recommended [Kenny 2000, Graham 2001].

1.1.5.6.3. Other pharmaceutical agents

A number of other pharmacological provocative agents have been tried with varying degrees of success, including sublingual isosorbide dinitrate [Zeng 1999], intravenous isosorbide dinitrate [Aerts 1999], edrophonium [Lurie 1993], clomipramine [Flevari 1998] and adenosine [Brignole 2000, Shen 1996, Perez-Paredes 1998]. More work is needed using these agents, however before they can be recommended for more general use.

1.1.5.6.4. Lower body negative pressure

Others have combined HUT with lower body negative pressure to provide a more physiological increase in orthostatic stress [El-Bedawi 1994]. This method has been shown to have high reproducibility and specificity [Hainsworth 1994] but is not yet in widespread use.

1.1.5.7. Positivity criteria

Since the advent of HUT as a clinical tool, a wide variety of criteria have been proposed for deeming positivity [Kapoor 1994]. A test is normally described as positive if a patient's original symptoms are reproduced in association with hypotension and/or bradycardia. The occurrence of hypotension and/or bradycardia in the absence of symptom reproduction is not currently regarded as a positive test [Kenny 2000]. The degree of hypotension and bradycardia required for a positive test

are again a matter of some debate and have varied with the use of provocative agents [Kapoor 1994], but a classification of VVS has been proposed according to BP and heart rate responses during HUT-induced pre-syncope (Table 1.3.) [Sutton 1992]. A positive response is usually described as cardioinhibitory if a marked bradycardia (≤ 40 bpm for > 10 seconds) or prolonged asystole (>3 seconds) occur in association with symptoms [Sutton 1992]. A positive response is generally defined as vasodepressor if symptoms occur with SBP < 80mmHg and HR maintained at a level no more than 10% below its peak value [Sutton 1992]. A positive response is normally regarded as mixed if SBP is <80mmHg and HR does not fall below 40bpm, falls below 40bpm for < 10 seconds or asystole of <3 seconds occurs in association with symptoms [Sutton 1992]. However, as mentioned above, these are descriptive classifications of a syndrome that is incompletely understood and are likely to undergo refinement as the precise pathophysiology becomes clearer.

1.1.5.8. Sensitivity, specificity & reproducibility

The sensitivity of HUT testing is difficult to elucidate as no 'gold standard' currently exists for the diagnosis of VVS with which HUT testing can be compared. Although the percentage of positive responses in patients with syncope of unknown origin is often referred to by the term 'sensitivity', this is incorrect due to the lack of an adequate reference standard. Approximately 50% of patients with unexplained syncope have a positive response to passive HUT testing but rates of between 26% and 90% have been reported [Kapoor 1994]. As mentioned above, higher tilt angles and an increased duration of testing may increase the yield of positive results [Kapoor 1994]. Isoproterenol appears to increase to number of positive responses to about 62% (range 39% to 87%), but assessment of the effect of isoproterenol is confounded

by the use of a higher tilt angle in most isoproterenol studies [Kapoor 1994]. Sublingual nitroglycerin has been reported to increase the positive yield from 34% to 73% [Kurbaan 1999], 25% to 51% [Raviele 1995], 45% to 79% [Natale 1998] and 11% to 59% [Del Rosso 1999].

The specificity of HUT results have been evaluated by performing the test in control subjects with no previous history of syncope. The situation is complicated by the fact that control subjects may have a predisposition to VVS but may not become symptomatic prior to enrolment in such studies [Kapoor 1994]. Specificity rates of between 0% and 100% have been reported for passive HUT testing, but the overall rate is approximately 90% [Kapoor 1994]. Specificity declines as longer durations of testing and higher doses of isoproterenol are used [Linzer 1997, Kapoor 1994]. Overall specificity of HUT testing with isoproterenol is approximately 75% (range 35% to 100%), with specificity worst in younger patients [Kapoor 1994]. The use of sublingual nitroglycerin with HUT testing has been reported to have a specificity of 94% [Raviele 1995, Del Rosso 1999] and does not appear to decrease specificity compared with a passive HUT test in older patients [Natale 1998]. False positive responses to HUT occur more commonly in younger subjects, possibly due to the age related decline in cardiopulmonary BRS [Grubb 1992b].

Reproducibility of the HUT test is a matter of importance with regard to assessing treatment regimes, but reproducibility studies are confounded by the widely differing protocols in existence. Nevertheless, negative responses may be more reproducible than positive responses (84% v 55%) when passive HUT is re-performed at 10 days [Ruiz 1996]. Immediate reproducibility of a positive passive test is reported to be approximately 75% [Fish 1992]. Negative HUT tests with isoproterenol have a reproducibility of 85% when performed 1-6 weeks apart, while positive test

reproduction may be as high as 90% [Sheldon 1992]. Immediate reproducibility of a negative isoproterenol HUT test result appears to be higher than a positive result (94% v 57% [de Buitleir 1993] and 100% v 80% [Chen 1992]). A negative HUT test with sublingual nitroglycerin provocation is 83% reproducible at 1-28 days while a positive test is 79% reproducible [Foglia-Manzillo 1999].

1.1.5.9. Testing in older patients

It was originally felt that VVS was an uncommon occurrence in older people, a hypothesis apparently supported by the demonstration of a reduced susceptibility of the elderly to syncope during postural tilt [Lipsitz 1989]. Indeed, physiological responses to HUT in healthy subjects may differ with advancing age. Stroke volume decreases and splanchnic vascular resistance increases to a greater degree than in younger subjects, while the increases in heart rate and forearm vascular resistance may be significantly less [Minson 1999]. Bootsma et al [1995], however, have demonstrated no age-related differences in the HR and BP responses of healthy subjects to HUT.

A number of studies have subsequently suggested that VVS is more frequent in older patients than generally recognised [Hackel 1991, Grubb 1992b,1993b, Marangoni 1996, Brembilla-Perrot 1996] and that HUT testing is a useful diagnostic tool in such patients [Marangoni 1996, McIntosh 1993, Bloomfield 1999, Brembilla-Perrot 1996]. When supervising HUT tests involving older subjects, however, the different symptomatology of the elderly during pre-syncope (see section 1.3.3) must be borne in mind [Grubb 1996a, Grubb 1993b, Lipsitz 1986].

Increasing age may be associated with different BP and HR behaviour prior to HUT-induced VVS, with greater falls in BP and smaller increases in HR being reported [Marangoni 1996].

The use of isoproterenol and sublingual nitroglycerin as provocative agents does not appear to affect the specificity of the HUT test in older age groups [Natale 1998, Bloomfield 1999], but nitroglycerin may yield more positive results than isoproterenol [Natale 1998]. The isoproterenol HUT test has been shown, however, to have excellent immediate reproducibility in older age groups [Kou 1997].

1.1.6. Treatment

Assessment of the efficacy of any intervention used to treat recurrent VVS is fraught with difficulties due to the relapsing and remitting nature of the condition, the fact that any tolerable intervention is unlikely to eliminate all events and symptoms and the variable reproducibility of the HUT test.

The majority of patients need no intervention other than reassurance and education regarding avoidance of precipitating factors and evasive action should pre-syncopal symptoms occur [Benditt 1999]. Discontinuation of medications with antihypertensive effects that may exacerbate vasodepression may improve matters [Benditt 1999]. Should recurrent episodes of VVS affect quality of life, further intervention may be considered including elastic support stockings [Grubb 1996a], fludrocortisone [Benditt 1999, Grubb 1996b, Scott 1995, Balaji 1994], increased dietary salt intake [El-Sayed 1996], β adrenergic blockers [Klingenheben 1999, Mahanonda 1995, Scott 1995, Lurie 1992, Sra 1992], midodrine (an α adrenergic agonist) [Klingenheben 1999, Sra 1997, Grubb 1999, Benditt 1998, Ward 1998],

serotonin reuptake inhibitors [Grubb 1993a, 1994, 1996a, Di Girolamo 1999b] and stress and anxiety management through biofeedback therapy [Benditt 1999, McGrady 1986]. Little benefit appears from using disopyramide [Morillo 1993], transdermal scopolamine [Lee 1996, Benditt 1999], ephedrine, dihydroergotamine [Benditt 1999, Grubb 1996b, Deal 1997], etilephrine [Raviele 1999], or theophyllines [Nelson 1991]. Permanent pacemakers with rate hysteresis have recently been shown to be useful in patients with the cardioinhibitory form of the syndrome [Ammirati 1998, Connolly 1999] and moderate exercise [Mtinangi 1998, 1999] and tilt training programs [Ector 1998, Di Girolamo 1999a] may be useful in patients with resistant forms of VVS.

A number of studies have demonstrated a progressive amelioration of symptoms related to VVS over time [Brignole 1992, Natale 1996, Morillo 1993]. It is unclear, however, if this is the natural history of the disorder or related to counselling and reassurance after diagnosis.

1.2. Cerebral blood flow

The human brain has a high metabolic demand for energy and, uniquely in humans, uses glucose as its sole substrate for energy metabolism [Warlow 1996]. Approximately 0.125kg of glucose is metabolised daily in the brain via the glycolytic pathway and tricarboxylic acid cycle [Warlow 1996]. Two molecules of pyruvate are formed from each molecule of glucose by the process of glycolysis. Two glycolytic pathways exist whereby molecules of adenosine triphosphate (ATP) are formed by a series of mitochondrial reactions either in the presence (aerobic glycolysis) or absence (anaerobic glycolysis) of oxygen. Aerobic glycolysis is the more efficient pathway, yielding 36 molecules of ATP from each molecule of glucose, while anaerobic

glycolysis yields only two. Inhibition of pyruvate oxidation during anaerobic glycolysis causes the reduction of pyruvate and the consequent accumulation of intracellular and extracellular lactic acid, inhibiting the ability of mitochondria to sequester calcium. To maintain integrity, neurones in the brain require a constant supply of ATP so that concentrations of the major intracellular cation, potassium, and major extracellular cations, calcium and sodium, are kept constant [Warlow 1996]. As the brain is unable to store energy, a constant supply of oxygenated blood and glucose is essential to preserve function and structural integrity.

The average human brain comprises approximately 2% of total body weight (~1.4 kg in a 65 kg adult) but receives 15-20% of the total cardiac output – a cerebral blood flow (CBF) of around 0.5L/kg/min. This equates to a cerebral metabolic rate of oxygen consumption of approximately 0.33 – 0.35 L/kg/min, or about 0.045 L/min of oxygen – 20% of the total oxygen consumption of the body at rest [Warlow 1996]. CBF and oxygen consumption is higher in people < 20 years and lower for those > 60 years.

In the resting brain, CBF is closely matched with the metabolic demands of cerebral neurones. Grey matter has a higher metabolic rate than white matter and, therefore, has a higher regional CBF. Local CBF may vary by between 10-20% depending on local brain function but, under steady state conditions, global CBF remains essentially constant [Lassen 1977, 1974, Aaslid 1987]. The physiological mechanism behind the close coupling of metabolism with CBF is unknown, but brain activity may produce local metabolites or neuronal discharges affecting the vasoactivity of local blood vessels.

Whole blood viscosity is mainly determined by haematocrit, and CBF has been shown to be inversely proportional to both haematocrit and whole blood viscosity, as well as

fibrinogen levels [Thomas 1982, Ameriso 1990]. It is thought that the inverse relationship of CBF with haematocrit is not due to sluggish blood flow at higher viscosities, but rather that the higher oxygen content of high-haematocrit blood allows the maintenance of oxygen delivery in the face of lower CBF.

CBF is primarily determined by the cerebral perfusion pressure (PP) at the base of the brain and by the cerebrovascular resistance (CVR), which is influenced mainly by the diameter of intracranial arteries as well as blood viscosity. In most body tissues, PP is the difference between the forward pressure exerted by the arterial system and the venous backpressure. This, however, is complicated by the fact that the brain is effectively contained in an enclosed space that retains its own intrinsic pressure, intracranial pressure (ICP). ICP, usually about 8mmHg in a supine adult, affects venous distension and arterial filling and has the effect of limiting CBF. CBF, therefore, can be represented by the equations:

$$CBF = \frac{PP}{CVR} = \frac{MAP - VP - ICP}{CVR}$$

where *MAP* is mean arterial pressure and *VP* is intracranial venous pressure (usually about 10mmHg).

From these equations, it is clear that, as intracranial PP changes, a constant CBF may be maintained by variations in CVR, mainly through alterations in the diameter of small intracranial arterioles or arteries, a process known as cerebral autoregulation.

1.3. Cerebral autoregulation

1.3.1. Historical perspective

Autoregulation refers to the intrinsic ability of an organ to maintain a constant blood flow despite changes in perfusion pressure (PP). Changes in BP and, hence, PP are counteracted by changes in vascular resistance, providing the organ with a constant supply of blood containing oxygen and vital nutrients.

The phoenomenon of autoregulation was first described by Bayliss [1902] with the aid of experiments on isolated canine hindlimbs. Lowering hindlimb PP caused a passive decrease in limb volume but restoration of PP caused an increase in limb volume to levels greater than baseline. The investigators suggested that these findings could be explained by local vasodilatation occurring during the period of hypoperfusion. This hypothesis of the intrinsic ability of an organ to alter vessel diameter was supported by Wacholder [1921] who demonstrated contraction of isolated segments of carotid artery 8-20 seconds after an increase in PP. Rein confirmed the ability of the canine renovascular bed to autoregulate in 1931 by showing preservation of renal blood flow throughout a considerable systemic BP range. The concept of a lower limit of PP, below which the ability of an organ to autoregulate is compromised, was described by Selkurt in 1946 using the canine kidney. As PP fell below 80mmHg, a pressure passive relationship developed whereby blood flow became dependent on PP. Shipley described the upper limit of the autoregulatory process using canine renovascular beds in 1951. Active autoregulation was subsequently demonstrated in a number of other organs including the heart, retina, intestine, liver, skeletal muscle and, perhaps the most studied organ, the brain.

Cerebral autoregulation (CA) was first described by Fog [1937] who demonstrated variations in the directly measured diameter of cat pial arterioles in response to manipulations of systemic BP. Such methods, however, involved long surgical

procedures which damaged the brain, often leading to the finding of impaired or absent CA and stimulating debate as to whether the process actually existed. The nitrous oxide gas inhalation technique was introduced by Kety in 1948 allowing the measurement of CBF under more physiological conditions and, for the first time, in humans. Harper [1965] used this method to demonstrate that CBF did not change significantly in normocapnic dogs when MAP was lowered to 90mmHg.

In 1959, Lassen used a number of small studies performed in the early 1950's with Kety's inert gas method to describe cerebral blood flow and oxygen consumption in man. These studies used a variety of patients, including those with essential hypertension and toxaemia of pregnancy, and a variety of methods, including the infusion of pressor and depressor pharmaceutical agents, tilting and spinal anaesthesia, to demonstrate that CA is also active in man. A number of these studies were methodologically flawed, as the effect of essential hypertension, toxaemia and many pharmaceutical pressor and depressor agents on CBF and CA are even still unknown. Nevertheless, these studies suggested that CBF remained constant at approximately 0.5L/kg/min while MAP was within the range 60-150mmHg but that a pressure passive relationship developed outside this range. Using these concepts, Lassen constructed the now classic autoregulatory plateau (Figure 1.1)

Some of these original studies combined CBF measurement with arteriovenous oxygen extraction assessment. This technique demonstrated that, although CBF passively followed MAP below the autoregulatory range, brain function was not affected until CBF fell below 0.2L/kg/min, due in the main to increased oxygen extraction by the brain. It soon became clear that, below this critical level, symptoms of cerebral hypoperfusion, such as dizziness, pallor and sweating, occurred and that, unless CBF was rapidly restored to higher levels, cerebral infarction would occur. If

the upper limit of the autoregulatory range was exceeded, a passive increase in CBF with MAP occurred, causing disruption of the blood-brain barrier with consequent brain oedema and impairment of function.

1.3.2. Mechanisms of Cerebral Autoregulation

Changes in MAP can be classified as either static or dynamic [Aaslid 1989, Tiecks 1995]. Static BP changes allow CA to be studied over a prolonged period, and, therefore, allow assessment of the overall efficiency of the system [Paulson 1990]. Dynamic BP changes, however, are followed by restoration of CBF to baseline within 8-20 seconds when CA is intact and such rapid step changes in BP may be used to assess the latency of the CA system [Paulson 1990]. This distinction between cerebral autoregulatory responses as either static or dynamic CA is important because responses may be effected by different physiological mechanisms and affected differently by pathological conditions such as acute ischaemic stroke [Tiecks 1995, Dawson 2000]. Baumbach [1985] also explored the temporal heterogenecity of CA and demonstrated that the blood-brain barrier was more susceptible to hypertensive disruption after rapid, rather than step-wise, increases in systemic BP.
Precisely how the brain alters vessel diameter to effect the process of CA remains unclear, but a number of theories have become well established.

1.3.2.1. Tissue perfusion theory

This early theory attempted to explain the phoenomenon of autoregulation through the response of venules to external pressure [Johnson 1964]. It was hypothesised that an increase in MAP, and hence CBF, increased extracellular tissue fluid production which, in turn, encroached on low pressure veins causing an increase in back pressure

to the arterial system, reducing PP and returning CBF to baseline levels. Such a passive mechanism suggests that CA should be immune to external manipulation with drugs, which does not appear to be the case (see section 1.3.3.5.). A number of other findings are also incompatible with the theory. Mathematical modelling has demonstrated that a pressure dependent mechanism could not explain the autoregulatory plateau [Koch 1964]. The theory does not account for Fog's findings of variations in the directly measured diameter of cat pial arterioles [1937] and the role of osmotic pressure on extracellular fluid formation has not been considered. Consequently, the tissue perfusion pressure theory as an underlying mechanism of CA has fallen from favour, but may have some merit in explaining the effects of ICP on PP.

1.3.2.2. Metabolic theory

Changes in cerebral PP lead to accumulation or clearance of vasoactive metabolites in the perivascular space. Oxygen and metabolites produced during cellular function, e.g. carbon dioxide, adenosine and hydrogen, potassium and calcium ions, have vasoactive effects, predominantly dilatory. The metabolic theory of CA suggests that periods of local cerebral hypoperfusion result in the release and accumulation of vasoactive chemicals that produce vasodilatation of cerebral vessels. Hypoxia [Kontos 1978b] and hypercapnia are two of the most powerful stimuli increasing global CBF. Hypocapnia reduces CBF and widens the plateau region of the static pressure autoregulation curve, representing an improvement in autoregulatory capacity [Paulson 1990]. Hypercapnia has the opposite effect with an upward shift of the static autoregulatory curve and disappearance of the plateau at very high levels of CO_2 [Harper 1966]. More recently, hypercapnia has also been shown to reduce

[Zhang 1998a, Panerai 1999b, Birch 1995] and hypocapnia to enhance [Birch 1995] the efficiency of dynamic CA.

Again, a number of weaknesses exist in the metabolic theory. Adenosine has been shown to increase during periods of hypoperfusion, but caffeine, an adenosine antagonist, has not been shown to date to change CBF [Kontos 1985]. Hypotension per se has not been shown to alter potassium and hydrogen ion concentrations [Kuchinsky 1978]. Both hypoxia and hypercapnia would require the release of a mediating substance to affect CVR and this would probably take longer than the 8-20 second time period seen for the dynamic CA response. Therefore, the metabolic theory cannot be completely rejected, especially when considering static CA, but other mechanisms must be explored to satisfactorily explain the phoenomenon of dynamic CA.

1.3.2.3. Myogenic theory

The myogenic theory states that the smooth muscle of cerebral vessels is responsive to changes in transmural pressure with small arteries and arterioles constricting or dilating in response to increases or decreases respectively in transmural pressure. In other words, the ability to vasoconstrict with hypertension and vasodilate with hypotension is an intrinsic property of cerebral blood vessels. This theory was first proposed by Bayliss in 1902 following examination of the effects of altered PP on denervated isolated canine hindlimbs. A myogenic mechanism would be rapid and help explain the response of the cerebrovasculature to dynamic BP changes, but precisely how the mechanism works is unclear. Stretch of smooth muscle in vascular walls could alter membrane permeability to ions such as calcium, cause changes in membrane potential and ultimately modify the status of actin and myosin filaments in

the smooth muscle [Paulson 1990]. Evidence for this hypothesis exists in the form of an increase in frequency and amplitude of spontaneous action potentials in rat arteries in response to rises in MAP [Harder 1985]. In addition, Thorin-Trescases et al [1997] demonstrated an inverse relationship between the diameter of human pial arterioles and the level of tone at an intraluminal pressure range of 60-90mmHg, a finding that also supports the involvement of a myogenic process in CA.

Wagner et al [1985], however, suggested that CA was a function of the cerebral PP gradient and could not be fully explained by a myogenic mechanism.

1.3.2.4. Neurogenic theory

The neurogenic hypothesis states that the autoregulatory adjustment of the calibre of resistance vessels is mediated by vascular innervation. This theory assumes that there is a reflex arc by which changes in cerebral PP control the diameter of resistance vessels via efferent extrinsic vasomotor nerves. There is substantial histological evidence for a dense neurological innervation of extraparenchymal and intraparenchymal tissues [Rosenblum 1971, Harper 1975]. In general, larger arteries are densely innervated with plexuses diminishing in size as vessels become smaller. The extrinsic nerves originate mainly from the cranial ganglia and consist predominantly of adrenergic fibres, especially around the anterior cerebral, middle cerebral, internal carotid and posterior communicating arteries. Constrictor α receptors and dilatory β_1 receptors have been identified in these nerves [Heistad 1978a] and in vitro and in vivo studies have demonstrated vasoconstriction of cerebral vessels in response to direct and intravenous administration of noradrenaline and inhibition of this vasoconstriction by the α-adrenergic blocker phenoxybenzamine

[Rosenblum 1971]. Stimulation and denervation of α-adrenergic perivascular sympathetic nerves at the level of the superior cervical ganglion results in changes in cerebral blood volume, intracranial pressure and the formation of cerebrospinal fluid [Heistad 1978a]. These findings may, however, be due to changes mediated in the large extracranial vessels rather than those concerned with CA and few studies have imaged small vessels to directly document calibre changes. Carotid baroceptor stimulation does not cause a change in CBF [Heistad 1976] and sectioning of the superior cervical sympathetic trunk distal to the superior cervical ganglion does not alter basal CBF [Heistad 1978b].

A large number of animal and human experiments have examined the role of the sympathetic system in CA by assessing CA and cerebral reactivity in response to pharmacological and non-invasive manipulation of BP, exsanguination and CO_2 inhalation [Eklöf 1971, Skinhøj 1972, 1973, Heistad 1978a, Hernandez-Perez 1975, Harper 1975, Roatta 1998]. Overall, these studies have demonstrated no effect of the sympathetic nervous system on CBF within the normal range (60-140mmHg) of systemic MAP. There is some evidence, however, that activity of the sympathetic nervous system extends the autoregulatory plateau at both extremes and may thus play a role in protecting the brain from extremes of hypo- and hyper-perfusion [Harper 1975, Hernandez-Perez 1975, MacKenzie 1977, Sadoshima 1985, Talman 1994]. Others have found that pharmacological blockade of the sympathetic nervous system does not alter the upper BP level of the autoregulatory plateau [Skinhøj 1973]. More recently, Roatta et al [1998] used the cold pressor test to demonstrate that a moderate sympathetic stimulus may affect both large and small cerebral vessels well below the accepted upper limit of the autoregulatory plateau.

The role of the parasympathetic system, which originates from the sphenopalatine and otic ganglia, is unclear. Parasympathetic stimulation in sympathetically denervated rats does not cause an increase in CBF, but parasympathetic denervation may extend the autoregulatory plateau at lower BP levels in rodents [Morita 1994].
In conclusion, the parasympathetic system appears to have little role to play in the control of CA. The sympathetic system also seems to play a minor role at physiologically normal systemic BP levels, but may, however, extend the range of CA by its action on extraparenchymal vessels.

1.3.2.5. Endothelial derived factor theory

This hypothesis states that endothelial derived factors mediate CA through increases or decreases in endothelial derived relaxing factor (EDRF) and endothelial derived constriction factor (EDCF). EDRF has recently been identified as nitric oxide (NO) [Moncada 1988] and has been proposed as playing an important role in the regulation of CBF [Cohen 1995, Iadecola 1994a, 1994b, Brian 1996, Toda 1996, Bryan 1995, Kontos 1993, Okamoto 1997a]. The findings that inhibitors of NO synthetase reduce basal CBF, and that NO concentrations do not appear to be affected by changes in oxygen or glucose metabolism, imply a role for NO in the maintenance of basal tone [Gardiner 1990, Prado 1992, Faraci 1991, Iadecola 1994a, 1994b]. NO may also mediate cerebral vascular responses to acetylcholine, substance P, bradykinin and α_2-adrenergic receptor agonists [Brian 1996, Toda 1996, Bryan 1995]. There is also evidence that NO contributes to the rise in CBF produced by hypercapnia [Iadecola 1994a, 1994b, Toda 1996, Okamoto 1997a] and inhalational anaesthetics [Koenig 1994, McPherson 1993, Okamoto 1997b], though NO synthetase inhibitors do not seem to inhibit the hypercapnic hyperaemic response in humans [White 1998].

Moreover, several studies have indicated that inhibitors of NO synthetase attenuate the CBF changes in response to electrical stimulation [Akgoren 1996], seizures [Toda 1996] and nociceptive stimulation [Cholet 1996]. Neuronal NO may also be released directly by nerve endings into the vascular adventitia resulting in the relaxation of vascular smooth muscle in the cerebral circulation [Bredt 1990, Rodrigo 1997, Yoshida 1994]. The vasodilator actions of NO in the cerebral circulation are generally thought to be due to the stimulation of guanylate cyclase / Ca^{2+}-activated K^+ channels in vascular smooth muscle cells [Cohen 1995, Loscalzo 1995]. Activation of these channels hyperpolarises vascular smooth muscle and limits Ca^{2+} influx through voltage gated channels [Cohen 1995]. Recent studies have used inhibitors of guanylate cyclase to suggest that the vasodilator response to NO in pial arterioles in vivo and in vitro is mediated by cGMP-dependent and cGMP-independent pathways [Alonso-Galicia 1999, Faraci 1999, Cohen 1995, Weisbrod 1998].

The role of NO in CA is contraversial. Some investigators have suggested that NO synthetase inhibitors abolish CA [Kobari 1994a, Tanaka 1993] but this is disputed by others [Iadecola 1994a, 1994b].

At least two other important endothelial products have been identified, prostacyclin (a vasodilator) and endothelin-1 (a vasoconstrictor) [Cohen 1995]. How these endothelial products affect CBF and CA is unclear, but endogenous endothelin-1 may have a role to play in the control of the vascular tone of human pial arteries [Thorin 1998]. Moreover, intravascular infusions of low doses of endothelin-1 cause cerebral microvessel vasoconstriction in cats, but infusions of larger doses cause vasodilation, probably through the induction of NO in cerebrovascular endothelium [Kobari 1994b]. Inhibitors of cyclooxygenase, such as indomethacin, reduce basal CBF probably by interfering with the vasodilatory actions of prostacyclin [Markus 1994].

It is not clear which of these mechanisms if any is predominantly responsible for CA. It may be that neurogenic, endothelial and metabolic factors modulate an intrinsic vascular myogenic response by influencing the rapidity of the response, the slope of the pressure-flow relationship and range of the autoregulatory plateau. It is also possible that cerebral blood vessels autoregulate by different mechanisms according to their location and size. This is supported by the findings of Baumbach et al [1985] who, suggested that CA displayed regional and segmental heterogenecity as well as the temporal heterogenicity mentioned earlier. Regional differences in CA were confirmed by the finding that brainstem CA was more effective than cerebral CA in the face of increases and decreases of cerebral PP. The same investigators also suggested that segmental CVR indicated that small cerebral vessels (<200μm in diameter) made significant contributions to CA in the MAP range of 80-100mmHg while the role of large cerebral arteries (>200μm in diameter) became increasingly important at higher MAP levels.

1.3.3. Factors that may affect cerebral autoregulation

CBF and CA are thought to be influenced not only by pathological states, but also by a number of other physiological and non-physiological parameters and it is essential that these parameters are considered when studying CA.

1.3.3.1. Carbon dioxide partial pressure

Arterial pCO_2 and, to a lesser extent cerebrospinal fluid pCO_2, have profound effects on CBF. As mentioned earlier, CO_2 has marked vasodilatory effects on the cerebrovasculature which add credence to the metabolic hypothesis of CA. Indeed,

inhalation of fixed concentrations of CO_2 (usually 5%) has been widely used as a method of measuring cerebral vasodilatory reserve capacity, also referred to as cerebral reactivity (CR) [Paulson 1972, Markwalder 1984, Ameriso 1994]. CR cannot be compared with CA, the response to changes in MAP, and, indeed, CR and CA may be affected differently by various processes - so called "dissociated vasoparalysis". Studies of CR have, however, shown that CBF increases with rises in pCO_2 and that there may be an exponential relationship between the two [Paulson 1972, Markwalder 1984, Ameriso 1994]. Previous animal work has suggested that the CBF response may be blunted at extremes of pCO_2 [Harper 1965].

In addition to effects on CBF, changes in pCO_2 have also been shown to profoundly affect CA. Hypocapnia reduces CBF and widens the plateau region of the static pressure autoregulation curve, representing an improvement in autoregulatory capacity (Figure 1.1.) [Paulson 1990]. Hypercapnia has the opposite effect with an upward shift of the static autoregulatory curve and disappearance of the plateau at very high levels of CO_2 (Figure 1.1.) [Harper 1966]. Aaslid et al confirmed the impairment of CA during hypercapnia and augmentation during hypocapnia with the use of the thigh-cuff technique in 1989. More recently, hypercapnia has also been shown to reduce [Zhang 1998a, Panerai 1999b, Birch 1995] and hypocapnia to enhance [Birch 1995] the efficiency of dynamic CA.

As pCO_2 has such profound effects on CA, we believe that CO_2 assessment is vital in any study of CA.

1.3.3.2. Age

The cardiovascular system demonstrates many age-related changes as evidenced by the well-recognized increase in systolic blood pressure (SBP) [Kannel 1978] and

decreases in systemic artery compliance, endothelial NO release and cardiac BRS with age [Fleg 1986, Gribbin 1971, Dawson 1999b, Tschudi 1996]. Aging, through the use of the nitrous oxide and Xenon clearance methods, has also been shown to be associated with a demise in CBF and CBF volume [Kety 1956, Naritomi 1979, Shaw 1984, Matsuda 1984]. Transcranial Doppler ultrasound has appeared to confirm these findings by demonstrating reduced cerebral blood flow velocities with advancing years [Martin 1994, Krejza 1999]. In addition, it has been suggested that CR also decreases with age and that coincident vascular risk factors augment the decrease [Yamamoto 1980, Yamaguchi 1979]. Davis et al [1983] contradicted these findings, however, by finding no age-related differences in CR assessed by CO_2 inhalation, although, contrary to others, they also claimed no reduction in cerebral white matter blood flow. A recent study used the breath-holding index to show an age-related decrease in CR between pre- and post-menopausal women [Matteis 1998]. No difference was shown between young and older men, however, and the findings in women may, therefore, reflect the influence of hormonal factors rather than age per se (see next section).

Senescent rats demonstrate a pressure passive relationship between CBF and BP, suggesting impairment of CA [Hoffman 1981], and this is accentuated in spontaneously hypertensive breeds, implying that age-related BP changes may be more important than age per se. The effects of age on CA in humans, however, are unknown and the hypothesis that the integrity of CA diminishes with age forms the basis of one of our studies. Nevertheless, in view of the known effects of age on CBF and CR, age should be a controlled factor in studies of CA until further evidence of the effect of age on CA is available.

1.3.3.3. Gender

Women have been shown to have higher levels of CBF until the menopause, a finding potentially attributable to female hormones, such as oestrogens or progestogens, or to the lower haematocrit, a factor compounded by menstrual blood loss [Kety 1956, Martin 1994, Karnik 1996]. Two studies assessing CR, one with CO_2 inhalation and the other with acetazolamide injection, demonstrated increased vasodilatory responses in pre-menopausal women [Karnik 1996, Kastrup 1998]. The effects of gender on CA, however, are unknown and, in view of the known effects on CBF and CR, gender should be a controlled factor in studies of CA.

1.3.3.4. Blood pressure

There is considerable experimental evidence that vascular histology changes as systemic BP levels increase. Smooth muscle hypertrophy and thickening of the extracellular matrix, through alterations in laminin, fibronectin and collagen IV, lead to an increase in the media to lumen ratio and changes in vascular resistance through reduced vascular stress (Laplace's Law) [Harper 1984, Faraci 1990, Slivka 1991, Nag 1997]. The effects of these changes on CBF are, however, unclear. No differences in CBF were demonstrated between spontaneously hypertensive rats and normotensive Wistar Kyoto rats [Hoffman 1981]. CBF was diminished, however, particularly in frontal cortical areas, in stroke-prone spontaneously hypertensive rats when compared to normotensive Wistar Kyoto rats and stroke-resistant spontaneously hypertensive rats [Yamori 1977]. These latter findings may suggest an influence of genotype or vascular disease on CBF rather than an influence of hypertension per se.

Human studies have been equally inconclusive. A number of investigators have found no change in CBF in hypertensive patients [Kety 1947, Faraci 1990, Thulin

1993]. The study of Kety et al [1947] also demonstrated that the oxygen extraction fraction was unchanged, but that cerebrovascular resistance increased with BP. Conversely, others have implied that CBF is reduced in hypertensive patients after finding reduced oxygen consumption with the use of an arteriovenous oxygen extraction technique [Strandgaard 1973]. Untreated hypertensive patients were shown to have lower CBF when compared with age and sex matched well-controlled hypertensives and normotensives [Nobili 1993]. This finding was confirmed by PET scanning and internal jugular monitoring [Fujishima 1995, Lambert 1996] methods which also uncovered regional differences in CBF, consisting of selectively larger decreases in CBF in the frontal cortex and basal ganglia.

The effect of hypertension on cerebral reactivity (CR) is also disputed. Tominaga et al [1976] found no alteration in the cerebrovascular response to inhaled CO_2 or hyperventilation in the pCO_2 range of 20-55mmHg, while more recent TCD studies have suggested that CR is impaired in hypertension [Maeda 1994].

CA has, however, been shown to be affected by hypertension, predominantly in the form of a shift in the static autoregulatory curve to the right (Figure 1.1.) [Strandgaard 1973, 1976, 1989, Hoffman 1981, Fujishima 1984]. There is evidence that this shift increases with longer durations of hypertension and that effective treatment may reverse the trend [Strandgaard 1976, 1989, Harper 1984, Slivka 1991, Nag 1997]. The shift in the autoregulatory curve to the right may have a protective function against severe hypertension, but it is unclear if the changes become permanent when present for a length of time or how soon after the instigation of treatment that reversal of the changes may be seen [Strandgaard 1976].

Despite a clear demonstration of a shift in the static autoregulatory curve to the right, it is unclear if CA is actually impaired by the shift. Faraci et al [1987] demonstrated

increased resistance in large and small cerebral vessels in cats, but only small vessels showed an increase in resistance in the brainstem. Severe hypertension, however, caused a fall in resistance in the cerebrum, suggesting impaired CA, but maintenance of high resistance in the brainstem vessels, again indicating possible regional differences in the effect of BP on CA.

A recent study in humans suggested that dynamic CA is preserved in untreated hypertensive patients [Blake 1999], but data concerning the effect of BP on dynamic CA is otherwise scarce.

In view of the uncertainty of the effects of BP on CA, BP should be a controlled factor in studies of CA.

1.3.3.5. Drug therapy

May different classes of drug affect CBF, CA and CR and much work has been done assessing the effects of antihypertensive agents.

Diuretics lower systemic BP without affecting CBF [Venkata 1987, Semplicini 1993, Landmark 1995], but do not appear to improve impaired CR in hypertensive subjects [Traub 1982]. Calcium antagonists also lower systemic BP without affecting CBF [Thulin 1993, Landmark 1995, Pandita-Gunawardena 1999] and, in addition, appear to correct the autoregulatory shift induced by hypertension (see section 1.3.3.4) [Fujishima 1995]. β adrenergic receptor blockers may increase resistance in the small cerebral vessels responsible for CA and lower the vasodilatory capacity to CO_2 challenge and hypotensive stress [Mathew 1973, Fujishima 1995]. Longer term administration at higher doses, however, may increase CBF through a vasodilatory action on the cerebral circulation [Globus 1983]. α adrenergic receptor blockers

reduce systemic BP with debate over whether CBF is subsequently increased [Mathew 1973, Fujishima 1995] or unchanged [Venkata 1987]. Angiotensin converting enzyme (ACE) inhibitors reduce systemic BP in humans without affecting CBF [Waldemar 1989, 1990, Semplicini 1993, Démolis 1993] and may correct the shift of the autoregulatory curve to the right [Waldemar 1989] resulting in an improvement in vasodilatory reserve to acetazolamide [Démolis 1993]. In addition, inhibitors of ACE may reduce the upper limit of static CA leading to a shortening of the autoregulatory plateau [Squire 1994].

Finally, the general anaesthetic agent propofol does not affect CA but isoflurane and desflurane may alter dynamic and then static CA [Strebel 1995].

1.3.3.6. Posture

Posture has been shown to have an effect on CBF. Transcranial Doppler ultrasonography has consistently shown reduced CBFV after HUT [Schondorf 1997, Stoll 1999, Cencetti 1997, Grubb 1991a], during lower body negative pressure [Bondar 1995,1994, Levine 1994, Giller 1992] and during active standing [Savin 1995] and higher CBFV during head-down tilt [Savin 1995]. Changes in CBFV may be due to a variety of different reasons, including altered systemic sympathetic activation [Bondar 1994, Levine 1994] or changes in the diameter of the MCA, although recent work has suggested that MCA calibre does not change during simulated orthostasis [Serrador 2000]. Furthermore, a direct relationship has been shown between the physiologically lower CO_2 levels after HUT and reduced CBFV [Cencetti 1997].

In spite of the CBF changes demonstrated on posture, little information exists on the effect of posture on CA. Using frequency domain analysis and lower body negative pressure, Zhang et al [1998b] suggested that CA may deteriorate during orthostatic

stress. Conclusions were based, however, on the transfer-function gain between pressure and velocity, the interpretation of which is a matter of some debate. In addition, coherence and phase results from the same work do not support worsening of CA with orthostatic stress. Methodology using rapid thigh cuff deflation has failed to demonstrate any deterioration in dynamic CA with 40° HUT [Leftheriotis 1998] but this angle of tilt is significantly lower than angles currently used for HUT testing [Kenny 2000]. More recently, infared spectroscopy has been used to demonstrate a significant decrease in cerebral oxygenation during active standing in healthy elderly subjects with no change in the cerebral oxygenation of younger subjects [Mehagnoul-Schipper 2000]. This could result from inferior CA in elderly subjects on standing, but cerebral oxygenation is not a surrogate for CA and only frontal oxygenation was measured in the study.

The precise effect, therefore, of changing posture on CA is unclear and requires further investigation.

1.3.3.7. Miscellaneous factors

Tobacco smokers have significantly lower CBF [Shaw 1984], a 48% reduction in vasodilatory capacity to CO_2, and a 24% reduction in vasoconstriction to 100% oxygen compared with healthy controls [Rogers 1984]. The act of smoking, however, increases CBF [Boyajian 2000] through mechanisms that are unclear.

Xenon inhalation studies have demonstrated reduced CBF in subjects with heavy alcohol consumption [Shaw 1984, Rogers 1983].

Patients with transient ischaemic attacks and hyperlipidaemia have been shown to have significantly lower CBF than similar patients with normal lipid profiles, but

normal subjects with hyperlipidaemia appear to have no significant trend towards reduced CBF [Meyer 1987].

Whole blood viscosity is mainly determined by haematocrit, and CBF has been shown to be inversely proportional to both haematocrit and whole blood viscosity, as well as fibrinogen levels [Thomas 1982, Nelson 1956, Ameriso 1990]. It is thought that the inverse relationship of CBF with haematocrit is not due to sluggish blood flow at higher viscosities, but rather that the higher oxygen content of high-haematocrit blood allows the maintenance of oxygen delivery in the face of lower CBF.

Although the above factors have been shown to affect CBF, their influence on CA is unknown. In view of these uncertainties, it is sensible to control for as many of these factors as possible when studying CA.

Figure 1.1. Autoregulatory curves of a normal subject at rest (black) and during hypercapnia (solid blue) and hypocapnia (dotted blue) and of a normocapnic hypertensive subject (red).

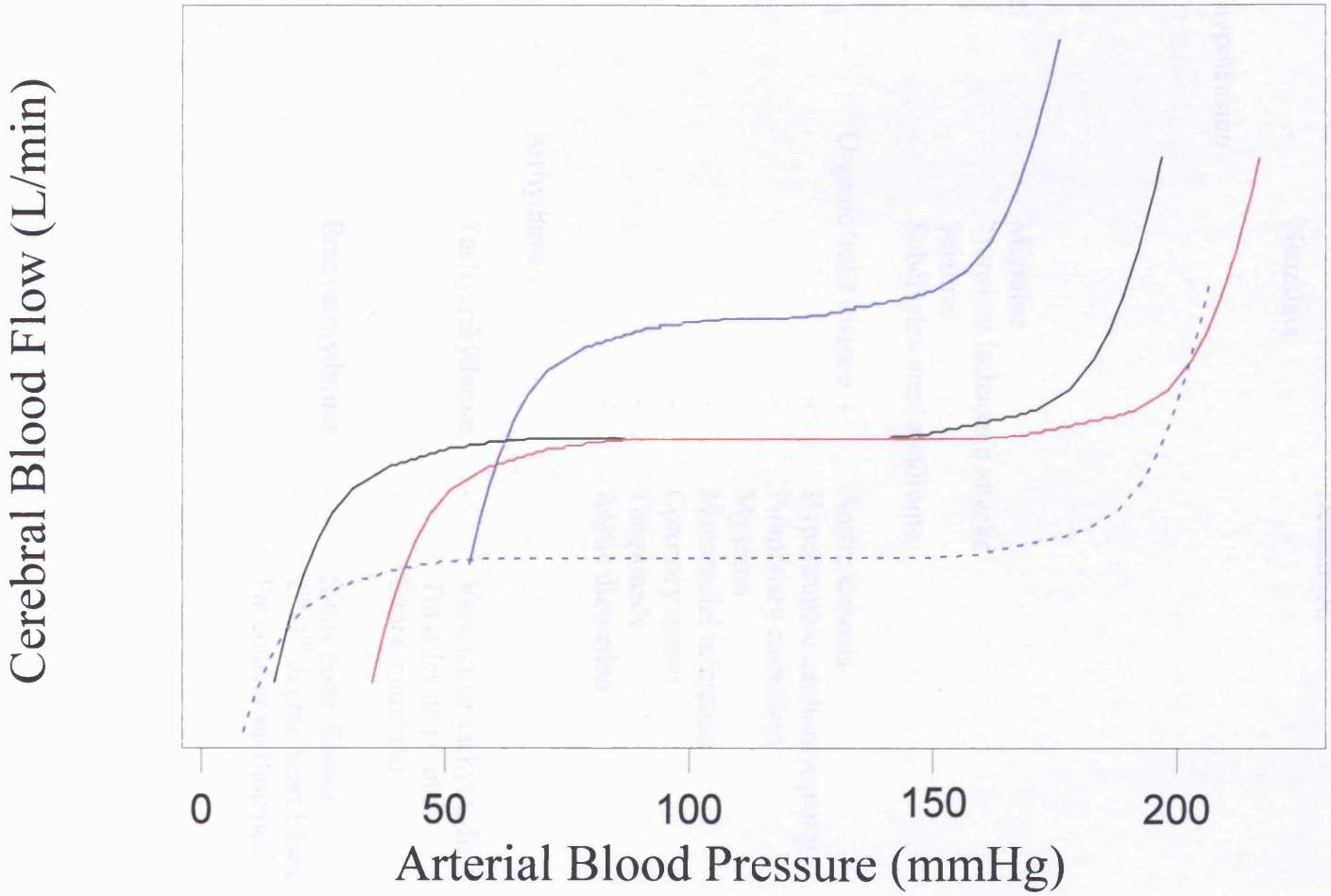


Figure 1.1.

