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Analysis and Biophysical Modelling of Baroreflex Stimulation with Applications in Syncope and Falls: A Neural Engineering Approach

By

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Supervised by

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&

Dr. Gerard Boyle

DECLARATION

I declare that this dissertation, except where otherwise stated, is entirely my own work and that it has not been submitted at this or any other university as an exercise for a degree. I agree that the library may lend or copy this thesis upon request.



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A handwritten signature in blue ink, appearing to read "Ciarán Finucane", written over a horizontal line.

Ciarán Finucane

September 2010

Abstract

Carotid Sinus Hypersensitivity (CSH) is an age related disorder, and a common cause of recurrent falls and syncope in the elderly. CSH is prevalent in patients with Dementia and Parkinson's disease and is a strong predictor of poor cognitive function compared to traditional risk factors such as stroke and hypertension. CSH is diagnosed in patients with unexplained falls or syncope, when carotid sinus massage (CSM) is accompanied by asystole greater than 3 seconds (cardioinhibitory subtype - CICS_H) or a fall in systolic blood pressure greater than 50mmHg (vasodepressor subtype - VDC_{SH}), or both (MXCS_H subtype) and no competing diagnosis. When symptomatic i.e. accompanied by loss of consciousness, Carotid Sinus Syndrome (CSS) is diagnosed. CSH is one of a number of so-called Neurocardiovascular instabilities (NCVI's) known to affect the older adult. Other NCVI's include orthostatic hypotension (OH) and vasovagal syncope (VVS). NCVI's are typically characterised by abnormal cardiovascular control leading to intermittent bouts of hypotension and/or bradycardia. The underlying pathophysiology of CSH is not well understood, although a number of hypotheses have been proposed.

The primary motivation of this thesis is to facilitate diagnosis and understanding of the pathophysiology of CSH, by harnessing information contained in non-invasive continuous blood pressure (BP) and electrocardiogram (ECG) recordings. In this case, the problem reduces to identifying the primary parameters that govern the neurocardiovascular control system, which are most likely to be involved in the pathogenesis of CSH. The technical fields of computational modelling, digital signal processing and control systems theory are used as the primary tools to explore this question.

My technical exposition is commenced by introducing the relevant anatomy and physiology relevant to CSH with particular emphasis on CSM, the current clinical choice of diagnosis, and a so-called test of baroreflex sensitivity. Computational models of autonomic control of the cardiovascular system and state of the art methods in measurement of baroreflex sensitivity are also discussed. A new mathematical model of CSM is proposed. Parameter tuning is employed to extend this model. This process allows us to hypothesize possible pathophysiological causes of CSH. A novel mathematical model of CSH is presented which is capable of accurately reproducing pathological blood pressure and heart rate responses to CSM including importantly an AV node component in cardiac control. Model simulations predict the possible existence of a number of distinct subtypes of CSH which have received little attention previously in syncope literature. These include two subtypes of the classical

cardioinhibitory CSH i.e. *chronotropic* and *dromotropic* CICSH and two novel subtypes of vasodepressor CSH i.e. *arterial* and *venous* VDCSH. Furthermore model based analysis also allows us to identify candidate biomarkers of CSH in a systematic fashion. A number of parameters are highlighted as paramount in reproducing a CSH response and include: baroreflex saturation level, baroreflex sensitivity, time constants governing response of venous and arterial limbs and the relative sensitivity of SA node and AV node to vagal stimulation.

Three large experimental studies investigating the pathophysiology of CSH are described invoking the application of non-invasive beat to beat measures of cardiovascular control in CSH diagnosis having been identified earlier as part of initial model analysis.

In the first of these studies the amplitude and frequency of blood pressure oscillations i.e. Mayer Waves are used as surrogate measures of baroreflex control of arterial and venous tone. Mayer wave characteristics were investigated in VDCSH. Blood pressure variability was found to be increased particularly at lower Mayer wave frequencies suggesting possible increases of baroreflex range and dominance of slower mechanisms governing blood pressure control in CSH a finding which would tend to agree with our earlier model predictions. A novel involvement of respiratory mechanisms in CSH was also suggested by the association found between altered Traube-Herring waves and CSH. Secondly we investigated baroreflex control of the SA node in CSH focussing for the first time on *both* the sensitivity and latency of responses found in CSH compared to controls. Sensitivity of the baroreflex was noted as unchanged however increased latency suggests slower dynamics dominate cardiac control of CSH, resulting in possibly slower recovery from large stimuli as encountered in CSM. Finally the thesis investigates the novel concept of baroreflex sensitivity variability as a means to investigate top-down modulation of baroreflex function and the involvement of central pathways in CSH pathophysiology. Interestingly the frequency content of baroreflex variability was found to be altered in CSH compared to control participants, suggesting possible alterations in central top-down modulation of baroreflex control in CSH. The thesis is then drawn to a close with conclusions and recommendations for future avenues of research.