Table 1.1. Causes of Syncope

- Reflex mediated
  - Vasovagal
  - Carotid sinus syndrome
  - Situational
    - Deglutition
    - Cough
    - Micturition
    - Defecation
  - Neuralgia
- Orthostatic hypotension
- Cerebral
- Psychogenic
- Neurological
  - Migraine
  - Transient ischaemic attacks
  - Seizures
  - Subclavian steal syndrome
- Cardiac
  - Organic heart disease
    - Aortic stenosis
    - Hypertrophic cardiomyopathy
    - Pulmonary embolism
    - Myxoma
    - Myocardial infarction
    - Coronary spasm
    - Tamponade
    - Aortic dissection
  - Arrhythmias
    - Tachyarrhythmias
      - Ventricular tachycardia
      - Torsades de pointes
      - Supraventricular
    - Bradyarrhythmias
      - Sinus node disease
      - $2^{nd}/3^{rd}$ degree heart block
      - Pacemaker malfunction
- Iatrogenic
- Idiopathic

Table 1.2. Investigations for Syncope

Investigation	Diagnostic Yield
Electrocardiography	5%
"Routine blood tests"	2-3%
24-hour Holter monitoring	19%
Echocardiography	5-10%
Tilt-table test & Carotid sinus massage	26-90%
Loop recorder	24-47%
Electroencephalography	1-2%
Electrophysiological studies	10-50%
Computed tomography of the brain	4%
Magnetic resonance imaging of the brain	4%
Exercise stress test	<1%
Thallium stress test	<1%
Psychiatric evaluation	5-24%
Carotid Doppler ultrasonography	6%
Transcranial Doppler ultrasonography	Unknown

Table 1.3. Classification of Vasovagal Syncope

Type 1 (mixed)

Systolic BP <80 mmHg and heart rate >40bpm

or

Systolic BP <80mmHg and heart rate <40 bpm for <10 seconds

or

Systolic BP <80mmHg and asystole for <3 seconds

Type 2 (cardioinhibitory)

Heart rate ≤40 beats per minute for >10 seconds *or* asystole for >3 seconds

2A BP falls prior to fall in heart rate

2B BP falls at or after onset of fall in heart rate

Type 3 (vasodepressor)

Systolic BP <80mmHg and heart rate >90% of its peak value at syncope

CHAPTER TWO

Methods

2.1. Measurement of Cerebral Blood Flow

Cerebral blood flow (CBF), as discussed in section 1.2, is primarily dependent on perfusion pressure (PP) and cerebrovascular resistance (CVR), but recent developments have suggested that the critical closing pressure (CrCP) of the cerebral circulation, i.e. the pressure below which blood flow in a vessel ceases, may have an important role to play [Dewey 1974, Dawson 1999a)]. CBF was first measured in animals using invasive methods such as bubble flow meters, but less invasive techniques had to be developed for use in human subjects. In this section, the most widely used techniques of measuring CBF in humans will be discussed, some of which are now largely of historical interest only, whilst concentrating on the currently most widely used technique, transcranial Doppler ultrasonography (TCD).

2.1.1. Nitrous Oxide Method

Initially described by Kety et al in 1948, this method employed the Fick principle and was the first method that could be applied to unanaesthetised subjects. The Fick principle states that the "quantity of any substance taken up in a given time by an organ from the blood that supplies it is equal to the amount of the substance carried to the organ by the arterial inflow minus the amount removed by the venous drainage in the same period", or:

$(Q_b)_u = (Q_a)_u - (Q_v)_u$

where $(Q_b)_u$ is the quantity of substance taken up by whole brain, $(Q_a)_u$ is the quantity contained in the arterial inflow and $(Q_v)_u$ is the quantity drained by the venous system. Nitrous oxide (N_2O), an inert gas, became the substance of choice for use with this technique because of its favourable solubility and diffusion characteristics. A low concentration was inhaled and CBF calculated using arterial and venous blood

samples acquired when equilibrium had been established, approximately 10 minutes after inhalation, according to the equations:

$$(Q_a)_u = TF \int_0^u A dt$$

$$(Q_v)_u = TF \int_0^u V dt$$

$$\therefore TF = \frac{(Q_b)_u}{\int_0^u (A - V) dt}$$

where A is the arterial concentration of N_2O, V the venous concentration and TF the total cerebral blood flow per minute. This technique was the first to approximate normal blood flow to be in the region of 0.5L/kg/minute, but had three inherent drawbacks. No compensation could be made for any inequalities that might exist in venous drainage by the two internal jugular bulbs, contamination of the venous drainage by extracerebral structures was an established risk and temporal resolution was extremely poor.

2.1.2. Xenon Inhalation / Injection Method

Devised in the 1960's, this method initially employed intracarotid bolus injections of radioactive ^{133}Xenon (Xe), but was later refined to utilise either inhaled or intravenously injected ^{133}Xe [Mallet 1965, Obrist 1975, Overgaard 1981, Bouma 1990]. Clearance curves of the γ radiation were measured by extracranial detectors, usually 8 in number, attached to the surface of the cranium. The intracarotid technique fell out of favour, not just because of its invasive nature, but also because it only allowed measurement of CBF in one anterior henisphere, unlike the inhalation and intravenous techniques which allowed examination of bilateral anterior and posterior circulations. All techniques employing ^{133}Xe were, however, limited by

poor temporal resolution and two other main limitations. Detectors only picked up changes occurring in the superficial brain structures and, therefore, yielded little in the way of anatomical information. In addition, hyperventilation often triggered by the process necessitated adjustment of CBF values for CO_2 levels.

2.1.3. Xenon enhanced computer tomography

This technique proved initially very attractive as it combined the use of computerised tomography to increase anatomical detail, especially of deep seated structures, with the use of non-radioactive Xe gas [Gur 1982]. Unlike earlier studies that assessed elimination, this technique assessed Xe uptake in different cerebral areas approximately 4 minutes after inhalation when equilibrium was thought to exist between end-tidal and arterial Xe levels. The high atomic number and high permeability across the blood-brain barrier the element allowed enhancement on CT scans at quite low inhaled concentrations. Calculation of CBF with this method, however, assumed uniform uptake throughout the brain substance but fast and slow flow areas led to inevitable error. While some mathematical compensation could be made for variations in uptake, substantial errors around pathological regions, e.g. between an infarct and its penumbra, severely limited its usefulness. Raised intracranial pressure was a recognised side effect of Xe and, once again, adjustment of CBF calculations for hyperventilation induced CO_2 changes was necessary. Temporal resolution was poor, and, in addition, difficulties with prototype CT scanners, such as high radiation dose, movement artefact and poor image resolution, compromised the safety and usefulness of the procedure.

2.1.4. Other radiological techniques

Positron emission tomography (PET), single photon enhanced computerised tomography (SPECT) and, more recently, phase contrast magnetic resonance angiography (PC MRA) [Patrick 1996] have emerged as exciting tools as they give information on cerebral metabolism as well as CBF with excellent morphological and anatomical detail. Expense and poor temporal resolution have, however, precluded their widespread use to date in the study of CBF and autoregulation.

2.1.5. Transcranial Doppler Ultrasonography

2.1.5.1. Physical and technical aspects

Christian Doppler first described the physical phoenomenon that has been named the Doppler principle when he noted that light waves were reflected at different frequencies when disturbed by a moving object. Satomura and Karubo first used the principle to study blood flow in 1960 and by 1965 Kato was using a transcranial Doppler (TCD) ultrasound technique to study CBF during neurosurgical procedures. Ultrasound refers to sound frequencies higher than 20 KHz. Current TCD techniques use a transducer (i.e. probe) with a peizoelectric crystal that generates ultrasound waves of a known frequency which are focused into a beam by a lens. When the beam is directed at a stream of moving red blood cells, the ultrasound waves are scattered and reflected back with a changed frequency to the transducer that also acts as a receiver. The change in frequency is known as the Doppler shift and is calculated according to the formula:

$$\Delta f = \frac{2(v\cos\theta)f_0}{c}$$

where Δf is the Doppler shift, v is the magnitude of scatter velocity, θ is the angle between the ultrasound beam and the direction of motion, f_0 is the original frequency

of the transmitted ultrasound beam and c is speed of propagation of ultrasound in soft tissues.

Because the sample volume contains a large number of cells causing different amounts of scatter, a spectrum of frequencies is relayed to the transducer. The maximum Δf is achieved by the highest cell velocity in the given time sample and the mean Δf reflects the mean velocity in the time sample [Gill 1985]. Accuracy is improved by the use of a Doppler beam that is uniform over the entire area of the insonated vessel [Evans 1982], and spatial resolution increased by the use of pulsed wave, rather than continuous wave, Doppler. The interface between the probe and the tissue being insonated is provided by a water-based coupling gel. Initial use of the technique for CBF measurement was hindered by the fact that most Doppler probes emitted a frequency that was absorbed or scattered by the cranial bones to such an extent that blood flow detection was impossible. However, 1982 saw the introduction of the PEDOF 2-MHz pulsed Doppler device which overcame these problems [Aaslid 1982] to allow measurement of blood flow velocity in large basal intracranial arteries. In addition, Aaslid appreciated the non-uniformity of the cranial bones and described the acoustic windows over the temporal, occipital and orbital bones. The introduction of a gated probe further improved the overall technique by allowing alteration of the depth of insonation and determination of the direction of blood flow either towards or away from the probe [Newell 1992].

Insonation may, however, prove technically impossible if an adequate acoustic window is not present, a finding commoner in older women and people of certain ethnic racial origins including the Chinese and Afro-Caribbean populations [Halsey 1990]. Detection rates in such subjects may be enhanced by increasing the probe

power from the usual 100mW/cm^2 to as much as 800mW/cm^2, but scalp discomfort and even burns may result from the use of such high powers [Halsey 1990].

2.1.5.2. Vessel identification and reproducibility

Aaslid [1982] described in detail the methods of insonation of the basal cerebral arteries comprising the Circle of Willis (Figure 2.1.) through the various acoustic windows (Figure 2.2). In doing so, he employed a 2-MHz probe with a high pass filter of 100 MHz, a low pass filter of 3.4-9 KHz, an emitted power of 350mW, a burst repetition of 6.8-18 KHz, a pulse length of 10μs and an emitting area of 1.5cm^2, i.e. 10 times the cross sectional area of the middle cerebral artery.

For the studies in this thesis, the proximal segment of the middle cerebral artery (MCA) was insonated, bilaterally when possible, through the transtemporal acoustic window using a SciMed QVL 120 TCD apparatus (Figure 2.3.). This is a purpose built, dual-channel machine as the use of two separate machines is practically impossible due to the asynchronicity of pulse repetition and frequency of both machines.

The transtemporal acoustic window lies immediately superior to the zygomatic arch, is comprised of a natural thinning of the temporal bone due to attenuation of the temporal squamosa, and is divided into three main functional areas - anterior, middle and posterior (Figure 2.2.). The posterior window is often the most successful point for MCA insonation and requires anterior and superior direction of the beam. Although as much as 39% of an ultrasound beam may be absorbed at this point, satisfactory insonation can be achieved in over 75% of subjects. In addition to the MCA, the terminal internal carotid artery (TICA), anterior and posterior cerebral arteries (ACA and PCA respectively) and the anterior and posterior communicating

arteries (ACoA and PCoA respectively) may be identified through the transcranial window. Accurate identification of vessels can be augmented by knowledge of the anatomy (Figure 2.1.), direction of flow, sampling depth and likely velocities [Aaslid 1982, Arnolds 1986, Martin 1994] of each vessel as well as the response of flow in each vessel to ipsilateral common carotid artery compression (Table 2.1.).

Using such methods, TCD has proven accurate in vessel identification and, if interhemispheric asymmetry is kept to a minimum, both inter- and intra-observer reproducibility is very good. Inter- and intra-observer reproducibility at 2 to 24 hours is <8% [Padayachee 1986, Totaro 1992, Demolis 1993, Baumgartneer 1994, Bay-Hansen 1997] and intra-observer reproducibility 13% at 2 months [Bay-Hansen 1997].

2.1.5.3. Validation as a method of measuring cerebral blood flow

CBF can be calculated from velocity measurements using the equation:

$$CBF = \sum_i v_i . \Delta A_i$$

where ΔA_i is the cross sectional area of the insonated vessel and v_i is the velocity of blood at the point cross section measured.

This calculation, however, assumes that there is no significant change in the diameter of the artery being insonated, that the angle of insonation is less than 30° (to reduce error in the calculation of velocity to <15%) and that the territory supplied by the artery in question is also constant. The angle of insonation is important as it can lead to significant underestimations of velocity a fact apparent in the equations:

$$\cos\theta^1 = \frac{\cos\theta}{\cos\eta}$$

$$V_t = \frac{V_{obs}}{\cos\theta}$$

where θ^1 is the measured angle, θ is the true angle, η is the angle of the vessel crossing the plane of imaging, V_t is the true velocity and V_{obs} is the observed velocity. The angle of insonation is generally assumed to be zero in most studies using TCD as it is impossible to measure it.

Changes in blood pressure and CO_2 and O_2 concentrations do not significantly alter the diameter of the MCA and other large basal cerebral arteries (<4%) but small distal vessels actively concerned with CA undergo considerable variation (>29%) [Hubner 1967, Giller 1993, Poulin 1996, Serrador 2000]. Attempts have been made to use Doppler spectral power to assess MCA vessel diameter during thigh cuff application and release [Aaslid 1989] and during hypocapnia and hypercapnia [Poulin 1996], but a recent study has cast doubt on the usefulness of this method of assessing vessel diameter [Deverson 2000]. A significant change in MCA diameter is unlikely, however, during thigh cuff inflation and release [Newell 1994b], lower body negative pressure [Serrador 2000], Valsalva manoeuver [Giller 1993, Tiecks 1996] or supine rest.

Because of the multiple assumptions, calculations of CBF from TCD measurements do not correlate well with values derived using the traditional methods of CBF measurement e.g. correlation between intravenous Xe clearance studies and TCD is 0.424 [Bishop 1986]. The correlation between CBF and velocities is much better, however, being approximately 0.63 between SPECT and TCD [Lindegaard 1987, Dahl 1992, Newell 1994b]. Even better correlation scores have resulted from comparisons between TCD velocities and CBF measurements during manoeuvres e.g. correlation between TCD velocities and Xe clearance is as high as 0.85 when testing cerebrovascular reactivity [Bishop 1986, Kontos 1989, Dahl 1992, Larsen 1994, Sugimori 1995]. Therefore, although TCD does not lend itself well to the absolute

calculation of CBF, velocity and changes in velocity correlate well with CBF results obtained using traditional techniques. Consequently, TCD-derived velocities from the main basal cerebral arteries (usually the MCA) have been widely used as a surrogate for CBF and to reflect changes in hemispheric CBF.

TCD machines can now display continuous beat-to-beat velocity profiles of basal cerebral arteries by performing power spectral analysis of the received signal using fast Fourier transformation (FFT) [Attinger 1966]. The information is displayed as an X-Y representation, the X-axis representing time and the Y-axis representing velocity in cm/s, with the intensity of the reflected signal represented by the brightness of the displayed velocity (Figure 2.4.). Conversion by spectral analysis yields an analogue output similar to the output from a non-invasive BP monitor, thus enabling measurement of beat-to-beat changes and the assessment of dynamic changes with a remarkable degree of temporal resolution [Aaslid 1982].

2.1.5.4. Calculation of indices of cerebrovascular resistance & critical closing pressure using transcranial Doppler ultrasound measured cerebral blood flow velocity

As discussed in section 1.2, cerebrovascular resistance (CVR), is one of the primary determinants of CBF and transcranial Doppler ultrasound has been used to derive various indices of CVR.

Gosling's pulsatility index (GPI) [1974] and Pourcelot's Resistance Index (PRI) [Planiol 1974] were among the first indices described:

$$GPI = (V_s - V_d) / V_m$$

$$PRI = (V_s - V_d) / V_s$$

where V_s, V_d and V_m represent systolic, diastolic and mean CBFV respectively.

The accuracy and tendency of these indices are practically identical in most applications, but GPI has probably been more widely used [Gomez 1999, Njemanze 1993, Daffertshafer 1995, Grubb 1998, Fredman 1995]. The attractiveness of these indices is that they may be derived from TCD recordings alone and do not require simultaneous measurement of arterial BP. The main drawback, however, is that both indices are small in magnitude and easily overshadowed by central cardiovascular factors [Aaslid 1992]. In addition, both indices were derived to reflect the interplay between the resistance and compliance components of the cerebrovascular bed, and neither index, therefore, directly reflects any physiological property such as CBFV, CVR or vasomotor tone [Aaslid 1992]. Moreover, a recent animal study has suggested that there may, in fact, be an inverse relationship between GPI and CVR [Czosnyka 1996a].

Classical CVR (CCVR) may be a more accurate index of CVR as it is calculated using the Poiseuille equation which takes arterial BP into account:

$$CCVR = \frac{Mean\ ABP}{Mean\ CBFV}$$

CCVR, unlike GPI and PRI, is therefore less likely to be overshadowed by central cardiovascular factors. Calculation of CCVR, however, makes the assumption that CBFV always intersects the ABP axis at 0mmHg (i.e. that blood flow continues even at very low levels of ABP), ignoring the critical closing pressure (CrCP) of the cerebral circulation (Figure 2.5.).

CrCP refers to the pressure below which blood flow in a vessel ceases and may have a profound effect on CBF [Burton 1951, Aaslid 1992, Dewey 1974, Dawson 1999a, Panerai 1995, 1996, 1999b, Garnham 1999, Carey 2000]. CrCP has an inverse relationship with CO_2 levels [Aaslid 1992, Panerai 1999b. Garnham 1999] and can change over a matter of seconds [Carey 2000]. Perhaps the most well described

method of calculating CrCP involves plotting the instantaneous relationship between CBFV and ABP for each cardiac cycle and performing linear regression to the ABP axis [Aaslid 1992, Panerai 1999b, 1995, Carey 2000, Garnham 1999, Dawson 1999a] (Figure 2.5., line 2). In addition, this method has been validated for very low levels of ABP [Carey 2000]. The point of intercept of the arterial BP axis represents the CrCP while the inverse of slope of the line represents the resistance-area product (RAP). RAP, therefore is a similar resistance index to CCVR, but probably superior as it allows for changes in CrCP. RAP may, therefore, be the best index of CVR as it allows for changes in both CrCP and ABP and it truly reflects the beat-to-beat changes in the instantaneous relationship between CBFV and arterial BP. Examination of Figure 2.5. should make it clear that changes in cerebral perfusion may occur through changes in CrCP without changes in RAP (line 3) and vice versa (line 1).

In conclusion, TCD is a relatively simple, well-tolerated, non-invasive technique for the assessment of CBF using basal cerebral artery blood flow velocities as a surrogate for CBF. It has been validated against traditional techniques, has a high degree of reproducibility and excellent temporal resolution, enabling assessment of both dynamic and static changes.

2.2. Non-invasive continuous blood pressure monitoring

Assessment of cerebral autoregulation (CA) requires measurement of the beat-to-beat response in CBF/MCAV to beat-to-beat changes in arterial BP. Intra-arterial monitoring remains the "gold standard" for continuous measurement of BP, but this is invasive, painful and entails inherent significant risks of thromboembolism,

haemorrhage, local and systemic infection and arterial dissection [Mangato 1979]. Servo-controlled plethysmomanometry permits non-invasive, continuous beat-to-beat recording of peripheral arterial BP and is based on the principles of "vascular unloading" and the "arterial volume clamp" first reported by Penaz [1973]. The development of fully automated instruments was a long awaited step forward in the technique of BP measurement. A number of commercially available, non-invasive, continuous BP monitors currently exist, including the Finapres 2300 system (Ohmeda, Colarado, USA) (Figure 2.6.).

The Finapres employs an infared finger photoplethysmograph surrounded by a fluid filled pressure cuff. An appropriately sized cuff is placed around each subject's finger, usually the middle finger of the non-dominant hand, and automatically inflated until the maximal plethysmographic finger pulsation is detected (Figure 2.6.). A finger volume is then calculated and the cuff aims to keep this value constant by a negative feedback loop (servo-adjust mechanism). Any adjustment reflects a change in arterial BP which is duly recalculated on a beat-to-beat basis. Results can be downloaded onto a computer, printed out or recorded directly onto a digital analogue tape (Figure 2.6.).

A number of studies have validated this system against intra-arterial brachial measurements in a variety of situatuions. Imholz et al [1988] found that the Finapres device reproduced intra-arterial BP patterns at rest faithfully, with values underestimated by 1 ± 10 mmHg, 9 ± 7 mmHg and 4 ± 6 mmHg for SBP, DBP and MAP respectively. Others have also examined the reliability of the Finapres in a variety of invasive and non-invasive physiological settings [Parati 1989, Lal 1995, Rongen 1995]. Manoeuvres used included the Valsalva manouevre, isometric hand grip, cold pressor test, mental arithmetic, passive leg tilt, lower body negative

pressure and passive and active standing, some of which have been employed during this research project. The Finapres tended to underestimate readings, particularly for SBP, in those studies but detected the same trends of change with accurate temporal representation. McAuley [1997], however, demonstrated that the Finapres SBP level was consistently and significantly higher than the intra-brachial value and that the difference increased during the cold pressor test. Omboni [1993] demonstrated that standard deviations of DBP, MAP and pulse interval were similar when assessed by Finapres and intra-arterial monitoring, whereas standard deviation of SBP was significantly overestimated by the Finapres. Bos [1992] found that Finapres measurements in patients with peripheral vascular disease were not always equal to intra-brachial measurements and that, during the Valsalva manoeuvre, the magnitude of BP response was sometimes over- or under-estimated by the Finapres device. Of particular interest, Jellema [1996] demonstrated that the Finapres device could be reliably used in clinical settings as a monitor of sudden changes in BP such as those induced by head-up tilt. Although arterial pressure waveforms change with head-up tilt, Petersen [1995] demonstrated that non-invasive plethysmography correlates very well with intra-arterial pressure recordings during head-up tilt. Most studies validating the Finapres device have been performed in subjects younger than 75 years, but validation has also been performed in the 71-83 years age group with comparable results [Rongen 1995].

The accuracy of the Finapres may be influenced by a number of factors. Jones [1993] demonstrated that SBP levels were underestimated when the finger cuff was applied too tightly and overestimated when applied too loosely. Finapres SBP may be significantly affected by fingertip temperature, probably as a result of local vasoconstriction of arteriovenous shunts, and finger warming may be a useful

procedure to improve the reliability of Finapres readings [Tanaka H 1993]. Hildebrandt [1991], however, found that heating of the fingertip distal to the Finapres cuff significantly decreased BP readings and concluded that heat-induced vasodilation may make Finapres readings unrepresentative of systemic BP. Other possible explanations for BP over- and under-estimation in the above studies include finger cuff malapplication, inappropriate cuff size, finger vasospasm and failure to position the hand at atrial level. In our subjects, an appropriate cuff size was chosen for each subject in agreement with the manufacturer's instructions and the hand and arm were supported at atrial level at all times using a custom designed arm-rest. All recordings were performed in a temperature controlled laboratory and BP readings were only accepted if they were within 15/10 mmHg of contralateral brachial readings.

In conclusion, the Finapres is currently the device of choice for non-invasive, continuous beat-to-beat BP monitoring, especially when measurement of relative changes, rather than absolute values, of BP is desired. It has been validated against intra-arterial measurements in older age groups and during a variety of manoeuvres, including head-up tilt.

2.3. Measurement of carbon dioxide partial pressure

As discussed previously, CO_2 has profound effects on CBF, through its stimulation of vasodilation, its depressive effect on critical closing pressure, and upward effect on the static autoregulatory curve. In any studies of CBF or CA, therefore, monitoring of CO_2 is essential. Arterial blood gas sampling is regarded as the "gold standard" of carbon dioxide partial pressure (pCO_2) measurement. However, this yields results for a single point in time only, and, like intra-arterial BP measurement, is not without

complications if repeatedly performed [Downs 1973, Bedford 1977]. Two recognised alternatives to arterial blood gas sampling are transcutaneous and end-tidal CO_2 measurement.

2.3.1. End-tidal carbon dioxide ($ETCO_2$) measurement

Capnography is a non-invasive technique allowing continuous measurement of expired or end-tidal CO_2 levels with the aid of infared spectroscopy [Ledingham]. Capnography uses microprocessor technology and the principle of infared absorption to measure $ETCO_2$ levels. Infared energy is a continuous band of electromagnetic radiation which borders the lower frequencies of visible light. CO_2 absorbs infared energy in direct proportion to the concentration of CO_2 present, and the amount of absorption may be measured by a photometer. Exhaled gas is channelled to the photometer via nasal canulae or, as in the case of our subjects, via a closely fitting face mask. A continuous beam of infared energy emitted by the photometer passes through the gas sample which absorbs frequencies specific to the individual gases present. A detector measures the reduced energy which has passed through the gas sample. A microprocessor analyses the detected values and displays CO_2 as a continuous waveform which may be displayed on a monitor or recorded onto a digital analogue tape (Figure 2.7.).

$ETCO_2$ levels may vary with changes in the rate of CO_2 production which is dependent on factors such as the work of breathing, CO_2 transport and elimination, nutritional support, cardiac output and the administration of exogenous CO_2 [Napolitano 1999, Weil 1985]. In subjects with healthy lungs, due to the effect of physiological dead space, an arterial/end-tidal CO_2 difference (usually $\leq$ 6mmHg) exists but in conditions of cardiovascular stability $ETCO_2$ levels bear a constant

relation to arterial CO_2 levels [Napolitano 1999]. Others have found that, in patients with normal pulmonary function and matching of ventilation-perfusion, $ETCO_2$ provides an accurate estimation of arterial pCO_2 [Hillier 1990, Tobias 1994, Campbell 1994, Napolitano 1999, Schmitz 1995, Rozycki 1998]. Capnography may, however, lose accuracy in very ill subjects [Schmitz 1995, Tobias 1997, Napolitano 1999], subjects with lung disease or unequal ventilation perfusion matching [Epstein 1985, Hand 1989, Sivan 1992], subjects with low tidal volumes [Tobias 1997] and during large decreases in cardiac output that may compromise alveolar blood flow [Weil 1985]. Capnography has been used in conjunction with the tilt table test [Serrador 1998, Yoshizaki 1998, Cencetti 1997, Novak 1998a, 1998b, Naschitz 1997] but there are unresolved issues regarding its use during a test that involves marked and sudden changes in cardiac output.

2.3.2. Transcutaneous carbon dioxide (TCO_2) measurement

A transcutaneous method (TINA, Radiometer, Copenhagen) [Larson 1993] of measuring CO_2 levels has been validated against arterial blood gas and arterialised ear lobe samples in a variety of situations [Trempler 1981, Mahutte 1984, Carter 1989, Sridhar 1993, Dawson 1998]. In neonates and infants with respiratory failure, transcutaneous CO_2 (TCO_2) monitoring has provided more accurate estimation of arterial pCO_2 than $ETCO_2$ monitoring [Tobias 1997, Rozycki 1998].

Prior to application, the TINA electrode is calibrated according to the manufacturer's instructions and heated to between 43° and 45° C, the recommended temperature range for adults. In our studies, a temperature of 43°C was chosen to minimise the risk of thermal injury to the skin. Optimal areas for TCO_2 measurement are the abdomen and chest due to high capillary density, ample capillary blood flow, thin

epidermis and no shunting effects. The chosen site is cleaned with alcohol and the electrode attached with an adhesive fixation ring and contact electrolyte fluid (Figure 2.8.). Typical physiological stabilisation time of a subject is 3-7 minutes for pCO_2 measurements but this may be increased by lower electrode temperatures.

The TINA electrode combines a heating element, two resistors acting as temperature sensors, a Clark-type oxygen electrode and a Severinghaus-type CO_2 electrode in a single unit. The temperature of the electrode is sensed by the resistor incorporated in the Ag/AgCl reference electrode. Due to high thermal conductivity of the silver body, the resistor responds quickly to any changes in temperature. The thermostating system maintains the electrode at the preset temperature. When the electrode is attached to the skin, the generated heat is transferred from the heating element via the silver body to the skin surface. The heating produces local vasodilatation and increases the permeability of the skin to oxygen and CO_2, rendering a measurement on the skin surface possible. The pCO_2 measurement is, in fact, a pH measurement. As CO_2 is released from the skin, it diffuses through the membrane into the electrolyte where it reacts with water forming carbonic acid which immediately dissociates into bicarbonate and hydrogen ions according to the equation:

$$H_2O + CO_2 \Leftrightarrow H_2CO_3 \Leftrightarrow H^+ + HCO_3^-$$

The changes in H^+ in the electrolyte imply changes in pH. As the pH in the electrolyte changes, the voltage between the glass electrode and the reference electrode changes. The pH change is converted to a pCO_2 reading on the basis of the linear relationship between pH and log pCO_2, as expressed by the Henderson-Hasselbach equation:

$$pH = pK + \log \frac{[HCO_3^-]}{a.pCO_2}$$

where pK is the dissociation constant of carbonic acid, $[HCO_3^-]$ is the concentration of bicarbonate ions, a is the solubility coefficient of dissolved CO_2 and pCO_2 is the partial pressure of CO_2. As no charged molecules can penetrate the membrane, the change in pH is strictly due to the CO_2 diffusion into the electrolyte. The potential measured across the combined electrode is fed into the pCO_2 channel where it is digitised. This digitised signal is then passed onto the microcomputer where it is converted to display pCO_2 in mmHg or kPa.

The biggest drawback with TCO_2 monitoring is poor temporal resolution, with gas diffusion contributing to a response time of up to 50 seconds [Steurer 1997]. This limitation may be surmounted, however, by monitoring for periods in excess of this time lag after an expected change. The accuracy of TCO_2 measurements during changes in cardiac output is also a matter of some debate [Steurer 1997] and cutaneous hypoperfusion during periods of hypotension or hypocapnia could potentially reduce CO_2 diffusion transcutaneously and affect accuracy [Steurer 1997]. Technical variables affecting the accuracy of TCO_2 readings, such as trapped air bubbles, damaged membranes and improper or inappropriate placement techniques, were avoided in this work by careful use of the equipment by well trained staff. Problems associated with patients which could potentially affect reading accuracy, such as the presence of oedema and the administration of vasoconstricting drugs, did not arise in subjects recruited for these studies.

In conclusion, in skilled hands, $ETCO_2$ and TCO_2 measurement provide acceptable alternatives to invasive techniques for arterial pCO_2 estimation.

2.4. Assessment of Cerebral Autoregulation

2.4.1. Assessment of static cerebral autoregulation

Lack of temporal resolution in measurements of CBF with traditional techniques meant that most studies of CA prior to the advent of TCD were of static CA. Original animal studies usually induced static BP changes by pharmacological manipulation, haemorrhage or reperfusion with autologous blood. Human studies have induced pressor changes of the order of 20 mmHg through the use of intravenous phenylephrine or noradrenaline [Larsen 1994, Tiecks 1995, Strebel 1995], and depressor changes with passive head-up tilt [Grubb 1991a, Schondorf 1997] or lower body negative pressure [Bondar 1994, 1995, Giller 1992, Levine 1994]. Cerebral responses to static pressor and depressor changes are usually considered separately, as cerebral vasoconstriction and vasodilation may involve different physiological mechanisms and be affected differently by pathological processes.

Studies of static CA usually involve calculation of an autoregulatory index (ARI) similar to that described by Tiecks et al [1995] where the percentage change in cerebrovascular resistance (CVR) per percentage change in BP is calculated. In our studies, data were manually selected to include a one-minute baseline period before the pressor or depressor stimulus as well as the subsequent period of static MAP change during the stimulus. CVR can be estimated for each window and the static ARI calculated, as previously described by Tiecks et al [13], using:

$$CVR = \frac{MAP}{MCAV}$$

$$\%\Delta CVR = \frac{CVR_{end} - CVR_{base}}{CVR_{base}}$$

$$\%\Delta MAP = \frac{MAP_{end} - MAP_{base}}{MAP_{base}}$$

$$StaticARI = \frac{\%\Delta CVR}{\%\Delta MAP} * 100\%$$

where MAP_{end} and CVR_{end} represent values at the end of the period of static BP rise, and MAP_{base} and CVR_{base} represent values during the baseline period. A change in CVR that would fully compensate for the MAP change yields a result of 100%, and no change in CVR, i.e. no autoregulation, would give a result of 0%. Tiecks [1995] considered a value of >50% to be normal. These principles are illustrated in Figure 2.9.

2.4.2. Assessment of dynamic CA

As discussed earlier, dynamic CA is a relatively new concept and is usually considered as a separate entity from static CA as it may be effected by different physiological mechanisms. Assessment of dynamic CA is enabled by the excellent temporal resolution of TCD which allows examination of CBF changes in response to pressor and depressor BP changes occurring over a matter of seconds. Methods of assessing dynamic CA using spontaneous BP changes at rest have theoretical advantages over the use of induced dynamic BP changes, as stimuli used to induce dynamic BP changes may also induce sympathetic stimulation or changes in CO_2 levels, both of which may affect the integrity of CA (see section 2.5.).

2.4.2.1. Aaslid's Method

Perhaps the most widely used method of assessing dynamic CA involves the principle of inducing a dynamic BP change and assessing the length of time it takes for CBF to recover to baseline levels [Aaslid 1989, Newell 1994b, Tiecks 1995]. The rate of recovery (dROR) is assessed by:

$$dROR = \frac{\Delta CVR}{\Delta Time} \div \Delta ABP$$

$$\Delta CVR = \frac{\Delta ABP}{\Delta CBF}$$

The dROR represents the percentage recovery per second, with most normal subjects achieving a dROR of ≥20% [Tiecks 1995]. The first studies described methods using rapid thigh-cuff deflation to induce a dynamic depressor change, but the methods are potentially applicable using other dynamic pressor and depressor stimuli, including spontaneous BP changes at rest.

Aaslid and Tiecks proposed a mathematical model to represent this principle to enable an autoregulatory index (ARI) to be calculated ranging from 0 (absent) to 9 (most efficient) [Tiecks 1995]. For an ABP change P(t), normalised by baseline values preceding the change, the relative pressure change dP(t) is given by [Tiecks 1995]:

$$dP(t) = \frac{P(t)}{1 - CrCP}$$

where $CrCP$ is the critical closing pressure assumed to be normalised by the baseline pressure. The relative velocity change predicted by the model is given by:

$$V_M(t) = 1 + dP(t) - K.x_2(t)$$

where K is a parameter reflecting system autoregulatory gain [Tiecks 1995] and x_2 (t) is an intermediate variable obtained from the following pair of equations:

$$x_1(t) = x_1(t-1) + \frac{dP(t) - x_2(t-1)}{f.T}$$

$$x_2(t) = x_2(t-1) + \frac{x_1(t) - 2D.x_2(t-1)}{f.T}$$

where f, D and T represent the sampling frequency, damping factor and time constant parameters respectively.

For each segment of data P(t), the model generated a corresponding predicted velocity $V_M(t)$ that was compared with the original data V(t) (Figure 2.10). Ten possible combinations of parameter values, corresponding to ARI values ranging from 0 to 9,

were tested and the one leading to the minimum square error corresponded to the solution adopted [Tiecks 1995].

A modification of these methods was subsequently described whereby the closest match is selected on the basis of the highest correlation coefficient [Dawson 2000] and fractional ARI values are obtained by parabolic interpolation around the point with least square error [Dawson 2000]. Unlike the least-squares method used by Aaslid and Tiecks [1995], this method does not rely on a specific value of critical closing pressure to select the closest match.

In this thesis, when applying these methods to induced and spontaneous ABP changes, data were marked manually at the point of initiation of the dynamic BP change. Only induced BP changes ≥ 10mmHg and spontaneous BP changes ≥ 5mmHg at rest were accepted as adequate dynamic stimuli, in keeping with the criteria adopted by others using similar methodology [Dawson 2000, Tiecks 1995, Strebel 1995, White 1997]. Subjects had to exhibit a synchronous and physiological change in BP and CBFV for all manual marks. A sample window of 30 seconds from the manual mark was used in all cases. In addition, these methods were also applied to one-minute segments of data from subjects when supine and in the head-up tilted positions.

These methods yield dynamic ARI values for right and left middle cerebral arteries for each individual for each dynamic BP change. As autoregulatory responses do not appear to depend on the cerebral hemisphere examined [Dawson 2000, Tiecks 1995, Strebel 1995], the mean of the two dynamic ARI values thus obtained was taken to be the ARI for each individual for each dynamic BP stimulus.

2.4.2.2. Frequency Domain Analysis

A number of methods have been recently devised, including frequency domain analysis, that allow quantification of dynamic CA from spontaneous BP changes at rest [Panerai 1998a, 1998b, 1999a, 1999b, Zhang 1998a,1998b]. Such methods of CA estimation are proving increasingly attractive, as mentioned previously, due to the uncertainty of the effects of induced dynamic BP changes on the integrity of CA. The use of spontaneous BP changes is also less noxious to subjects and poses less risk to patients potentially at risk from the induction of acute hypotensive or hypertensive changes e.g. patients post acute stroke or subarachnoid hemorrhage and those with carotid stenosis. In addition, assessment of CA at rest is possible over longer periods than with induced BP changes and has the potential, therefore, to yield more accurate results.

In this thesis, frequency domain analysis was performed on supine rest recordings of CBFV and ABP. Neglecting the effects of intracranial pressure and critical closing pressure [Dewey 1974, Panerai 1993], at a stable operating point, the relationship between CBFV and ABP can be written as:

$$V_O = \frac{P_O}{R_O} \qquad (1)$$

where R_o represents the resistance-area product [Evans 1988]. For a small change in ABP, Δp, CA increases R_o by an amount Δr, and CBFV also changes by an amount Δv.

For small values of Δr and Δv, the product $\Delta r.\Delta v$ can be neglected, and it is possible to write:

$$V_O + \Delta v = \frac{P_O + \Delta p}{R_O + \Delta r} \qquad (2)$$

$$\frac{\Delta v}{V_o} \cong \frac{\Delta p}{P_o} - \frac{\Delta r}{R_o} \qquad (3)$$

With perfect autoregulation, Δr compensates the Δp change and $\Delta v = 0$. At the other extreme, in the absence of autoregulation, $\Delta r = 0$, and the relative change in velocity is the same as in ABP. In either case, the above approximation becomes an equality, because the product $\Delta r.\Delta v = 0$.

Given the linear properties of Fourier transform [Bendat 1986], equation 3 can be written in the frequency domain as:

$$\frac{V(f)}{V_o} = \frac{P(f)}{P_o} - \frac{R(f)}{R_o} \qquad (4)$$

Assuming that changes in resistance are the result of changes in CBFV, it is possible to postulate a dynamic relationship between these two quantities in the form of a transfer function $G(f)$, or:

$$R(f) = G(f).V(f) \qquad (5)$$

Substituting in equation 4 and rearranging:

$$\frac{V(f)}{P(f)} = \frac{1}{R_o + V_o.G(f)} = H(f) \qquad (6)$$

where $H(f)$ is the transfer function between ABP and CBFV. The function $G(f)$ can be regarded as the feedback gain of autoregulation [Panerai 1996]. When $G(f) = 0$, autoregulation is absent, and changes in ABP are completely transmitted to CBFV. At the other extreme, when the gain is high, $H(f)$ is small, and the CBFV changes are equally small. Reynolds et al [1997] have provided a detailed analysis of the power spectra of $V(f)$ and $P(f)$ in neonates.

In our studies, cross spectral analysis of supine rest recordings of CBFV and ABP was performed with a segment of 512 samples selected from each record corresponding to the region with maximum ABP variability. For a segment of data with 256 samples, a

20% cosine tapered window was applied to *v(n)* and *p(n)*, and the corresponding discrete Fourier transforms *V(f)* and *P(f)* computed with a FFT algorithm. The cross-spectrum was computed as [Bendat 1986]:

$$G_{PV}(f) = E[P(f).P(f)] \quad (7)$$

where the expected value of the complex product E [$P(f)$.P(f)] was obtained by smoothing the spectra with a nine-point triangular moving average window and by averaging two segments of data. Similarly, the power spectra of *p(n)* was computed as:

$$G_{PP}(f) = E[P(f).P(f)] \quad (8)$$

The squared coherence function was estimated by [Bendat 1986]:

$$\gamma^2(f) = \frac{|G_{PV}(f)|^2}{G_{VV}(f).G_{PP}(f)} \quad (9)$$

and the transfer function was given by:

$$H(f) = \frac{G_{PV}(f)}{G_{PP}(f)} \quad (10)$$

From the real and imaginary parts of *H(f)* the amplitude and phase of the frequency response was calculated as:

$$|H(f)| = \left[H_R(f)^2 + H_I(f)^2\right]^{1/2} \quad (11)$$

$$\phi(f) = \tan^{-1}\frac{H_I(f)}{H_R(f)} \quad (12)$$

The frequency response was multiplied by a cosine-shaped low-pass filter with cut-off frequency at 1.0 Hz and the impulse response $h_{PV}(n)$ was obtained by the inverse Fourier transform using the same FFT algorithm. The step response was obtained by integration of $h_{PV}(n)$ for positive values of time.

Frequency domain analysis has been used to demonstrate impairment of dynamic CA in premature neonates, hypercapnia and severe carotid artery stenosis [Panerai 1998a, 1998b, 1999b]. High coherence between MCA BP and CBFV suggests that BP changes are transmitted passively to the cerebral circulation, indicating impaired CA. On the other hand, active CA will attenuate CBFV changes in response to BP changes and coherence will fall. Reduced coherence at very low frequencies (<0.1 Hz) has been shown to be indicative of active dynamic CA [Panerai 1998a, 1999b, Zhang 1998a, 1998b] (Figure 2.11a.). In subjects with normal CA, oscillations in CBFV lead BP oscillations by a positive phase angle i.e. changes in CBFV occur before those in systemic BP [Panerai 1998a, 1999b, Zhang 1998a, 1998b]. In subjects with impaired dynamic CA, the phase angle becomes less positive [Panerai 1998a, 1998b, 1999b, Zhang 1998a, 1998b] (Figure 2.11b.) and deterioration of CA may be reflected more markedly in the phase rather than in the amplitude frequency response [Panerai 1998a, 1998b] which may demonstrate an increase at low frequencies if CA is impaired (Figure 2.11c.).

The impulse response function represents the CBFV response to a very short, impulse-like disturbance in ABP. Impulse response plots show an initial positive wave and subsequent negative deflection in CBFV when dynamic CA is active, with impairment leading to blunting or disappearance of the negative deflection [Panerai 1998a, 1998b, 1999, Zhang 1998a, 1998b] (Figure 2.11d.). Step response plots demonstrate a return of CBFV to baseline values when dynamic CA is intact and higher values when impaired [Panerai 1998a, 1998b, 1999b, Zhang 1998a, 1998b] (Figure 2.11e.).

In summary, both induced and spontaneous pressor and depressor BP changes can be used with Aaslid's model and frequency domain analysis to assess the integrity of dynamic CA.

2.5. Methods used to induce static and dynamic BP changes

In this work, a number of methods were used to induce pressor and depressor BP changes so that CA could be investigated (Table 2.2.). In this section, I will discuss the practical aspects and physiology of the various tests, along with any known effects of the tests themselves on CBF.