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Nomenclature

ACh – Acetylcholine	D - minimum of maximum frequency shift envelope (k
Alx – Pulse wave augmentation index	DB – Deep breathing
AN region - Merging zone between atria and AV node	DBP – Diastolic blood pressure
ANP - Atrial natriuretic peptide	DBP var – Standard deviation of DBP
ANS – Autonomic Nervous System	DEG/ENaC - Degenerin/Epithelial sodium (Na ⁺) channel
AOO -Area of overlap between Ellipses	DLB –Dementia with Lewy bodies
AP –atrial pressure	DMN - Dorsal motor nucleus of the vagus
AR – Autoregressive	ECG – Electrocardiogram.
AS – Active Stand	Edls - Left-Atrium End Diastolic Elastance
ATP – Adenosine triphosphate	EDV - End Diastolic Volume
AVN – Atrioventricular node	EMG – Electromyogram
AVP – Arginine vasopressin	Epi – Epinephrine
bnst - bed nucleus of the stria terminalis complex	Esla - Left-Atrium End Systolic Elastance
BP – Blood Pressure.	Eslv - Left-Ventricle End Systolic Elastance
BRS – Baroreflex sensitivity	ESV - End Systolic Volume
BRS- - Baroreflex sensitivity - down-going pairs only.	fpi - frequency at which this peak
BRS+ - Baroreflex sensitivity - up-going pairs only.	GABA- γ -aminobutyric acid
CO ₂ - Carbon dioxide	H ⁺ - Hydrogen ion concentrations
Ca - Aortic compliance	HF – High frequency band
Cac - Cerebral Artery compliance	HF _{α} -high frequency α -coefficient
Caf - Finger arteries compliance	HR – Heart rate
Cal - Leg arteries compliance	HR var – Standard deviation of HR
CAN – Central autonomic network	HUT – Head Up Tilt
Cau - Thoracic and Abdominal artery compliance	ICA – Internal carotid artery
CBF - Cerebral blood flow	ICP - Intracranial pressure
CBV - Cerebral blood volume	IML - Intermediolateral column of the spinal cord
CCA - Common carotid artery	IWM - average intensity weighted mean Doppler shift frequency (kHz)
CICSH – Cardioinhibitory Carotid Sinus Hypersensitivity	IWM – Instantaneous intensity weighted mean
CICSH+ - borderline cardioinhibitory CSH	K ⁺ - Potassium ion concentration
CICSH++- definite cardioinhibitory CSH	Ke - Left-Ventricle End Diastolic Elastance curve exponen
CNA - the central nucleus of the amygdale	LF – Low frequency band
CNS – Central nervous system	LF _{α} - low frequency α -coefficient
COF –centre of frequency	LTF - the lateral tegmental field
CPP – Cerebral perfusion pressure	M - average maximum frequency (kHz)
CS – Carotid Sinus	MAF – Instantaneous maximum frequency
CSF - Cerebrospinal fluid	MAP – Mean arterial pressure
CSH – Carotid Sinus Hypersensitivity.	MAP var – Standard deviation of MAP
CSM – Carotid Sinus Massage.	MARC – Model Augmented Research Cycle.
CV – Cardiovascular.	MRI – Magnetic Resonance Imaging
Cv - Vena cava compliance	MSE - Mean squared error (MSE)
Cvc - Cerebral vein compliance	MXCSH – Mixed CSH.
Cvl - Leg vein compliance	N region -Mid-portion
CVLM - Caudal ventrolateral medulla	NA – Nucleus ambiguus
Cvu - Thoracic and Abdominal vein compliance	NANC – Non cholinergic

NCVI – Neurocardiovascular Instability.
NE – Norepinephrine
NH region - Transition zone with AVN and bundle of His
NO - Nitric oxide
NTS - the nucleus of the solitary tract
O2 - Oxygen
OH – Orthostatic Hypotension.
P Cells – Pacemaker Cells
PaCO₂- Arterial PCO₂
PAG - the periaqueductal grey matter
PD – Parkinsons disease
PED – Post excitatory depression
PEEP - Positive end expiratory pressure
PI - Gosling’s pulsatility index RI
Pi - Peak power spectral density
PI var – Standard deviation of PI
PI_{orig} - Gosling’s original Pulsatility index
PNS – Parasympathetic nervous system
Polv - Left-Ventricle End Diastolic Elastance curve scaling constant
PVN - Paraventricular nucleus
RAAS - Renin-Angiotensin-Aldosterone
Rac - Cerebral artery resistance
Racp - Cerebral peripheral resistance
Raf – finger and arm arteries
Rafp – Finger resistance
Ral – Leg arteries
Ralp – Leg resistance
Rau - Arteries serving abdominal organs (Splanchnic and Extrasplanchnic)
Raup - Abdominal Organs (Splanchnic and Extrasplanchnic)
RI - Pourcelot’s resistance index
ROC – Receiver operating curve
RR - ECG RR Interval
Rv –Vena cava
Rvl – Leg veins
RVLM - Rostral ventrolateral medulla
Rvu - Upper body veins
S - maximum of maximum frequency shift envelope (kHz)
SA – Sinoatrial node
SBP – Systolic blood pressure
SBP var – Standard deviation of SBP
SCM – sternocleidomastoid
SIZ - Spike initiation zone of the nerve
SNA – sympathetic nerve activity
SNS – Sympathetic nervous system
SON - Supraoptic nucleus
SSRI – Serotonin Reuptake inhibitors
SV – Stroke Volume
T - Transitional Cells
TPR – Total peripheral resistance
Tsa - Atrial contraction duration
Ts-v - Timing between atrial and ventricular contractions
Tsv - Ventricular contraction duration
US – Ultrasound
VDCSH – Vasodepressor Carotid Sinus Hypersensitivity.
VDCSH+ - borderline vasodepressor CSH
VDCSH++ - definite vasodepressor CSH
VIP – Vasoactive intestinal peptide
VLM - the ventrolateral
VM – Valsalva manoeuvre
VM -ventromedial medulla
Voa – Aortic unstressed volume
Voac - Cerebral Artery unstressed volume
Voaf - Finger arteries unstressed volume
Voal - Leg arteries unstressed volume
Voau - Thoracic and Abdominal unstressed volume
Vov – Vena cava unstressed volume
Vovc – Cerebral unstressed volume
Vovl - Leg veins compliance unstressed volume
Vovu - Thoracic and Abdominal unstressed volume
VVI – Dual chamber pacing
VVS– Vasovagal Syncope.
xBRS – Cross correlation Baroreflex sensitivity

CHAPTER 1

1.1 Introduction

The primary impetus of this thesis is to improve diagnosis and understanding of Carotid Sinus Hypersensitivity, a common cause of syncope and unexplained falls in the older adult. A brief literature review of relevant mathematical modelling and physiological material is presented in this chapter, setting the scene for the current thesis.

CHAPTER 1

1.1 Introduction

Carotid Sinus Hypersensitivity (CSH) is an age related disorder and a common cause of recurrent falls and syncope in the elderly (Humm and Mathias 2006). CSH has also been noted as prevalent in patients with Dementia and Parkinson's disease and is a strong predictor of poor cognitive function when compared to traditional risk factors such as stroke and hypertension (Kenny, Kalaria et al. 2002). CSH is diagnosed in patients with unexplained falls or syncope, when carotid sinus massage (CSM) is accompanied by asystole > 3 seconds (cardioinhibitory subtype - CISH) or a fall in systolic blood pressure > 50 mmHg (vasodepressor subtype - VDCSH), or both (mixed subtype - MXCSH) and no competing diagnosis (Moya, Sutton et al. 2009). When symptomatic i.e. accompanied by loss of consciousness, Carotid Sinus Syndrome (CSS) is diagnosed. CSH is one of a number of so-called Neurocardiovascular instabilities (NCVI's) known to affect the older adult (Kenny, Kalaria et al. 2002). Other NCVI's include orthostatic hypotension (OH) (Cooper and Hainsworth 2001) and vasovagal syncope (VVS) (Tan, Newton et al. 2008; Tan, Newton et al. 2009). NCVI's are typically characterised by abnormal cardiovascular control, leading to intermittent bouts of hypotension and/or bradycardia. The underlying pathophysiology of CSH is not well understood, although a number of hypotheses have been proposed (O'Mahony 1995; Tea, Mansourati et al. 1996).

The primary motivation of this thesis is to facilitate diagnosis and understanding of pathophysiology of CSH, by harnessing information contained in non-invasive continuous blood pressure (BP) and electrocardiogram (ECG) recordings. In this case, the problem reduces to identifying the primary parameters that govern the neurocardiovascular control system, which are most likely to be involved in the pathogenesis of CSH. The technical fields of computational modelling (Crampin, Halstead et al. 2004) and control systems theory (de Paor and Ringwood 2006) are now sufficiently well developed to aid us in exploring these questions and are used as the primary technical tools throughout this thesis. This approach is not dissimilar to that advocated by the emerging systems biology field (Cowley 2004).

A mathematical model is a succinct summary of our current knowledge about the function of a system. Development of a cardiovascular model (CV) has many benefits. Simulated CV systems find applications in diagnostics (Smith, Chase et al. 2004), clinical education (Giannessi, Ursino et al. 2008), therapy selection, refinement, and drug discovery (Banks, Holm et al. 2009). The modelling process also encourages hypothesis generation affording

one the ability to perform thought experiments and test hypotheses at a systems level that would be otherwise unethical or impractical to pursue. This allows refinement of clinical ideas and planning of practical experiments at a fraction of normal time and cost. Furthermore the added understanding this system level approach brings, may lead to prediction of new behaviours and the classification of new clinical entities.

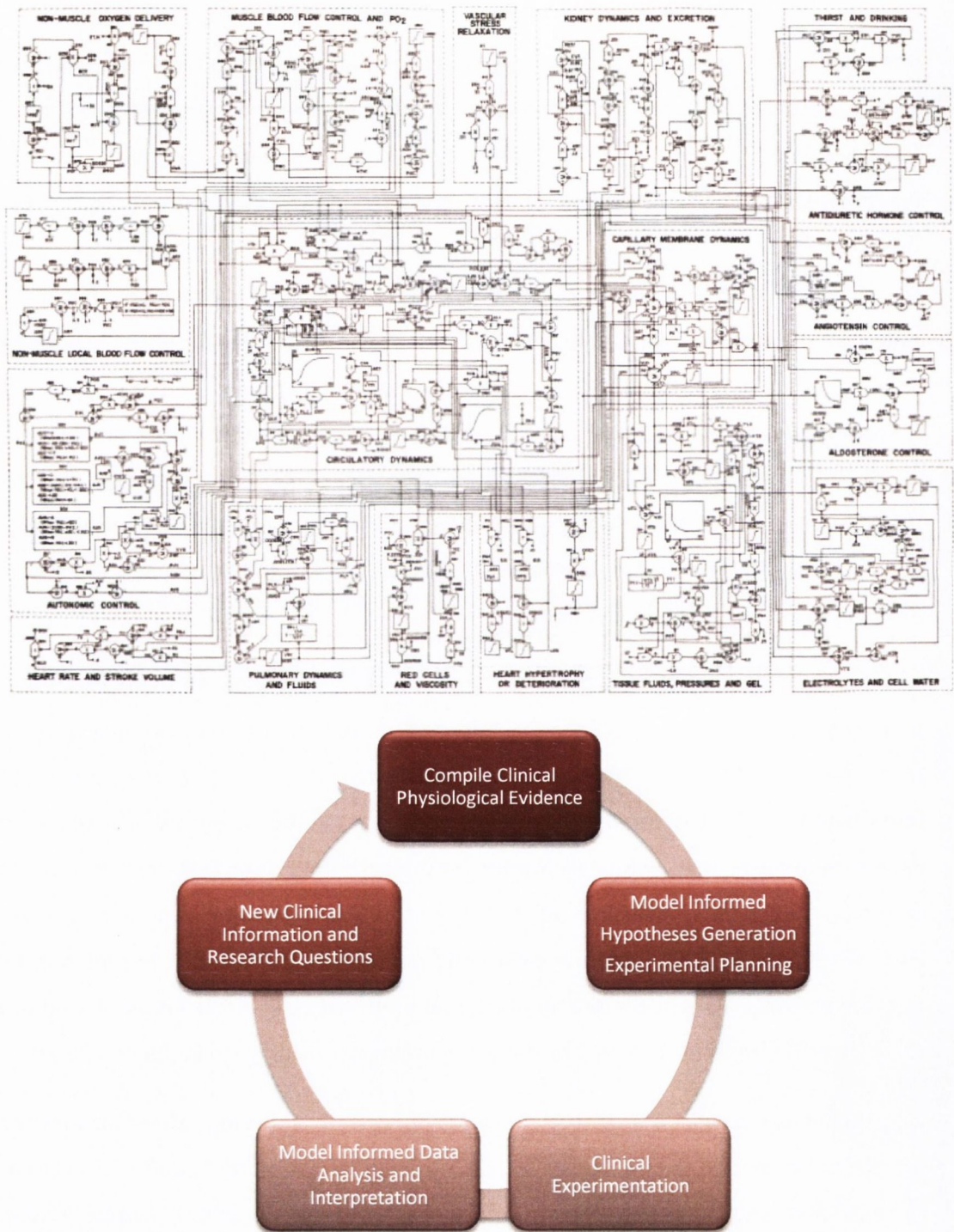


Figure 1.1: The Model Augmented Research Cycle (MARC) (Bottom). Guyton's Comprehensive model of human cardiovascular control system (Top).