2.5.1. Thigh-cuff inflation and release - static pressor and dynamic depressor stimuli (Figure 2.12.)

This technique was first described by Aaslid [1989] as a non-invasive, non-pharmacological method of effecting a rapid fall in MAP for the purpose of CA assessment. The original description of the technique involved inflation of bilateral thigh-cuffs to 30mmHg above systolic BP for 3 minutes with subsequent rapid release achieving a mean fall in MAP of >20mmHg lasting >15 seconds. Subsequent work has validated this technique in a number of subject groups [Tiecks 1995, Strebel 1995, Dawson 2000], while illustrating that inflation to systolic BP levels or just above for 90 seconds produces BP falls of similar magnitude without causing as much patient discomfort.

In addition, it became clear that the period of thigh-cuff inflation caused a static rise in MAP, with a less marked rise in heart rate, presumably reflecting sympathetic stimulation due to discomfort. Consequently, this technique can be used as a means of inducing static and dynamic BP changes, but there are a number of drawbacks.

Sympathetic stimulation, as discussed in section 1.3.2.4., may have effects on CA and compromise results but there is evidence that changes in sympathetic nervous system activity may not affect CBF in the BP range likely to be examined by thigh-cuff inflation and release i.e. 60-140mmHg [Roatta 1998, Eklöf 1971, Skinhøj 1972, 1973, Heistad 1978a, Hernandez-Perez 1975, Harper 1975]. A build up of blood rich in CO_2 and other potential metabolites in the legs during inflation with subsequent arrival in the brain after release is another potential confounding factor, but this may be minimised by using the shorter inflation period. The shorter inflation period may also help to minimise factors related to the subject that may also affect CA results, such as inadvertent breath holding or Valsalva manoeuvre performance during the test.

2.5.2. Valsalva manoeuvre - a dynamic pressor stimulus (Figure 2.13.)

The Valsalva manoeuvre, or forced expiration against a closed glottis, causes marked systemic haemodynamic changes that may be described in four separate phases. Phase I represents the start of the strain and is associated with a rise in ABP because of increased intrathoracic pressure. During phase II, as atrial filling decreases, a compensatory sympathetic response leads to an increase in heart rate, cardiac output and BP. When release of the strain causes a sudden fall in intrathoracic pressure (phase III), a sharp fall in BP is rapidly followed by a large BP overshoot due to the persistent sympathetic activity and high peripheral resistance (phase IV). BP levels gradually return to baseline over the next 30-60 seconds [Hamilton 1936]. The MCAV responds to these BP changes and the velocity changes can be used to calculate an autoregulatory index [Tiecks 1996].

The standard method of performing the manoeuvre is to blow into a syringe fitted with a constant bleed device which is attached to a transducer to record intrathoracic pressure. Subjects aim to achieve 40mmHg pressure for 15 seconds after a normal inspiratory breath [Palmero 1981, Smith 1987].

Phase IV of the manoeuvre is easily recognisable and reproducible, and, therefore, has been used as a dynamic pressor stimulus to derive indices of dynamic CA [Tiecks 1996]. Again, there are potential drawbacks when using the manoeuvre for calculating autoregulatory indices as the influences of raised intracranial pressure during strain and hypercapnia while breath holding on such indices are unknown.

2.5.3. Lower body negative pressure and release - static depressor and dynamic pressor stimuli (Figure 2.14.)

Lower body negative pressure (LBNP) is achieved by placing a subject's lower body in an air-tight box and sealing at the level of the iliac crests. Negative pressure is then applied with a pump, such as a domestic vacuum cleaner, to create negative pressure relative to the rest of the body in the lower body. The pressure is monitored with the aid of a manometer in series and can be varied according to the protocol required to be hypotensive (usually >-20mmHg) or non-hypotensive (usually < -10 to -15mmHg). Negative pressure has the effect of triggering venous pooling in the lower limbs and pelvis and causing a central hypovolaemic state with a fall in cardiac output and stroke volume [Stevens 1965]. Pooling of blood during LBNP of between -30 and -50 mmHg has been estimated at between 0.5 to 1.0 litres [Wolthuis 1970]. Non-hypotensive LBNP activates arterial high pressure baroreceptors and extraarterial low pressure cardiopulmonary mechanoreceptors leading to maintenance of MAP through an increase in heart rate and total peripheral resistance (TPR) [Stevens 1965, Wolthuis

1974]. As the degree and duration of LBNP increase, the capacity of these mechanisms to compensate is exceeded and MAP starts to decline (hypotensive LBNP), often to the point of syncope [Stevens 1965, Bondar 1994, 1995]. Gender and age related differences have been demonstrated in the responses to LBNP, with men demonstrating more calf pooling and women more thoracic impedance [Frey 1988]. Heart rate and TPR responses have been shown to diminish with age [Frey 1988] while athletes have a reduced tolerance to LBNP, possibly due to a high vagal tone or a decreased sympathoadrenal response [Raven 1993,1984].

If pressure is carefully controlled, a static decline in BP can be achieved. Rapid release of LBNP causes a sudden rise in circulating volume and, in conjunction with the persistent elevation in TPR, results in a dynamic rise in BP.

Many studies have examined the effect of LBNP on CBF, primarily in fit young men [Giller 1992, Ueno 1993, Bondar 1994, 1995, Levine 1994, Balldin 1996, Zhang 1998b]. Most investigators have demonstrated a decrease in MCAV with increasingly negative pressures and some have used indices of cerebrovascular resistance to suggest that the decrease in MCAV is due to cerebral vasoconstriction [Giller 1992, Levine 1994, Bondar 1995]. Consequently, hypotheses of sympathetic induced vasoconstriction overriding CA gained favour, especially as vasoconstriction was also demonstrated in the renal vascular bed [Hirsch 1989]. Cerebral vasoconstriction during LBNP may due to hypocapnia rather than sympathetic nerve activity [Zhang 1998b]. It is possible, therefore, that CA may actually improve during LBNP, due to CO_2 changes, rather than being compromised (see section 1.2.3.1). CO_2 and sympathetic changes, therefore, may limit the usefulness of LBNP as a BP stimulus for CA assessment.

In summary, the above manoeuvres may be employed as static and dynamic pressor and depressor stimuli to assess CA. It is important to use pressor and depressor and static and dynamic stimuli as CA responses to these different stimuli may be different and be affected differently by pathology. It is clear that the above BP stimuli may stimulate the autonomic nervous system and evoke changes in pCO_2 to some degree, making interpretation of results difficult. For these reasons, spontaneous pressor and depressor BP changes at rest may prove more useful when studying CA.

2.6. Study protocol

The initial part of the protocol of all studies described in this thesis was identical and is outlined here.

Subjects avoided caffeine containing products, nicotine and alcohol for at least 12 hours prior to the studies. They wore loose comfortable clothing and attended in the morning between 09.00 and 11.00 a minimum of 2 hours after a light breakfast. All recordings were made in a dedicated research room kept at constant ambient temperature (21-24°C) with external stimuli minimised.

Subjects lay supine on a padded table (Figure 2.3.) capable of being manually tilted with their head supported by two pillows. After lying supine for 10 minutes, three semi-automated BP readings were taken 1minute apart (Omron 711, Japan). The mean of the last 2 readings, providing pressures differed by less than 10 mmHg, was taken as the baseline casual BP measurement. A surface 3 lead ECG was fitted for measurement of heart rate and arterial BP was measured continuously and non-invasively from the middle finger of the non-dominant hand using a servo-controlled plethysmograph (Finapres 2300, Ohmeda, USA, Figure 2.6, Section 2.2). An

appropriate cuff size was chosen and the hand supported at the level of the right atrium using a custom-made arm rest.

Transcutaneous carbon dioxide (CO_2) partial pressure was measured using a transcutaneous gas monitor (TINA, Radiometer, Copenhagen, Figure 2.8, Section 2.3.2) validated previously [Dawson 1998]. The probe was applied, as outlined in section 2.3.2., to the skin of each subject at heart level in the anterior axillary line (Figure 2.8.).

To measure CBFV, both middle cerebral arteries were identified and insonated as described by in section 2.1.5. [Aaslid 1982] using bilateral 2MHz pulse transcranial Doppler ultrasound (SciMed QVL 842X, Bristol, UK). Both Doppler probes were held in place using a custom designed adjustable head frame and the velocity waveform spectra were visually displayed to aid positioning (Figure 2.3.). The Doppler frequency shift and the other parameters were recorded onto a digital audio-tape (Sony Digital Instrumentation Cassette Recorder PC-108M).

Once the subjects had rested supine for a minimum of 30 minutes and the Finapres and TCO_2 traces had stabilized (<10% variation over 5 minutes), recording was started. Subjects were asked to lie still and to refrain from talking during the recordings.

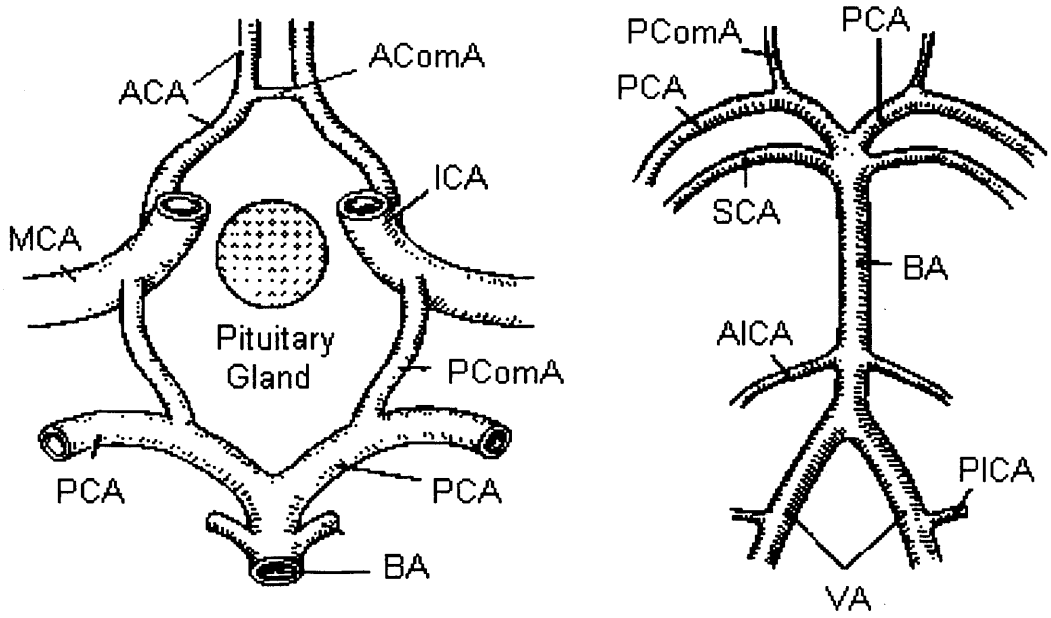
2.7. Data analysis

Preliminary analysis of data recorded onto digital audio tapes was identical in all studies described in this thesis and is described here. Data were downloaded in real time onto a dedicated personal computer. A Fast Fourier Transform method was used to convert the Doppler signals into maximum frequency velocity envelopes. A

window of 5ms was used to achieve temporal resolution. The Finapres, TCO_2 and ECG output signals were directly converted at 200 Hz.

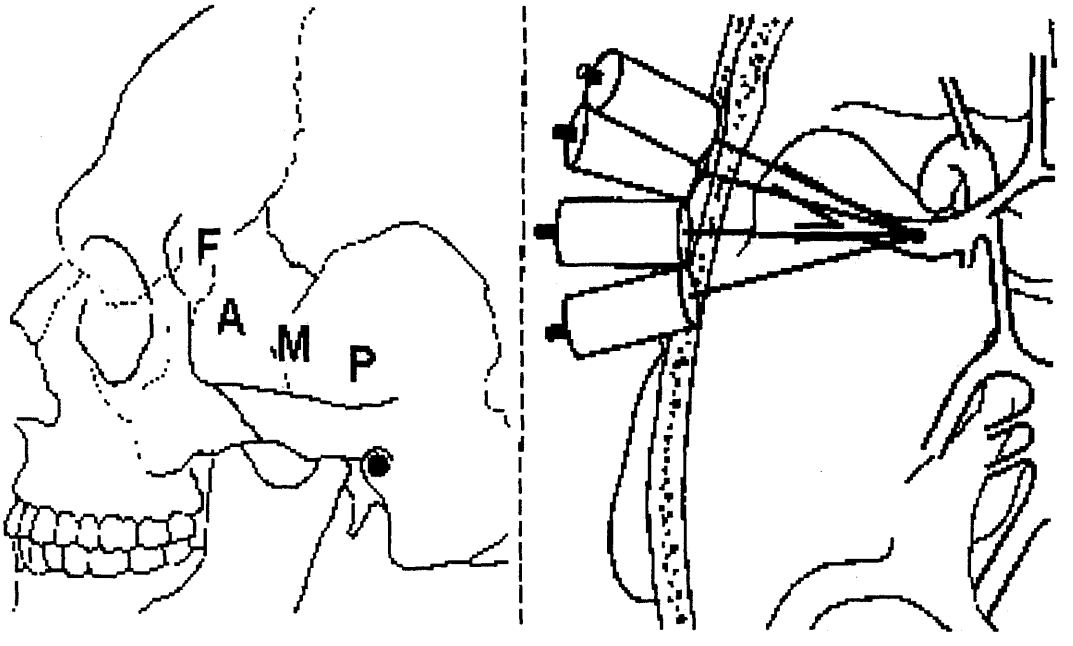
Data were visually inspected, the BP trace was calibrated and artefactual data spikes were removed by linear interpolation. Each cardiac cycle was automatically marked to determine the R-R interval from the ECG tracing with ectopic beats being manually marked and removed by linear interpolation. Ectopic beats occurring with a frequency of more than one per 30 seconds led to rejection of the data. Using spline interpolation (equivalent to a third order polynomial) and resampling the data at 0.2 seconds, a uniform time base for all the data was achieved. Estimates of systolic, diastolic and mean BP, systolic, diastolic and mean CBFV, pulse interval and TCO_2 were made for each cardiac cycle.

Figure 2.1. Circle of Willis



ACA	=	anterior communicating artery
PCA	=	posterior communicating artery
BA	=	basilar artery
VA	=	vertebral artery
ICA	=	internal carotid artery
PComA	=	posterior communicating artery
AcomA	=	anterior communicating artery
MCA	=	middle cerebral artery
PICA	=	posterior inferior cerebellar artery
AICA	=	anterior inferior cerebellar artery

Figure 2.2. Transtemporal Acoustic Windows



F	=	frontal
A	=	anterior
M	=	middle
P	=	posterior

Figure 2.3. A subject undergoing transcranial Doppler ultrasound with the SciMed 120 QVL apparatus

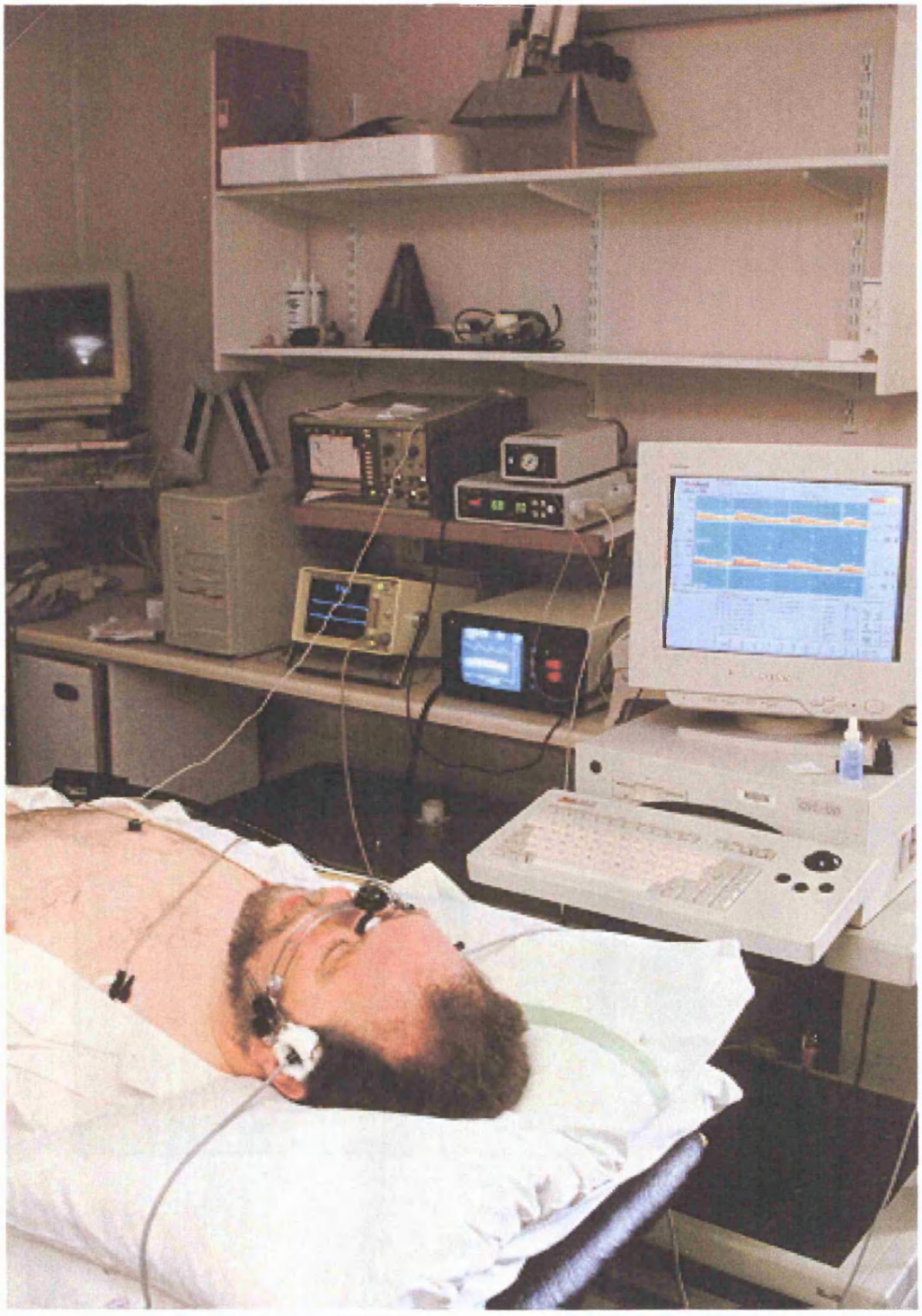


Figure 2.4. Continuous middle cerebral artery blood flow velocity profiles as displayed using the Scimed QVL 120 transcranial Doppler ultrasound apparatus

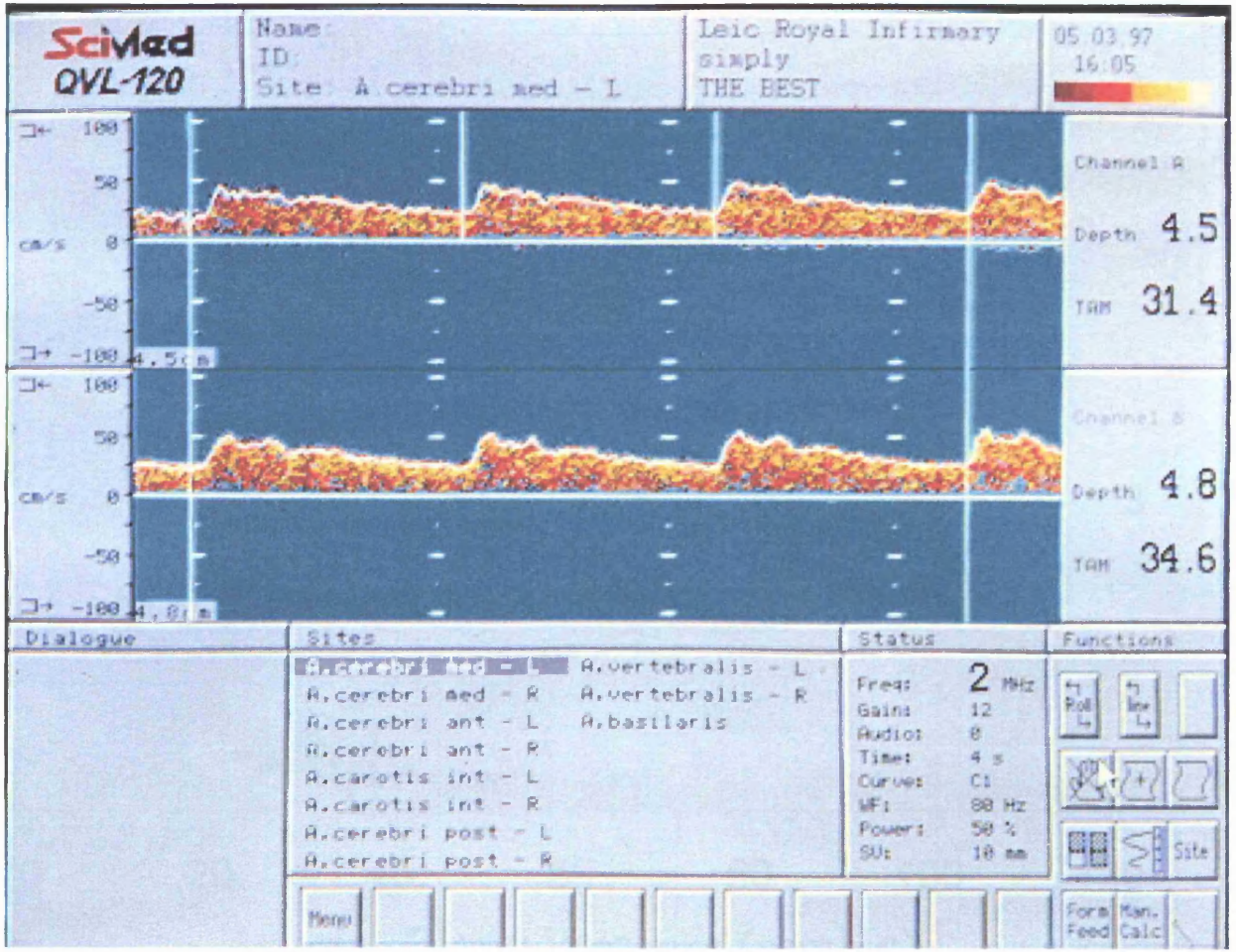


Figure 2.4.

Figure 2.5. Method of Calculation of CrCP and RAP

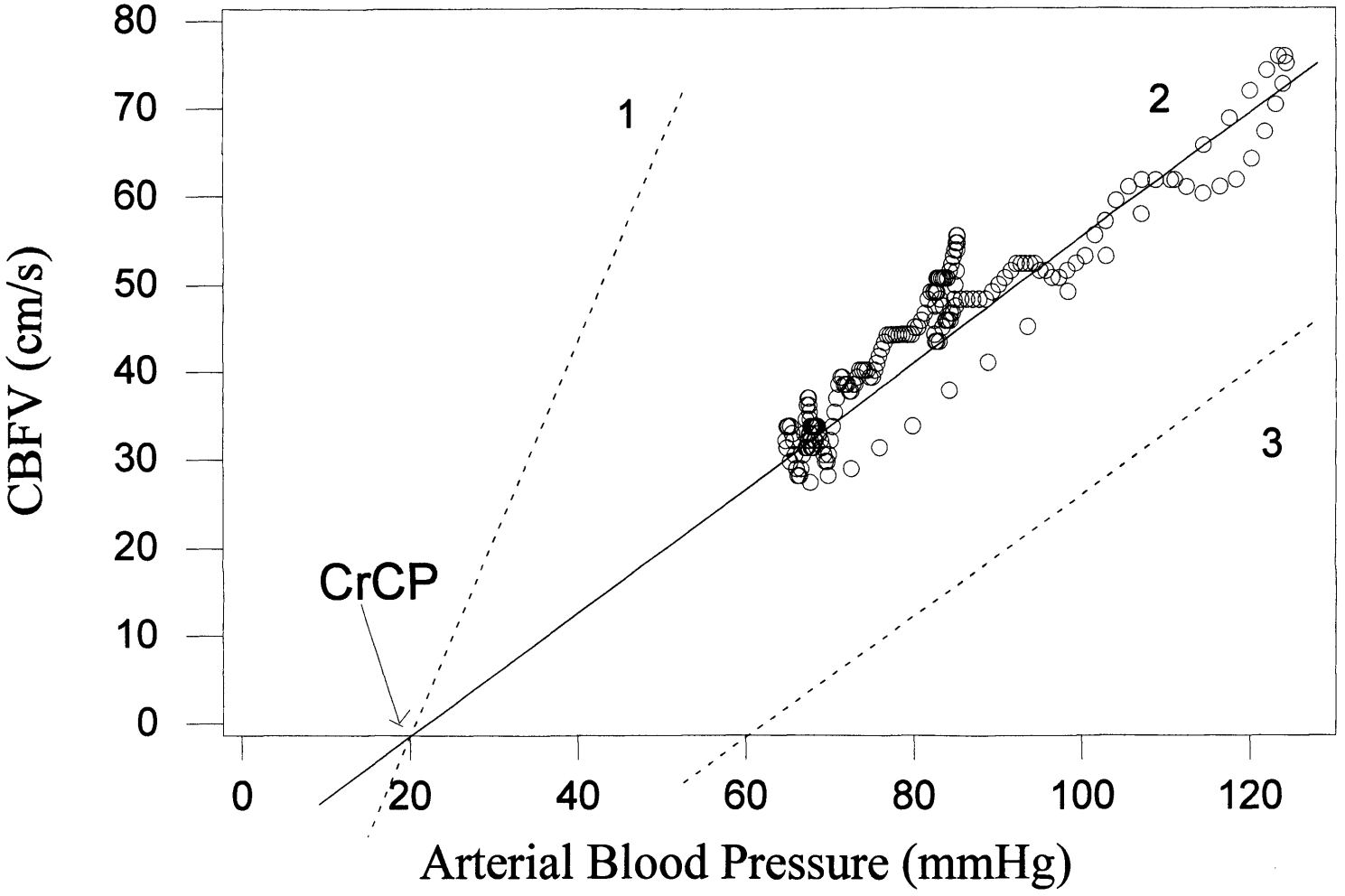


Figure 2.5.

Figure 2.6. The Ohmeda 2300 Finapres device with cuff applied to the middle finger of the non-dominant hand

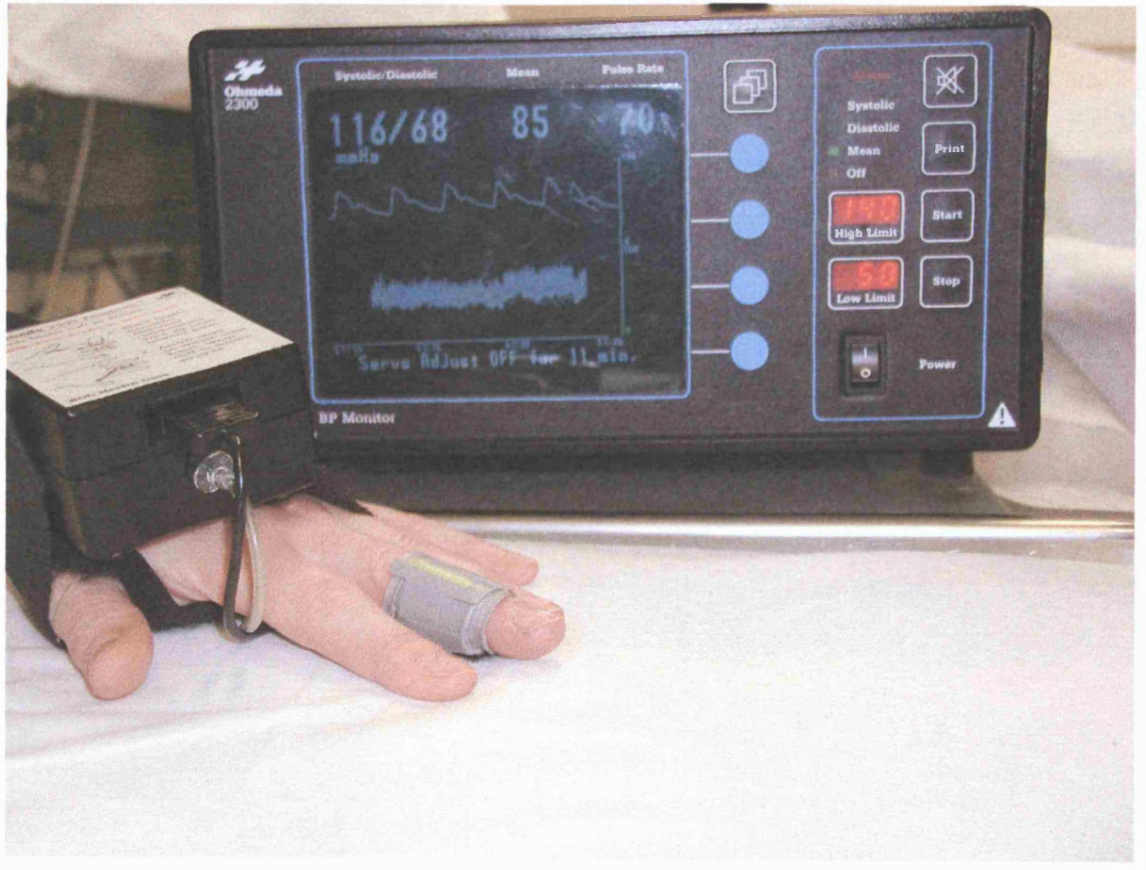


Figure 2.6.

Figure 2.7. End-tidal carbon dioxide monitoring with the Capnogard infa-red capnograph and face-mask

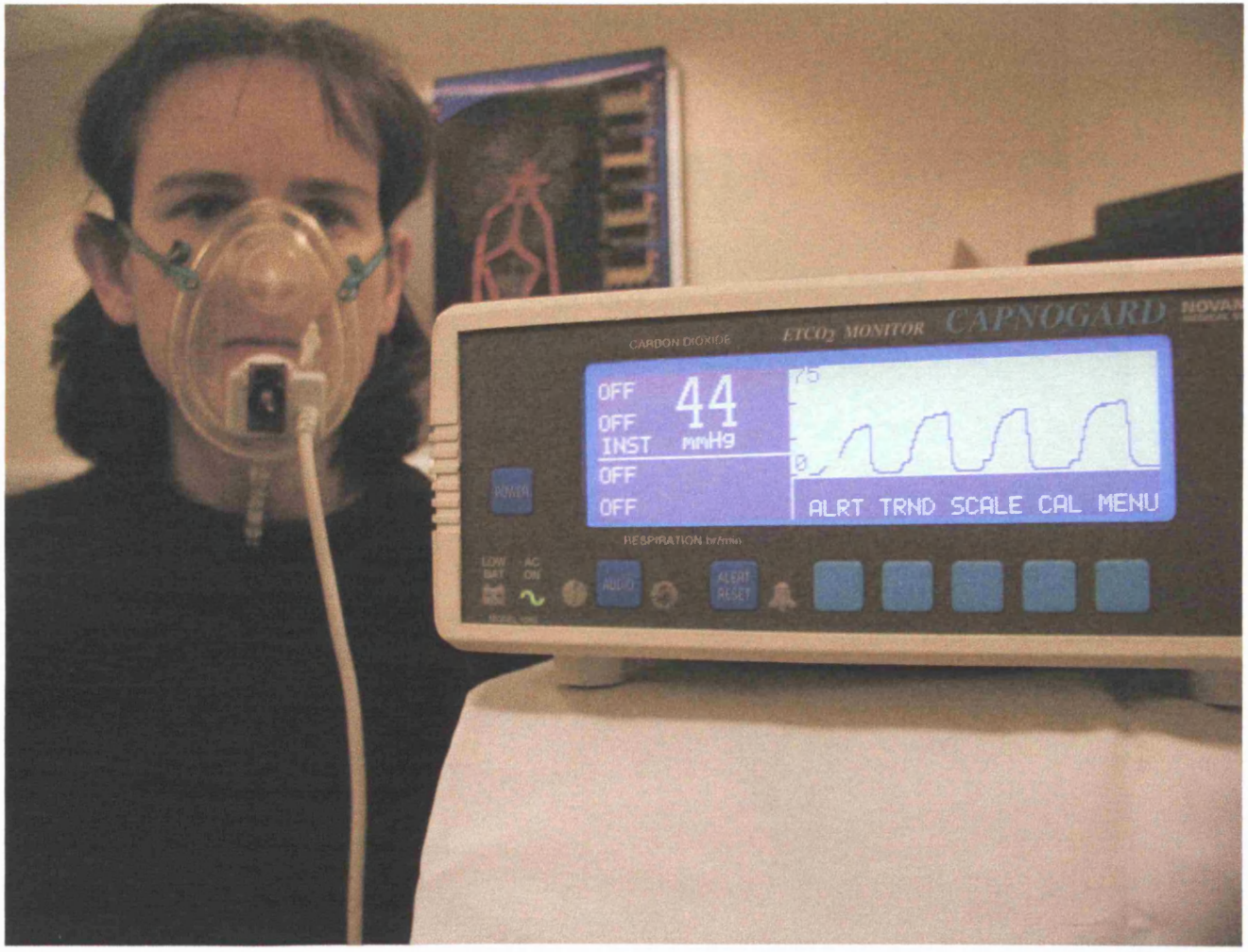


Figure 2.7.

Figure 2.8. TINA transcutaneous gas monitor with probe attached to the skin at heart level in the anterior axillary line

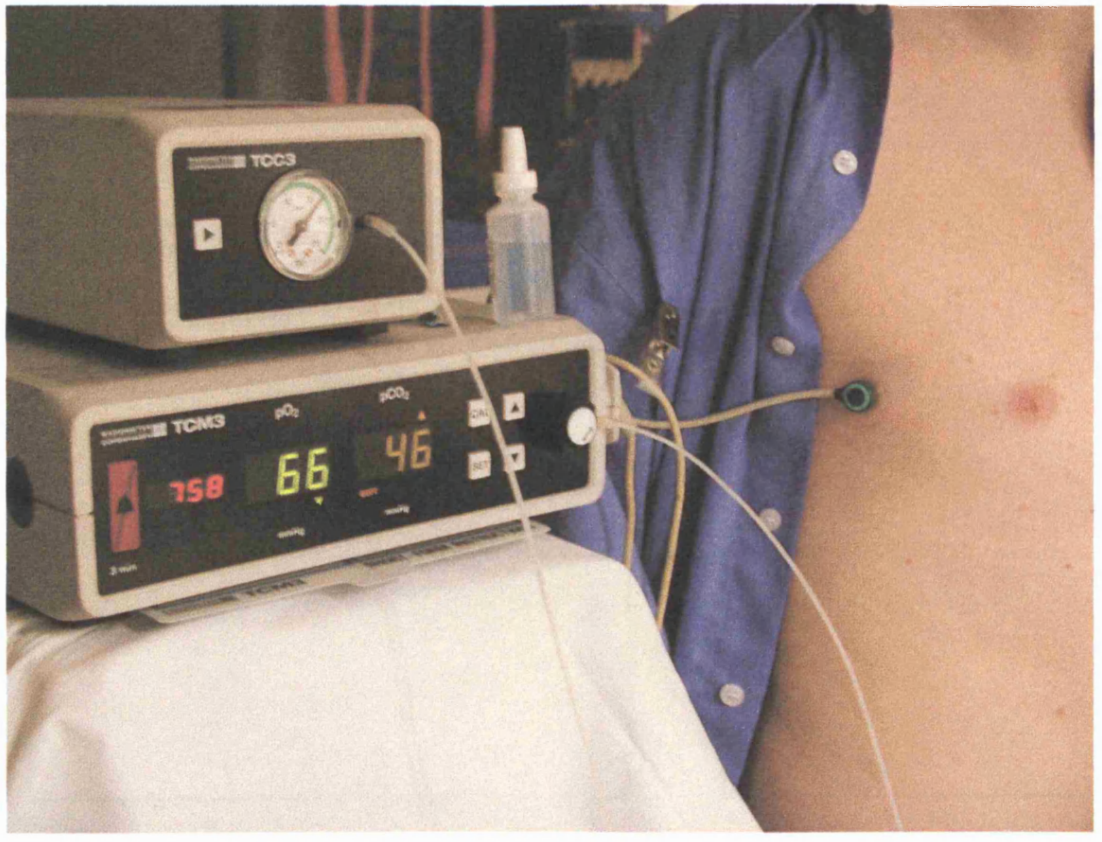
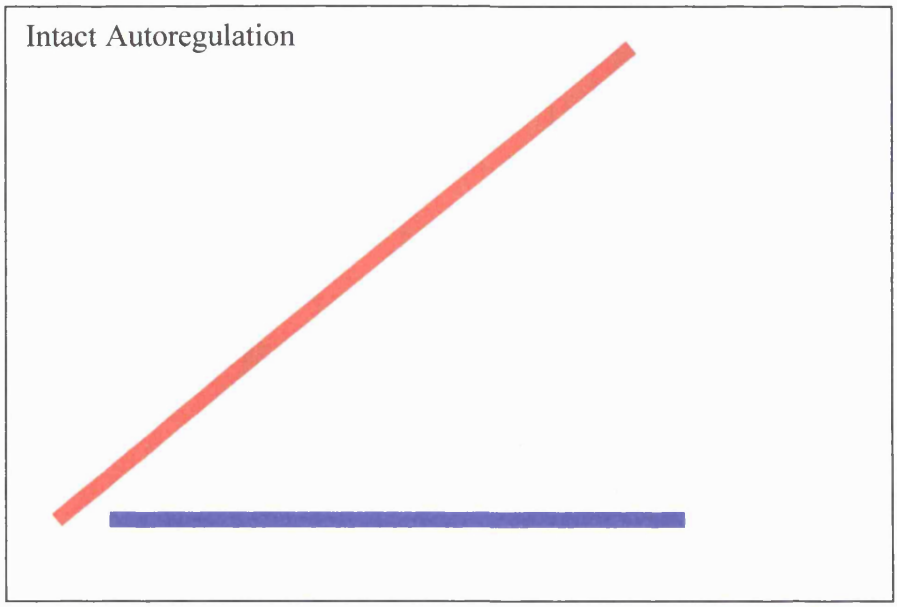
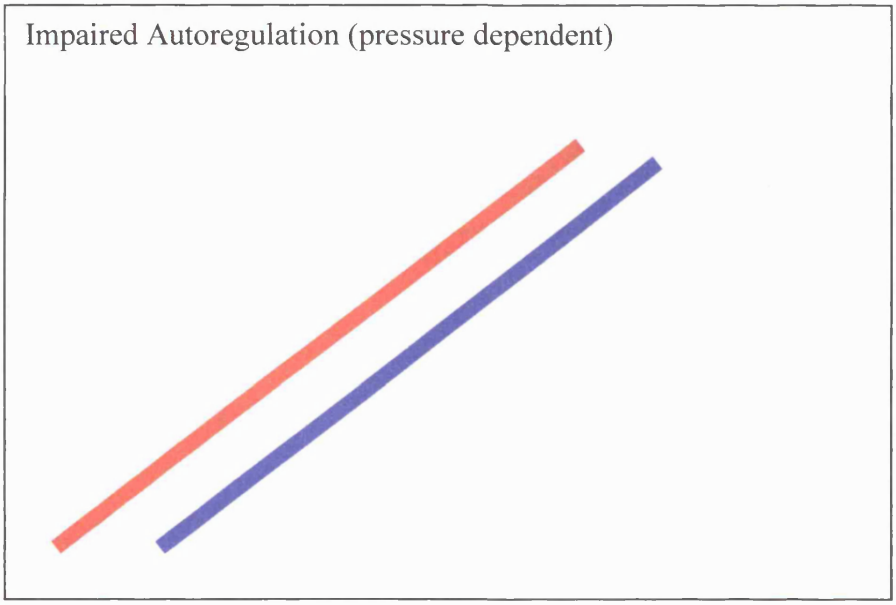


Figure 2.8.

Figure 2.9. Static Cerebral Autoregulatory Changes



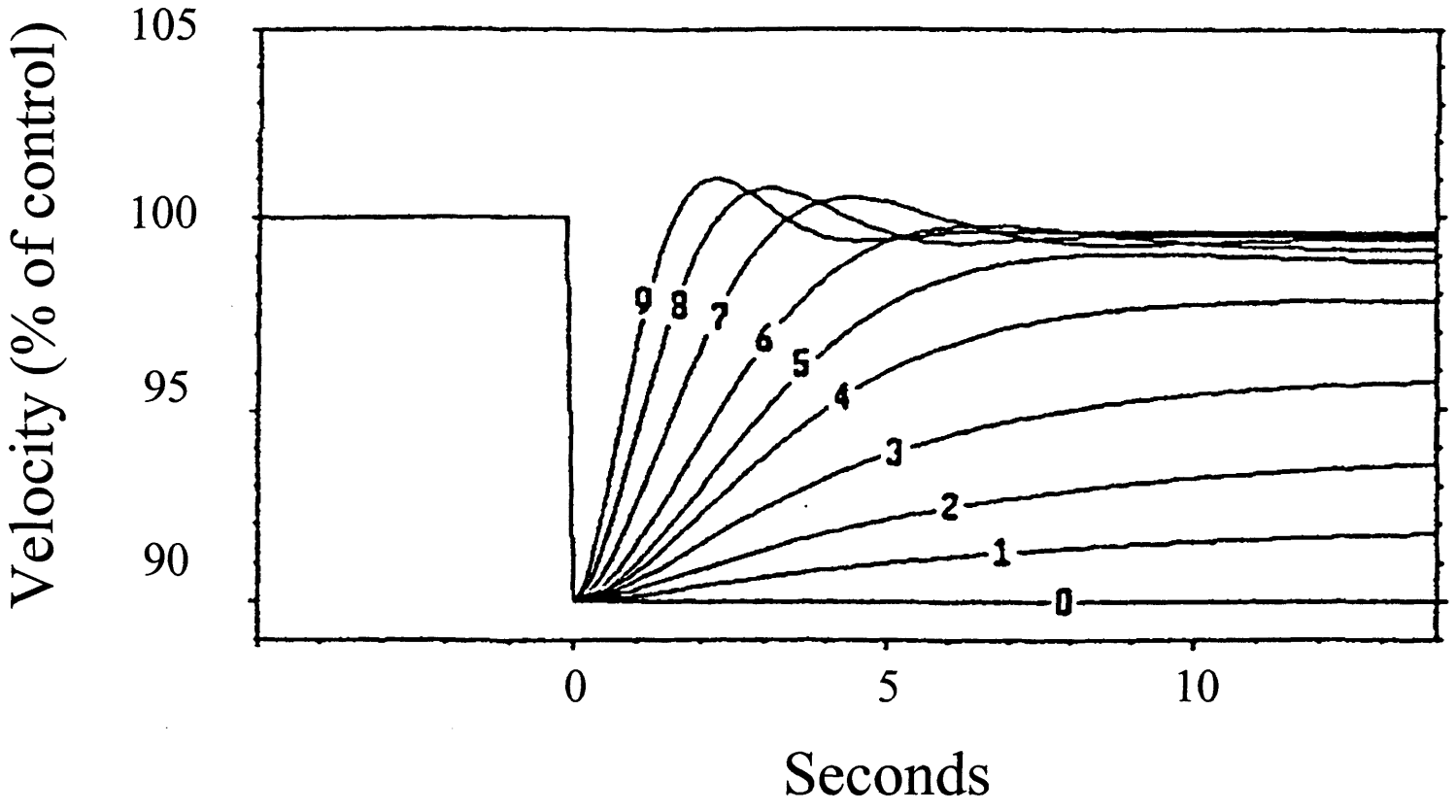
Time



Time

MAP CBFV

Figure 2.10. Aaslid's Model



Mathematical model curves of dynamic cerebral autoregulation in response to a step change in BP.

Figure 2.10.