An appreciation of the system function in the framework of a mathematical model contributes to the selection of appropriate physiological measurement methods and optimum signal processing and analysis approaches (Mukkamala, Toska et al. 2003). Finally the process of modelling results in the assimilation, management and synopsis of clinically relevant information pertaining to system function, and provides a succinct tool for exploring the relationship between data obtained in large scale studies (Heldt, Shim et al. 2002).

An important point, often forgotten, is the environment in which this process occurs. Models are commonly developed in relative isolation in laboratories far removed from the realities of a clinical setting, with loose collaboration occurring at a distance between clinicians and engineers. Ideally, the modelling process should be a natural extension of the clinical research process, working symbiotically alongside clinical experimentation through an iterative process of modelling-supported hypotheses and clinical testing. A prime example of how successful this process can be is the life's work of Arthur Guyton (Arthur C. Guyton 1996). Being a Physicist, Physiologist and Clinician he appreciated and leveraged this approach to produce some of the most advanced and clinically accepted models of circulatory control to date (Figure 1.1).

As part of this thesis, working as a Medical Physicist and Neural Engineer, the author had the enviable position of working at the front line of clinical research alongside patients and clinicians on a regular basis. This fostered the development of strong working relationships with clinicians and patients, which allowed the germination and iteration of clinically grounded ideas and hypotheses.

Capturing the essence of CSH (and all NCVI's) in a mathematical model requires a biophysical description of an intricate cardiovascular and neuroregulatory system. CSH and all NCVI's require a particular model emphasis on cardiac, vascular and cerebral autoregulatory control. A successful model ought to be capable of accurately simulating cardiovascular responses to typical clinical stimuli used to examine NCVI including carotid sinus massage (CSM) (Wieling, van Lieshout et al. 1993; Moya, Sutton et al. 2009), active standing (AS) (Wieling, van Lieshout et al. 1993), head up tilt-table testing (HUT) (Kenny, O'Shea et al. 2000), deep breathing (DB) and the Valsalva manoeuvre (VM) (Malik 1998). The focus of this thesis will be the short-term (< 5 minutes) CV regulatory mechanisms. Note HUT involves longer periods and so only the initial response to tilting will be accurately examined.

This is a difficult task. Our goal is complicated by the non-linear, tempo spatially multi-scale, and distributed nature of the system. Since the ultimate goal of modelling is to encapsulate the important underlying principles of system function it is neither technically nor scientifically practical to attempt to simulate the complete spectrum of behaviour of the cardiovascular system. The selection of model scale (temporal and spatial) and model structure (lumped or distributed, linear or non-linear) in the modelling task is paramount and specific to the research question at hand. However probably the most powerful tool in the hands of the modeler is the art of judicious simplification. This is even more powerful when informed by an accurate knowledge of relevant physiology.

To this end a brief overview of anatomy and physiology appropriate to CSH is described in section 1.2. Work in the field of modern cardiovascular modelling has been ongoing for some decades, a review of which is given in Section 1.3. However no models to date have explored CSH. This subject forms the basis of Chapters 3 of this thesis.

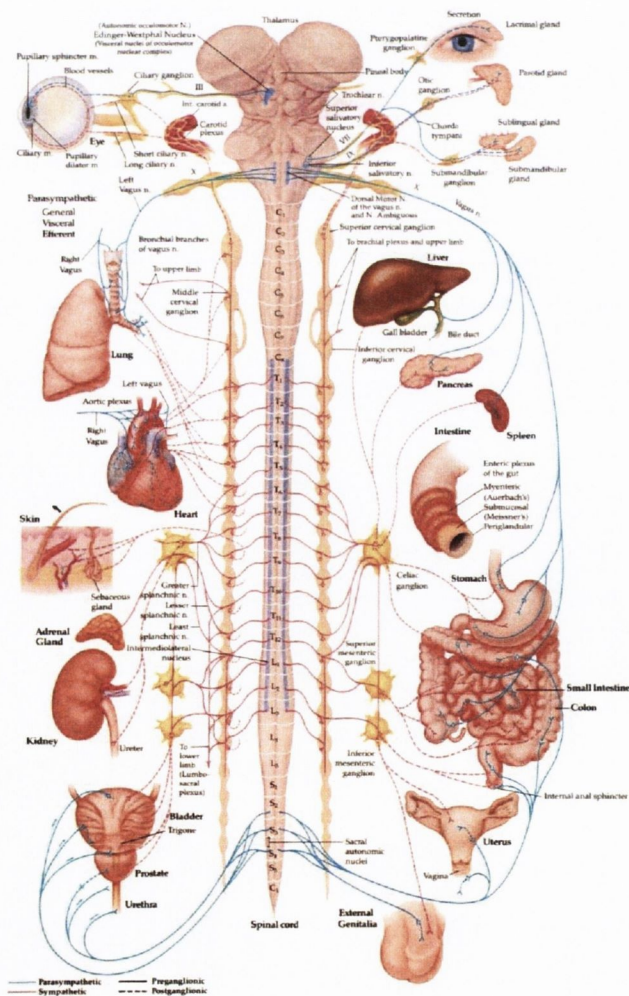


Figure 1.2: Autonomic Nervous System innervation

1.2 Autonomic System Physiology

The autonomic nervous system (ANS) in combination with the endocrine system makes up the neural-hormonal axis which provides central governance of short and long-term cardiovascular control. Local control is also achieved at specific vascular beds via specialised autoregulatory processes e.g. located in the brain and kidney. The ANS consists of a complex network of afferent chemoreceptors and mechanoreceptors which innervate all organs of the body, a central autonomic network (CAN) providing central integration and control of autonomic function and an array of efferent output organs connected to the central nervous system via parasympathetic (PNS)* and sympathetic (SNS) pathways. Together these systems act in synergy to produce involuntary (and voluntary) control of many bodily functions i.e. heart rate and vascular tone control, body temperature, tear and saliva production, gut motility, pupillary and sphincter control (See Figure 1.2) (Bannister and Mathias 1993).

Classical ANS wisdom states that the PNS and SNS reciprocally modulate the activity of a given organ (Low 2008). PNS activity is generally associated with relaxation and/or resting conditions, with SNS activity being responsible for fight or flight responses – i.e. stress responses. Connections found throughout the CAN allow higher level emotional and cognitive brain areas to exert control over the ANS effectors, thus completing the so-called *Mind-Body* axis. Psychological and cognitive phenomena such as dizziness, anxiety, stress and depression are thus all associated with autonomic symptoms and cardiovascular responses (Low 2008).

Neurotransmitters play a crucial role in relaying neural information to other neurons and effector organs and global modulation of neuronal excitability (Ganong 2005). A number of neurotransmitters are important in the ANS. These traditionally include acetylcholine (ACh) and norepinephrine (NE) and epinephrine (Epi).

ACh is released by all preganglionic axons at synapses in ganglia (PNS or cholinergic neurons). ACh is typically released by many PNS postganglionic neurons. Sympathetic postganglionic axons generally release norepinephrine (adrenergic neurons) causing vessel constriction, but sudomotor and muscle vasodilator axons release ACh. Neurotransmitters released by the non-adrenergic, non-cholinergic (NANC) include vasoactive intestinal peptide (VIP), nitric oxide (NO), adenosine triphosphate (ATP) and neuropeptide Y.

* PNS system is often also referred to as the vagal system.

Fast central neurotransmission is typically governed by excitatory amino acids such as glutamate and inhibitory amino acids such as γ -aminobutyric acid (GABA). Other neurotransmitters such as ACh, noradrenaline, other monoamines, and adenosine act to globally modulate neuronal excitability (Ganong 2005).

1.2.1 Autonomic Cardiovascular Control

Short-term reflex cardiovascular control is achieved through the coordination of a subset of autonomic afferent receptors, central nuclei and efferent neural pathways and effector organs. The combined effect is a summation of a number of primary reflex arcs. Arterial baroreceptors located in the carotid and aortic arteries, and cardiopulmonary mechanoreceptors located within the walls of the heart and cardiopulmonary system, all provide primary sensory input to this system. Action potentials from these areas are transmitted via glossopharyngeal, vagal and spinal sympathetic afferent nerve fibres to the brainstem. These fibres synapse in functionally organised areas of the dorsolateral and dorsomedial areas of the nucleus tractus solitarius (NTS) (Low 2008).

The NTS subsequently influences the principal hind brain nuclei governing efferent PNS and ANS activity i.e. cardiac and vasomotor brainstem nuclei. Projections from the NTS connect to preganglionic neurons in the dorsal motor nucleus of the vagus (DMN) and neurons in the nucleus ambiguus (NA) which allows direct parasympathetic slowing of heart rate (Chapleau, Li et al. 2001).

Neurons in the NTS also project to the caudal ventrolateral medulla (CVLM), which sends inhibitory projections to neurons in the rostral ventrolateral medulla (RVLM). RVLM neurons subsequently project to sympathetic preganglionic neurons in the intermediolateral column of the spinal cord (IML). These connections allow vasodilatation and heart rate slowing to be achieved through relatively slow (compared to PNS activity) sympathetic withdrawal via baroreceptor activation (Bannister and Mathias 1993).

Baroreceptor activity also influences vasopressin release from the paraventricular nucleus (PVN) and the supraoptic nucleus (SON) through the NTS-CVLM circuitry, which plays a role in long term volume and blood pressure control together with sympathetic-renal pathways and the renin-angiotensin-aldosterone system (RAAS) (Low 2008).

Through reciprocal bottom-up and top-down connections this arc can be modulated by and can modulate activity in the CAN e.g. cortical and superior positioned sub-cortical nuclei such as the amygdala and hypothalamus (Benarroch 1993). According to Karemaker et al

(Karemaker and Wesseling 2008), absolute sympathetic tone is set by central areas and passes through an NTS gating mechanism which modulates tone reflexively. Figure 1.3 depicts the major elements of short-term cardiovascular control. Note however this is a simplified representation of the architecture of this system.

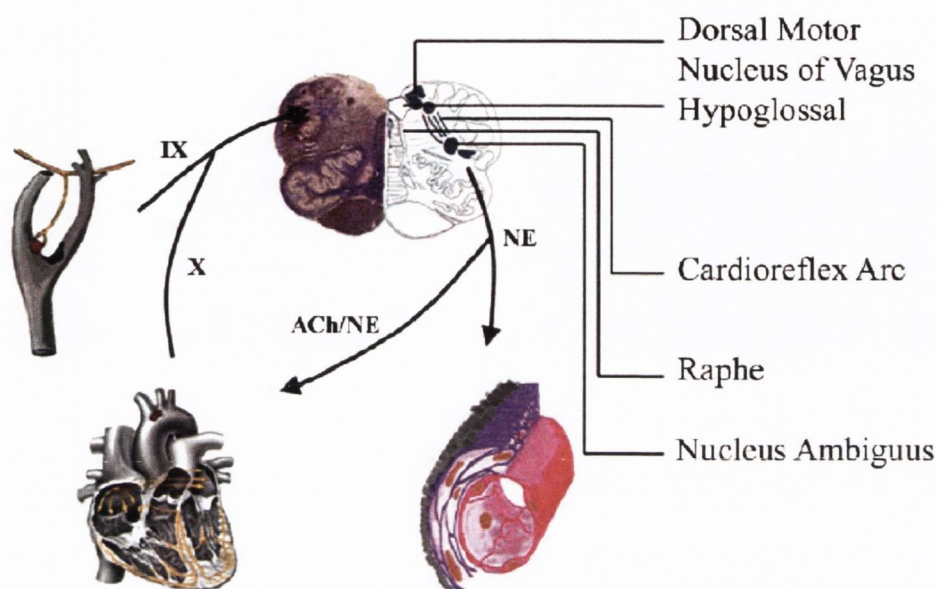


Figure 1.3: Central and peripheral areas of the cardiovascular control system. Carotid sinus and aortic baroreceptor and cardiopulmonary afferents when triggered send nerve impulses via the vagus and glossopharyngeal nerve to medullary brainstem centres, stimulating vagal efferent nerves and vasodilatation. See text for a more detailed description.

In order to simulate the response to CSM and other clinical tests of autonomic cardiovascular control an understanding of the important underlying local and global circuits (i.e. baroreceptors and effector organ control) affected in clinical testing is now detailed.