Figure 2.11a. Coherence function plots of a subject with normal CA (black) and a subject with impaired CA (red)

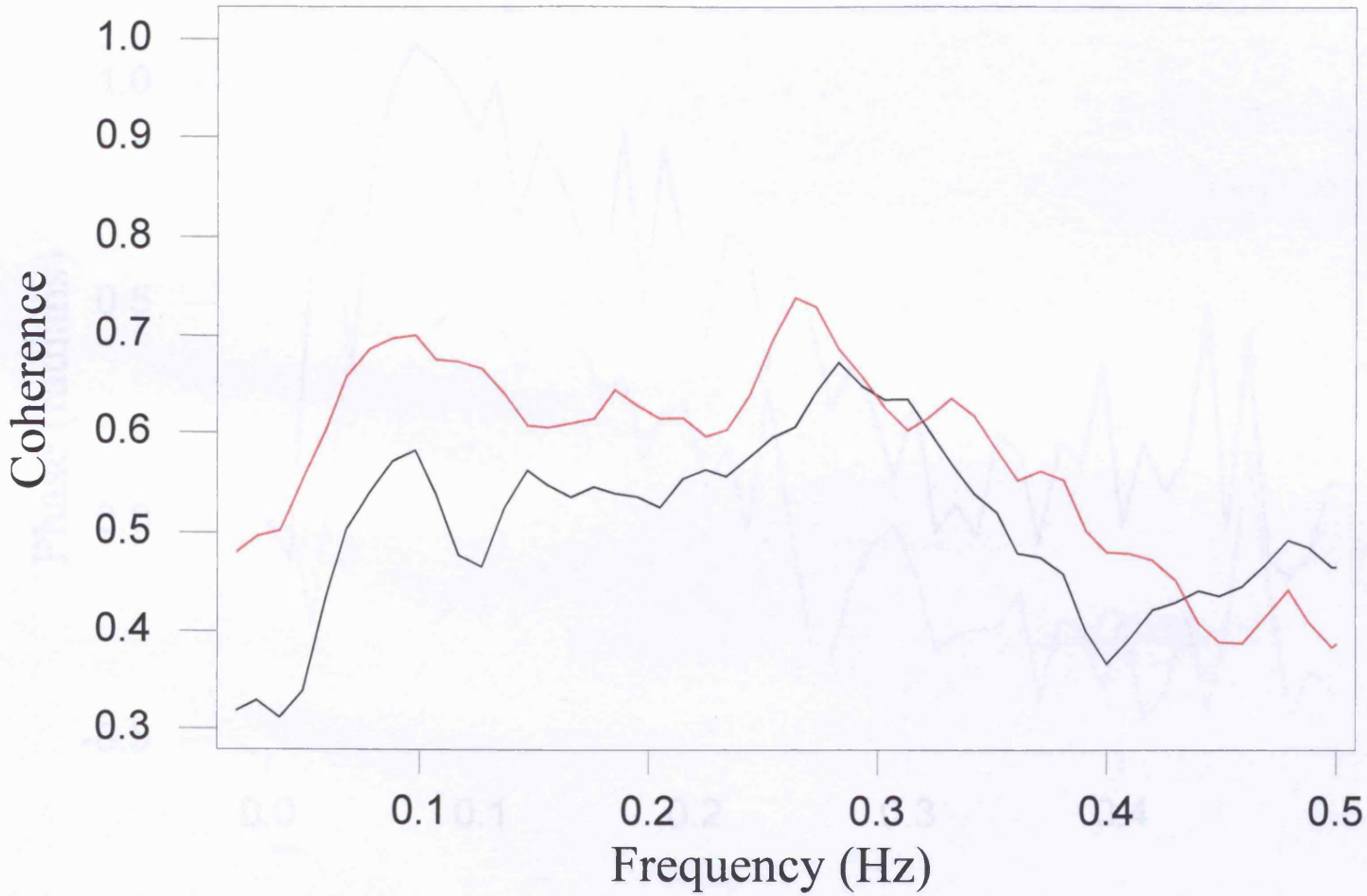


Figure 2.11a.

Figure 2.11b. Phase frequency responses of a subject with normal CA (black) and a subject with impaired CA (red)

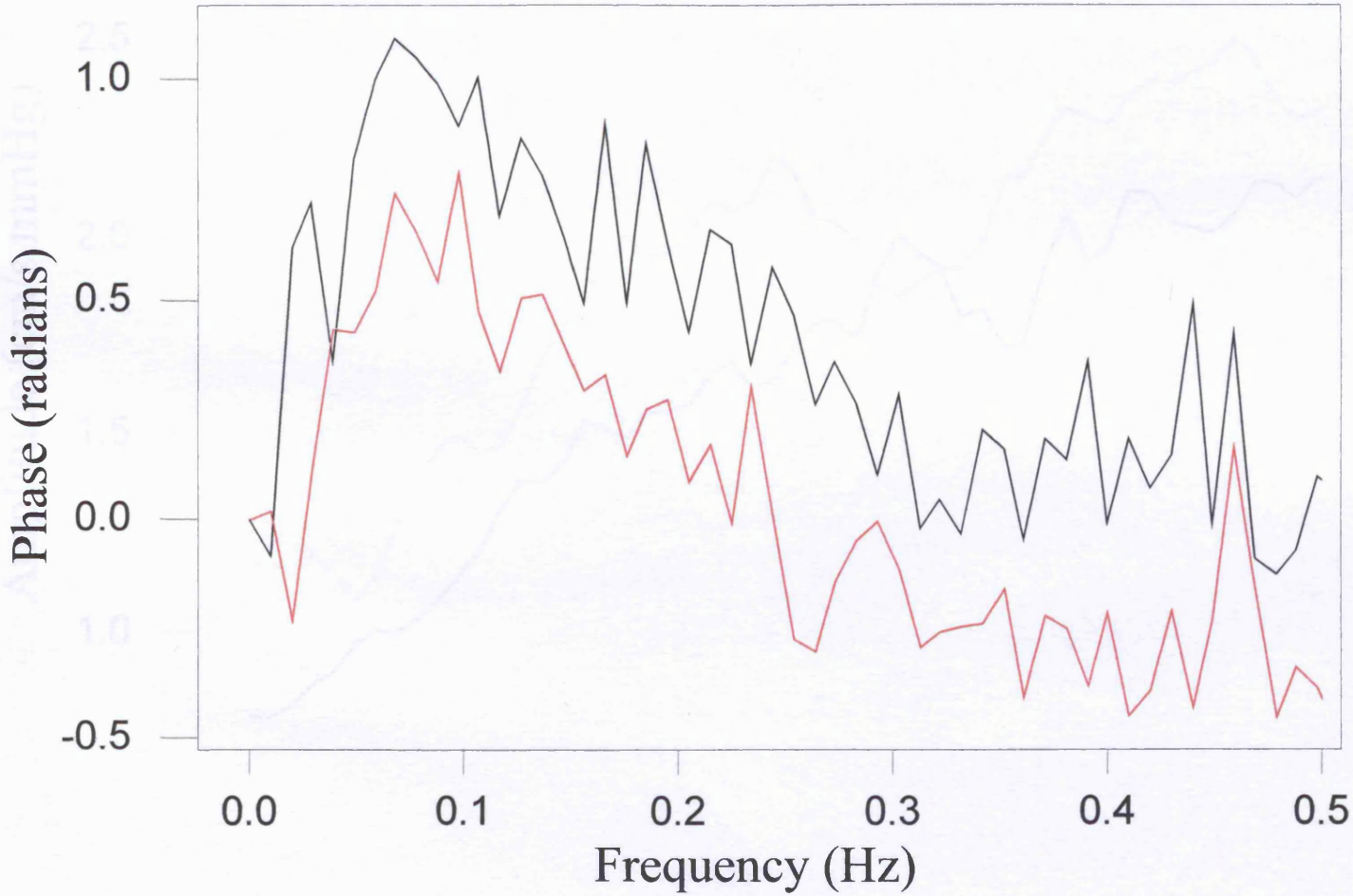


Figure 2.11b.

Figure 2.11c. Amplitude plots of a subject with normal CA (black) and a subject with impaired CA (red)

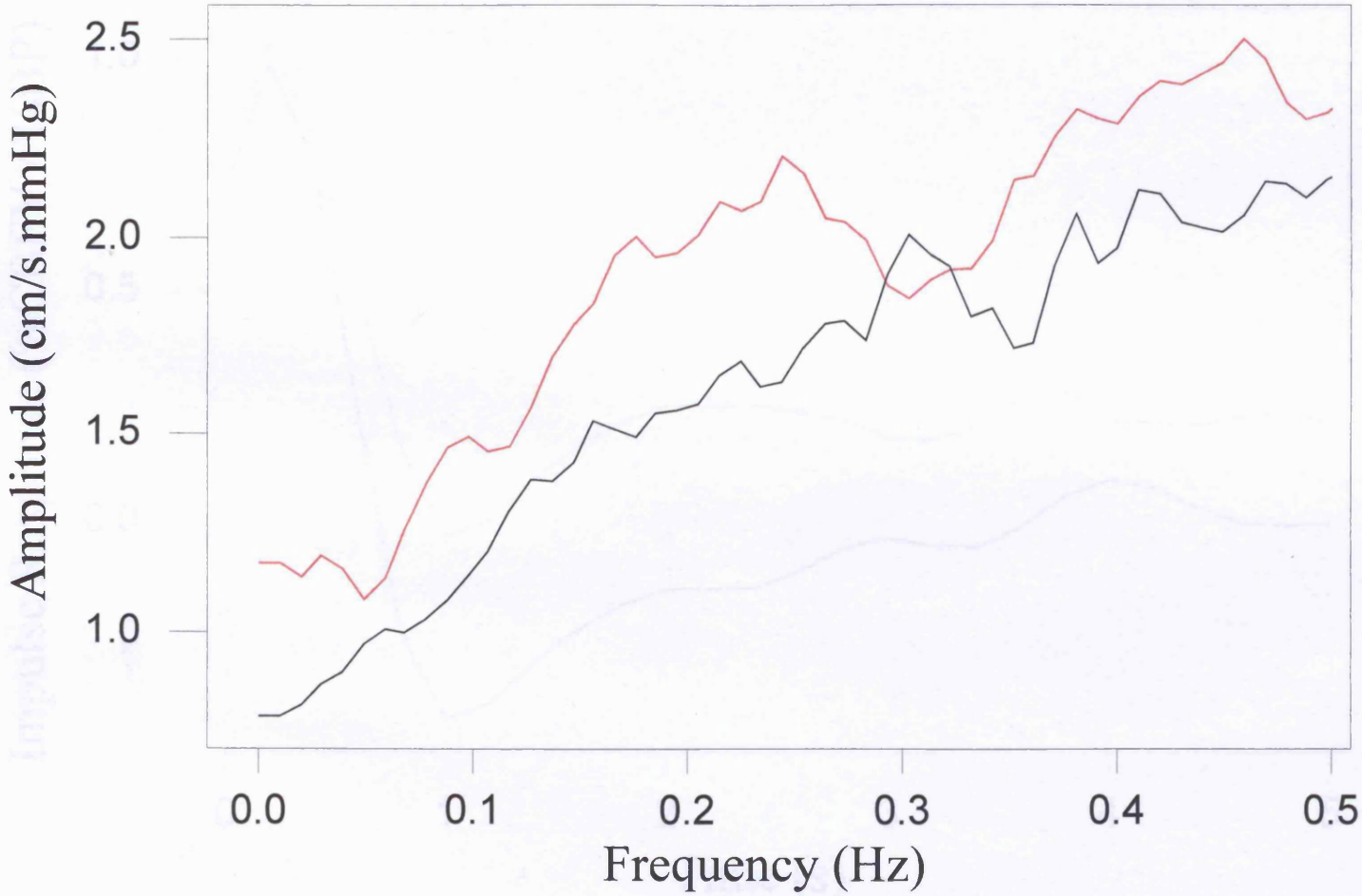


Figure 2.11c.

Figure 2.11d. Impulse response plots of a subject with normal CA (black) and a subject with impaired CA (red)

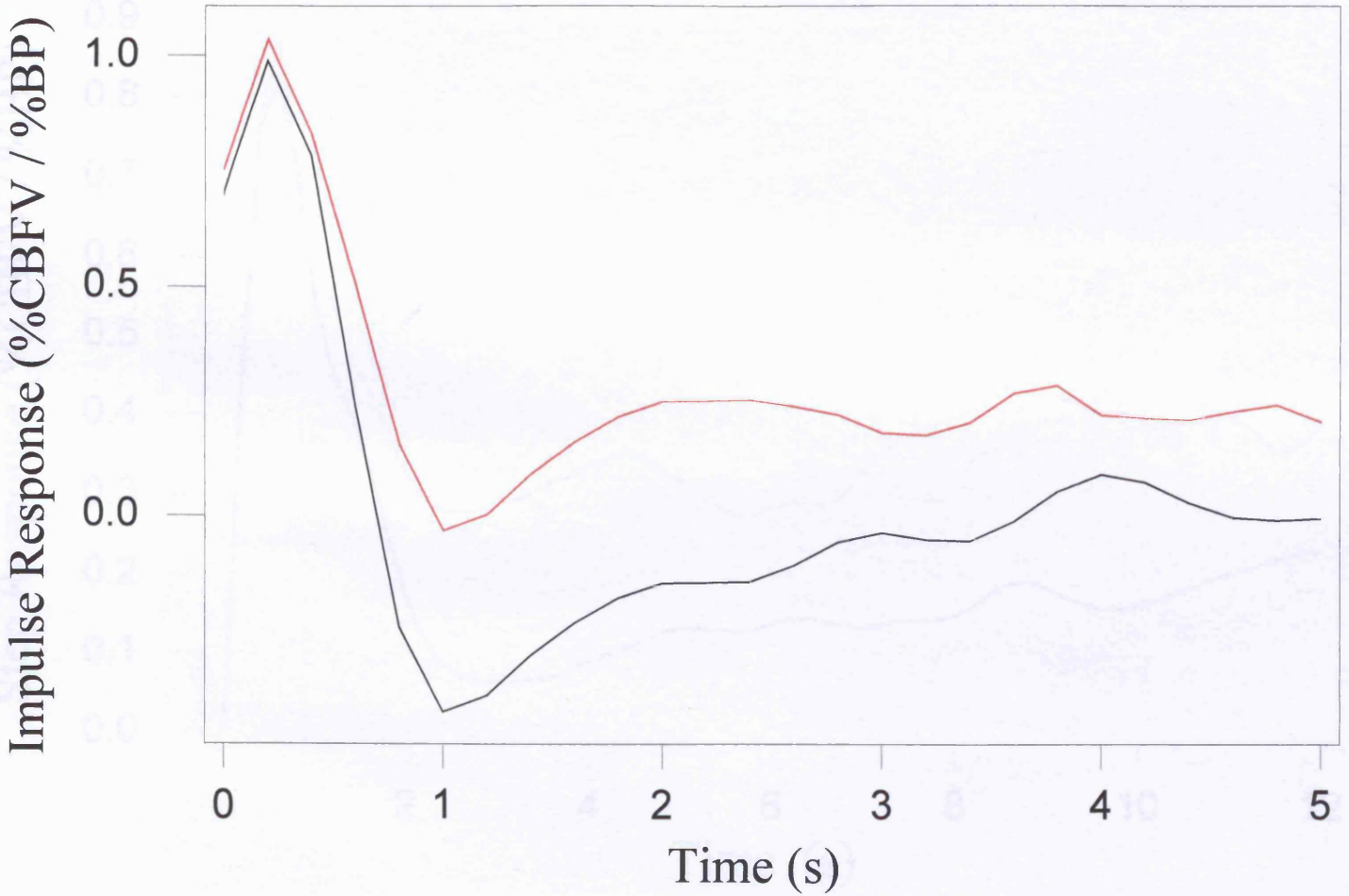


Figure 2.11d.

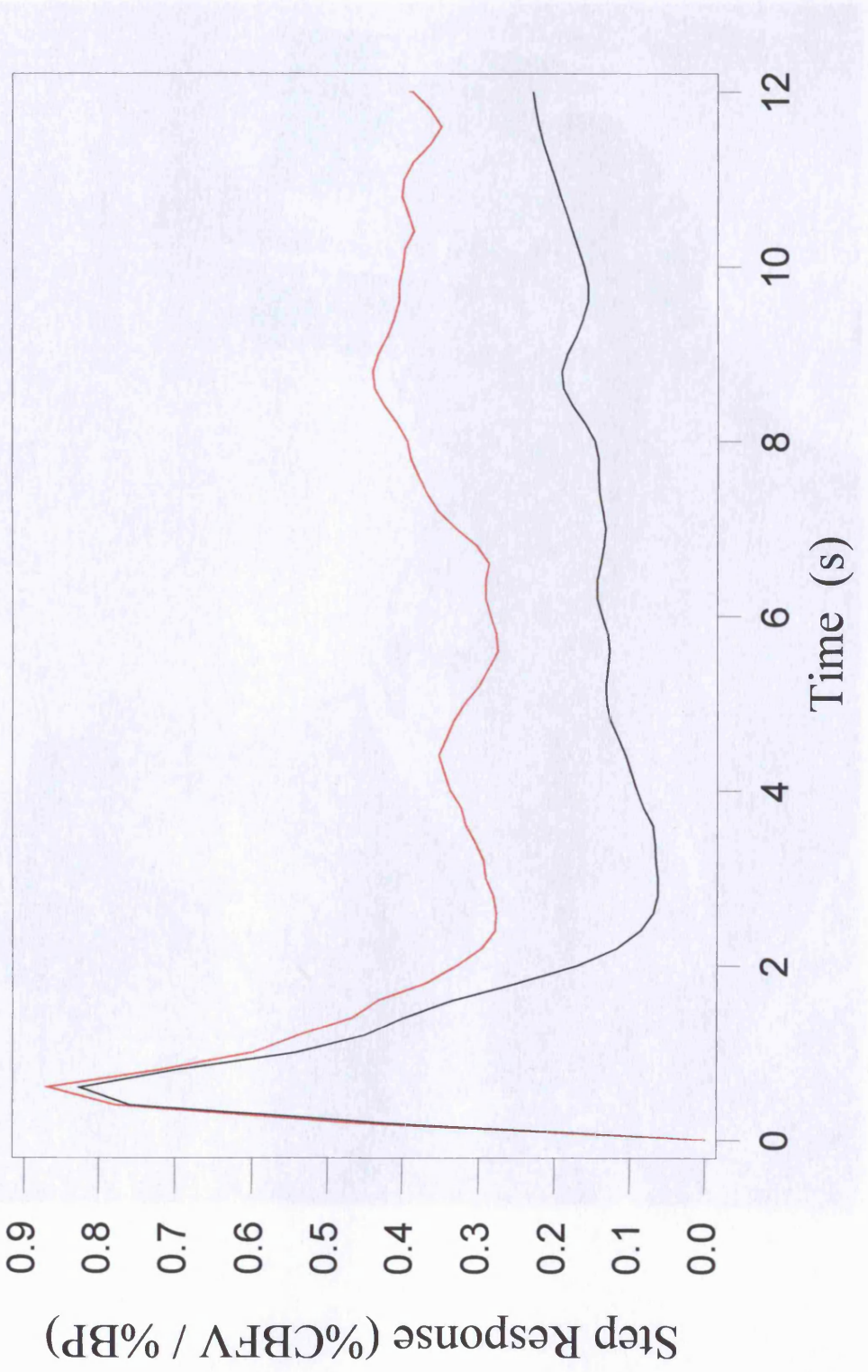


Figure 2.11e. Step response plots of a subject with normal CA (black) and a subject with impaired CA (red)

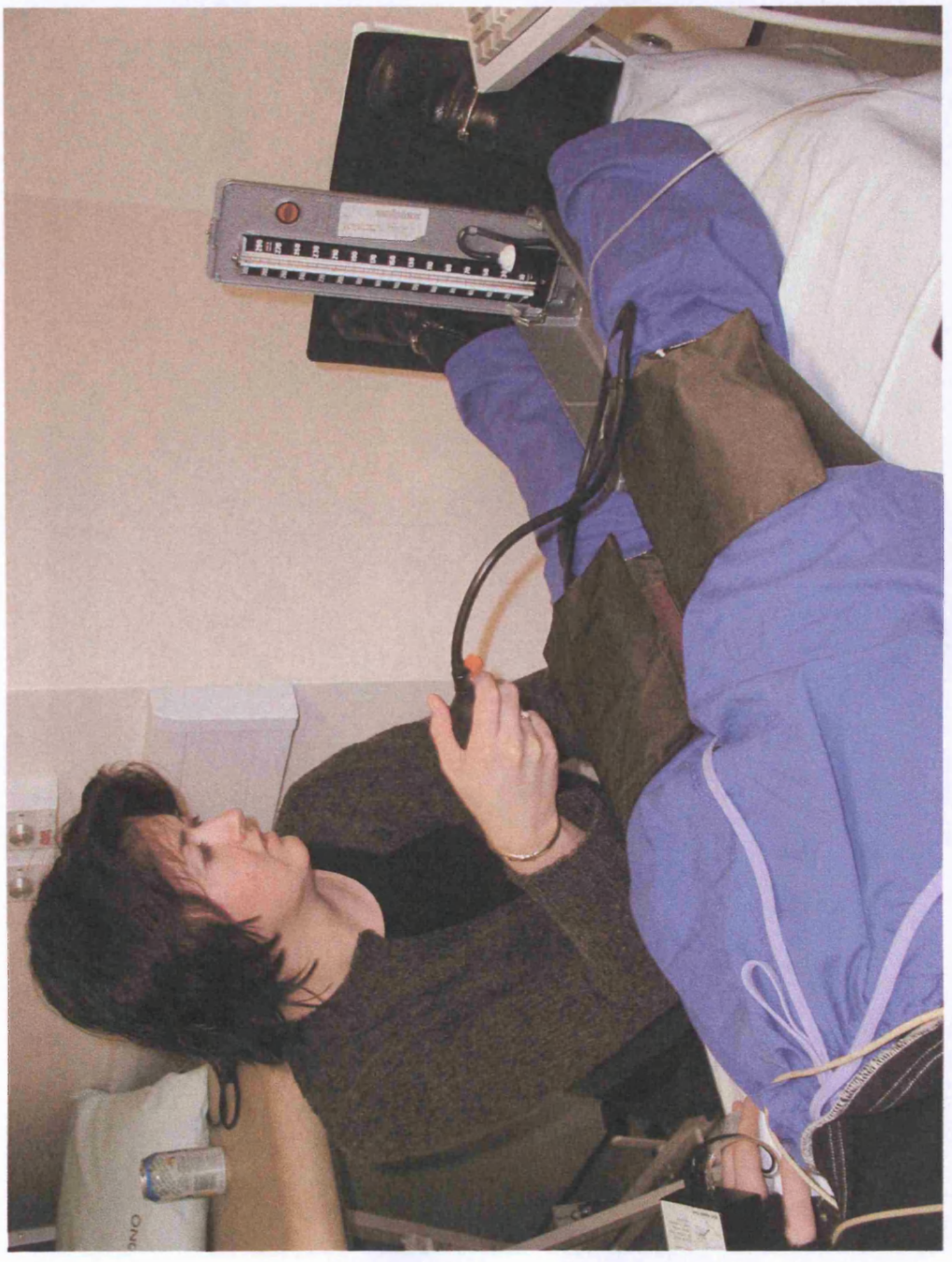


Figure 2.12. A volunteer undergoing thigh-cuff inflation

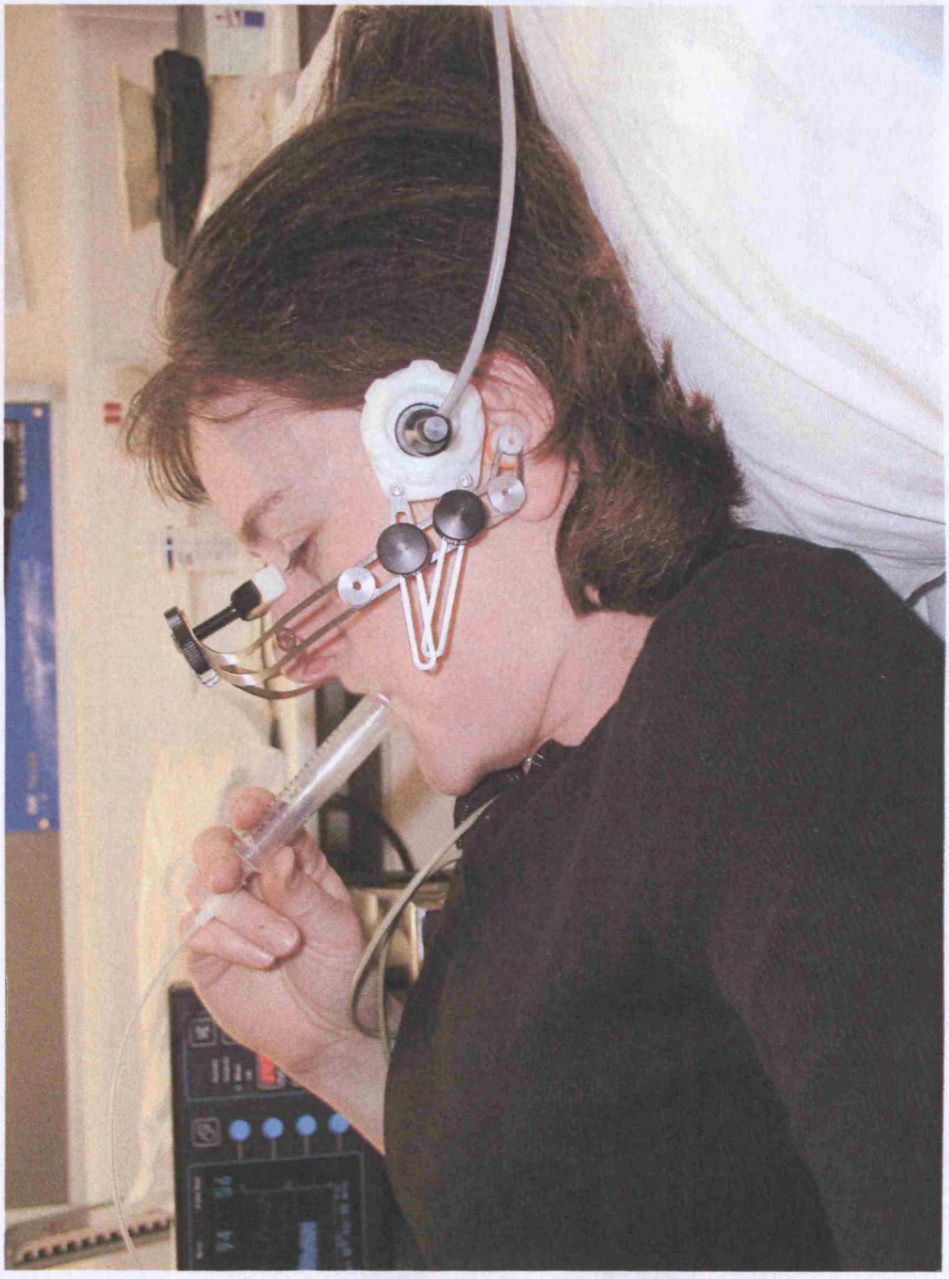


Figure 2.13. A volunteer performing a Valsalva manoeuvre

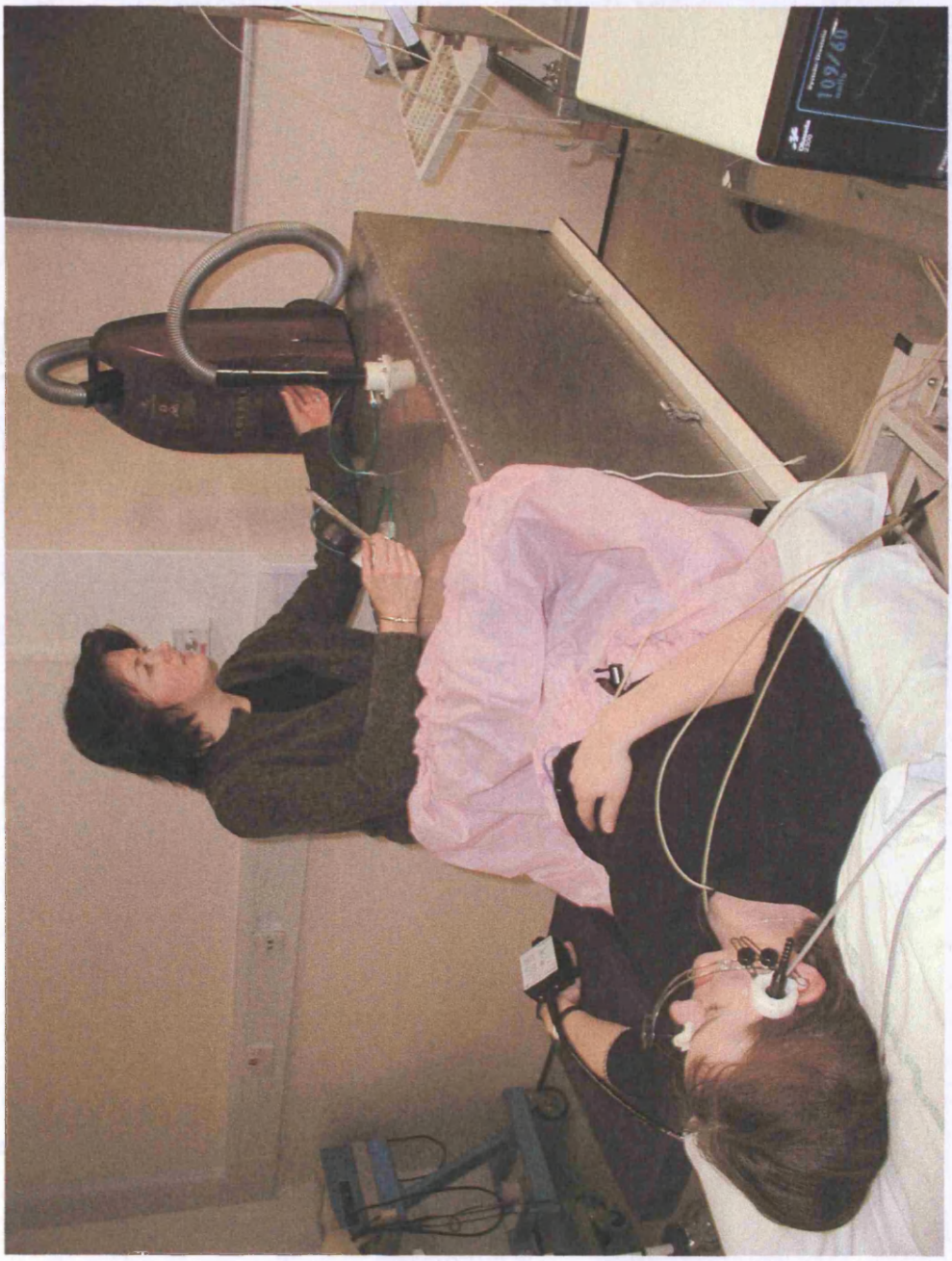


Figure 2.14. Application of lower body negative pressure

Artery	Transducer Position	Depth of sampling (mm)	Direction of Flow	Spatial Relationship ACA/MCA Bifurcation	Mean Velocity (cm/sec)	Response to Ipsilateral Carotid Compression
MCA	Transtemporal	30-60	Toward	Same	55 ± 12	↓
ACA/MCA Bifurcation	Transtemporal	55-65	Bidirectional	-	-	↓
ACA	Transtemporal	60-80	Away	Anterior & Superior	50 ± 11	↓
Proximal PCA	Transtemporal	60-70	Toward	Posterior & Inferior	39 ± 10	↔↑
Distal PCA	Transtemporal	60-70	Away	Posterior & Inferior	40 ± 10	↔↓
TICA	Transtemporal	55-65	Toward	Inferior	39 ± 9	↓
OA	Transorbital	40-60	Toward	-	21 ± 5	↓
VA	Transforaminal	60-90	Away	-	38 ± 10	-
BA	Transforaminal	80-120	Away	-	41 ± 10	-

Table 2.1. Identification of basal cerebral arteries

ACA = anterior cerebral artery
MCA = middle cerebral artery
PCA = posterior cerebral artery
TICA = terminal internal carotid artery
OA = ophthalmic artery
VA = vertebral artery
BA = basilar artery

Table 2.2. Static and Dynamic Pressor & Depressor Changes

Stimulus	Induced	Static	Dynamic	Pressor	Depressor
Thigh cuff inflation	✓	✓	×	✓	×
Thigh cuff release	✓	×	✓	×	✓
Lower body negative pressure	✓	✓	×	×	✓
Lower body negative pressure release	✓	×	✓	✓	×
Phase IV of the Valsalva manoeuvre	✓	×	✓	✓	×
Spontaneous BP changes at rest	×	×	✓	✓	✓

CHAPTER THREE

Effect of Ageing on Cerebral Autoregulation

3.1. Summary

Normal ageing is associated with marked changes in the cardiovascular and cerebrovascular systems. Although cerebral autoregulation (CA) is impaired in certain disease states, the effect of age per se on CA in humans is unknown.

27 young subjects (≤ 40 years) and 27 older subjects (≥ 55 years), matched for sex and systolic blood pressure (BP), underwent measurement of cerebral blood flow velocity using transcranial Doppler ultrasound and non-invasive beat-to-beat arterial BP measurement during induced and spontaneous static and dynamic BP stimuli. Standard static and dynamic autoregulatory index (ARI) values were derived for each spontaneous and induced static and dynamic BP stimulus as well as cardiac baroreceptor sensitivity (BRS) and step response values for the two groups.

The mean age of the young group was 29 ± 5 years and older group was 68 ± 5 years. Cardiac BRS was reduced in the older group (8.6 ± 4.5 v 16.9 ± 8.8 ms/mmHg, $p<0.0001$). However, no age-related differences were demonstrated in step response plots or in ARI values for pressor (0.80) or depressor (0.48) static or dynamic ($p=0.62$) BP stimuli ($p=0.62$). Mean dynamic ARI values for all stimuli combined were 4.9 ± 1.8 for the young group and 5.0 ± 2.3 for the older group. Mean static ARI values were 54 ± 30% for the young group and 56 ± 32% for the older group.

Although increasing age is associated with a decrease in cardiac BRS and CBFV, dynamic CA, as assessed using step response analysis as well as cerebral blood flow responses to transient and induced static and dynamic BP stimuli, is unaffected by ageing.

3.2. Background

The cardiovascular system demonstrates many age-related changes as evidenced by the well-recognised increase in systolic blood pressure (SBP) [Kannel 1978] and decreases in systemic artery compliance and cardiac BRS with age [Fleg 1986, Gribbin 1971]. Ageing may also be associated with changes in cerebrovascular haemodynamics with both cerebral blood flow volume and cerebral blood flow velocities being reported as declining with advancing years [Matsuda 1984, Krejza 1999].

Cerebral autoregulation (CA) refers to the inherent ability of the cerebral blood vessels to keep cerebral blood flow (CBF) constant for a wide range of systemic BP levels [Lassen 1959, Paulson 1990]. CA occurs with a substantial degree of temporal heterogeneity in that physiological adjustments of CBF occur both quickly and slowly. Dynamic CA refers to the ability to maintain CBF in the face of BP changes occurring over a matter of seconds and reflects the latency of the cerebral vasoregulatory system. Static CA refers to CBF adjustments in response to more prolonged BP changes and is a measure of the overall efficiency of the system. Dynamic CA is impaired in a variety of disease states including post head-injury [Czosnyka 1996, Smielewski 1997, Steiger 1994], subarachnoid haemorrhage [Smielewski 1995], acute ischaemic stroke [Dawson 2000] and severe carotid artery disease [White 1997]. It has been suggested that static and dynamic CA may have different control mechanisms, and that dynamic CA may be more susceptible to damage in pathological states [Tiecks 1995] as seen following acute ischaemic stroke [Dawson 2000]. As disease states likely to affect CA are more common in the elderly, it is important to know if ageing per se affects CA.

The advent of transcranial Doppler ultrasonography has facilitated the non-invasive measurement of CBF haemodynamics by allowing cerebral blood flow velocity

(CBFV) changes in response to static and dynamic BP changes, and hence CA, to be calculated [Tiecks 1995, Aaslid 1989]. Methods of CA estimation using spontaneous BP changes may have advantages over methods using induced BP changes. Such methods include the new step response methodology [Panerai 1998a, 1999b, Zhang 1998a], and do not induce sympathetic stimulation or hypocapnia, both of which may affect the integrity of CA (see sections 1.3.2.4. & 1.3.3.1.). The use of spontaneous BP changes is also less noxious to subjects and poses less risk to patients potentially at risk from the induction of acute hypotensive or hypertensive changes e.g. patients post acute stroke or subarachnoid haemorrhage and those with carotid stenosis. Although the effect of ageing on CA has been studied in animals [Hoffman 1981], the effects of physiological ageing on CA in humans are unknown. This study was designed to assess the effect of human ageing on static and dynamic CA to spontaneous and induced pressor and depressor stimuli.

3.3. Objectives

1. To assess the effect of normal ageing on static cerebral autoregulation.
2. To assess the effect of normal ageing on dynamic cerebral autoregulation.
3. To examine the effect of the magnitude of pressor and depressor changes on static and dynamic CA.

3.4. Methods

3.4.1. Subjects

Subjects were recruited from a volunteer register in the department and from departmental staff. All were healthy, on no medications and free from cardiovascular, cerebrovascular or autonomic disease as based on history and clinical examination.

Significant silent carotid stenosis was excluded on the basis of bilateral neck auscultation and the absence of typical transcranial Doppler ultrasound findings [Wilterdink 1997]. Subjects were assigned by age to a young group (≤ 40 years) or an older group (≥ 55 years) being pair-matched for sex, body mass index (BMI) (within 2.0 kg/m^2) and systolic BP (within 10mmHg) using BP measurements made according to the protocol described in section 2.6.

3.4.2. Study Protocol

All subjects underwent the initial preparatory protocol outlined in section 2.6. After resting supine for a minimum of 30 minutes and when the Finapres and TCO_2 traces had stabilized (<10% variation over 5 minutes), two baseline recordings of at least 5 minutes each were made during supine rest for each subject. Subsequently, the pressor and depressor stimuli were applied in random order with a baseline recording of 60 seconds before and after each test.

3.4.2.1. Static pressor stimulus

Bilateral thigh cuffs were applied and inflated to suprasystolic pressures for 90 seconds with thigh cuff pressure monitored using a mercury sphygmomanometer, as described in section 2.5.1.

3.4.2.2. Static depressor stimulus

The lower limbs of the subjects were sealed at the level of the iliac crests in a custom designed box and lower body negative pressure (LBNP) applied (range 15-58

mmHg), as described in section 2.5.3, for 5 minutes to cause a fall of at least 10 mmHg in systolic BP.

3.4.2.3. Dynamic pressor stimuli

I) LBNP release – After 5 minutes of the static depressor BP stimulus outlined above (3.4.2.2.), atmospheric pressure was suddenly restored to the box by disconnecting the pressure box.

II) Valsalva manoeuvre (phase IV) - Subjects were asked to perform a Valsalva manoeuvre lasting 15 seconds whilst supine by blowing into a tube connected to a transducer, as described in section 2.5.2, which registered intrathoracic pressures to aid compliance. After completion, subjects lay quietly for one minute while recording continued. This procedure was repeated twice so that each subject performed 3 Valsalva manoeuvres one minute apart.

III) Three spontaneous rises in BP >5mmHg were selected at random from each of the two 5-minute rest recordings. A total of six spontaneous pressor changes were, therefore, selected for each subject and the mean value taken.

3.4.2.4. Dynamic depressor stimuli

I) Thigh cuff release – After 90 seconds of the static pressor BP stimulus outlined above (section 3.4.2.1), the cuffs were rapidly deflated while recording continued for a further minute. This test was repeated in some patients to increase the likelihood of obtaining a BP fall of >10 mmHg.

II) Three spontaneous falls in BP >5mmHg were selected at random from each of the two rest recordings. A total of six spontaneous depressor changes were, therefore, selected for each subject.

3.4.3. Data analysis

Data were initially analysed as outlined in section 2.7. In addition, ectopic beats occurring in the 15-second window prior to or after induced and spontaneous pressor and depressor BP changes led to the rejection of the data.

3.4.4. Determination of cerebral autoregulation

3.4.4.1. Determination of static CA

Indices of static CA ranging from 0% (absent) to 100% (most efficient) were derived using the methods outlined in section 2.4.1. Data were manually selected to include a one-minute baseline period before the pressor or depressor stimuli as well as the subsequent period of static MAP change during the stimuli.

3.4.4.2. Determination of dynamic CA using Aaslid's model

Dynamic CA was graded by generating a dynamic autoregulatory index (ARI), ranging from 0 (absent) to 9 (most efficient), for each subject for each dynamic pressor and depressor stimulus using the methods outlined in sectioned 2.4.2.1. Data were marked manually at the point of initiation of the dynamic BP change. Only induced BP changes ≥ 10mmHg and spontaneous BP changes ≥ 5mmHg at rest were accepted as adequate dynamic stimuli. Subjects had to exhibit a synchronous and physiological change in BP and MCA CBFV for all manual marks. A sample window of 30 seconds from the manual mark was used in all cases. Each dynamic BP stimulus yielded an ARI for right and left middle cerebral arteries for each individual. The mean of the two ARI values thus obtained was taken to be the ARI for that individual for that dynamic BP stimulus. For thigh cuff release, phase IV of the Valsalva manoeuvre and spontaneous pressor and depressor changes the mean of the

ARI values derived for each adequate stimulus was taken to be the ARI for that dynamic BP stimulus.

3.4.4.3. Determination of dynamic CA using step response analysis

The step response of both young and older groups was derived using frequency domain analysis as outlined in section 2.4.2.2.

3.4.5. Determination of cardiac baroreceptor sensitivity

The PI and SBP series were analyzed by means of power spectral analysis with a fast Fourier transform with 512 samples. The data segments used were extracted under visual inspection from the most stable segment of each rest recording. The beat-to-beat series of PI and SBP were interpolated with a third-order polynomial and resampled with an interval of 0.5s to produce signals with a uniform time axis. The power spectra were obtained as the average of three recordings for each subject and were smoothed with a 13-point triangular window. This produced estimate of power spectra of PI and SBP, coherence function and frequency response between PI and SBP with 58 degrees of freedom. Coherence between BP and PI variability reflects the amount of linear coupling between the two spectra and is, therefore, comparable to the correlation coefficient in regression analysis [Robinson 1997]. A coherence value >0.4 was considered significant [Panerai 1997]. Power spectral analysis estimates of cardiac BRS were obtained by calculation of the α-index (square root of the powers of PI to BP) for the low frequency band (0.05 to 0.15 Hz). To correct for variability in total and very low frequency (0.02 to 0.05 Hz) powers, the low frequency power spectra for PI and SBP were calculated in normalised units [Montano 1994] as follows:

Power = Absolute power / (total power – very low frequency power)*100

3.4.6. Statistical Analysis

Data were analysed using SAS version 6.12 and Minitab 12 software packages. Results are presented as mean ± standard deviation (range) and statistical significance set at $p<0.05$ level.

With all 5 dynamic BP stimuli, it was assumed that missing data were lost in random fashion i.e. that the probability of a missing ARI was not a function of the subject's ARI. A normal distribution was assumed and a good approximation to this was demonstrated by a plot of residuals. Using mixed modelling age by stimulus interaction, age effect, estimated difference (young v old) and stimulus effect were calculated.

As the two groups were pair-matched, Student's paired t-tests were used to compare ARI values derived for each BP stimulus between the two groups to see whether any individual test demonstrated a difference.

The differences between ARI values derived from the 5 different stimuli were estimated using a mixed model for repeated measures data. Different covariance patterns were investigated using Akaike's Information Criterion. Multiple pairwise testing was adjusted for using Tukey's method.

Mean step responses and their standard errors were calculated for both young and older groups [Panerai 1998a, 1999b]. The step responses at 5 seconds were compared between the two groups using Student's paired t-tests.

Static CA indices were compared between the young and older groups using Student's paired t tests.