1.2.1.1 Baroreceptors

Baroreceptors are a collection of non-encapsulated nerve endings positioned in the adventitial layer of arterial walls (Brown 1980). CSM directly stimulates receptors embedded in the wall of the carotid sinus, a dilated, structurally compliant area of the internal carotid artery (ICA) located just superior to the carotid bifurcation. Aortic baroreceptors, situated in the transverse arch of the aorta also play an indirect role in the reflex response to CSM.

Despite their name, baroreceptors are strain not pressure sensitive (Angell James, 1971), responding to vessel wall deformation, via a mechanoelectrical transduction process. Nerve endings are viscoelastically coupled to the arterial walls in which they are embedded. The

exact biochemical mechanisms of transduction are not definitively known (Chapleau, Li et al. 2001).

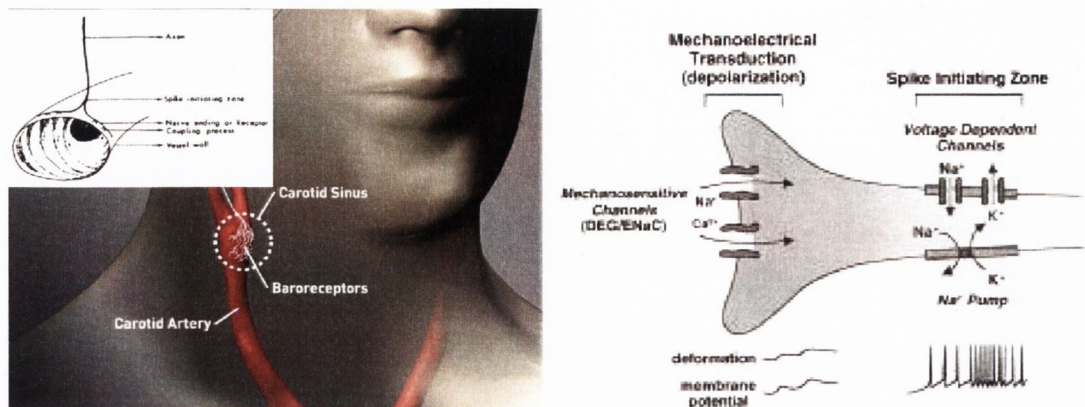


Figure 1.4: Carotid Sinus Baroreceptors embedded in walls of internal carotid artery (Left). Mechanoelectrical transduction process involved in baroreception (Right).

However recent results suggest Degenerin/Epithelial sodium (Na^+) channels (DEG/ENaC) tethered to the vessel connective tissue are gated by membrane tension. Increases in tension increase nerve cell permeability to Na^+ and calcium (Ca^{2+}) ions resulting in nerve cell depolarisation, with a nerve potential linearly related to the magnitude of sensory stimulation (Chapleau, Li et al. 2001). Like all generator potentials, its magnitude decays exponentially with distance from nerve ending.

To transmit information longer distances, generator potentials are frequency modulated (i.e. firing frequency is related to stimulation level) at the spike initiation zone of the nerve (SIZ). Supra-threshold depolarization initiates a rapid spiking cell depolarization event known as an action potential (Chapleau and Abboud 2001). Action potentials are transmitted rapidly over long distance to areas of the CNS along myelinated nerve fibres, and at slower conduction velocities along unmyelinated fibres via an energy driven active transmission process (Arthur C. Guyton 1996).

The baroreceptor sensitivity i.e. the degree to which pressure driven changes in strain are converted to increases in carotid sinus nerve firing frequency is dependent on such factors as vessel wall compliance, visco-elastic coupling characteristics, Na^+ pump activation , potassium (K^+) channel activation, and paracrine and autocrine factors (Prostacyclin, Nitric Oxide, Reactive Oxygen Species, Platelet Factors (Chapleau, Li et al. 2001). These factors are all candidates for local modulation of this mechano-electrical transduction process in health and disease.

Owing largely to the seminal baroreflex studies of Bronk-Stella (Bronk and Stella 1932), Landgren (Landgren 1952), Neil (Neil 1973), Angell-James (Angell-James 1971), Brown (Brown, Saum et al. 1976), Chapleau (Chapleau and Abboud 1987) and Abboud (Abboud and Chapleau 1988) and Eckberg and Sleight (Eckberg 1992) a number of important properties of the baroreceptor steady-state and transient behaviour have been elucidated and are worth mentioning in the context of CSM. The rate of afferent impulses increases with arterial pressure commencing at a *threshold* pressure and reaching a *saturation* rate of 120-140 impulses per second (Figure 1.4).

Receptors also discharge at pressures below this threshold provided the rate of change in pressure is sufficiently high. Angell-James reported widely varying threshold and saturation pressures between different nerve fibres in the rabbit aorta (Figure 1.5). Baroreceptors discharge synchronously with blood pressure pulses (Bronk and Stella 1932), with an initial rapid burst of impulses occurring during upstroke, followed by a gradual decrease of impulse rate and silence during diastole (Figure 1.5).

Step increases in pressure are followed by overshoot and adaptation (decay) to a new steady-state firing frequency (Brown 1980), while step decreases in pressure result in a firing cessation known as post excitatory depression (PED) followed by resumption to new steady-state firing frequency (Figure 1.5). Certain baroreceptors are also known to *reset their threshold and saturation* levels in the face of sustained hypertension and/or hypotension, thus adapting to the prevailing mean arterial pressure (Brown 1980). The mechanisms governing adaptation and resetting are still unknown. Viscoelastic creep, autocrine and paracrine factor modulation of membrane properties and central NTS changes are among the suggested mechanisms (Chapleau, Li et al. 2001).

When endovascular pressure in the sinus is increased, the persistent tonic discharge traversing sympathetic nerves from the stellate ganglion to the heart is diminished. If the increased pressure within the sinus is maintained, complete inhibition continues for some seconds, after which there is escape and return of sympathetic discharge (Lown and Levine 1961). The duration of inhibition and speed of escape are a function of the pressure level. Inhibition is also bilateral. When the carotid sinus is suddenly distended vagal activity accounts for the initial slowing, however decreased sympathetic activity which emerges more gradually becomes the major restraining influence with continued stimulation (Lown and Levine 1961).

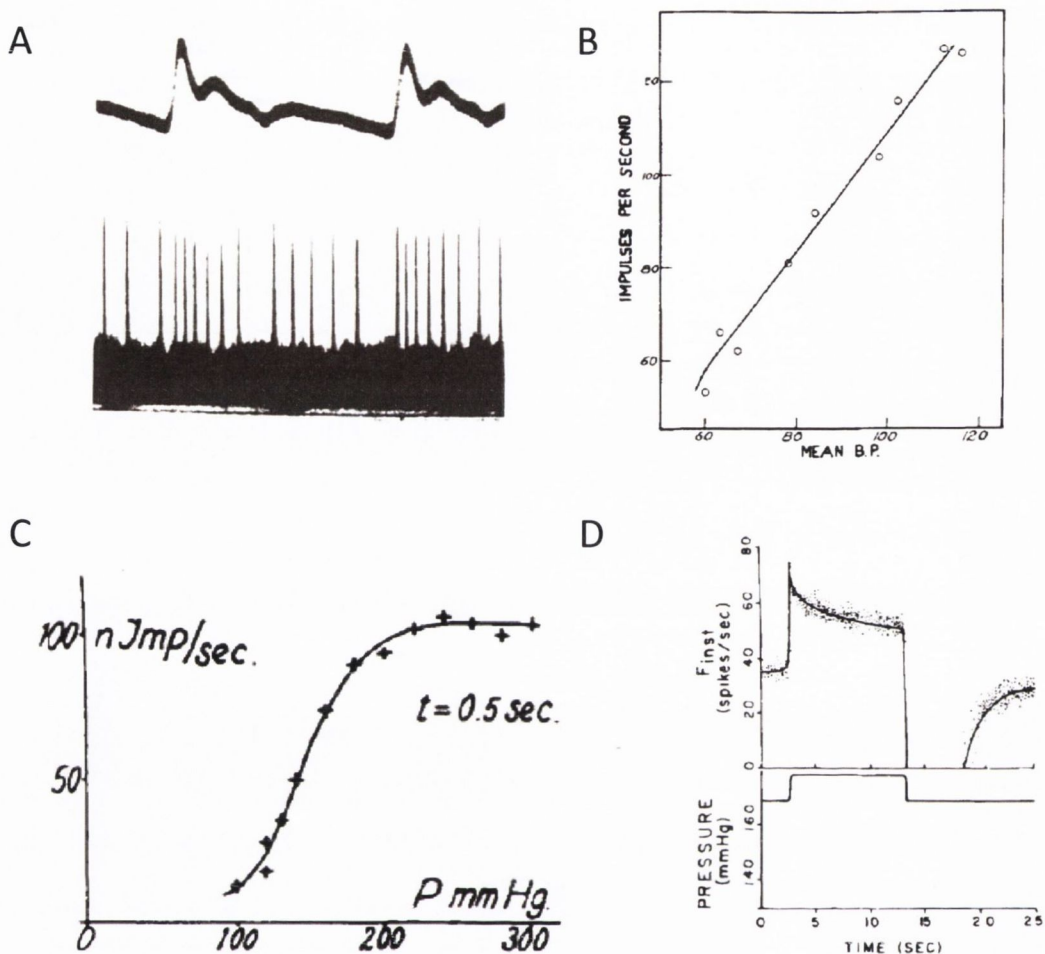


Figure 1.5: Baroreceptor properties. A) During systole increases in pressure correspond to pulsatile increases in baroreceptor single nerve firing frequency and a period of silence during diastole B) The relationship between firing frequency and mean BP is linear in the range 80 to 120mmHg C) Single nerve fibres demonstrate threshold and saturation behaviour D) Responses to step increases in BP demonstrate overshoot followed by adaptation while a step decrease in pressure results in post excitatory depression, followed by return to steady state firing frequency.

Not all myelinated fibres are the same. Baroreceptor subtypes include large myelinated 'A' fibres which typically operate at a lower threshold pressure (30-90mmHg), and fire in synchrony with each arterial pulse. Narrower unmyelinated 'C' fibres are activated at higher pressures of 70-140mmHg (Brown 1980). In a similar fashion, fibre saturation pressures differ widely. Of note some unmyelinated fibres are only activated at physiologically high pressures and show irregular firing patterns, presumably functioning as a pressure driven

safety valve (Brown 1980). These were noted as having extremely high vagal responses. Eckberg and Sleight also noted that some 'C' fibres directly innervate vagal efferents, bypassing central NTS nerve processing and central modulation (Eckberg 1992). Ultimately afferent nerves carry a combination of fibre types, with 'A' fibres contributing to normal baroreflex activity, and 'C' fibres progressively recruited at higher pressures. The relative contribution in hypertension of 'A' and 'C' fibres tend to equalise (Angell-James and George 1980).

Frequency responses of myelinated fibres have a band-pass filter characteristic with a resonant peak at frequencies corresponding to the heart rate, followed by a progressive drop off of gain at high frequencies, while unmyelinated fibres have a low-pass characteristic with relatively low 3dB corner frequency (Figure 1.6).

For a detailed overview of baroreflex function properties the interested reader is referred to the excellent monograph by Eckberg and Sleight (Eckberg 1992).

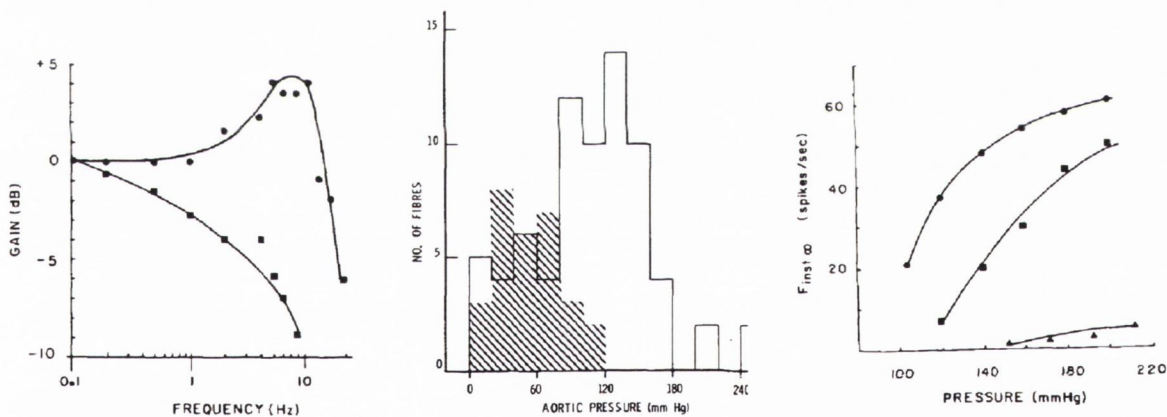


Figure 1.6: (Left) Frequency response of myelinated (circle) and unmyelinated fibres (square). (Centre) Distribution of single fibre thresholds in normal (shaded) and hypertensive rats (unshaded) Pressure stimulus response of myelinated (circle), common unmyelinated (square) and irregularly firing unmyelinated fibres (triangle)