3.5. Results

Demographic and baseline data for the young (n=27) and older groups (n=27) are contained in Table 3.1. Despite matching for systolic BP and BMI, both parameters were significantly higher in the older group ($p < 0.001$ and $p=0.003$ respectively), but mean BP and diastolic BP were similar in the two groups. Baseline mean CBFV was significantly higher in the younger group ($p=0.006$) as was mean baseline cardiac BRS ($p<0.0001$).

The average BP changes achieved by the different static and dynamic stimuli are shown in Table 3.2. Regression analysis failed to show a significant correlation between ARI values and the magnitude of dynamic ($p=0.82$) or static ($p=0.39$) BP change.

No differences were demonstrated between the young and older groups for static pressor or depressor ARI values (Table 3.2.). Mixed modelling did not demonstrate any variation of the effect of age on ARI values according to the dynamic stimulus used (age by stimulus interaction), $p=0.36$.

When a constant effect across all dynamic stimuli was assumed, no age effect was shown ($p=0.62$) with the estimated difference in ARI between young and older groups being -0.18 (95% CI; -0.93 to 0.56). No significant differences were shown between the two groups for ARI values derived using any of the 5 dynamic BP stimuli (see Table 3.2.).

When age effect was excluded from the final model and the effect of dynamic stimulus on ARI values was estimated for young and older subjects combined, a significant effect was demonstrated ($p=0.033$). Further comparison, using Tukey's method of adjusting p values for multiple comparisons, showed that ARI values derived from thigh cuff release were significantly greater those from LBNP release

(difference=1.27, 95%CI 0.03-2.50, p=0.042), though no other significant differences were found.

When all dynamic ARI values were combined, the young group had a mean ARI value of 4.9 ± 1.8 compared to 5.0 ± 2.3 for the older group (difference = -0.1; 95% CI –0.6 t 0.7; p=0.88).

Mean step response plots for the two groups, including standard errors, are displayed in Figure 3.1. No significant differences were shown between the step responses of the groups at 5 seconds (103.5 v 102.9, difference=0.6, p=0.37).

3.6. Discussion

Certain important aspects of cerebral haemodynamics have been shown to change with age, with CBF volume and CBFV decreasing and cerebral arterial vessels widening in diameter [Matsuda 1984, Krejza 1999]. The reasons behind the decline in CBF and CBFV with age are unknown but may be due to the increase in arterial vessel diameter [Matsuda 1984] or decreasing metabolic demand [Murphy 1996]. Dynamic, as opposed to static, CA has been shown to be the more vulnerable component to impairment in certain disease states [Dawson 2000, Tiecks 1995] and, as pathological changes become more prevalent with age, it is important to know if age per se causes deterioration in CA. That such changes take place in old age may have clinical importance and help explain, for example, the poor correlation between postural symptoms and systemic BP changes to standing in the elderly and in certain syncope syndromes [Wynne 1996]. In this study, no change was demonstrated in static CA with age and, despite the use of two different methodologies (Aaslid's model and frequency domain analysis), pressor and depressor BP stimuli and induced and spontaneous static and dynamic BP changes, no differences were demonstrated in

static or dynamic CA with age. Similar methods have detected impaired dynamic CA in carotid artery stenosis [Panerai 1998b], after acute ischaemic stroke [Dawson 2000], in neonates [Panerai 1998a] and during hypercapnia [Panerai 1999b]. The older group had lower cardiac BRS and mean CBFV values than their younger counterparts, suggesting that the "normal" ageing process in other cardiovascular and cerebrovascular parameters was present in the subjects recruited [Gribbin 1971, Krejza 1999, Fuledsi 1997].

3.6.1. Pressor and depressor changes

Thigh cuff inflation, as a static pressor stimulus, and thigh cuff release and the Valsalva manoeuvre, as dynamic pressor and depressor stimuli respectively, have previously been used to assess CA [Dawson 2000, Tiecks 1995, 1996, White 1997]. Thigh cuff release is probably the most widely applied dynamic BP stimulus, but it is unknown if ARI values are dependent on the type of stimulus used, the direction of BP change (pressor or depressor) or the magnitude of BP change induced. The author is unaware of any previous reports of the use of LBNP release or spontaneous transient changes in BP at rest with Aaslid's model to assess CA. Although we have demonstrated significant differences between ARI values derived using different dynamic BP stimuli (thigh cuff release and LBNP release), no age-related differences were found.

3.6.2. Autoregulatory indices

Although Aaslid's dynamic ARI is an arbitrary model, it does give important clinical information, e.g. acute ischaemic stroke patients have dynamic ARI values in the order of 2.0 lower than age and BP matched controls [Dawson 2000]. Similar

methods have shown dynamic ARI values to be a mean of 2.6 lower than control values in patients with carotid artery disease [White 1997]. The static and dynamic ARI values in this study are consistent with those published previously [Dawson 2000, White 1997, Tiecks 1995, Mahony 2000] and demonstrate a dynamic ARI difference of only –0.18 between young and older groups with a 95% confidence interval of –0.93 to 0.56. These confidence intervals are of a magnitude that suggest that there are is no clinically significant age-related deterioration in dynamic CA.

3.6.3. Magnitude of blood pressure changes

The magnitudes of dynamic BP changes were significantly greater in the young for phase IV of the Valsalva manoeuvre but no differences were shown for any of the other dynamic BP stimuli. No significant correlation was found, however, between the magnitude of static and dynamic BP changes and ARI values. It is also worth noting that phase IV of the Valsalva manoeuvre caused the largest dynamic BP changes in both groups but yielded neither the highest nor lowest ARI values. Static BP changes between the two static stimuli are not comparable due to the protocol of LBNP application adopted.

3.6.4. Step response analysis

Step response analysis has been used to demonstrate impairment of dynamic CA in premature neonates [Panerai 1998a], hypercapnia [Panerai 1999b] and severe carotid artery stenosis [Panerai 1998b]. Step response plots characteristically demonstrate a return of CBFV to baseline values when dynamic CA is intact and higher values when impaired. The step response plots were remarkably similar for the two groups and indicate an active autoregulation in both groups.

3.6.5. Age and cerebrovascular function

Kastrup [1998] found that cerebrovascular CO_2 reactivity was not affected by ageing in men but decreased with age in women. A sub-analysis of the female subjects in this study demonstrated no differences in dynamic CA with age. It has to be remembered, however, that CO_2 reactivity and dynamic CA are different entities, the former possibly representing only one of the elements of the latter. If post-menopausal differences in CO_2 reactivity truly exist, they do not appear to affect the integrity of dynamic CA.

This is the first study to show that ageing does not impair CA while demonstrating that ageing does alter other cardiovascular and cerebrovascular haemodynamic parameters i.e. cardiac BRS and CBFV. CA is a function of multiple physiological processes including metabolic, myogenic, neuronal and, possibly, nitric oxide (NO) and endothelin-mediated endothelial mechanisms [White 1998, Thorin 1998]. It is interesting that, although arterial compliance [Fleg 1986], CBFV [Krejza 1999], CBF [Matsuda 1984] and, possibly, endothelium-mediated vascular relaxation [Hongo 1988] decline with age, the ability of the cerebrovasculature to compensate for BP changes remains undiminished. This suggests that the CA system may have an in-built reserve that allows for degeneration of the individual elements with time. If this is the case, it is possible that CA reserve may deteriorate with age and that impairment of CA may only be uncovered if the reserve is stretched to capacity e.g. at BP or age extremes, with large BP changes or in disease states. CBFV values in the young and older groups were comparable to values reported elsewhere and demonstrated the significant age-related decline one would expect [Krejza 1999, Fuledsi 1997]. It is unknown if the magnitude of CBFV has any effect on CA, but it would appear not to

be the case in this study as ARI values were similar in our young and old groups even though mean CBFV was significantly lower in the older group.

3.6.6. Limitations

Despite matching, the older group as a whole had a small though significantly higher systolic BP than the young group but mean BP and diastolic BP were well matched between the group pairs. Increasing BP levels cause a shift in the static autoregulatory curve to the right [Strandgaard 1973, 1976, 1989, Hoffman 1981, Fujishima 1984], but there is no evidence that increases in systemic BP levels impair or facilitate dynamic CA [Blake 2000]. Similarly, there is no evidence that increases in BMI are associated with changes in dynamic CA. If such changes did occur with increasing BMI, one could hypothesise that they would be mediated by increases in arterial BP, but this parameter has been reasonably well controlled.

The static and dynamic BP stimuli used in this study for assessing CA probably did not produce big enough BP changes to exceed the upper and lower BP limits within which CA is active, and the possibility of a narrowing with age of the BP plateau could not be addressed. In addition, only two static BP stimuli were employed resulting in quite large confidence intervals and the conclusions that can be drawn regarding the effect of ageing on static CA are, therefore, somewhat limited.

The major limitation of this work, and indeed, any work using similar methodology, is that we have measured cerebral blood flow velocity rather than cerebral blood flow. Changes in CBF can only be reliably deduced from CBFV changes if the diameter of the insonated vessel remains unchanged [Aaslid 1982], but reliable, non-invasive assessment of vessel diameter has proven notoriously elusive. A number of authors have used the spectral power of Doppler signals to show that MCA diameter does not

change during thigh cuff application and release [Aaslid 1989] and during hypocapnia and hypercapnia [Poulin 1996], but a recent study has cast doubt on the usefulness of this method of assessing vessel diameter [Deverson 2000]. Significant change in MCA diameter is unlikely, however, during thigh cuff application and release [Newell 1994], Valsalva manoeuvre [Tiecks 1996], LBNP [Serrador 2000] or supine rest. Nevertheless, MCA diameter was not directly measured and caution must therefore be exercised in interpreting the results.

In addition to inducing BP changes, the different static and dynamic stimuli may result in other important physiological changes such as hypocapnia secondary to hyperventilation, hypercapnia during the Valsalva manoeuvre due to apnoea and, possibly, varying degrees of increased sympathetic nervous system activity between stimuli. Hypocapnia has been shown to augment dynamic CA [Aaslid 1989], but no age-related differences in CO_2 levels were found at rest. The effect of increased systemic SNSA on dynamic CA is unclear (see section 1.2.2.4.), nor is it known if the effect of sympathetic nerves on cerebral blood vessels changes with ageing. An age-related deterioration would, however, probably impair CA and result in lower ARI values in the older age group. As the degree of change in CO_2 and sympathetic nervous system activity, and the effects on CA, of thigh cuff application and release, Valsalva manoeuvre and LBNP application and release are unknown, the statistical methods used allowed for the fact that ARI values derived from different dynamic stimuli may not be directly comparable. In view of these uncertainties, methods of assessing dynamic CA using spontaneous BP changes at rest, using Aaslid's model or step response analysis, may appear more attractive.

3.7. Conclusions

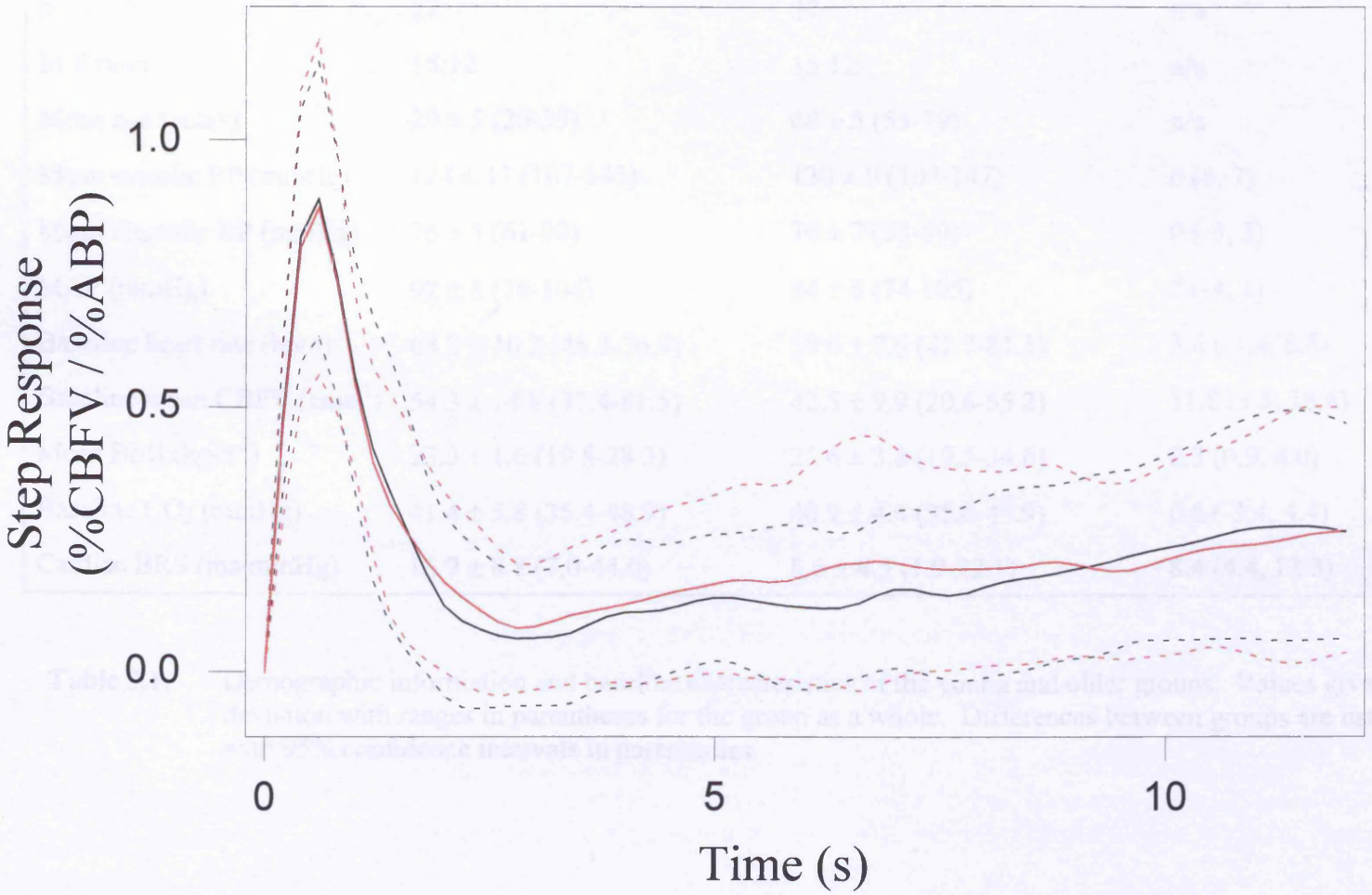
1. Static and dynamic CA, as assessed using induced and spontaneous pressor and depressor changes, are unaffected by ageing.

2. No relationship exists between the magnitude of induced and spontaneous BP changes and indices of static and dynamic CA.

3. Dynamic ARI values derived using thigh cuff release are significantly greater than those derived using LBNP release.

4. Further studies using other methods are needed to precisely define the autoregulatory curve in older persons.

Figure 3.1. Mean step responses (solid lines) and standard errors (dotted lines) of young group (black lines) and older group (red lines)



	Young group	Older group	Difference (95%CI)	p value
n	27	27	n/a	n/a
M:F ratio	15:12	15:12	n/a	n/a
Mean age (years)	29 ± 5 (20-39)	68 ± 5 (55-79)	n/a	n/a
Mean systolic BP (mmHg)	124 ± 11 (107-145)	130 ± 9 (107-147)	6 (5, 7)	<0.001
Mean diastolic BP (mmHg)	76 ± 8 (61-90)	76 ± 7 (58-89)	0 (-3, 3)	0.98
MAP (mmHg)	92 ± 8 (76-104)	94 ± 8 (74-105)	2 (-4, 1)	0.10
Baseline heart rate (bpm)	63.2 ± 10.2 (45.2-76.4)	59.6 ± 7.6 (42.7-81.1)	3.6 (-1.4, 8.5)	0.15
Baseline mean CBFV (cms^{-1})	54.3 ± 14.8 (37.4-81.5)	42.5 ± 9.9 (20.6-55.2)	11.8 (3.5, 18.6)	0.006
Mean BMI (kgm^{-2})	23.3 ± 1.6 (19.8-28.3)	25.6 ± 3.8 (19.5-34.6)	2.3 (0.9, 4.0)	0.003
Baseline CO_2 (mmHg)	41.4 ± 5.8 (35.4-48.9)	40.9 ± 4.4 (35.0-45.9)	0.5 (-3.4, 4.4)	0.80
Cardiac BRS (ms/mmHg)	16.9 ± 8.8 (7.0-44.0)	8.6 ± 4.5 (1.9-22.1)	8.4 (4.4, 12.3)	<0.0001

Table 3.1. Demographic information and baseline characteristics of the young and older groups. Values given are mean ± standard deviation with ranges in parentheses for the group as a whole. Differences between groups are listed as mean differences with 95% confidence intervals in parentheses.

BP stimulus		n	Younger BP change (mmHg)	Older BP change (mmHg)	Difference (95% CI)	p value	Younger mean ARI	Older mean ARI	Difference (95% CI)	p value
Static	Thigh cuff inflation	27	19 ± 8	22 ± 9	3 (-3, 6)	0.44	57 ± 32%	55 ± 35%	2 (-13, 17)	0.80
	LBNP	14	-18 ± 6	- 20 ± 7	-2 (-5, 2)	0.31	52 ± 29%	57 ± 31%	-5 (-15, 10)	0.48
Dynamic	Spontaneous pressor changes	27	9 ± 3 *	8 ± 2 *	1 (-0.5, 2.5)	0.16	4.4 ± 1.5	4.0 ± 2.3	0.4 (-0.9, 1.5)	0.34
	Spontaneous depressor changes	27	-9 ± 3 *	-9 ± 4 *	0 (-1.3, 2.1)	0.67	5.0 ± 1.9	4.7 ± 2.5	0.3 (-1.0, 1.4)	0.63
	Thigh cuff release	19	-16 ± 3 †	-16 ± 6 †	0 (-1.3, 4.8)	0.91	5.4 ± 1.1	6.2 ± 2.4	-0.8 (-1.9, 1.5)	0.13
	LBNP release	11	17 ± 7	14 ± 3	3 (-0.9, 7.6)	0.11	4.1 ± 2.0	4.5 ± 2.6	-0.4 (-2.3, 1.5)	0.62
	Valsalva manoeuvre (phase IV)	18	28 ± 14 ‡	20 ± 6 ‡	8 (1.7, 13.9)	0.02	5.2 ± 2.6	5.2 ± 2.7	0 (-1.9, 2.0)	0.94

Table 3.2. Differences between groups in MAP changes and ARI values for each BP stimulus.
n = the number of matched pairs where data were available.
Comparisons were made using the Student's paired t-test.

* Represents the mean of all values > 5mmHg derived from the rest recordings.
† Represents the mean of all values > 10 mmHg derived from the thigh cuff recordings.
‡ Represents the mean of all values > 10 mmHg derived from the three Valsalva recordings.

CHAPTER FOUR

Baseline Cerebral Autoregulation in Patients With Recurrent Vasovagal Syncope

4.1. Summary

Cerebral vasoconstriction has been reported prior to VVS, suggesting that CA may be impaired during pre-syncope. It is unclear, however, whether patients with recurrent VVS have abnormalities of CA at rest as well as during orthostatic stress.

17 patients with recurrent VVS and 17 normal control subjects were pair-matched for age, sex and systolic blood pressure (BP). Bilateral middle cerebral artery blood flow velocities were measured supine using transcranial Doppler ultrasound and BP measured by non-invasive beat-to-beat monitoring. Static and dynamic autoregulatory indices were calculated for each subject using spontaneous BP changes at rest and pressor and depressor BP changes induced by thigh-cuff inflation and release. Frequency domain analysis of rest recordings was also used to investigate dynamic CA.

No differences were demonstrated in static autoregulatory indices between the patient (56±39%) and control (59±37%) groups (p=0.7). Dynamic autoregulatory indices derived from mean values for both thigh-cuff release and spontaneous BP changes were similar for both patient (5.6 ± 1.7) and control (5.7 ± 1.5) groups (difference 0.2; 95% CI –0.6 to 0.4; p=0.56) and frequency domain analysis also failed to find any differences between groups.

Static and dynamic CA are preserved at rest in patients with recurrent VVS and cannot be used to predict the presence of recurrent VVS.

4.2. Background

Vasovagal syncope (VVS) is the commonest form of syncope encountered in medical practice [Kapoor 1990, 1994, Driscoll 1997]. The presence of VVS does not

necessarily imply a specific underlying cardiovascular pathology and can occur in normal individuals in a variety of circumstances [Van Lieshout 1991, Jorgensen 1993, el-Bedawi 1994a, Lightfoot 1995, Bondar 1995]. Prior to VVS, systolic blood pressure (BP), diastolic BP and total peripheral resistance decline in association with pre-syncopal symptoms such as dizziness, nausea, diaphoresis and diplopia until syncope and loss of consciousness occur [Van Lieshout 1991, Novak 1996, de Jong-Vos van Steenwijk 1995, Novak 1996, Hainsworth 1991, Fitzpatrick 1993] (see section 1.1.3.2.).

Dynamic CA refers to the ability to maintain cerebral blood flow in the face of BP changes occurring over a matter of seconds whereas static CA refers to cerebral blood flow adjustments in response to more prolonged BP changes (see section 1.3.). Irrespective of the pathophysiology involved in VVS, it is thought that the loss of consciousness during syncope is caused by cerebral hypoperfusion [Van Lieshout 1991, Sung 2000, Grubb 1991a, 1998, Fredman 1995, Giller 1992, Levine 1994, Schondorf 1997]. It is possible, therefore, that an impairment of CA may be contributing to the symptoms of VVS. In support of this hypothesis, a number of studies have used transcranial Doppler ultrasound with either head-up tilt (HUT) or incremental lower body negative pressure to suggest that paradoxical cerebral vasoconstriction may occur prior to VVS [Driscoll 1997, el-Bedawi 1994a, Sung 2000, Grubb 1991a, 1998, Fredman 1995, Giller 1992, Levine 1994]. More recently, however, others have suggested that cerebrovascular resistance (CVR) falls prior to syncope and that CA is, therefore, preserved in VVS [Schondorf 1997].

Transcranial Doppler ultrasound has facilitated the non-invasive measurement of cerebral blood flow velocity (CBFV) changes in response to static and dynamic BP changes, allowing indices of CA to be calculated [Tiecks 1995, Aaslid 1989] (see

section 2.4.). Methods of CA estimation from spontaneous BP and CBFV changes, e.g. frequency domain analysis [Panerai 1998a, 1999b, Zhang 1998a], may have advantages over methods using induced BP changes (see section 2.4.2.2.) as they do not induce sympathetic stimulation or changes in arterial CO_2, both of which may occur with other methods, such as the Valsalva manoeuvre, and may affect the integrity of CA. The use of spontaneous BP changes is also less noxious to subjects and poses less potential risk from the induction of acute hypotensive or hypertensive changes, particularly in patients with carotid artery stenosis and post acute ischaemic stroke.

As CA may be impaired during pre-syncope, induced and spontaneous static and dynamic changes in BP were used to investigate the hypothesis that abnormalities of CA detected during supine rest can predict recurrent episodes of VVS.

4.3. Objectives

1. To assess if differences exist during supine rest in static cerebral autoregulation between patients with recurrent VVS and controls.
2. To assess if differences exist during supine rest in dynamic cerebral autoregulation between patients with recurrent VVS and controls.

4.4. Methods

4.4.1. Subjects

17 patients with a history of recurrent VVS were recruited from a specialist out-patient syncope clinic (mean age = 48 ± 22 years; range 15-82). The diagnosis was made on the basis of reproduction of syncope in association with the symptoms of referral and the characteristic haemodynamic profile [Van Lieshout 1991] by a 70°

HUT test of 30-minutes maximum duration without pharmacological provocation. Mean time to syncope was 816 ± 550 seconds (range 65-1790 seconds). In addition, each patient had other possible causes of syncope excluded by a combination of careful history and physical examination, full neurological assessment, standard laboratory tests, 12-lead surface ECG, supine and orthostatic BP measurements, bilateral supine and erect carotid sinus massage, 24-hour Holter recording, 2-dimensional echocardiography and standard autonomic function tests [Ewing 1981]. Other cardiac and neurological investigations, such as electroencephalography, exercise stress testing, angiography, Doppler flowmetry of cervical vessels, electrophysiologic study and computed tomography or magnetic resonance imaging of the brain, were performed when clinically indicated. In addition, inclusion criteria included: at least 3 syncopal episodes in the previous 2 years; the last syncopal episode occurring within 6 months of recruitment; an interval of >6 months between the first and last episode.

The patient group was pair-matched for age, sex and systolic BP within 10 mmHg with 17 control subjects recruited from a volunteer register in the department and from departmental staff. Control subjects were healthy and had no previous history of syncope or pre-syncope (as assessed by history and physical examination, full neurological assessment and standard autonomic function tests) and had remained asymptomatic during a previous 30-minute 70^{o} HUT test without pharmacological provocation. None of the patients or control subjects was taking any medication known to affect the cardiovascular system.

4.4.2. Study Protocol

All subjects underwent the initial preparatory protocol outlined in section 2.6.

The servo-adjust mechanism of the Finapres was then switched off and a baseline recording of 10 minutes was made with the subjects lying quietly. The servo-adjust mechanism of the Finapres was then switched on and bilateral thigh cuffs applied. The servo-adjust mechanism was again switched off and recording recommenced. After one minute, the thigh cuffs were inflated to 20mmHg above systolic BP for 90 seconds with thigh cuff pressure monitored using a mercury sphygmomanometer (see section 2.5.1). The cuffs were then rapidly deflated while recording continued for a further minute. After the recording, the Finapres servo-adjust mechanism was again switched off, the thigh cuffs reapplied, and the inflation/deflation cycle repeated in all subjects for a second time.

4.4.3. Data analysis

Data were initially analysed as outlined in section 2.7. In addition, ectopic beats occurring in the 15-second window prior to or after the point of thigh cuff release led to the rejection of the data.

4.4.4. Determination of Dynamic Cerebral Autoregulation using Aaslid's Method

Data were manually marked at the point of thigh cuff release and, in addition, four spontaneous dynamic pressor and four spontaneous dynamic depressor changes were marked using the 10-minute rest recording. Dynamic CA was graded by generating an autoregulatory index (ARI) ranging in value from 0 (absent) to 9 (most efficient) using the methods outlined in section 2.4.2.1. Only a dynamic BP fall $\geq$ 10mmHg after thigh cuff release and spontaneous BP changes $\geq$ 5mmHg at rest were accepted

as adequate dynamic stimuli. Subjects also had to exhibit a synchronous and physiological change in BP and CBFV for all manual marks.

Each dynamic BP stimulus yielded a dynamic ARI for the right and left MCA of each individual. The mean of the two dynamic ARI values thus obtained was taken to be the ARI for that individual for that dynamic BP stimulus. The mean of the two dynamic ARI values thus derived from the two thigh cuff releases for each subject was taken as the dynamic ARI for that subject for thigh cuff release. Similarly, the mean of the four dynamic ARI values derived using spontaneous pressor and depressor changes was taken as the dynamic ARI for each subject for spontaneous pressor and depressor changes.

4.4.5. Determination of Static Cerebral Autoregulation

ARI values were derived for each subject for the static pressor response induced by thigh cuff inflation as described in section 2.4.1. Data were manually selected to include the one-minute baseline period before thigh cuff inflation and 90 second period of static mean arterial BP (MAP) rise after inflation. A BP rise ≥10mmHg was considered to be an adequate static stimulus. Each static BP rise yielded an ARI for the right and left MCA of each subject. The mean of these two ARI values was taken to be the static ARI for each static pressor stimulus. The mean of the two static ARI values thus derived from the two thigh cuff inflations for each subject was taken as the static ARI for that subject.

4.4.6. Frequency Domain analysis

Frequency domain analysis was performed using the methods outlined in section 2.4.2.2.

4.4.7. Statistical analysis

As patients and controls were pair matched, demographic details and baseline characteristics of the two groups were compared using the Student's paired t-test.
A normal distribution of static and dynamic ARI values was assumed and a good approximation to this was demonstrated by a plot of residuals. Dynamic ARI values were compared between the three dynamic BP stimuli and between the two groups using two-way analysis of variance. Static ARI values were compared between the two groups using the Student's paired t-test.
For frequency domain analysis, Student's paired-t tests were applied to individual spectral harmonics of coherence, amplitude and frequency response in the range 0.02 – 0.2 Hz, and also for the trough values of the impulse response, and at different times along the step response.
Data were analysed using Minitab 12 software package. Results are presented as mean ± standard deviation (range). Statistical significance was set at $p< 0.05$ level.

4.5. Results

The demographic details and baseline charateristics of the two groups are contained in Table 4.1. No significant differences were demonstrated between the groups for age, body mass index, baseline mean CBFV, TCO_2 or casual systolic and diastolic blood pressure, though baseline heart rate tended to be slightly higher in the control group (68 ± 8 v 63 ± 10 beats per minute; p=0.06).

No significant differences were demonstrated between ARI values derived from the three dynamic BP changes (Table 4.2.), though ARI values derived from thigh cuff release tended to be higher than those derived from spontaneous pressor (difference = 0.9; 95% CI –0.1 to 1.8) and depressor (difference = 0.7; 95% CI -0.3 to 1.6) changes at rest (p=0.07). Overall, mean dynamic ARI values were 5.6 ± 1.7 for the patient group and 5.7 ± 1.5 for the control group, with no significant difference between the two groups (difference = -0.2; 95% CI –0.6 to 0.4; p=0.56). No differences were found between the groups for static ARI values or for dynamic ARI values derived from individual dynamic stimuli (Table 4.2.).

Mean values of coherence, amplitude and phase responses for the two groups were similar throughout the ranges studied, as shown in Figures 4.1., 4.2. and 4.3. respectively. The impulse and step responses of the two groups were also similar (see Figures 4.4. & 4.5.).

4.6. Discussion

Using both static and dynamic models of CA [Tiecks 1995, Panerai 1998a, 1999b, Zhang 1998a], as well as induced and spontaneous BP changes, no differences were demonstrated during supine rest between patients with stringently diagnosed recurrent VVS and pair-matched healthy controls. Using similar methods and volunteer numbers, others have previously detected impaired dynamic CA in patients with severe carotid artery stenosis [White 1997], after acute ischaemic stroke [Dawson 2000], in neonates [Panerai 1998b] and during hypercapnia [Panerai 1999b]. In addition, the confidence intervals for dynamic ARI values suggest that with this study

size there are no clinically significant differences in dynamic CA between the two groups.

4.6.1. Cerebral autoregulation during pre-syncope

In view of the fact that the loss of consciousness during syncope is probably caused by cerebral hypoperfusion [Van Lieshout 1991, Sung 2000, Grubb 1991a, 1998, Fredman 1995, Giller 1992, Levine 1994, Schondorf 1997], the hypothesis that CA is impaired in patients with recurrent VVS, and that this impairment may be the primary problem in such patients, is an attractive one. Recent studies have appeared to support this hypothesis by demonstrating paradoxical increases in CVR during pre-syncope [Driscoll 1997, el-Bedawi 1994a, Sung 2000, Grubb 1991a, 1998, Fredman 1995, Giller 1992, Levine 1994]. More recently, however, others have suggested that CA may indeed be preserved prior to VVS [Schondorf 1997]. These results suggest that CA is normal at rest in patients with recurrent VVS and baseline CA measurements do not, therefore, predict the presence of VVS.

4.6.2. Autoregulatory Indices

Although Aaslid's method of calculating an ARI is an arbitrary model, it does give important clinical information, e.g. acute ischaemic stroke patients have dynamic ARI values in the order of 2.0 lower than age and BP matched controls [Dawson 2000]. Similar methods have shown dynamic ARI values to be a mean of 2.6 lower than control values in patients with carotid artery disease [White 1997]. The static and dynamic ARI values in this study are consistent with those published previously [Tiecks 1995, Dawson 2000, White 1997, Mahony 2000] and suggest that CA in patients with recurrent VVS is normal when supine.

4.6.3. Static & Dynamic Blood Pressure Stimuli

Thigh cuff release is probably the most widely applied dynamic BP stimulus, but it is unknown if ARI values are dependent on the type of dynamic stimulus used or the direction of BP change (pressor or depressor). It is also unclear whether induced BP changes alter physiological parameters that are known to affect CA, such as arterial CO_2 levels and systemic sympathetic nervous system activity, and whether these changes could potentially affect ARI values. In view of the uncertainties surrounding methods involving induced dynamic BP changes, both induced and spontaneous BP changes and two different methodologies of assessing dynamic CA were employed in this study but still failed to show any differences between patients and controls.

4.6.4. Frequency Domain Analysis

Frequency domain analysis has been used to demonstrate impairment of dynamic CA in premature neonates, hypercapnia and severe carotid artery stenosis [Panerai 1998a, 1998b, 1999b]. High coherence between arterial BP and CBFV suggests that BP changes are transmitted passively to the cerebral circulation, indicating impaired CA. On the other hand, active CA will attenuate CBFV changes in response to BP changes and coherence will fall. Reduced coherence at very low frequencies (<0.05 Hz) has been shown to be indicative of active dynamic CA [Panerai 1998a, 1999b, Zhang 1998a] but both patient and control groups demonstrated similar coherence values at all frequencies. In subjects with normal CA, oscillations in CBFV lead BP oscillations by a positive phase angle i.e. changes in CBFV occur before those in systemic BP [Panerai 1998a, 1999b, Zhang 1998a]. In subjects with impaired dynamic CA, the phase angle becomes less positive [Panerai 1998a, 1998b] but similar phase frequency responses were present in both groups. Amplitude frequency

responses were also similar in both groups, but Panerai [1998a, 1998b] observed that deterioration of CA is reflected more markedly in the phase rather than in the amplitude frequency response. Impulse response plots show an initial positive wave and subsequent negative deflection in CBFV when dynamic CA is active [Panerai 1998a, 1998b, 1999b, Zhang 1998a] with impairment leading to blunting or disappearance of the negative deflection [Panerai 1998a, 1998b, 1999b, Zhang 1998a]. Step response plots demonstrate a return of CBFV to baseline values when dynamic CA is intact and higher values when impaired [Panerai 1998a, 1998b, 1999b, Zhang 1998a]. The impulse response and step response plots were similar for patients and controls and indicate active autoregulation in both groups.

4.6.5. Limiting Factors

Only one pressor stimulus (thigh cuff inflation) was used to assess static CA and the confidence intervals are consequently not narrow enough to exclude clinically significant differences in static CA between the two groups. This is unlikely, however, as dynamic CA is probably more susceptible to impairment than static CA [Tiecks 1995, Dawson 2000] and this was normal in both groups. Nevertheless, the findings with regard to static CA need to be confirmed using other established methodologies.

This study did not attempt to assess CA changes during pre-syncope and, in view of apparently contradictory evidence in this regard [Driscoll 1997, el-Bedawi 1994a, Sung 2000, Grubb 1991a, 1998, Fredman 1995, Giller 1992, Levine 1994, Schondorf 1997], further investigation of CA during pre-syncope is warranted (see Chapters 5 and 6). Previous work in the area has relied on calculations of CVR to illustrate apparent cerebral arterial vasoconstriction or vasodilation but such indices may not

accurately reflect cerebrovascular changes [Schondorf 1997, Czosnyka 1996, Aaslid 1992]. It may be that the lower limit of CA occurs at a higher arterial BP in patients with recurrent VVS than normal controls (i.e. that the CA curve is shifted to the right) or that the autoregulatory plateau is narrowed in such patients, but the methodology of this study did not permit the testing of these hypotheses.

Although this study shows that both static and dynamic CA appear to be normal at rest in patients with recurrent VVS, the possibility that CA may deteriorate in patients with recurrent VVS during orthostasis was not addressed. Zhang [1998b] used lower body negative pressure and frequency domain analysis to suggest that CA deteriorates in normal subjects during orthostatic stress. Leftheriotis [1998], however, used thigh cuff release during HUT to suggest that dynamic CA is preserved during orthostasis, but the angle of tilt was only 40°. The hypothesis that orthostasis itself impairs CA in patients with recurrent VVS was not addressed by this study and this is an important area requiring further investigation.

The major limitation of this work, and indeed, any work using similar methodology, is that CBFV rather than CBF was measured. Changes in CBF can only be reliably deduced from velocity changes if the diameter of the insonated vessel remains unchanged [Aaslid 1982]. Significant changes in MCA diameter have not, however, been demonstrated during thigh cuff application and release [Newell 1994] or during supine rest. Nevertheless, MCA diameter was not directly measured in this study and caution must therefore be exercised in interpreting our results.

4.7. Conclusions

1. Static and dynamic CA, assessed using spontaneous and induced pressor and depressor BP changes, are normal during supine rest in patients with recurrent VVS.

Measurements of static or dynamic CA during supine rest cannot, therefore, be used to predict recurrent episodes of VVS.

Figure 4.1. Mean coherence values of the patient group (red line) and control group (black line). A representative sample standard error bar is included for the coherence values of the patient group at 0.06 Hz.

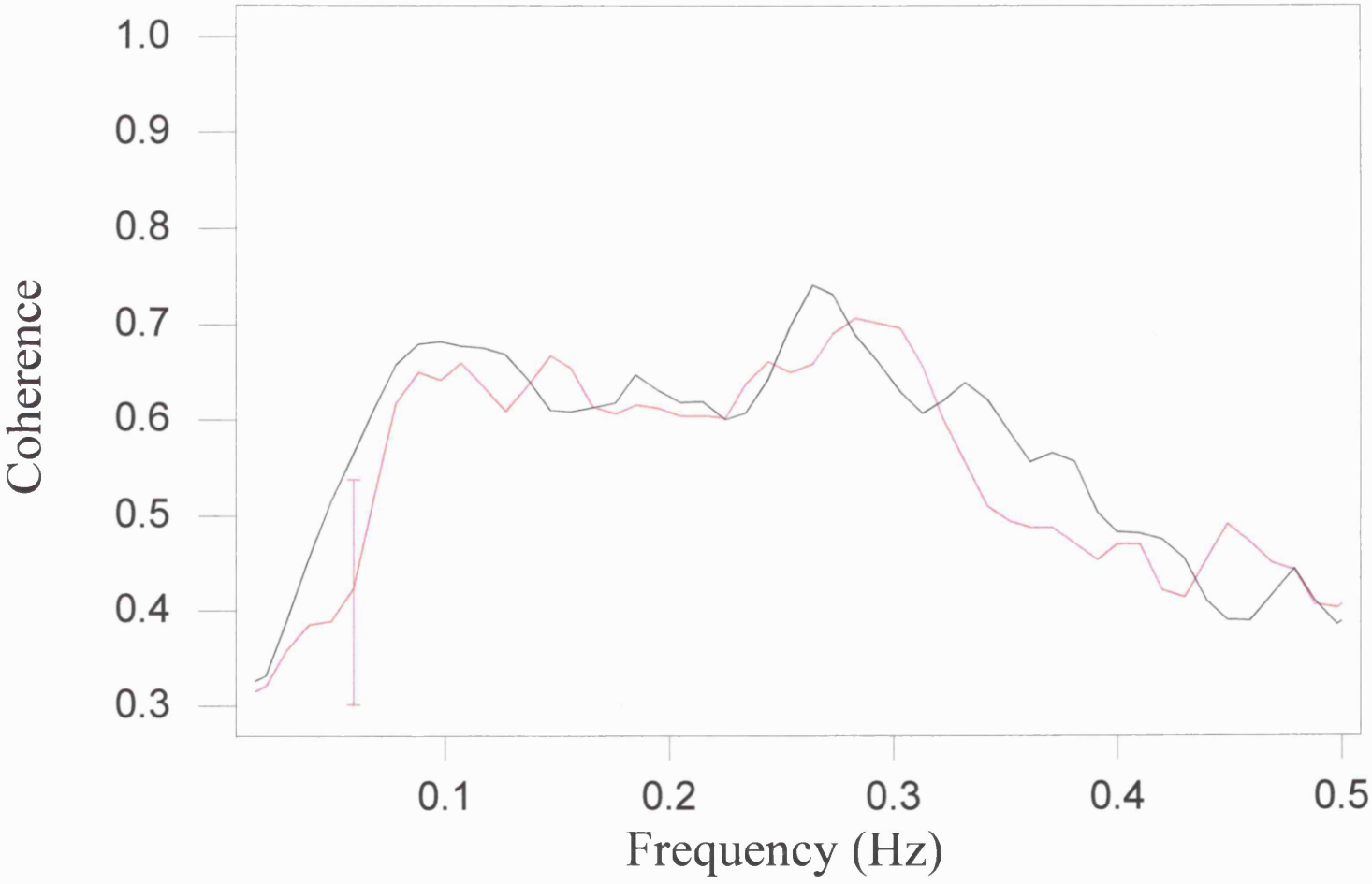


Figure 4.2. Mean values of phase frequency response of the patient group (red line) and control group (black line). A representative sample standard error bar is included for the phase values of the patient group at 0.06 Hz.

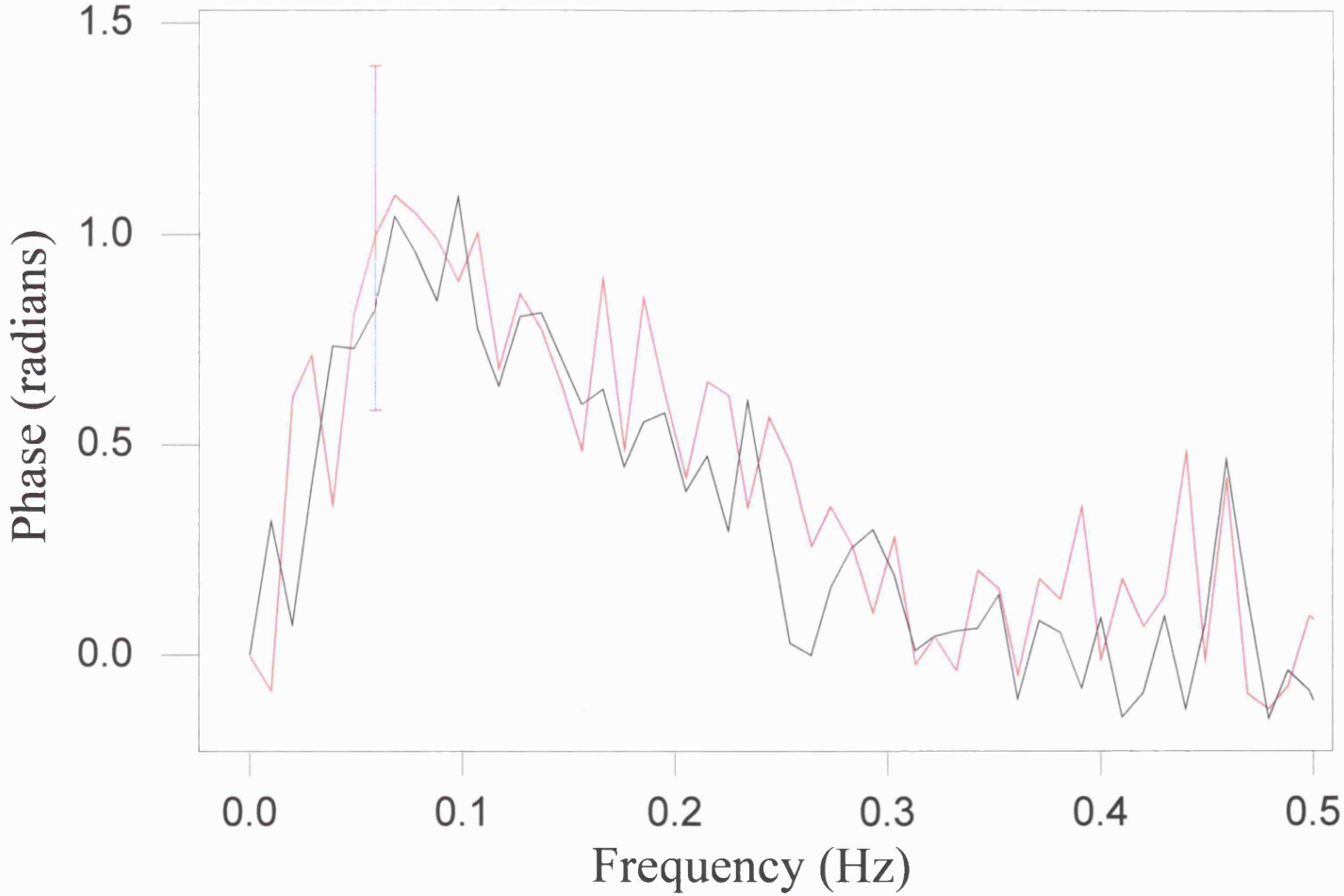


Figure 4.3. Mean values of amplitude frequency response of the patient group (red line) and control group (black line). A representative sample standard error bar is included for the amplitude values of the patient group at 0.06 Hz.

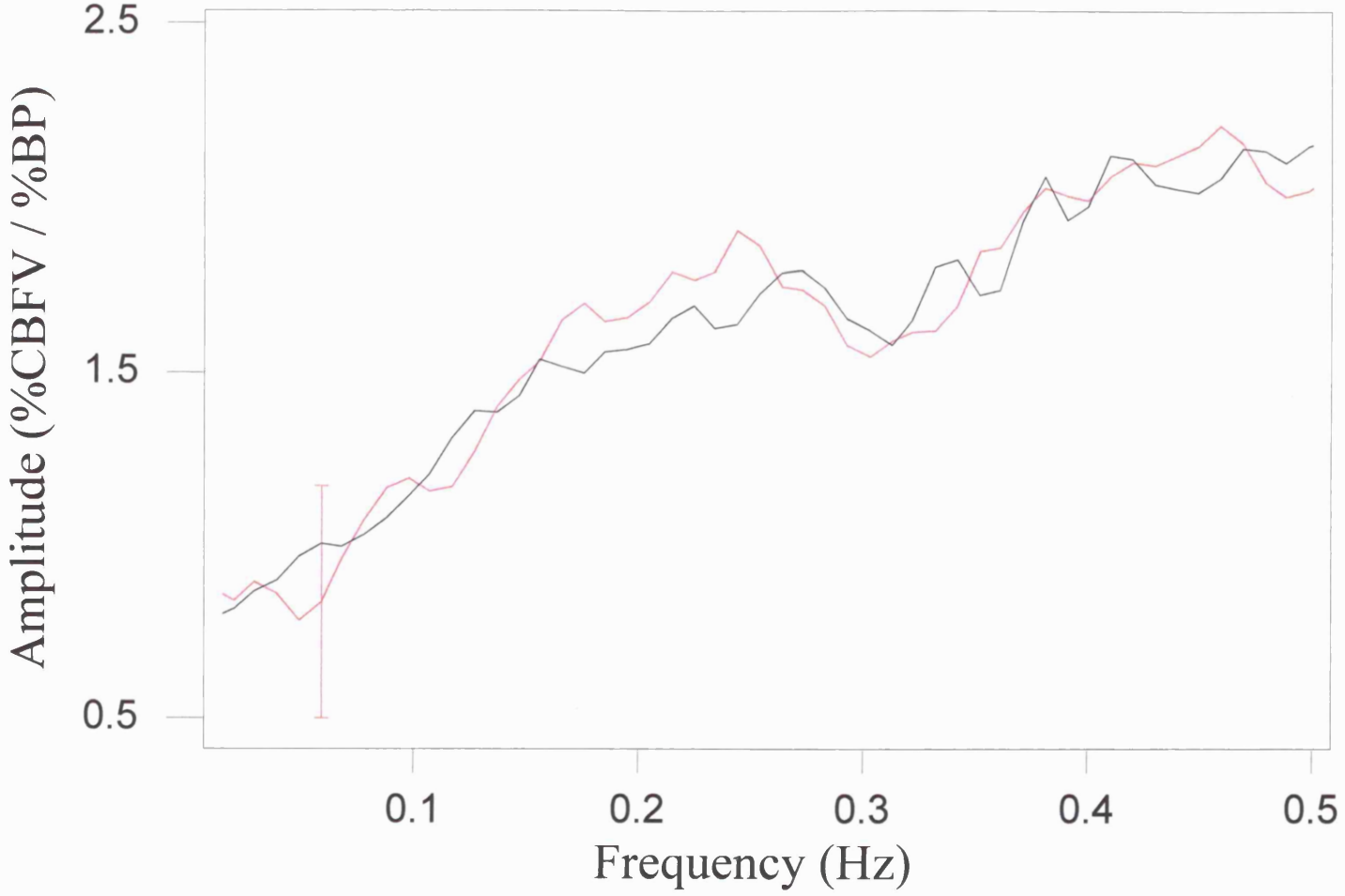


Figure 4.3.

Figure 4.4. Mean impulse responses (solid lines) and standard errors (dotted lines) of the patient group (red lines) and control group (black lines).

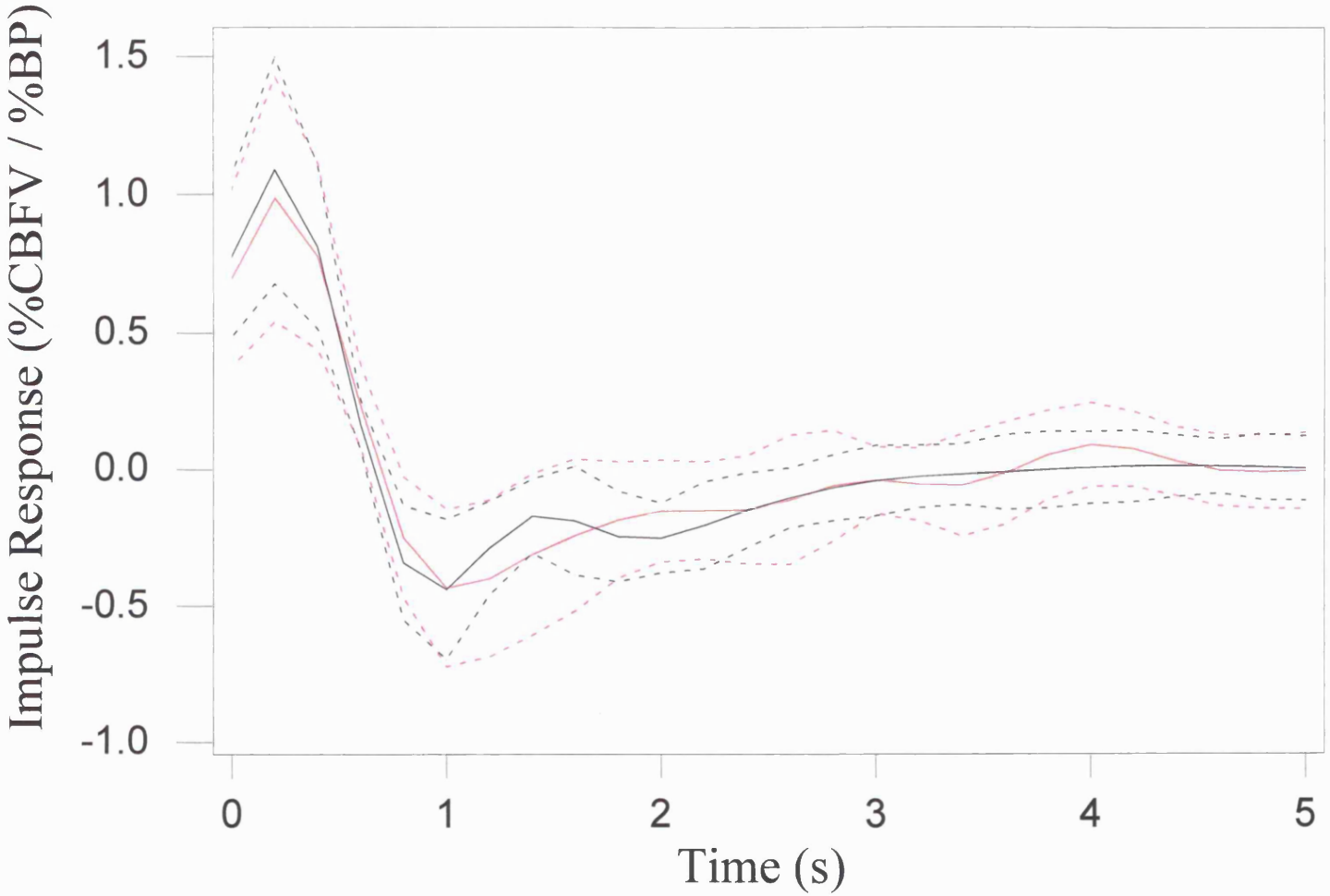


Figure 4.4.

Figure 4.5. Mean step responses (solid lines) and standard errors (dotted lines) of the patient group (red lines) and control group (black lines).

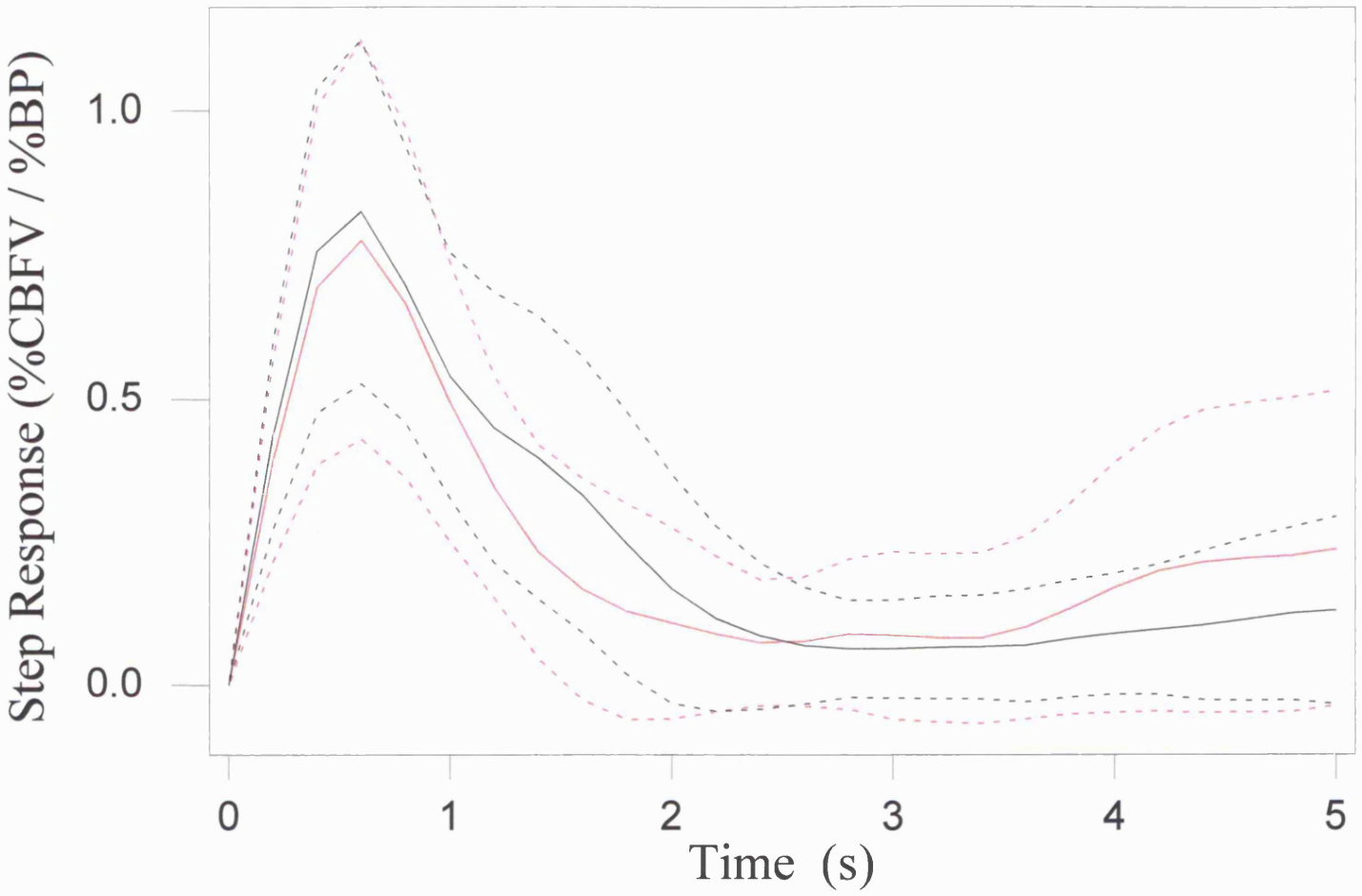


Figure 4.5.

Parameter	Patients	Controls	Difference (95% CI)	p value
Age (years)	48 ± 22 (15-82)	49 ± 20 (19-90)	-1 (-5.38, 2.55)	0.46
Systolic BP (mmHg)	131 ± 21 (98-179)	129 ± 17 (105-163)	2 (-9, 14)	0.68
Diastolic BP (mmHg)	76 ± 11 (60-98)	79 ± 10 (63-103)	-3 (-8, 3)	0.18
Heart rate (bpm)	63 ± 10 (46-78)	68 ± 8 (52-82)	-5 (-10, 1)	0.06
Mean CBFV (cms^{-1})	53 ± 14 (34-83)	59 ± 12 (41-83)	-6 (-14, 2)	0.13
Transcutaneous CO_2 (mmHg)	41.1 ± 4.7 (29.1-47.0)	41.8 ± 3.9 (34.5-47.9)	-0.7 (-3.8, 2.4)	0.61
BMI (kg/m^{-2})	22.0 ± 2.8 (16.9-27.8)	23.8 ± 3.7 (16.8-30.3)	-1.8 (-4.3, 0.6)	0.13

Table 4.1. Demographic and baseline characteristics of the patient and control groups compared using Student's paired t-tests.

Values are displayed as mean ± standard deviation with ranges in parentheses.

BP stimulus	ARI			Difference (95% CI)	p value
	Patients & Controls	Patients	Controls		
Thigh cuff release (dynamic)	6.2 ± 1.4	6.1 ± 1.4	6.3 ± 1.5	-0.2 (-1.1, 0.7)	0.565
Rest pressor changes (dynamic)	5.3 ± 1.7	5.0 ± 1.8	5.5 ± 1.6	-0.5 (-1.7, 0.7)	0.396
Rest depressor changes (dynamic)	5.5 ± 1.7	5.6 ± 1.9	5.4 ± 1.4	0.2 (-1.0, 1.3)	0.738
Thigh cuff inflation (static)	N/A	56 ± 39 %	59 ± 37 %	-3 % (-18, 12)	0.702

Table 4.2. Dynamic and static ARI values of patient and control groups. Values displayed are mean ± standard deviation. Differences shown are for the values between patient and control groups.

CHAPTER FIVE

Cerebral Autoregulatory Responses To Head-Up Tilt in Normal Subjects & Patients With Recurrent Vasovagal Syncope

5.1. Summary

In chapter four, it was recorded that no abnormalities were detected in static or dynamic cerebral autoregulation (CA) in patients with recurrent vasovagal syncope (VVS) during supine rest. The effect of orthostatic stress, however, on dynamic CA in patients with recurrent VVS and normal subjects is unclear and in this chapter the dynamic CA responses of both groups to head-up tilt (HUT) are studied.

17 patients with recurrent VVS and 17 pair-matched control subjects underwent 70° HUT for up to 30 minutes. Bilateral middle cerebral artery blood flow velocities (CBFV) were measured using transcranial Doppler ultrasound along with non-invasive beat-to-beat blood pressure (BP), heart rate (HR) and transcutaneous (TCO_2) and end-tidal ($ETCO_2$) carbon dioxide concentrations. Indices of dynamic CA were derived for periods before, during and after HUT. Eight normal subjects with no previous clinical history of syncope but who developed VVS using an identical protocol were also studied.

CBFV, TCO_2 and $ETCO_2$ levels declined significantly after HUT in all groups ($p<0.0001$). Dynamic CA indices were unchanged throughout HUT in non-syncopal control subjects and were initially unchanged in patients, but deteriorated significantly in patients and syncopal controls in the sixty seconds before ($p=0.027$ and $p=0.012$ respectively) and sixty seconds after ($p=0.002$ and $p=0.007$ respectively) returning supine following symptom onset. In non-syncopal controls, changes in TCO_2 after HUT were significantly correlated with changes in mean CFBV ($p=0.011$) and inversely correlated with indices of dynamic CA ($p=0.027$).

Dynamic CA, therefore, is preserved in patients and control subjects initially after HUT. Cerebral autoregulatory function remains intact in non-syncopal control subjects during prolonged orthostasis, but deteriorates in patients and syncopal

controls immediately before and after VVS. An inverse relationship exists between TCO_2 changes and indices of dynamic CA after HUT in normal subjects, suggesting that orthostasis-induced hypocapnia may help to preserve dynamic CA.

5.2. Background

Hypotension prior to VVS is probably precipitated by sympathetic nervous system withdrawal and increased vagal activity [Mosqueda-Garcia 1997, Morillo 1997, Lewis 1932] but loss of consciousness during syncope is probably caused by cerebral hypoperfusion [Van Lieshout 1991, Bondar 1995, Sung 2000, Grubb 1991a, Giller 1992, Levine 1994, Schondorf 1997], suggesting that an impairment of CA may contribute to the symptoms of VVS. In chapter four, however, no abnormalities were detected during supine rest in static or dynamic CA in patients with recurrent VVS. CBF velocity (CBFV) has been shown to fall significantly during orthostatic stress with HUT and lower body negative pressure (LBNP) in normal subjects [Bondar 1995, Sung 2000, Grubb 1991a, Giller 1992, Levine 1994, Schondorf 1997, Cencetti 1997]. Arterial, end-tidal and transcutaneous carbon dioxide (CO_2) levels have also been shown to fall significantly in normal subjects immediately following HUT [Cencetti 1997, Serrador 1998, Anthonisen 1965, Bjurstedt 1962, Yoshizaki 1998] and Cencetti [1997] has shown a significant link between the declines in CBFV and CO_2 after HUT. Hypocapnia reduces CBF, improves dynamic CA [Panerai 1999b] and widens the plateau region of the static pressure autoregulation curve, representing an improvement in autoregulatory capacity [Paulson 1990] (see section 1.3.3.1.). Despite the fall in CBFV during orthostatic stress, its effect on dynamic CA is unclear with both intact [Leftheriotis 1998, Lipsitz 2000] and impaired [Zhang 1998b] CA being reported in normal subjects. Leftheriotis [1998] demonstrated preserved

dynamic CA in normal subjects in response to rapid thigh cuff release during 40° head-up tilt. This angle of tilt exerts less orthostatic stress, however, than the angles of 60-90° in more widespread usage. Zhang [1998b] employed lower body negative pressure (LBNP) and an increased low-frequency transfer function gain to demonstrate deterioration in dynamic CA during high levels of orthostatic stress in normal subjects. The issue is complicated by the facts that there may be differences in cerebrovascular and cardiovascular responses between HUT and LBNP [Bondar 1995] and that the significance of changes in transfer function gain are a matter of some debate [Panerai 1998a]. More recently, Lipsitz [2000] looked at standing changes from sitting in elderly controls and previously treated hypertensives and found similar responses to those found in young, healthy controls.

This study investigated the dynamic CA responses to HUT-induced orthostatic stress in normal subjects and patients with recurrent VVS, hypothesising that dynamic CA would remain intact during orthostatic stress in normal subjects but would deteriorate in patients with recurrent VVS.

5.3. Objectives

1. To assess the dynamic cerebral autoregulatory responses of normal subjects and patients with recurrent VVS to HUT.

2. To assess the relationship between dynamic CA changes and physiological CO_2 changes in normal subjects after HUT.

5.4. Methods

5.4.1. Subjects

17 patients with a history of recurrent VVS according to the same inclusion and exclusion criteria outlined in section 4.4.1. were recruited from an out-patient specialist Syncope Clinic.

The patient group was pair-matched for age, sex and systolic BP within 10 mmHg with 17 control subjects (non-syncopal control group) recruited from a volunteer register in the department and from departmental staff. Control subjects were healthy (as assessed by history and physical examination, full neurological assessment and standard autonomic function tests), had no previous history of syncope or pre-syncope and had remained asymptomatic during a previous 30 minute 70° HUT. In addition, we studied 8 subjects who were otherwise similar to the controls but developed VVS (mean time to syncope = 1102 ± 612 seconds; range 185-1800 seconds) during HUT using an identical protocol to that outlined below (syncopal control group). None of the patients or control subjects was taking any medication known to affect the cardiovascular system.

5.4.2. Study Protocol

All subjects underwent the initial preparatory protocol outlined in section 2.6. In addition, end-tidal CO_2 was measured via a closely fitting face-mask and an infra-red capnograph (Capnogard, Novametrix) as described in section 2.3.1. (Figure 2.7). The vertical height in centimetres (Ht) from the point of insonation of the right MCA to the second intercostal space was also recorded for each subject.

After resting supine for a minimum of 30 minutes to obtain stable values (<10% variation over 5 minutes), a 5-minute baseline recording was made. The subjects then underwent HUT within three seconds to an angle of 70° for 30 minutes or until syncope was imminent. The Finapres cuff was kept at heart level at all times before,

during and after HUT with the aid of an adjustable arm-rest. In order to minimise discomfort and improve compliance with the study protocol, $ETCO_2$ measurements were discontinued 5 minutes after tilt in all subjects. The imminence of syncope was recognised by the occurrence of a subjective sensation of impending syncope in association with the typical hemodynamic profile [Van Lieshout 1991]. For ethical reasons, all pre-syncopal subjects were replaced supine prior to loss of consciousness, the point at which subjects were replaced supine being taken as the point of syncope. The point of syncope was synchronised for all subjects using a mark generated by an electrical device each time the tilt table passed through 45°. Recording continued for a further 5 minutes after returning supine.

5.4.3. Data Analysis

Data were initially analysed as outlined in section 2.7. with estimates of systolic, diastolic and mean arterial BP, systolic, diastolic and mean CBFV , pulse interval (PI), TCO_2 and $ETCO_2$ being made for each cardiac cycle.

Using methods described in section 2.4.2.1, an estimation of a dynamic autoregulatory index (ARI) ranging from 0 (absent) to 9 (most efficient) was made for the 1-minute period before tilt, first and third minutes after tilt, third last and last minutes before returning supine and first and third minutes after returning supine for each subject. MCA mean pressure (MCAMP) during HUT was estimated from MAP by subtracting the hydrostatic pressure (Ht * 0.735 * sin 70°). Detailed averaged profiles of all parameters were calculated for both groups for the 1-minute period before and 3-minute period after HUT.

The model allowed calculation of correlation coefficients assessing how closely measured CBFV fitted the model predicted velocity [Panerai 1999a] for each subject during each time period.

5.4.4 Statistical analysis

Demographic details and baseline characteristics of the three groups were compared using one-way analysis of variance. The between group and within subject changes of the patient and non-syncopal control groups were modeled for each outcome measure using a mixed model for repeated measures data. Model selection was by changes in the log likelihood and denominator degrees of freedom were calculated using Satterthwaite's method [Satterthwaite 1946]. Different covariance patterns were investigated using Akaike's Information Criterion [Akaike 1973].

To investigate the relationship between TCO_2 changes and ARI and mean CBFV changes after HUT in non-syncopal control subjects, changes in TCO_2 after HUT were treated as a covariate in a repeated measures model using CBFV and ARI values as the dependent variables. ARI values immediately before and after syncope were compared between the syncopal control group and other groups using Student's 2 sample t-tests. Data were analysed using SAS version 6.12 and Minitab 12 software packages. Statistical significance was set at $p<0.05$ level.

5.5. Results

No significant differences were demonstrated between the three groups in demographic details and baseline characteristics (Table 5.1.). All 17 patients developed syncope within 30 minutes of HUT (mean time to syncope = 816 ± 550 s; range 65-1790 s). All 17 control subjects remained asymptomatic during the 30

minutes of HUT. Actual data records for a non-syncopal control subject before and after tilting and a patient before and after syncope are displayed in Figures 5.1. and 5.2. respectively.

Changes in MCA mean CBFV from baseline for the patient and non-syncopal control groups are contained in Table 5.2, changes in MCAMP and MAP in Table 5.3, changes in pulse interval in Table 5.4. and changes in TCO_2 and $ETCO_2$ in Table 5.5. Mean MCAMP and mean CBFV changes for the 1-minute period before HUT and 3-minute period after HUT for both patient and non-syncopal control groups are displayed in Figure 5.3. Mean $ETCO_2$ and TCO_2 changes for the same period are displayed in Figure 5.4.

Mean CBFV was significantly lower in patients than non-syncopal controls 3 minutes before syncope (difference=8.9 cm/s; 95% CI 0 to 18; p=0.044) and at syncope (difference=24.6 cm/s; 95% CI 16 to 33; p<0.0001) but was similar at all other times (see Table 5.2.). MCAMP was lower in patients than non-syncopal controls at syncope (difference=52.5 mmHg; 95%CI 45 to 60; p<0.0001) but was similar at all other times (see table 5.3.). No differences were demonstrated between patients and non-syncopal controls in TCO_2 (p=0.31) and $ETCO_2$ (p=0.10) values at any stage.

Mean dynamic ARI values of the patient and non-syncopal control groups for the 7 chosen time points are contained in Table 5.6. ARI values were similar to pre-HUT values both during and after HUT in non-syncopal control subjects (Table 5.6.). Patient dynamic ARI values were similar to non-syncopal control values at baseline and initially after HUT but were significantly lower during the last minute before syncope and the first minute after syncope (Table 5.6.).

ARI values of the 8 control subjects who developed VVS were similar to patient values during the last minute before (3.1 ± 2.2 v 3.6 ± 3.0; difference = -0.5; 95% CI – 1.3 to 0.3; p=0.25) and first minute after (2.1 ± 1.7 v 2.3 ± 1.8; difference = -0.2; 95% CI –1.0 to 0.6; p=0.60) syncope and significantly lower than non-syncopal control values during the same periods (p=0.012 and p=0.007 respectively).

Correlation coefficients reflecting model accuracy did not differ between groups and were similar to baseline coefficients pre- and post-syncope (Table 5.6.).

A significant relationship was demonstrated between TCO_2 changes and mean CBFV changes (p=0.011; $r^2 = 0.46$) and a significant inverse relationship was shown between TCO_2 changes and ARI values (p=0.027; $r^2 = 0.12$) after HUT in non-syncopal control subjects.

5.6. Discussion

This study has not demonstrated any deterioration in dynamic CA during orthostatic stress in normal subjects and has shown that dynamic CA is initially preserved after HUT in patients susceptible to VVS. Dynamic CA has been shown, however, to deteriorate in patients and control subjects during pre-syncope and to remain impaired during the immediate post-syncopal period. In addition, the results suggest that an inverse relationship exists between CO_2 changes and changes in indices of dynamic CA after HUT in normal subjects, a finding consistent with the conclusions of others that hypocapnia physiologically improves autoregulatory function [Paulson 1990, Panerai 1999b]. Baseline ARI values in this study are comparable to values previously derived using similar methods [Panerai 1999a, 2001] and suggest that baseline dynamic CA is normal in all groups studied. As well as these new findings,

this study confirms that CBFV and CO_2 levels decline significantly in normal subjects after passive HUT [Bondar 1995, Sung 2000, Grubb 1991a, Giller 1992, Levine 1994, Schondorf 1997, Cencetti 1997, Serrador 1998, Anthonisen 1965, Bjurstedt 1962, Yoshizaki 1998] and reveals that similar changes occur initially after HUT in patients with recurrent VVS. Finally, the results also appear to confirm the significant relationship between CO_2 and CBFV changes after HUT in normal subjects first demonstrated by Cencetti [1997].

5.6.1. Dynamic cerebral autoregulation during orthostatic stress

Zhang [1998b] used frequency domain analysis and LBNP to demonstrate that dynamic CA may deteriorate in normal subjects during high levels of orthostatic stress. An increased low-frequency CBFV/arterial BP transfer function gain was shown during pre-syncope, suggesting a closer relationship between CBFV and ABP and, therefore, impairment of dynamic CA. There may be important differences, however, between HUT and LBNP in cardiovascular and cerebrovascular responses [Bondar 1995] and the significance of changes in transfer function gain are the subject of some debate [Panerai 1998b]. For the latter reason, dynamic CA was assessed in this study employing ARI values derived from Aaslid's model rather than using frequency domain analysis.

More recently, Leftheriotis [1998] used rapid thigh cuff deflation to demonstrate preserved dynamic CA in normal subjects 5 minutes after 40° head-up tilt. In many ways, this study forms a link between the studies of Zhang [1998b] and Leftheriotis [1998] and shows that the findings of all three studies are compatible with each other. The finding of Zhang [1998b] that dynamic CA deteriorates in normal subjects during pre-syncope is supported by our demonstration of decreased ARI values during pre-

syncope in the syncopal control group. In addition, we have demonstrated that similar changes occur in patients with recurrent VVS. The conclusion of Leftheriotis [1998] that dynamic CA is preserved in normal subjects at low levels of orthostatic stress is similarly supported by our initial data after HUT, which also demonstrate similar preservation of dynamic CA in patients with recurrent VVS.

5.6.2. Dynamic cerebral autoregulation and carbon dioxide changes after HUT

This work appears to confirm the findings of Cencetti [1997] that CBFV changes in normal subjects after HUT are significantly linked to physiological hypocapnia. Hypocapnia has previously been suggested as helping to facilitate dynamic CA [Paulson 1990, Panerai 1999b] and the suggestion of a significant inverse link between changes in TCO_2 and dynamic ARI values supports this hypothesis. It is possible, therefore, that the preservation of dynamic ARI values after HUT may be facilitated by the physiologically lower CO_2 levels seen during orthostasis but this warrants further investigation as the r^2 value reported (0.12) is unimpressive.

5.6.3. Dynamic cerebral autoregulation during pre-syncope

As loss of consciousness during syncope is probably caused by cerebral hypoperfusion [Van Lieshout 1991, Bondar 1995, Sung 2000, Grubb 1991a, Giller 1992, Levine 1994, Schondorf 1997], the hypothesis that impaired CA is the underlying problem in patients with recurrent VVS is an attractive one. The findings of preserved ARI values in patients during supine rest (see Chapter 4) and initially after HUT and similarly impaired ARI values in normal subjects immediately before and after syncope tend to refute this hypothesis. The reason for impairment of dynamic ARI values during the peri-syncopal period is unclear, but is most likely to

result from MCAMP falling outside the proposed autoregulatory range of 60-150mmHg [Paulson 1990] during this period (Table 5.3.). Another potential reason for impairment of dynamic CA before and after syncope is a build up of cerebral metabolites (including CO_2) during a period of relative hypoxia, but our methods did not allow us to explore this hypothesis.

5.6.4. Model validity and accuracy

The model proposed by Aaslid and Tiecks [Tiecks 1995] was initially developed using hypotension induced by rapid thigh cuff deflation, but has been previously applied to spontaneous BP changes at rest [Panerai 1999a, 2001] and shown to be valid. Correlation coefficients between measured and model predicted CBFV were similar to previously reported coefficients [Panerai 1999a] and did not differ immediately before or after syncope, suggesting that the model is accurate and valid at low extremes of CBFV and MCAMP.

5.6.5. Limiting factors

The major limiting factor of this work is the indirect measure of MCAMP. Although arterial pressure waveforms change with head-up tilt, non-invasive plethysmography correlates very well with intra-arterial pressure recordings during head-up tilt [Petersen 1995]. A direct measurement of MCA pressure is impossible without very invasive procedures which would, in themselves, affect the interpretation of such work. As original work with the model [Panerai 1999a, 2001] used MCA pressure derived using Finapres monitoring as the input parameter and assumed that fluctuations in perfusion pressure were reflected, in the main, by MCA pressure fluctuations, it is important that MCA pressure is used when calculating ARI values.

Intracranial pressure changes after HUT are likely to be relatively small [Drummond 2000] and similar in syncopal and non-syncopal subjects alike, and changes in venous pressure will occur to an equal and proportionate degree as arterial pressure. In the absence of better, non-invasive alternatives, therefore, calculations using non-invasive plethysmography provide acceptable estimates of MCA pressure.

Our calculations also assume that MCA diameter remains constant during HUT and in the pre-syncopal period. MCA calibre does not change during simulated orthostatic stress [Serrador 2000] and changes in CO_2 concentrations to the degree demonstrated by us would not be expected to significantly affect MCA diameter [Giller 1993]. Profound hypotension during pre-syncope, however, could potentially cause MCA myogenic vasodilation and influence CBFV, but the methodology employed did not allow assessment of this possibility. As MCA diameter was not directly measured during this study, caution must, therefore, be exercised when interpreting the results.

TCO_2 measurements correlate highly with arterial CO_2 levels but rely on gas diffusion and, therefore, have poor dynamic response characteristics (section 2.3.2.). In addition, doubts exist about the accuracy of end-tidal and transcutaneous CO_2 measurements during changes in cardiac output [Steurer 1997]. The TCO_2 measurements reported in this study, however, were taken over stable one-minute periods and are consistent with the findings of others [Cencetti 1997, Anthonisen 1965, Bjurstedt 1962, Yoshizaki 1998], suggesting that they are a fair reflection of arterial CO_2 levels.

5.7. Conclusions

1. Dynamic CA is preserved initially after HUT in normal subjects and patients with recurrent VVS with identical cardiovascular, cerebrovascular and carbon dioxide changes demonstrated in both groups.

2. A significant inverse relationship exists between CO_2 changes and dynamic ARI changes after HUT in normal subjects consistent with the hypothesis that hypocapnia facilitates dynamic CA. This inverse relationship suggests a potential mechanism whereby dynamic CA may be preserved during orthostatic stress.

3. Dynamic CA deteriorates during pre-syncope and remains impaired during the early post-syncopal period in both patients and syncopal control subjects. The reasons for impairment of dynamic CA during and after pre-syncope are unclear, however, and require further investigation.

Figure 5.1.
Data record of a non-syncopal control subject around the point of HUT at time 0.

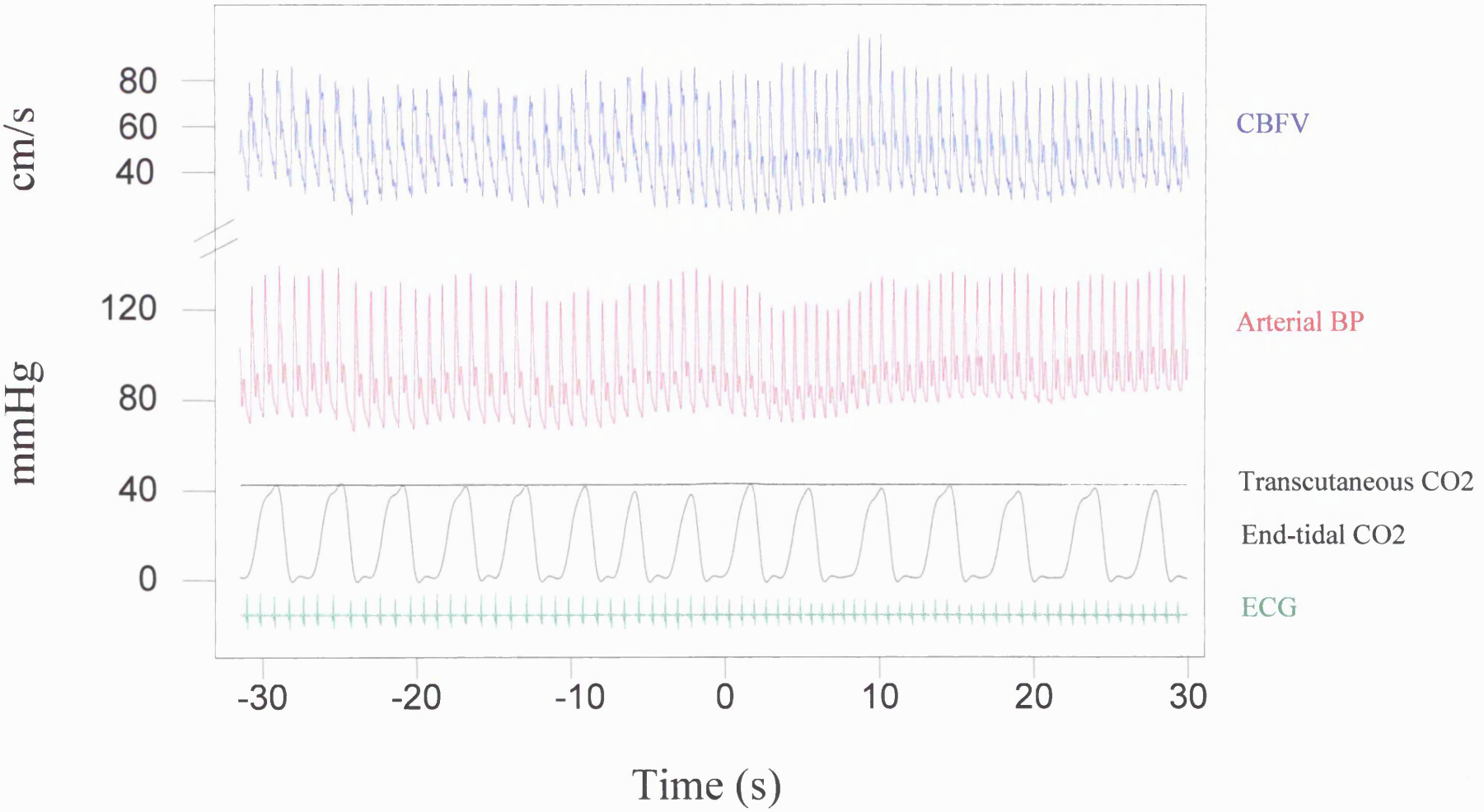


Figure 5.1.

Figure 5.2.
Data record of a patient around the point of syncope at time 0.

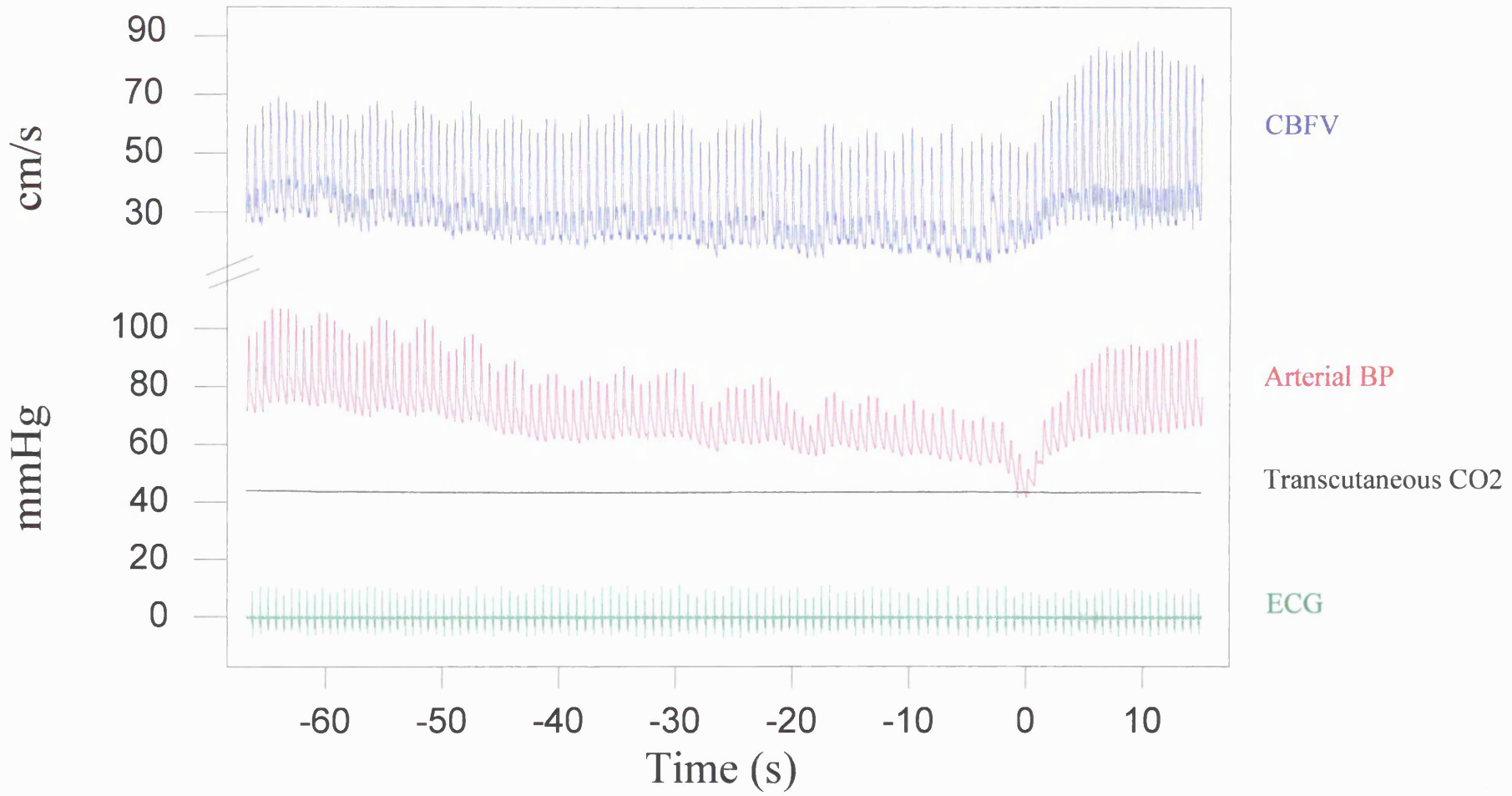


Figure 5.2.

Figure 5.3.
Mean MCAMP (solid lines) and mean CBFV (dotted lines) changes for the patient group (red lines) and control group (black lines) for the 1-minute period before and 3-minute period after HUT at time 0.

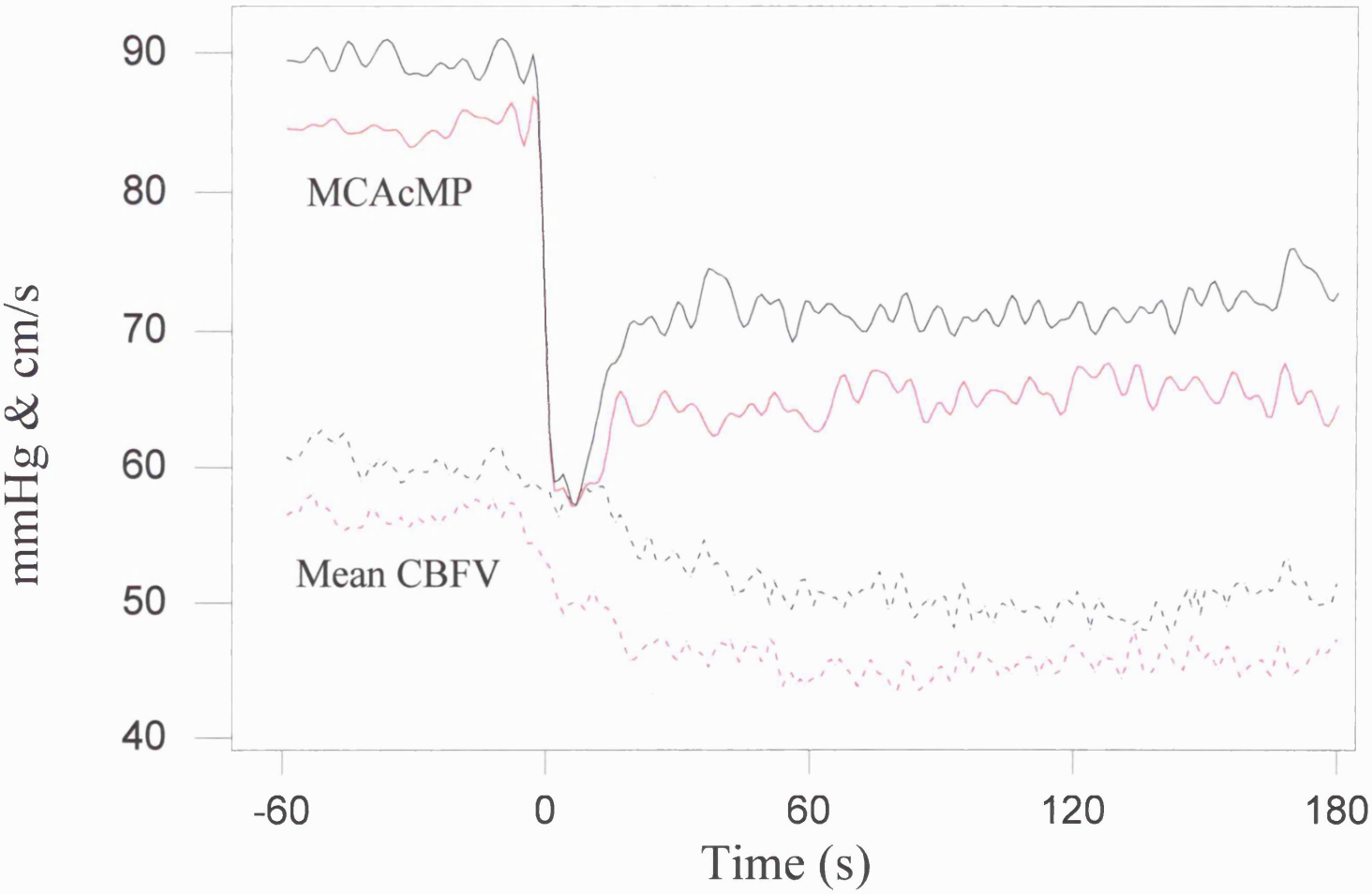


Figure 5.3.

Figure 5.4.
Mean TCO2 (solid lines) and ETCO2 (dotted lines) changes for the patient group (red lines) and control group (black lines) for the 1-minute period before and 3-minute period after HUT at time 0.

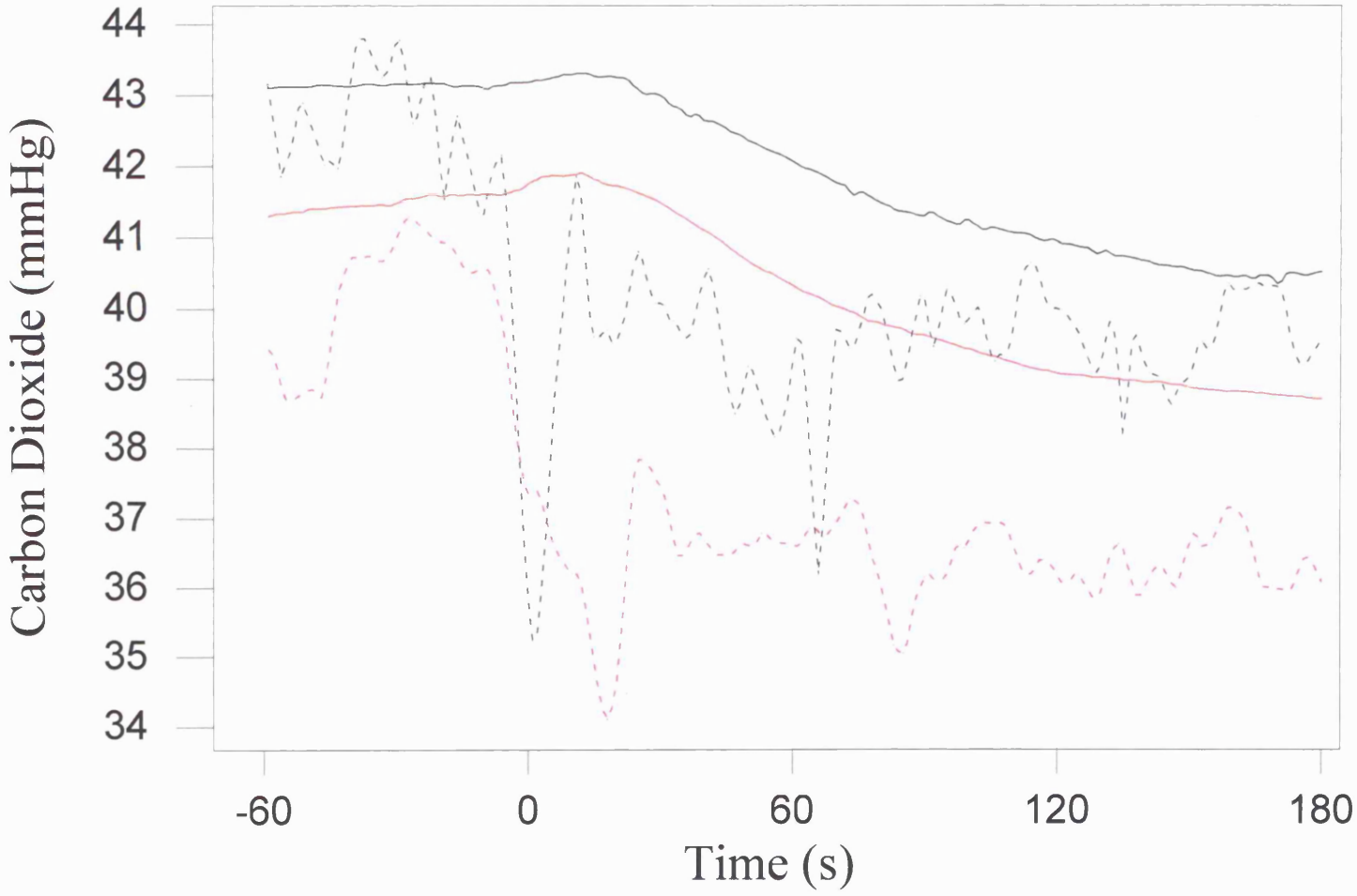


Figure 5.4.

Parameter	Patients	Non-Syncopal Controls	Syncopal Controls	p value
n	17	17	8	N/A
Age (years)	48 ± 22 (15-82)	49 ± 20 (19-90)	55 ± 22 (21-87)	0.63
Systolic BP (mmHg)	128 ± 21 (98-155)	127 ± 17 (105-152)	129 ± 19 (102-158)	0.96
Diastolic BP (mmHg)	75 ± 11 (60-89)	78 ± 10 (63-90)	81 ± 11 (62-91)	0.42
Heart rate (beats per minute)	63 ± 10 (46-78)	68 ± 8 (52-82)	66 ± 7 (56-81)	0.23
Mean CBFV (cms^{-1})	57 ± 16 (34-83)	61 ± 16 (41-83)	60 ± 17 (45-79)	0.37
Transcutaneous CO_2 (mmHg)	41.1 ± 4.7 (29.1-47.0)	41.8 ± 3.9 (34.5-47.9)	41.5 ± 4.8 (36.6-46.1)	0.80
Height (m)	1.71 ± 0.09 (1.50 – 1.90)	1.69 ± 0.08 (1.54 – 1.82)	1.69 ± 0.07 (1.57-1.80)	0.83
Body mass index (kg/m^{-2})	22.0 ± 2.8 (16.9-27.8)	23.8 ± 3.7 (16.8-30.3)	23.9 ± 2.7 (19.8-28.4)	0.12

Table 5.1. Demographic and baseline characteristics of the patient group, non-syncopal control group and syncopal control groups. Values are displayed as mean ± standard deviation with ranges in parentheses. No differences were demonstrated between the 3 groups for any baseline parameter.

	Time*	A	B	C	D	E	F	G
Mean CBFV (cm/s)	Controls	59±15	50±12	51±11	49±11	54±15	55±15	57±15
		Diff	-9	-9	-10	-5	-4.8	-3
		95% CI	-5, -14	-5, -13	-5, -16	-12, 1	-10, 1	-8, 2
		p value	<0.0001	<0.0001	0.0008	0.11	0.063	0.26
	Patients	56±16	44±12	47±11	41±13	29±9	49±15	51±15
		Diff	-12	-9	-15	-26	-7	-5
		95% CI	-7, -16	-4, -13	-10, -21	-20, -33	-2, -12	-10, 1
		p value	<0.0001	0.0002	<0.0001	<0.0001	0.0064	0.069

Table 5.2. Mean CBFV of the patient and non-syncopal control groups before, during and after HUT. Differences cited are from baseline. Values are displayed as mean ± SD.

	Time*	A	B	C	D	E	F	G
MCAMP (mmHg)	Controls	89±16	72±14	73±16	69±14	68±12	90±14	91±15
		Diff	-17	-17	-20	-22	0.2	2
		95% CI	-12, -23	-12, -22	-13, -27	-16, -27	-5, 5	-4, 7
		p value	<0.0001	<0.0001	<0.0001	<0.0001	0.94	0.58
	Patients	85±15	63±20	65±20	60±17	15±10	86±15	91±18
		Diff	-22	-20	-25	-69	1	-7
		95% CI	-16, -27	-15, -25	-17, -32	-64, -75	-4, 6	1, 12
		p value	<0.0001	<0.0001	<0.0001	<0.0001	0.58	0.027
MAP (mmHg)	Controls	89±16	91±14	92±16	88±14	87±12	90±14	91±15
		Diff	2	3	-1	-2	1	2
		95% CI	-4, 7	-2, 8	-8, 6	-7, 4	-5, 5	-4, 7
		p value	0.57	0.38	0.91	0.69	0.94	0.58
	Patients	85±15	82±20	84±20	79±17	34±10	86±15	91±18
		Diff	-3	-1	-6	-51	1	-7
		95% CI	-8, 3	-6, 4	-13, 2	-46, -57	-4, 6	1, 12
		p value	0.32	0.89	0.096	<0.0001	0.58	0.027

Table 5.3. MCAMP and MAP of the patient and non-syncopal control groups before, during and after HUT. Differences cited are from baseline. Values are displayed as mean ± SD.

* A = 1 minute before HUT (baseline)
B = 1 minute after HUT
C = 3 minutes after HUT
D = 3 minutes prior to being returning supine
E = 1 minute prior to being returned supine
F = 1 minute after being returned supine
G = 3 minutes after being returned supine

	Time*	A	B	C	D	E	F	G
Pulse interval (ms)	Controls	898±134	755±93	753±102	701±104	721±117	882±98	929±151
		Diff	143	145	198	177	16	-31
		95% CI	80, 206	102, 189	151, 244	130, 224	-35, 67	-90, 29
		p value	<0.0001	<0.0001	<0.0001	<0.0001	0.515	0.292
	Patients	1007±192	866±196	788±197	729±190	975±756	1022±206	1060±273
		Diff	141	219	278	32	-16	-54
		95% CI	66, 217	136, 301	193, 363	-295, 359	-52, 20	-135, 26
		p value	0.001	<0.0001	<0.0001	0.838	0.363	0.188

Table 5.4. Pulse interval changes of the patient and non-syncopal control groups before, during and after HUT. Differences cited are from baseline. Values are displayed as mean ± SD.

	Time*	A	B	C	D	E	F	G
Trans-cutaneous CO_2 (mmHg)	Controls	42.0±6.2	41.0±6.3	39.5±6.6	40.0±5.8	39.9±5.7	40.7±5.7	40.9±5.6
	Patients	41.3±6.3	40.3±6.6	38.7±6.2	38.6±6.2	37.5±6.2	37.8±6.0	38.5±5.5
	Patients & Controls	Diff	-1.0	-2.5	-2.3	-2.9	-2.4	-2.0
		95%CI	-0.6, -1.4	-1.9, -3.2	-1.2, -3.5	-1.7, -4.2	-1.2, -3.6	-0.9, -3.1
		p value	<0.0001	<0.0001	0.0002	<0.0001	0.0002	0.001
End-tidal CO_2 (mmHg)	Controls	43.2±5.3	39.2±7.2	39.6±6.1				
	Patients	39.4±6.7	36.7±5.6	36.1±7.6				
	Patients & Controls	Diff	-3.4	-3.5				
		95% CI	-1.9, 4.9	-1.5, -5.5				
		p value	<0.0001	0.0014				

Table 5.5. Transcutaneous and end-tidal CO_2 changes of the patient and non-syncopal control groups before, during and after HUT. Differences cited are from baseline. Values are displayed as mean ± SD.

* A = 1 minute before HUT (baseline)
B = 1 minute after HUT
C = 3 minutes after HUT
D = 3 minutes prior to being returning supine
E = 1 minute prior to being returned supine
F = 1 minute after being returned supine
G = 3 minutes after being returned supine

*Time Period	Patients (n=17)				Non-Syncopal Controls (n=17)				Controls v Patients	
	ARI	Difference from A (95% CI)	p value	Correlation Coefficient	ARI	Difference from A (95% CI)	p value	Correlation Coefficient	Difference	p value
A	4.4 ± 2.7	-	-	0.69 ± 0.16	4.2 ± 2.7	-	-	0.63 ± 0.16	-0.3 (-1.9, 1.4)	0.75
B	5.5 ± 2.6	1.1 (-0.5, 2.6)	0.17	0.62 ± 0.21	4.9 ± 2.9	0.7 (-0.8, 2.2)	0.36	0.62 ± 0.19	-0.6 (-2.3, 1.0)	0.46
C	6.2 ± 1.4	1.7 (0.2, 3.2)	0.025	0.73 ± 0.16	5.4 ± 2.6	1.2 (-0.3, 2.7)	0.12	0.74 ± 0.19	-0.8 (-2.4, 0.9)	0.35
D	5.4 ± 2.5	0.9 (-0.6, 2.5,)	0.22	0.68 ± 0.16	5.5 ± 2.3	1.3 (-0.2, 2.8)	0.096	0.68 ± 0.13	0.1 (-1.6, 1.7)	0.92
E	3.6 ± 3.0	0.9 (-0.6, 2.4)	0.24	0.69 ± 0.18	5.4 ± 2.0	1.2 (-0.3, 2.7)	0.12	0.69 ± 0.14	1.9 (0.2, 3.5)	0.027
F	2.3 ± 1.8	-2.1 (-0.6, -3.6)	0.0066	0.74 ± 0.19	4.9 ± 2.3	0.8 (-0.8, 1.8)	0.33	0.62 ± 0.21	2.6 (1.0, 4.2)	0.0021
G	5.3 ± 2.6	0.9 (-0.7, 2.4)	0.26	0.64 ± 0.22	5.4 ± 1.8	-1.2 (-0.3, 2.7)	0.12	0.66 ± 0.12	0.1 (1.6, 1.7)	0.94

Table 5.6. Comparison of dynamic ARI values between different time periods for both patient and non-syncopal control subjects. Correlation coefficients are given for how closely measured CBFV fitted the model predicted CBFV for each time period. Values are given as mean ± standard deviation.

* A = last minute before HUT (baseline)
B = first minute after HUT
C = third minute after HUT
D = third last minute of tilt prior to being returning supine
E = last minute of tilt prior to being returned supine
F = first minute after being returned supine
G = third minute after being returned supine

CHAPTER SIX

Carbon Dioxide, Critical Closing Pressure & Cerebral Haemodynamics During Pre-Syncope

6.1. Summary

In the previous chapter, indices of dynamic CA were shown to deteriorate during pre-syncope in normal subjects and patients with recurrent VVS. The reason for such deterioration is unclear but may be due to MCA mean BP falling outside the reported autoregulatory range of 60 – 150 mmHg [Paulson 1990]. This study, therefore, looked more closely at the changes in a number of cerebrovascular parameters during pre-syncope, and their potential underlying mechanisms, to help explain the deterioration in dynamic CA.

65 normal subjects with no previous history of syncope and 16 patients with recurrent VVS were subjected to 70° HUT for 30 minutes or until syncope was imminent. Bilateral MCA CBFV was measured using TCD ultrasound along with simultaneous measures of MCA BP, heart rate, $ETCO_2$ and TCO_2. All 16 patients and 14 of the control subjects developed VVS during HUT with similar pre-syncopal changes in both groups. During pre-syncope, mean CBFV declined predominantly due to a decrease in diastolic rather than systolic CBFV. CO_2 levels and indices of CVR decreased during pre-syncope while CrCP increased to levels approaching MCA diastolic BP before decreasing precipitously on syncope.

The rise in CrCP, possibly due to progressive hypocapnia, provides an explanation for the selective impairment of diastolic CBFV during pre-syncope. Rises in CrCP, therefore, may counteract the autoregulatory falls in CVR leading to impaired CA during pre-syncope. The fact that similar pre-syncopal cerebrovascular changes occur in normal subjects and patients with recurrent VVS suggests that impaired CA is unlikely to be the primary problem in patients.

6.2. Background

Irrespective of the pathophysiology involved in VVS (see section 1.1.3.), it is thought that loss of consciousness during syncope is caused by cerebral hypoperfusion [Van Lieshout 1991, Sung 2000, Grubb 1991a,1998]. In chapter 5, dynamic CA was shown to deteriorate during pre-syncope induced by HUT in normal subjects and patients with recurrent VVS, suggesting that impaired dynamic CA during pre-syncope may contribute to the pathophysiology of VVS by failing to preserve CBF. The reasons for deteriorating dynamic CA during pre-syncope are, however, unclear. A number of studies have suggested that paradoxical cerebral vasoconstriction may occur prior to syncope [Sung 2000, Grubb 1991a,1998, Levine 1994] but these studies have, in the main, used Gosling's pulsatility index (GPI) as a marker for rises in cerebrovascular resistance (CVR) [Sung 2000, Grubb 1991a,1998, Levine 1994]. As arterial BP is not taken into account in its calculation, GPI may be poorly applicable to the cerebral circulation [Czosnyka 1996, Schondorf 1997, Aaslid 1992] and, more recently, others have used Poiseuille's Law and classical CVR (CCVR) to suggest that CVR actually falls prior to VVS [Schondorf 1997]. Calculations of CCVR assume, however, that blood flow continues in cerebral vessels at arterial BP levels approaching 0mmHg, an assumption that is almost certainly untrue [Dewey 1974, Panerai 1995,1999b]. It is more likely that CBF ceases at arterial pressures above 0mmHg due to vessel wall collapse, and this pressure below which flow in a blood vessel ceases is termed critical closing pressure (CrCP) [Dewey 1974, Panerai 1995,1999b]. CrCP has an inverse relationship with carbon dioxide (CO_2) concentrations [Panerai 1999b, Garnham 1999], can change markedly over a matter of seconds [Carey 2000a] and may have a profound effect on cerebral blood flow [Dewey 1974, Panerai 1995,1999b, Carey 2000a, Czosnyka 1999, Panerai 1996,

Evans 1988]. Resistance-area product (RAP) is an index of CVR which, unlike CCVR, allows for CrCP by not making the assumption that cerebral blood flow velocity (CBFV) intercepts the arterial BP axis at 0mmHg [Panerai 1999b, Carey 2000a, Czosnyka 1999, Panerai 1996, Evans 1988].

Using these more accurate modeling techniques, the hypothesis that changes in CrCP, RAP and CO_2 may help to explain cerebral haemodynamics prior to VVS was investigated.

6.3. Objectives

1. To assess the pre-syncopal cerebrovascular responses of normal subjects and patients with recurrent VVS.
2. To assess pre-syncopal $ETCO_2$ and TCO_2 changes in both groups.
3. To assess pre-syncopal RAP and CCVR changes in both groups.
4. To assess pre-syncopal CrCP changes in both groups.

6.4. Methods

6.4.1. Subjects

16 patients with a history of recurrent VVS diagnosed according to the criteria outlined in section 4.4.1. were recruited from a specialist out-patient syncope clinic. 65 control subjects were also recruited from a volunteer register in the department and from departmental staff. Control subjects were healthy as assessed by history and physical examination, full neurological assessment and standard autonomic function tests. None of the patients or control subjects was taking any medication known to have cardiovascular or cerebrovascular effects.

6.4.2. Study Protocol

All subjects underwent the initial preparatory protocol outlined in section 2.6. In addition, end-tidal CO_2 was measured via a closely fitting face-mask and an infra-red capnograph (Capnogard, Novametrix) as described in section 2.3.1. (Figure 2.7). The vertical height in centimetres (Ht) from the point of insonation of the right MCA to the second intercostal space was also recorded for each subject. Subjects then underwent a head-up tilt protocol identical to that outlined in section 5.4.2. Once again, in order to minimise discomfort and improve compliance with the study protocol, $ETCO_2$ measurements were discontinued 5 minutes after tilt in all subjects. For ethical reasons, all pre-syncopal subjects were replaced supine prior to loss of consciousness and the point at which subjects were replaced supine was taken as time 0.

6.4.3. Data Analysis

Data were initially analysed as outlined in section 2.7. with estimates of SBP, DBP, MAP, systolic, diastolic and mean CBFV , pulse interval (PI), TCO_2 and $ETCO_2$ being made for each cardiac cycle. MCA systolic pressure (MCASP), MCA diastolic pressure (MCADP) and MCA mean pressure (MCAMP) during HUT were estimated from SBP, DBP and MAP respectively by subtracting the hydrostatic pressure (Ht * 0.735 * sin 70°).

CCVR and GPI were calculated for each cycle using the formulae (section 2.1.5.4.):

CCVR = MCAMP / MCBFV

GPI = (SCBFV – DCBFV) / MCBFV

CrCP and RAP were calculated for each cardiac cycle by plotting the instantaneous CBFV waveform as a function of MCA BP and performing linear regression analysis,

as described in section 2.1.5.4. [Panerai 1999b, Carey 2000a, Czosnyka 1999, Panerai 1996, Evans 1988]. The slope of the regression line represents the inverse of RAP while the arterial BP axis intercept of the regression line determines the CrCP (Figure 2.5.) [Panerai 1999b, Carey 2000a, Czosnyka 1999, Panerai 1996, Evans 1988]. Time 0 was synchronised for all subjects using a mark generated by an electrical device each time the tilt table passed through 45°. All files were inspected individually and detailed averaged profiles of all parameters calculated for the four-minute period from –180s to +60s for both syncopal patients and syncopal control subjects.

6.4.4. Statistical analysis

Demographic details and baseline characteristics of the syncopal patient group, syncopal control group and non-syncopal control group were compared using one-way analysis of variance. The between group differences and changes between parameter values at -180 s and time 0 were modeled for each outcome using a mixed model for repeated measures (SAS proc Mixed). Model selection was by changes in the log likelihood and denominator degrees of freedom were calculated using Satterthwaite's method [Satterthwaite 1946]. Different covariance patterns were investigated using Akaike's Information Criterion [Akaike 1973]. Due to skewing of variables, parameter values of the non-syncopal control group at the mean time to syncope of the patient group were compared with parameter values at time 0 of the syncopal patients and syncopal controls using the Kruskal-Wallis test with between group differences assessed using Wilcoxon's signed rank tests.

6.5. Results

All 16 of the patients with recurrent VVS (syncopal patients) and 14 of the control subjects (syncopal controls) developed VVS. No significant differences were demonstrated in baseline characteristics between the 16 syncopal patients, 14 syncopal controls and 51 control subjects who did not develop VVS (non-syncopal controls) (Table 6.1.). Imminent syncope tended to occur sooner after HUT in the patient group than in the control group, but the difference was not significant (302 seconds; 95% CI –116 to 737; p=0.17). No significant differences were demonstrated during pre-syncope between the syncopal patient group and syncopal control group for any parameter examined.

Changes in pre-syncopal parameters for the syncopal patient group and syncopal control group between -180 s and time 0 are shown in Table 6.2. Mean MCASP, MCAMP and MCADP and mean PI for the two groups for the four-minute period between –180s and +60s are displayed in Figures 6.1 and 6.2 respectively. SCBFV, MCBFV and DCBFV for the same period are displayed in Figure 6.3, mean RAP and CCVR in Figure 6.4, mean GPI in Figure 6.5, mean $ETCO_2$ and TCO_2 in Figure 6.6 and mean CrCP and MCADP in Figure 6.7. Changes in the instantaneous pressure-velocity relationships of a representative patient for the cardiac cycles at –180s and –20s are displayed in Figure 6.8.

SCBFV, DCBFV and MCBFV fell significantly during pre-syncope in both groups, though the fall in DCBFV was greater than the fall in SCBFV in both the syncopal patient group (41.2 ± 23.1% v 7.3 ± 16.5%, p<0.0001) and the syncopal control group

(44.5 ± 19.8 % v 6.3 ± 12.9%, p<0.0001) and accounted for most of the fall in MCBFV (Table 6.2. & Figure 6.3.).

Although TCO_2 data were available for all subjects, pre-syncopal $ETCO_2$ results are available for 7 subjects only (5 patients and 2 controls) who developed syncope within 5 minutes of HUT. Despite the small numbers, $ETCO_2$ demonstrated a significant decline (41.2 ± 3.7 mmHg v 37.4 ± 4.1 mmHg; difference 3.8 mmHg, 95%CI 0.9 to 6.6, p=0.017) during pre-syncope in the 7 subjects (Figure 6.6.).

CrCP rose significantly during pre-syncope in both groups, approaching MCADP (Table 6.2 & Figure 6.7) before falling precipitously on syncope.

757 seconds after HUT (the mean time to syncope of the patient group) all parameter values of the non-syncopal control group were significantly higher (p<0.0001) than values at time 0 in the syncopal patient and syncopal control groups, except for CrCP and GPI which were significantly lower (p<0.0001) (Table 6.2). These findings were unchanged irrespective of the time after HUT chosen for the non-syncopal control group (results not presented).

6.6. Discussion

This study has demonstrated the previously unreported findings during pre-syncope of progressive hypocapnia, rising CrCP, falling RAP and similar pre-syncopal changes in patients with recurrent VVS and control subjects. The demonstration of a rise in CrCP, an important factor in the control of CBF, during pre-syncope may help to explain complex and seemingly contradictory pre-syncopal cerebral haemodynamics in the light of a new hypothesis – increases in CrCP during pre-syncope, possibly due

to progressive hypocapnia, selectively impair diastolic CBF, thereby counteracting autoregulatory decreases in CVR and causing impaired CA prior to VVS.

6.6.1. Carbon Dioxide changes during pre-syncope

Changes in ventilation and CO_2 levels prior to syncope are complex. Schondorf [1997] demonstrated no change in respiratory rate prior to syncope but CO_2 concentrations were not measured. Novak [1998] demonstrated that hypocapnia, caused by hyperventilation resulting from an increased tidal depth without an increased rate, occurs in patients with orthostatic intolerance subjected to head-up tilt. Lipsitz [1998] indicated that hyperventilation probably occurred prior to VVS by illustrating an increase in respiratory amplitude without any change in respiratory rate, but, again, CO_2 levels were not measured. Taken in conjunction with the demonstration of falling CO_2 concentrations prior to syncope, it would appear that hypocapnia due to an increase in respiratory amplitude may form an intrinsic part of the pathophysiology of VVS. This is unsurprising as an increase in respiratory depth is a well-known pressor mechanism causing venoconstriction and increased preload [Shepherd 1981]. Gilliat [1948] has also reported a spinal vasoconstrictor reflex activated by deep inspiration which may lead to increases in systemic BP.

6.6.2. Pre-syncopal changes in cerebrovascular resistance

Pathophysiological hypocapnia prior to VVS might be expected to cause cerebral vasoconstriction and lead to the reduction in CBFV found and, taking GPI as an index of CVR, this would appear to be so. Calculations of GPI do not, however, take systemic BP levels or CrCP into account and probably do not, therefore, accurately reflect changes in CVR [Czosnyka 1996, Schondorf 1997, Aaslid 1992]. Indeed,

there may be an inverse relationship [Czosnyka 1996]. In this study, however, GPI was calculated (with a rise demonstrated during pre-syncope) to illustrate that the findings are consistent with those of others who have studied VVS.

CCVR in probably a more reliable index of CVR as its calculation takes BP into account and this work would seem confirm the findings of Schondorf et al [11] that CCVR decreases during pre-syncope. Calculation of CCVR, however, assumes that the CrCP of the cerebral circulation is 0mmHg and constant, and both of these assumptions are most unlikely to be true. RAP is probably the best available index of CVR as CrCP is taken into account in its calculation and it truly reflects the beat-to-beat changes in the instantaneous relationship between CBFV and arterial BP [Panerai 1999b, Carey 2000a, Czosnyka 1999, Panerai 1996, Evans 1988]. In this study, a previously unreported substantial decline in RAP was shown during pre-syncope, similar to the decline in CCVR, suggesting that distal arteriolar vasodilatation is taking place. The relative preservation of SCBFV that was demonstrated in the face of a precipitously falling SBP, would appear to confirm the presence of cerebral vasodilatation during pre-syncope.

6.6.3. Pre-syncopal changes in critical closing pressure

If cerebral arteriolar vasodilatation is occurring, why are MCBFV and DCBFV not being maintained? These results suggest that changes in CrCP during the pre-syncopal period as well as the low MCADP may be responsible. CrCP is seen to consistently rise during pre-syncope, possibly due to the simultaneous decline in CO_2 levels [Panerai 1999, Garnham 1999, Aaslid 1992], before abruptly falling immediately prior to syncope (Figure 6.7.). DCBFV is seen to decrease by a much greater amount than SCBFV during pre-syncope (Table 6.2. & Figure 6.3.), even

though MCASP declines in much the same fashion as MCADP (Figure 6.1.). This finding has been previously reported by others [Sung 2000, Grubb 1991a, Schondorf 1997] and accounts for the rise in GPI during pre-syncope (Figure 6.5.). The reason for the sharp decline in DCBFV despite active vasodilatation can be explained by CrCP approaching MCADP during pre-syncope (Figure 6.7.). The convergence of CrCP and MCADP probably results in a substantial number of downstream vessels collapsing during diastole leading to severe curtailment of DCBFV (Figures 6.3. & 6.7.). As PI rises in late pre-syncope (Table 6.2. & Figure 6.2.), diastole comprises a relatively greater proportion of the cardiac cycle and this may compound the problem of reduced CBF during diastole. Rises in CrCP, therefore, seem to counteract the effects of cerebral arteriolar vasodilatation by reducing CBF during diastole.

6.6.4. Carbon dioxide and critical closing pressure during pre-syncope

Increasing respiratory depth prior to syncope, therefore, may help maintain systemic BP but may have deleterious effects on CBF through the action of hypocapnia on CrCP. Novak [1998] found that rebreathing CO_2 has the effect of abolishing symptoms and improving CBFV and CVR in patients with orthostatic hypotension subjected to orthostatic stress. It has been suggested that higher CO_2 concentrations may work by inducing cerebral vasodilatation, and this study suggests that this may occur through an action on CrCP. Whether employing rebreathing techniques to increase CO_2 levels would be an appropriate treatment for patients with recurrent VVS is worthy of further investigation.

6.6.5. Similar changes in patients and syncopal controls

The findings of this study suggest that changes in the pre-syncopal period are similar for patients with recurrent VVS and control subjects who have VVS induced by head-up tilt. It is unlikely, therefore, that impaired control of CBF is the primary problem in patients with recurrent VVS, but this warrants further investigation.

6.6.6. Limiting factors

The major limiting factor of this work, similar to the work in chapter five, remains the inability to directly measure MCA BP. As discussed in section 5.6.5., non-invasive plethysmography correlates very well with intra-arterial pressure recordings during HUT [Petersen 1995] and intracranial pressure changes after HUT are likely to be relatively small [Drummond 2000] and similar in syncopal and non-syncopal subjects alike. Changes in venous pressure will occur to an equal and proportionate degree as arterial pressure and, in the absence of better, non-invasive alternatives, therefore, calculations using non-invasive plethysmography provide acceptable estimates of MCA pressure.

Calculations also make the assumption analogous to that in chapter five that both MCA diameter and intracranial pressure remain constant in the pre-syncopal period. As discussed in section 5.6.5., simulated orthostasis does not affect MCA calibre [Serrador 2000] and changes in CO_2 concentrations to the degree demonstrated in this study would not be expected to affect MCA diameter [Hubner 1967, Giller 1993] or intracranial pressure [Drummond 2000]. Similarly, profound hypotension during pre-syncope could potentially cause MCA myogenic vasodilatation and influence CBFV, but the methodology employed did not allow assessment of this possibility.

While TCO_2 and $ETCO_2$ measurements accurately reflect arterial CO_2 measurements in the steady state, some doubts remain over accuracy during hyperventilation and

changes in cardiac output [Steurer 1997, Weil 1985]. In addition, temporal resolution is poor with TCO_2 measurements, but the facts that TCO_2 levels continued to decline in pre-syncopal subjects for ~40s after time 0 (Figure 6.6), that $ETCO_2$ levels also declined during pre-syncope (Figure 6.6) and that others have demonstrated hyperventilation during pre-syncope [Lipsitz 1998], suggest that the conclusion that progressive hypocapnia occurs during pre-syncope is correct. Hypocapnia is known to increase CrCP [Aaslid 1992, Panerai 1999b,Garnham 1999, Czosnyka 1999], but the poor temporal resolution of the TCO_2 measurements prevented assessment of whether the rise in CrCP during pre-syncope was causally linked to the CO_2 changes and this is worthy of further study.

6.7. Conclusions

1. Similar pre-syncopal cerebrovascular and CO_2 changes occur in normal subjects and patients with recurrent VVS. Impaired CA is unlikely, therefore, to be the primary problem in patients with recurrent VVS.

2. End-tidal and transcutaneous CO_2 levels decline progressively during pre-syncope, but further work is needed to assess if one or both of these parameters accurately reflect pre-syncopal arterial CO_2 changes.

3. RAP, probably the best index of CVR as it is calculated taking CrCP and systemic BP into account, declines significantly during pre-syncope. CCVR, declines in a similar fashion during pre-syncope, but GPI rises mainly due to a marked fall in diastolic CBFV.

4. CrCP rises during pre-syncope, possibly due to progressive hypocapnia, but further work is needed to assess if there is, indeed, a causal relationship.

5. The rise in CrCP and low MCA diastolic pressure may account for the selective fall in diastolic CBFV during pre-syncope and lead to impairment of dynamic CA by attenuating reductions in CVR.

6. As hypercapnia is known to increase CrCP, there may be a role for rebreathing in the treatment of VVS with hypercapnia-induced rises in CrCP potentially facilitating better diastolic CBF during pre-syncope.

Figure 6.1.
Mean MCASP, MCADP and MCAMP 3 minutes prior to, and 1 minute after, being replaced supine at time 0 of 16 syncopal patients (red lines) and 14 syncopal controls (black lines).

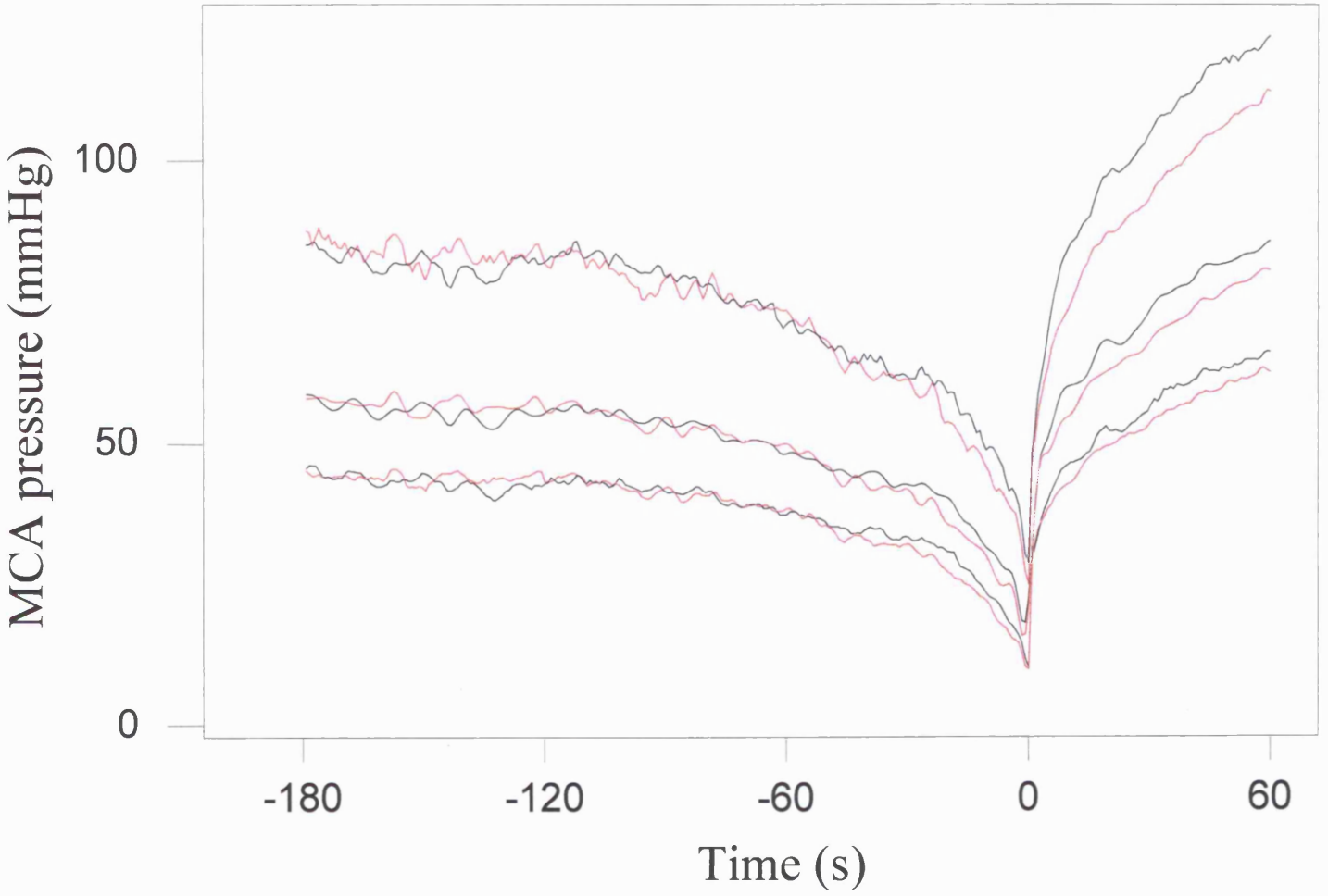


Figure 6.1.

Figure 6.2.
Mean PI changes 3 minutes prior to, and one minute after, being replaced supine at time 0 of 16 syncopal patients (red lines) and 14 syncopal controls (black lines).

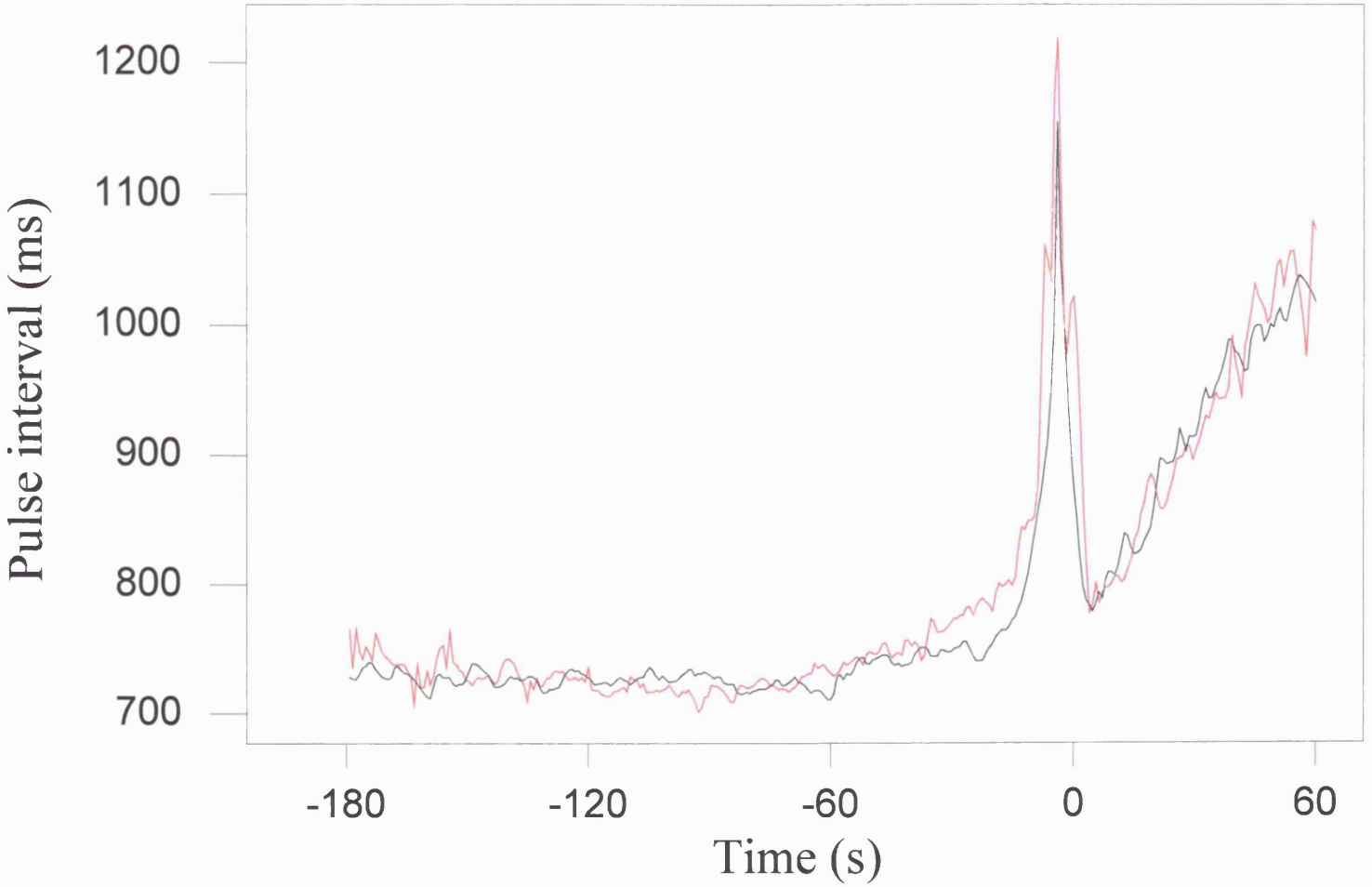


Figure 6.3.
Mean SCBFV, MCBFV and DCBFV changes 3 minutes prior to, and one minute after, being replaced supine at time 0 of 16 syncopal patients (red lines) and 14 syncopal controls (black lines).

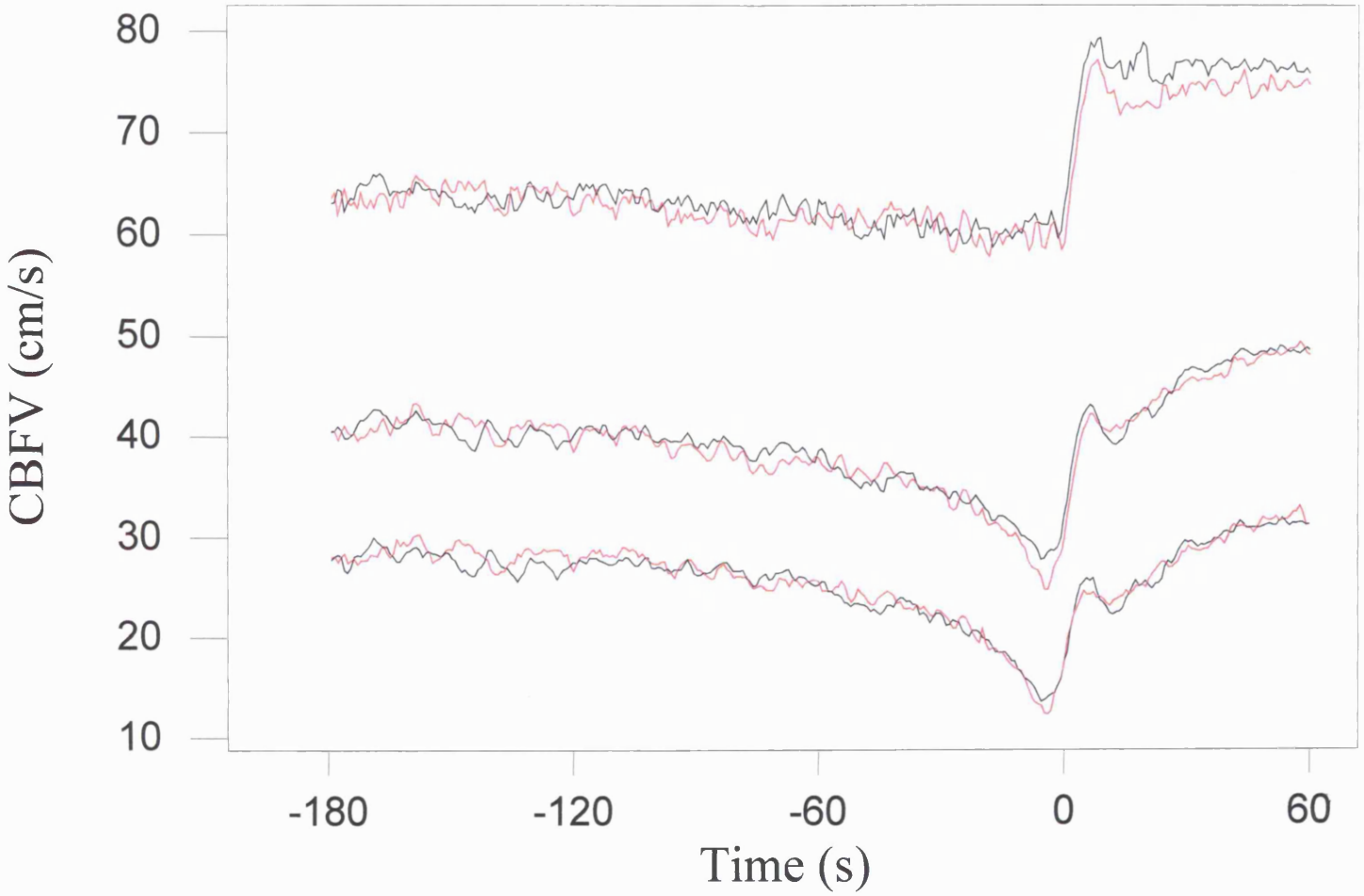


Figure 6.3.

Figure 6.4.
Mean RAP (solid lines) and CCVR (dotted lines) changes 3 minutes before, and 1 minute after, being replaced supine at time 0 of 16 syncopal patients (red lines) and 14 syncopal controls (black lines).

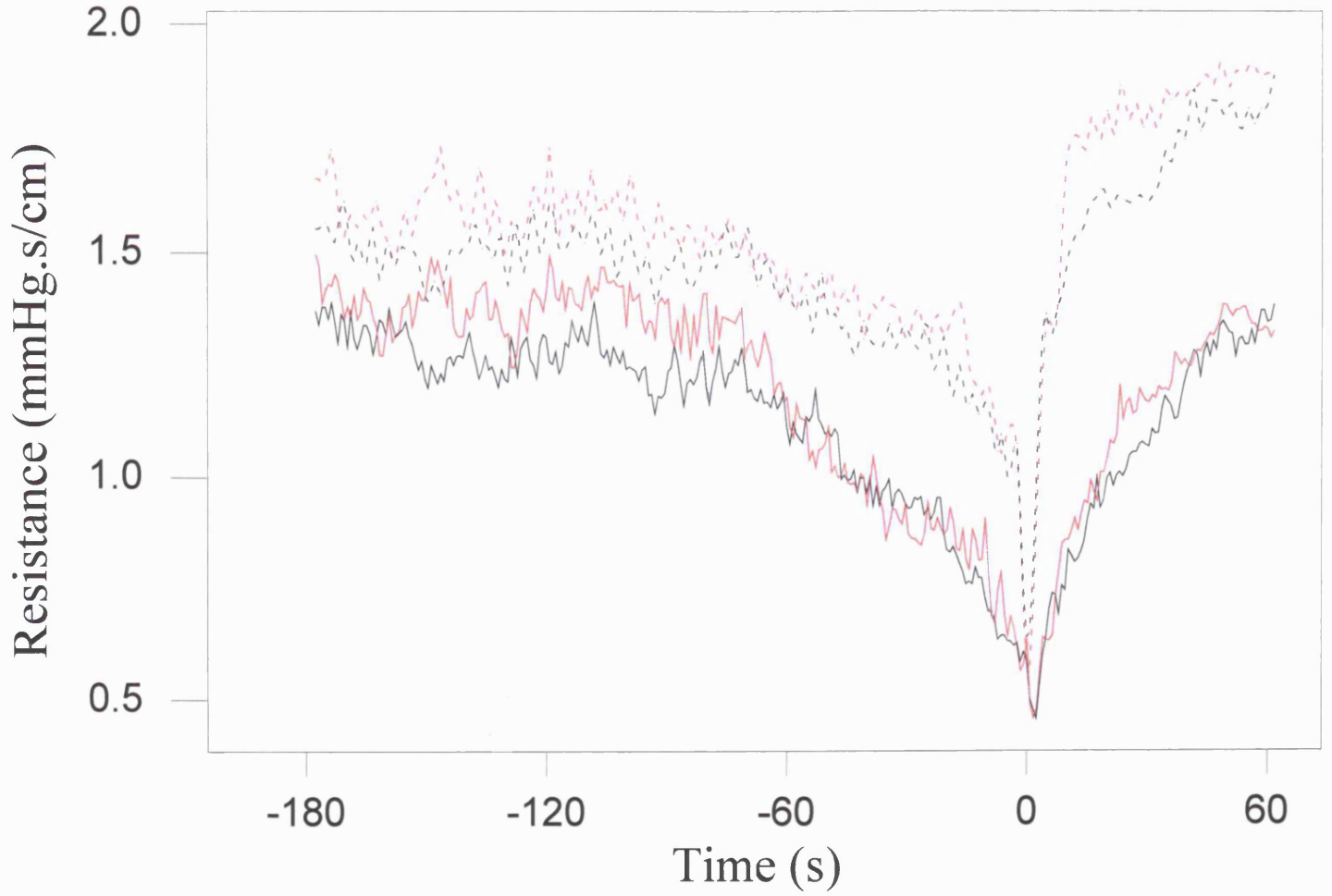


Figure 6.4.

Figure 6.5.
Mean GPI changes 3 minutes prior to, and 1 minute after, being replaced supine at time 0 of 16 syncopal patients (red lines) and 14 syncopal controls (black lines).

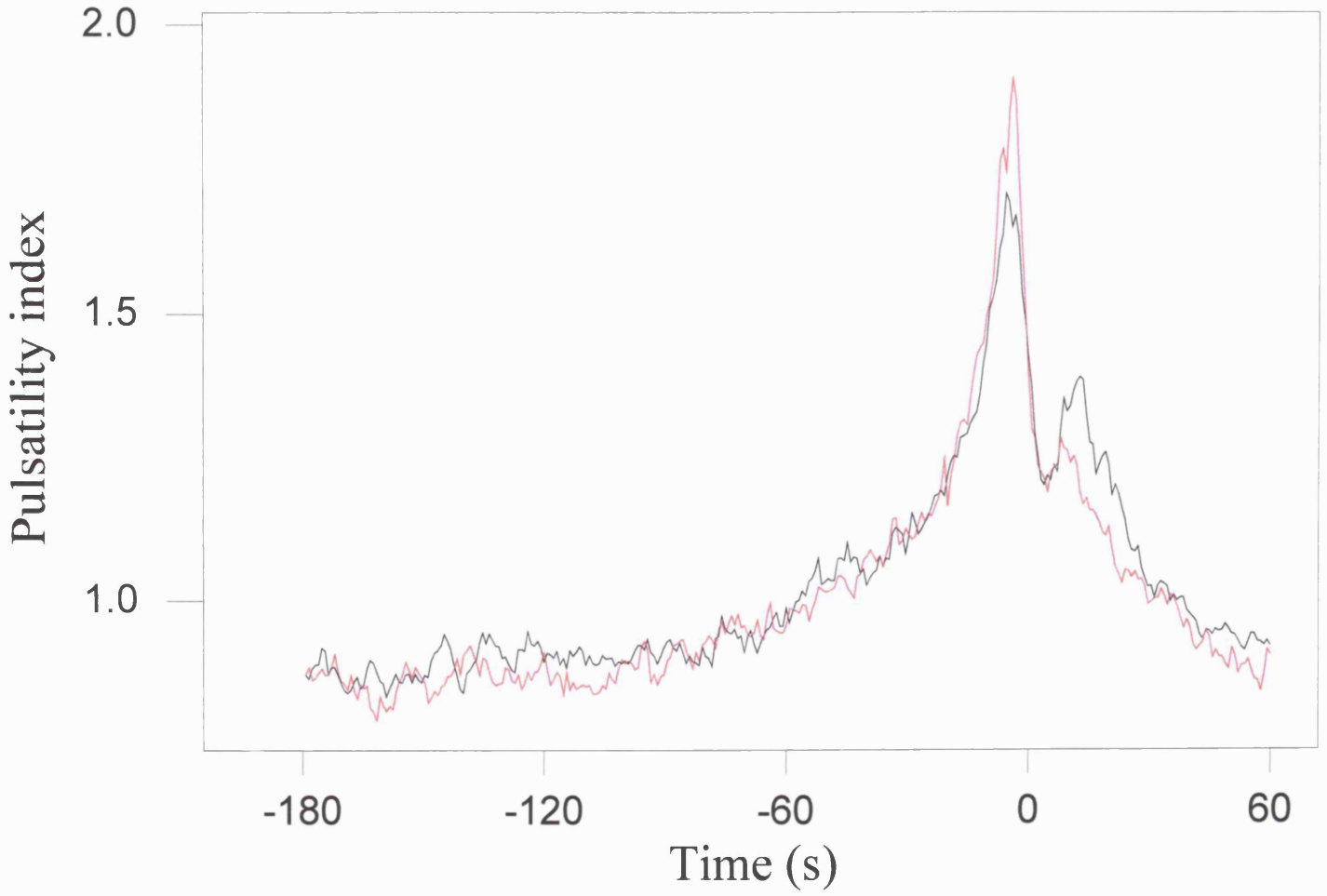


Figure 6.5.

Figure 6.6.
Mean TCO2 changes of 16 syncopal patients (red line) and 14 syncopal controls (black line) and mean ETCO2 changes (blue dotted line) of 7 subjects (2 controls and 5 patients) 3 minutes prior to, and 1 minute after being replaced supine at time 0.

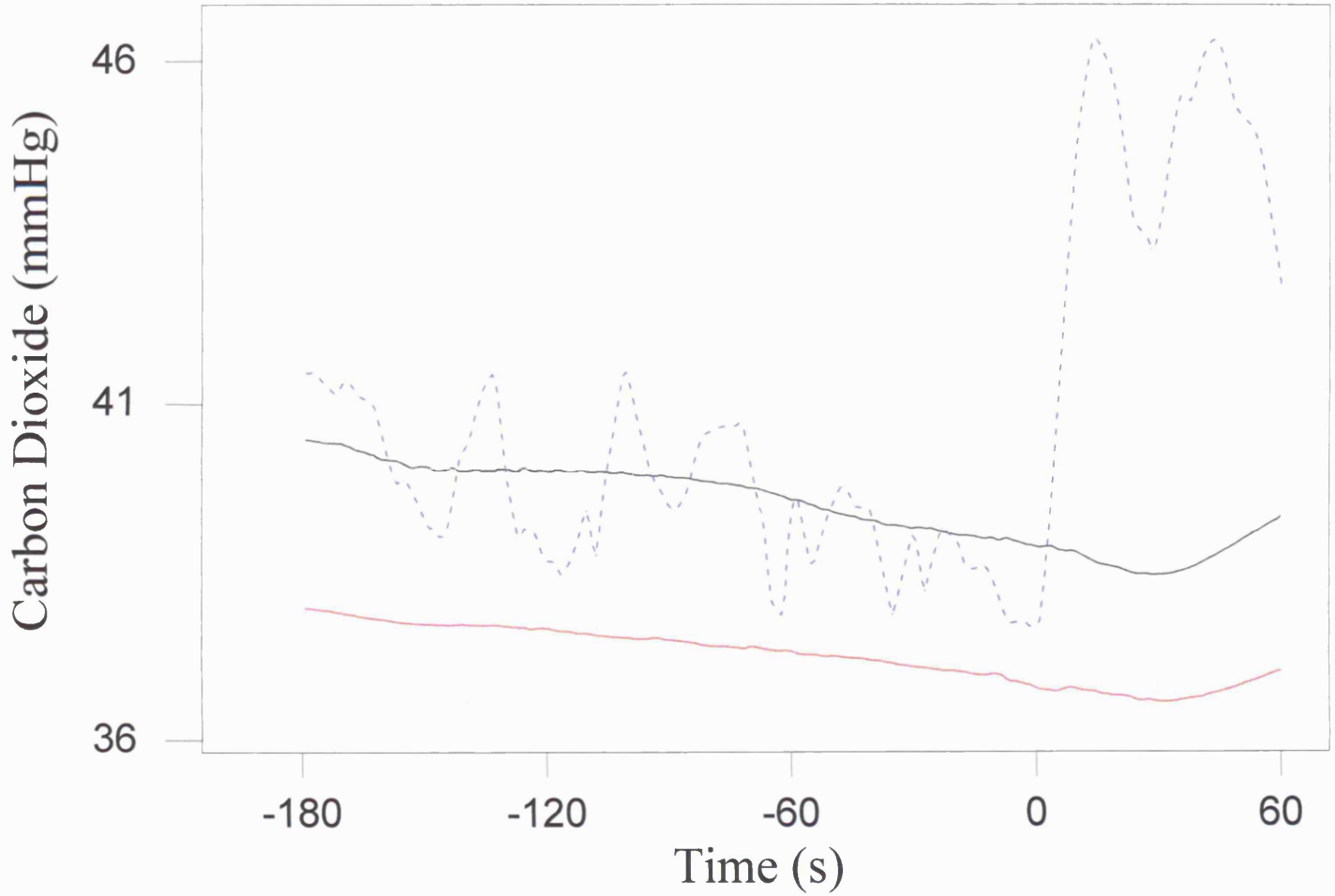


Figure 6.6.

Figure 6.7.
Mean CrCP (solid lines) and MCADP (dotted lines) changes 3 minutes prior to, and 1 minute after, being replaced supine at time 0 of 16 syncopal patients (red lines) and 14 syncopal controls (black lines).

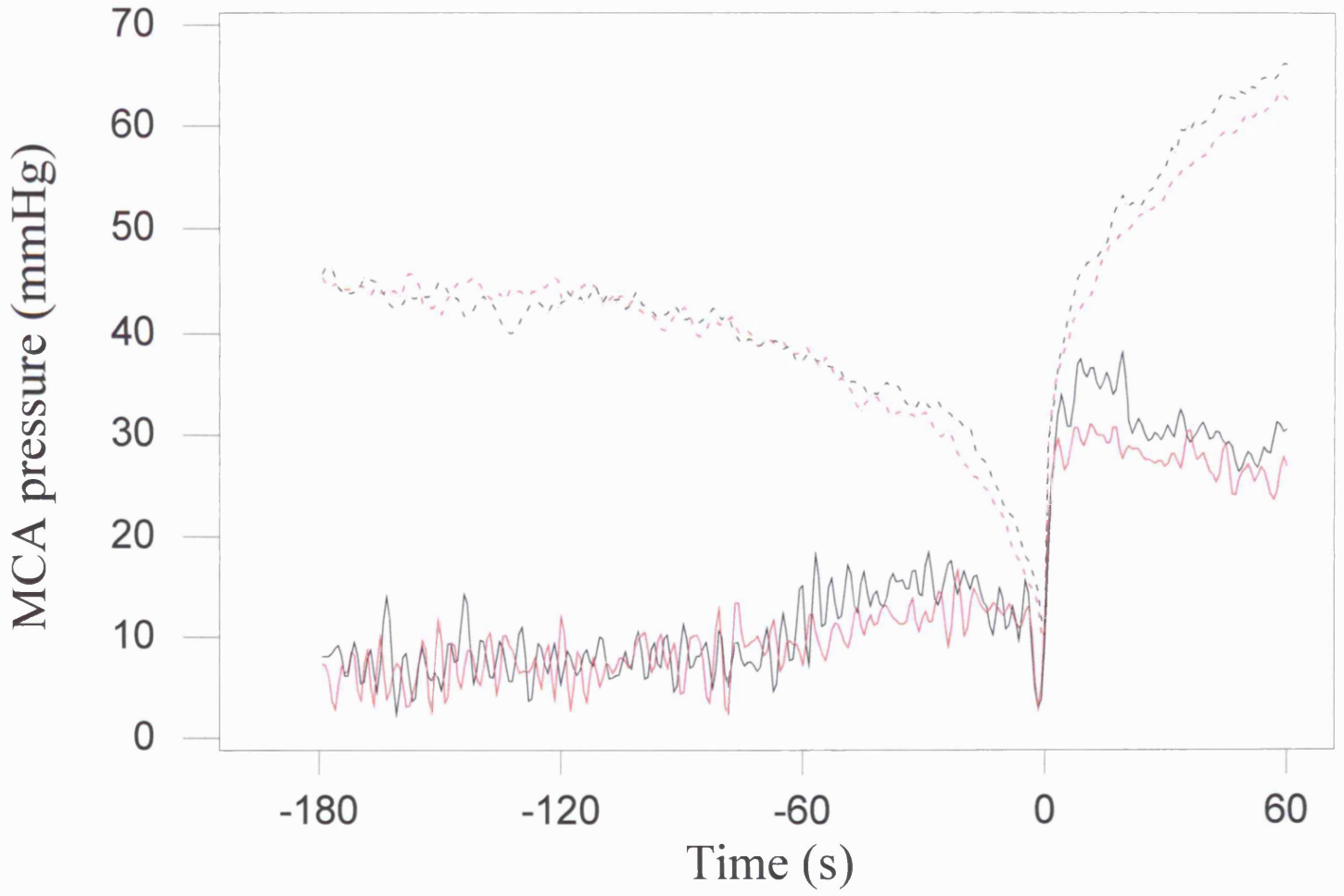


Figure 6.7.

Figure 6.8.
Instantaneous pressure-velocity relationships of a representative patient for the cardiac cycles at -180s (circles) and -20s (triangles). Linear regression analysis demonstrates a CrCP of 23mmHg at -20s which is higher than the CrCP of 11mmHg at -180s despite arterial blood pressure being lower.

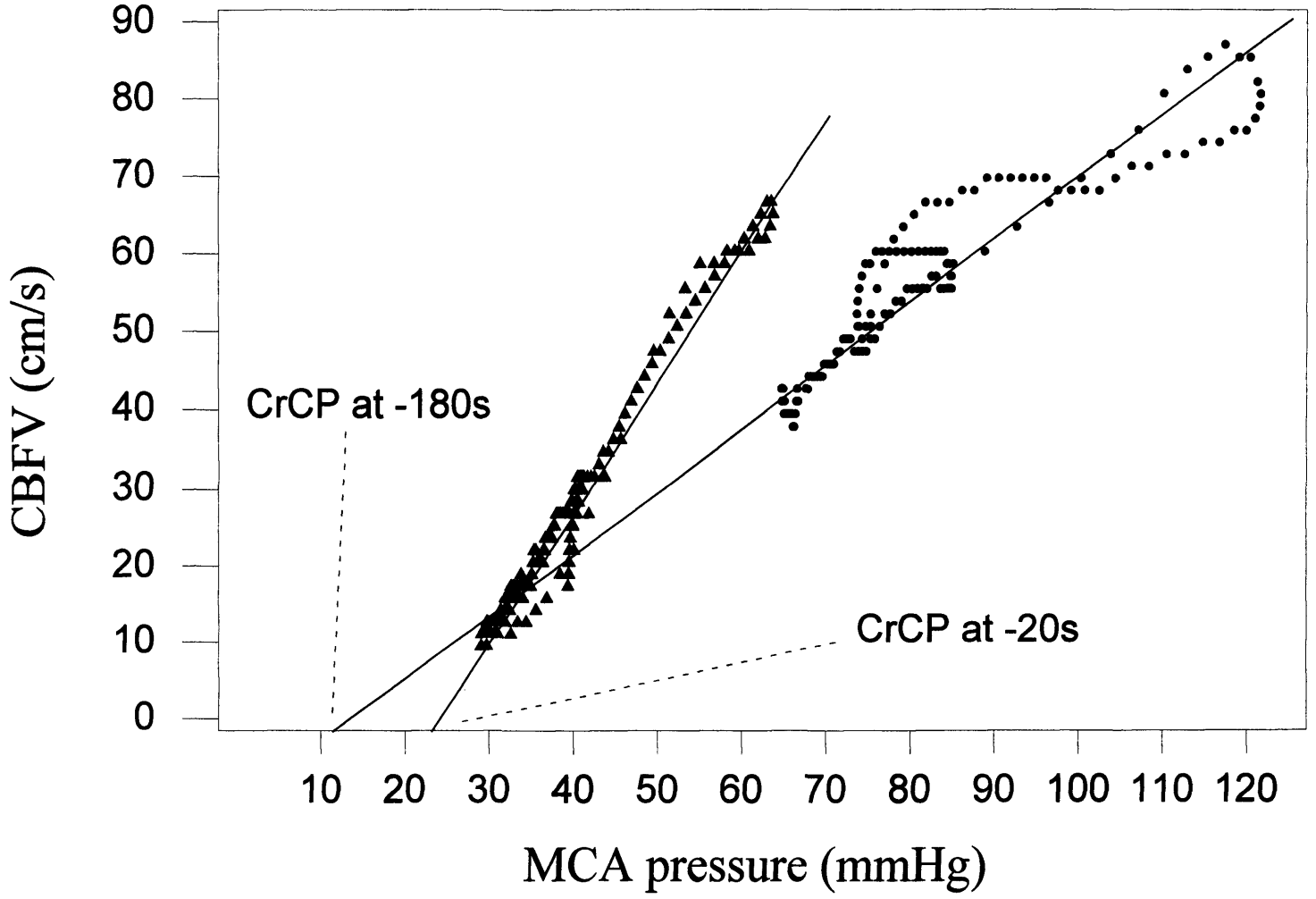


Figure 6.8.

Parameter	Syncopal Patients	Syncopal Controls	Non-syncopal Controls
n	16	14	51
Age (years)	52 ± 22 (17-86)	53 ± 22 (21-87)	53 ± 22 (20-90)
Male : Female	7:9	6:8	24:27
Systolic BP (mmHg)	132 ± 21 (105-179)	127 ± 19 (94-151)	130 ± 18 (103-166)
Diastolic BP (mmHg)	76 ± 11 (60 – 97)	79 ± 12 (62 – 92)	79 ± 11 (61-98)
Heart Rate (bpm)	62 ± 10 (46-78)	65 ± 7 (53-76)	66 ± 10 (49-102)
Body mass index (kgm^{-2})	22.4 ± 3.2 (16.9-27.8)	23.9 ± 2.8 (19.8-28.4)	24.5± 3.3 (16.8-30.8)
Mean CBFV (cms^{-1})	51 ± 16 (21-83)	52 ± 15 (29-78)	55 ± 17 (22-86)
TCO_2 (mmHg)	40.9 ± 4.9 (30.1-47.0)	42.8 ± 3.8 (33.3-46.8)	41.9 ± 5.6 (29.6-50.8)
$ETCO_2$ (mmHg)	42.1 ± 4.7 (32.2-49.3)	43.7 ± 5.2 (32.9-50.4)	42.2 ± 4.5 (34.0-51.4)
Time to syncope (s)	757 ± 539 (61-1768)	1059 ± 615 (185-1800)	N/A

Table 6.1. Demographic data and baseline characteristics of syncopal patients, syncopal control and non-syncopal control subjects. No differences were shown between the 3 groups for any parameter.

Parameter	Syncopal Controls				Syncopal Patients				Non-Syncopal Controls
	-180 s	Time 0	Difference, (95% CI)	p value	-180 s	Time 0	Difference, (95% CI)	p value	757 s after HUT*
MCBFV (cm/s)	41 ± 12	28 ± 8	-13, (-10,-16)	<0.0001	41 ± 13	29 ± 8	-12, (-8,-15)	<0.0001	52 ± 13
SCBFV (cm/s)	65 ± 15	60 ± 16	-5, (-2,-9)	0.041	64 ± 17	59 ± 18	-5, (-0.9,-8.1)	0.017	80 ± 17
DCBFV (cm/s)	28 ± 11	15 ± 5	-13, (-10,-17)	<0.0001	28 ± 11	16 ± 6	-12, (-8,-16)	<0.0001	35 ± 10
MCAMP (mmHg)	60 ± 15	18 ± 17	-42, (-32,-53)	<0.0001	62 ± 15	15 ± 11	-47, (-41,-53)	<0.0001	73 ± 16
MCASP (mmHg)	91 ± 17	34 ± 24	-57, (-43,-70)	<0.0001	90 ± 20	34 ± 14	-56, (-47,-65)	<0.0001	112 ± 27
MCADP (mmHg)	47 ± 12	14 ± 13	-33, (-25,-42)	<0.0001	49 ± 15	13 ± 10	-35, (-29,-42)	<0.0001	54 ± 13
† CrCP (mmHg)	5.1 ± 13.8	11.6 ±10.8	6.5, (1.2,11.8)	0.018	7.7 ± 17.2	14.5 ±14.7	6.8, (0.2,13.4)	0.044	2 ± 16
RAP (mmHg.s/cm)	1.4 ± 0.5	0.6 ± 0.6	-0.8, (-0.6,-1.0)	<0.0001	1.4 ± 0.8	0.6 ± 0.4	-0.8, (-0.6,-1.1)	<0.0001	1.5 ± 0.7
CCVR(mmHg.s/cm)	1.5 ± 0.4	0.6 ± 0.6	-0.9, (-0.8,-1.1)	<0.0001	1.7 ± 0.7	0.6 ± 0.4	-1.1, (-0.9,-1.3)	<0.0001	1.5 ± 0.5
TCO_2 (mmHg)	40.7 ± 5.0	39.3 ± 4.8	-1.4, (-0.4,-2.5)	0.011	38.2 ± 6.2	36.9 ± 6.5	-1.3, (-0.3,-2.2)	0.014	40.8 ± 3.7
PI (ms)	789 ± 142	1219 ±253	430, (294,620)	<0.0001	730 ± 188	1153 ±538	423, (291,742)	<0.001	753 ± 102
GPI	0.95 ± 0.32	1.60 ±0.52	0.65, (0.43,0.87)	<0.0001	0.94 ± 0.27	1.50 ±0.39	0.56, (0.39,0.73)	<0.0001	0.88 ± 0.17

Table 6.2. Cardiovascular and cerebrovascular parameters at -180s and time 0 of 16 syncopal patients and 14 syncopal controls.
*Also the average time to syncope of the syncopal patient group
†Compares values at -180s with values at -20s.

SCBFV, MCBFV, DCBFV = systolic, mean and diastolic cerebral blood flow velocity respectively
MCASP, MCAMP, MCADP = middle cerebral artery systolic, mean and diastolic pressure respectively
CrCP = middle cerebral artery critical closing pressure
RAP = resistance-area product
CCVR = classical cerebrovascular resistance
TCO_2 = transcutaneous carbon dioxide
PI = pulse interval
GPI = Gosling's pulsatility index

CHAPTER SEVEN

Conclusions of the Thesis

The work described in this thesis sought to explore cardiovascular and cerebrovascular responses in orthostatically induced syncopal and non-syncopal subjects in order to investigate the hypothesis that impaired cerebral autoregulation (CA) contributes to the pathophysiology of vasovagal syncope (VVS). More specifically, the effects of ageing and orthostatic stress on CA were assessed along with cerebrovascular and cardiovascular function in syncopal subjects at rest and during pre-syncope.

7.1. Summary of Results

Chapter 1 reviewed the literature regarding the historical aspects, epidemiology, pathophysiology, clinical characteristics, investigation, treatment and prognosis of VVS. In addition, literature on the physiological entity of CA, the inherent ability of the cerebral blood vessels to keep cerebral blood flow (CBF) constant for a wide range of systemic blood pressure (BP) levels, was reviewed in association with current understandings of the role of CA in the pathophysiology of VVS. CA occurs with a substantial degree of temporal heterogeneity and dynamic CA refers to the ability to maintain CBF in the face of BP changes occurring over a matter of seconds, reflecting the latency of the cerebral vasoregulatory system. Static CA refers to CBF adjustments in response to more prolonged BP changes and is a measure of the overall efficiency of the system. Static and dynamic CA may have different control mechanisms and dynamic CA may be more susceptible to damage in pathological states [Tiecks 1995, Dawson 2000]. It was noted that CBF has been shown to be impaired during pre-syncope [Janosik 1992, Bondar 1995, Sung 2000, Grubb 1991a, 1998, Levine 1994, Giller 1992] but that controversy over cerebrovascular resistance (CVR) clouded the issue over whether the impairment of CBF is due to abnormalities

of CA [Janosik 1992, Bondar 1995, Sung 2000, Grubb 1991a, 1998, Levine 1994, Giller 1992, Czosnyka 1996b, Schondorf 1997, Aaslid 1992]. Literature concerning the effect of orthostatic stress on CA in normal subjects and patients with recurrent VVS was discussed and felt to be scanty and disadvantaged by poor methodology. Chapter 2 reviewed the methods used in the studies of this thesis to measure systemic blood pressure (BP), CBF velocity (CBFV) and carbon dioxide (CO_2) continuously and non-invasively. Finger plethysmography using the Finapres device provides an accurate assessment of rapid changes in arterial BP compared to intra-arterial measurements, though exact BP levels may differ between methods [Imholz 1988, Rongen 1995, Petersen 1995, Omboni 1993, Jellema 1996]. Although arterial pressure waveforms change with head-up tilt, non-invasive plethysmography also correlates very well with intra-arterial pressure recordings during head-up tilt]. Because of multiple assumptions, including a constant diameter of the insonated vessel and an insonation angle of 0°, calculations of CBF from transcranial Doppler ultrasound (TCD) measurements do not correlate well with values derived using the traditional methods of CBF measurement, such as intravenous Xe clearance studies (see section 2.1.5.3.) [Bishop 1986]. The correlation between CBF and TCD measured CBF velocities is much better, however, especially during physiological manoeuvres. As CBF velocity and changes in velocity correlate well with CBF results obtained using traditional techniques, and because the temporal resolution is excellent, TCD has become the method of choice for the non-invasive assessment of rapid changes in CBF.

The temporal resolution of end tidal-CO_2 measurements is excellent, but as transcutaneous CO_2 measurements rely on gas diffusion, temporal resolution is poor (see section 2.3.2.). Transcutaneous [Trempler 1981, Mahutte 1984, Carter 1989,

Sridhar 1993, Dawson 1998] and end-tidal [Hillier 1990, Tobias 1994, Campbell 1994, Napolitano 1999, Schmitz 1995, Rozycki 1998] CO_2 measurements, however, give accurate non-invasive estimates of arterial CO_2 in the steady state (see section 2.3.).

Also in Chapter 2, thigh cuff inflation and release, Valsalva manoeuvre and lower body negative pressure (LBNP) application and release were reviewed as methods of inducing static and dynamic pressor and depressor changes and techniques of assessing the efficiency of static and dynamic CA using such induced BP changes were discussed. Drawbacks of using induced BP changes to assess CA and the potential advantages of using spontaneous BP changes at rest to assess dynamic CA were also evaluated. Finally, indices of CVR in current usage and their validity and methods of calculation were reviewed in detail.

Systemic BP levels are known to increase with age [Kannel 1978] while arterial compliance [Fleg 1986], cardiac baroreceptor sensitivity (BRS) [Gribbin 1971], CBF [Matsuda 1984] and CBFV [Krejza 1999] are lower in older subjects, but the effect of age on CA is unknown. As an age-related deterioration in CA could potentially explain the increased prevalence of syncope syndromes in older people, Chapter 3 investigated the effect of physiological ageing on CA. Twenty-seven young (<40 years) subjects were pair-matched for sex, systolic BP and body-mass index with twenty-seven older (>55 years) subjects, with young recruits being a mean of 39 years younger. Although age-related differences in cardiac BRS and CBFV were demonstrated between the two groups, no deterioration in static or dynamic CA was shown in older subjects despite the use of spontaneous and induced pressor and depressor BP changes. Induced and spontaneous BP changes were of a similar

magnitude in both groups except for phase IV of the Valsalva manoeuvre which had a greater pressor effect in the younger group. Despite this, no correlation was shown between the magnitude of BP changes and autoregulatory index (ARI) values. ARI values derived using thigh cuff release were significantly higher than those derived using LBNP release, but this was a consistent finding in both groups. The confidence intervals reported suggest that no clinically significant age-related deterioration occurs in dynamic CA but the wider confidence intervals for static ARI values mean that conclusions regarding the absence of an age-related deterioration in static CA are less robust.

The hypothesis that impaired cerebral autoregulatory function may contribute to the pathophysiology of syncope in patients with recurrent VVS arose because of reported reductions in CBFV during pre-syncope [Janosik 1992, Bondar 1995, Sung 2000, Grubb 1991a, 1998, Levine 1994, Giller 1992]. Chapter 4, therefore, addressed the possibility that abnormalities of CA during supine rest may predict the development of VVS. Static CA (assessed using thigh cuff inflation) and dynamic CA (assessed using thigh cuff release and spontaneous BP changes at rest with both Aaslid's model and frequency domain analysis) were found to be comparable in 17 patients with recurrent VVS and 17 pair-matched controls.

Although abnormalities of CA do not appear, therefore, to be present in patients with recurrent VVS during supine rest, the possibility remained that orthostatic stress could compromise CA in such patients. Indeed, conflicting evidence exists regarding the effect of orthostatic stress on CA in normal subjects with both preserved [Leftheriotis 1998, Lipsitz 2000] and impaired [Zhang 1998b] dynamic CA being reported.

Chapter 5, therefore, explored the effect of orthostatic stress induced by 70° head-up tilt (HUT) on dynamic CA in normal subjects and patients with recurrent VVS. Autoregulatory responses were identical in both groups before and immediately after HUT with patients and controls demonstrating preservation of indices of dynamic CA. ARI values subsequently deteriorated, however, during pre-syncope in patients and syncopal control subjects and remained impaired during the first minute after returning supine. In addition, a significant inverse relationship was found between dynamic ARI values and CO_2 changes after HUT in normal subjects, supporting the findings of others that hypocapnia improves autoregulatory capacity [Paulson 1990, Birch 1995, Aaslid 1989]. This relationship was not explored in patients or during pre-syncope due to the effect of critical closing pressure (CrCP) on CBFV discussed in Chapter 6.

The reasons for impairment of dynamic CA in the peri-syncopal period are unclear and Chapter 6 examined pre-syncopal changes in a number of cerebrovascular and cardiovascular parameters to help explain the findings. Impairment of CBFV during pre-syncope in patients and syncopal controls was seen to be primarily due to a reduction in diastolic CBFV in the face of a relative preservation of systolic CBFV. Two indices of CVR were demonstrated to fall markedly during pre-syncope, suggesting that active cerebral vasodilatation was taking place. The CrCP of the cerebral circulation rose significantly during pre-syncope, providing an explanation for the selective impairment of diastolic CBFV. As hypocapnia is known to increase CrCP, the progressive hypocapnia demonstrated during pre-syncope in both groups could potentially explain the concomitant rise in CrCP, but the methods used could not determine if this link was causal. Finally, no differences in cerebrovascular or

cardiovascular parameters were demonstrated between patients and syncopal controls at any stage, suggesting that abnormalities of CA are not the primary pathophysiological problem in patients with recurrent VVS.

7.2. Study limitations

The author has attempted to highlight the limitations of these studies in each chapter and has mentioned some of them in the above summary.

All work involving transcranial Doppler ultrasound, including these studies, makes the assumption that the diameter of the insonated vessel remains constant throughout the duration of the study. Changes in CBF can only be reliably deduced from CBFV changes if the calibre of the insonated vessel is constant [Aaslid 1982], but reliable, non-invasive assessment of vessel diameter has proven notoriously elusive. A number of authors have used the spectral power of Doppler signals to show that MCA diameter does not change during thigh cuff application and release [Aaslid 1989] and during hypocapnia and hypercapnia [Poulin 1996], but a recent study has cast doubt on the usefulness of this method of assessing vessel diameter [Deverson 2000]. Significant change in MCA diameter is unlikely, however, during thigh cuff application and release [Newell 1994], Valsalva manoeuvre [Tiecks 1996], LBNP [Serrador 2000] or supine rest. Profound hypotension during pre-syncope, however, could potentially cause MCA myogenic vasodilatation and influence CBFV and as MCA diameter was not directly measured during these studies, caution must be exercised when interpreting the results.

One of the major limiting factors of this work is the indirect measure of MCA pressure during HUT in Chapters 5 and 6. Although arterial pressure waveforms

change with HUT, non-invasive plethysmography correlates very well with intra-arterial pressure recordings during HUT [Petersen 1995]. A direct measurement of MCA pressure is impossible without very invasive procedures which would, in themselves, affect the interpretation of such work. Intracranial pressure changes after HUT are likely to be relatively small [Drummond 2000] and similar in syncopal and non-syncopal subjects alike, and changes in venous pressure will occur to an equal and proportionate degree as arterial pressure. In the absence of better, non-invasive alternatives, therefore, calculations using non-invasive plethysmography provide reasonable estimates of MCA pressure during HUT.

Transcutaneous CO_2 measurements correlate highly with arterial CO_2 levels but rely on gas diffusion and, therefore, have poor dynamic response characteristics (section 2.3.2.). In addition, doubts exist about the accuracy of transcutaneous and end-tidal CO_2 measurements during changes in cardiac output [Steurer 1997]. In the steady state, as in Chapters 3 and 4, these limitations do not present any problems, but difficulties arise due to the temporal delay and cardiac output changes induced by HUT and pre-syncope in Chapters 5 and 6. The transcutaneous CO_2 measurements reported in Chapter 5, however, were taken over stable one-minute periods and are consistent with the findings of others [Cencetti 1997, Anthonisen 1965, Bjurstedt 1962, Yoshizaki 1998], suggesting that they are a fair reflection of arterial CO_2 levels. With reference to transcutaneous and end-tidal CO_2 measurements in Chapter 6, the facts that transcutaneous CO_2 levels continued to decline in syncopal subjects after returning supine, that end-tidal CO_2 levels also declined during pre-syncope and that others have demonstrated hyperventilation during pre-syncope [Lipsitz 1998], suggest that the conclusion that progressive hypocapnia occurs during pre-syncope is correct.

Nevertheless, a repeat of these studies with intra-arterial measures of CO_2 may be useful, though such invasive manoeuvres may present difficulties with the interpretation of HUT results [Kenny 2000, McIntosh 1994].

In Chapters 3 and 4, static and dynamic CA were assessed using spontaneous and induced BP changes that were probably not of a large enough magnitude to exceed the upper and lower BP limits within which CA is active. BP changes were, however, within "normal" physiological limits that one might encounter clinically, but the possibility of a narrowing or a shift of the BP plateau in older normal subjects and patients with recurrent VVS was not addressed. In addition, only two static BP stimuli were employed in Chapter 3 and only one in Chapter 4 resulting in relatively wide confidence intervals and a consequent dilution of conclusions regarding static CA. Further work is, therefore, required to precisely delineate the cerebral autoregulatory curve in older subjects and patients with recurrent VVS.

7.3. Prospects for further studies

The findings of this thesis have important implications for future research into physiological ageing and the pathophysiology of syncope.

Results presented in Chapters 3, 4 and 5 are supportive of the view that CA is normal in older subjects and patients with recurrent VVS. Further work is needed, however, to confirm the findings in relation to static CA and, in addition, static and dynamic CA need to be assessed at extremes of arterial BP to more clearly define the autoregulatory curve of both groups. Because of the findings with regard to dynamic CA in Chapter 3, investigators assessing dynamic CA with similar methods in the future may feel tempted to dispense with controlling for age as a confounding factor,

but this cannot be recommended until the autoregulatory curve of older subjects is more clearly defined.

The discovery of preserved dynamic CA during orthostatic stress until pre-syncope intervenes in normal subjects and patients with recurrent VVS is an important finding. Only one method of assessing dynamic CA was used, however, and the findings require confirmation using other methods of quantifying dynamic CA. In addition, no attempt was made to assess the integrity of static CA during orthostatic stress and this is worthy of future investigation.

The findings in Chapter 6 of progressive hypocapnia during pre-syncope in association with a rise in CrCP and selective impairment of diastolic CBFV raises the possibility that rebreathing may be of benefit in patients with recurrent VVS. Increasing CO_2 levels through rebreathing has the potential to decrease CrCP and to allow better CBF during diastole with the possible result of reducing symptoms and increasing the time to syncope. Rebreathing would be an easy, inexpensive technique with little risk and is worthy of further study in either physiological or clinical trials. The efficacy of current treatments for VVS can be difficult to assess in view of the relapsing and remitting nature of the condition, the fact that any tolerable intervention is unlikely to eliminate all events and symptoms and the variable reproducibility of the HUT test (section 1.1.6.). Much further work is needed to quantify the clinical and physiological responses to pharmacological and non-pharmacological therapies in current usage for patients with recurrent VVS. More information about the effects of such interventions on CA and other cerebrovascular and cardiovascular parameters,

such as baroreceptor sensitivity, may help the development of newer and more consistently beneficial treatments.

As intra-arterial CO_2 measurements are invasive, painful, not without risk [Downs 1973, Bedford 1977], have the potential to affect HUT results [Kenny 2000, McIntosh 1994] and are still difficult on a beat to beat basis, further work is needed to advance non-invasive techniques of assessing CO_2 levels, such as end-tidal and transcutaneous methods. As the effects of CO_2 on cerebral haemodynamics are profound (section 1.2.3.1.), CO_2 measurement is essential in studies designed to explore CBF and an improvement in non-invasive techniques would greatly enhance understanding of the relationship between CO_2 and CBF. More particularly, such an improvement may help answer the question raised in Chapter 6 as to whether there is a causal relationship between progressive hypocapnia and rising CrCP during pre-syncope.

7.4. Conclusion

This work suggests that the high prevalence of VVS in older age groups cannot be explained by 'physiologically' deteriorating CA as no age-related declines in static or dynamic CA were detected. The studies have also identified that abnormalities of dynamic CA exist during pre-syncope induced in normal subjects and patients with recurrent VVS, possibly due to hypocapnia-induced rises in cerebrovascular CrCP, but suggest that CA is otherwise normal in patients with recurrent VVS. As no differences were demonstrated in pre-syncopal cerebrovascular changes between normal subjects and patients at any stage, it is possible that impaired dynamic CA contributes to the pathophysiology of VVS but is unlikely to be the primary problem in patients with recurrent VVS. Further studies are needed, however, to confirm these

findings and to explore the interesting hypothesis that rebreathing may be of benefit in patients with recurrent VVS.

APPENDIX

Publications arising from this thesis

Carey BJ, Eames PJ, Blake MJ, Panerai RB, Potter JF.

Dynamic cerebral autoregulation is unaffected by aging.

Stroke. 2000; 31:2895-2900.

Carey BJ, Manktelow BN, Panerai RB, Potter JF.

Cerebral autoregulatory responses to head-up tilt in normal subjects and patients with recurrent vasovagal syncope.

Circulation. 2001;104:898-902.

Carey BJ, Eames PJ, Panerai RB, Potter JF.

Carbon dioxide, critical closing pressure and cerebral haemodynamics prior to vasovagal syncope in humans.

Clinical Science. 2001;101:351-358.

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