1.2.1.2 Baroreflex

The circuitry of the baroreflex has been studied extensively (Dampney 1994; Spyer 1994) and has been alluded to already. Baroreceptor stimulated NTS neurons initiate a feedback loop that ultimately results in excitation of cardiovagal neurons in the NA and inhibition of sympathoexcitatory neurons in the RVLM. Sympathoinhibitory information from

barosensitive NTS neurons is relayed through propriospinal neurons in the CVLM, which in turn inhibit sympatho-excitatory neurons of the RVLM. Cardiovagal activation involves direct excitation of NA neurons by the NTS input. Barosensitive NTS neurons also give rise to an ascending projection that leads to local GABAergic inhibition of AVP-secreting magnocellular neurons of the hypothalamus which leads to decreased water retention and decreased blood pressure.

The combined effect of all baroreceptor activity from right/left carotid arteries and the aortic arch gives rise to the baroreflex, probably the most important short-term regulator of blood pressure. Rises in arterial pressure cause increased afferent activity, travelling through glossopharyngeal and vagal nerves. Efferent effects include decreased heart rate due to vagal activation and sympathetic withdrawal, and peripheral vasodilatation of resistance and capacitance vessels. Acute BP drops result in tachycardia and vasoconstriction of vascular beds. The Renin-Angiotensin-Aldosterone (RAAS) system is also activated bringing about a slow rise in intravascular volume (Low 2008).

The integrated baroreflex response is a summation of the activity of all recruited single-fibre activity and is essentially a mass action response. Thus the macroscopic (i.e. multifibre) steady-state relationship between carotid blood pressure changes and heart and/or vascular tone does not demonstrate an abrupt threshold and saturation. Instead a more continuous classical sigmoidal relationship (Figure 1.7) due to quasi-continuous recruitment of single nerve fibres with different thresholds over the pressure range of interest arises.

Furthermore according to Hainsworth (Hainsworth and Al-Shamma 1988), activation from separate baroreflex sites (e.g. left/right CS and aortic baroreceptors) results in simple addition of the separate macroscopic stimulus-response curves. As noted, resetting is thought to occur but recent evidence indicates that not all receptors reset their activity and thus contain information regarding the prevailing blood pressure. On the basis of this evidence it is likely that some baroreceptors are responsible for buffering short-term fluctuations in BP while others play a role in long-term regulation. This area is currently a hot-topic for debate (Rose 2007).

The response latency of the baroreflex is 0.75 seconds for heart rate changes, while sympathetic effects on the heart occur more slowly (after circa. 2 seconds). Maximal vascular changes on the arterial side occur in the order of 3-5 seconds while venous changes can take up to 30 seconds to respond. It is also known to modulate sympathetic nerves to

the atrioventricular node (AVN) and the myocardium, controlling the conductivity and contractility of the heart.

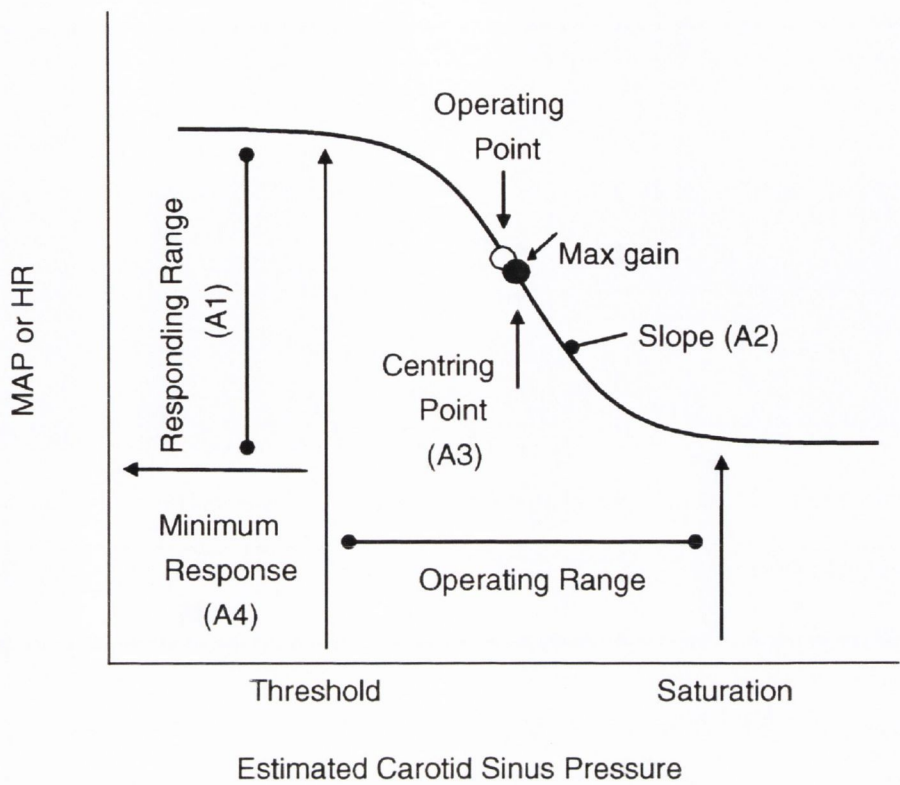


Figure 1.7: Classical baroreflex curve, resulting from a summation of activity of all single-fibres

1.2.1.3 Cardiopulmonary Receptors, Bezold-Jarisch and Bainbridge Reflexes

In a manner akin to high pressure arterial baroreceptors, the cardiopulmonary afferents allow reflex adjustments to be made from the low pressure cardiopulmonary side of the circulatory system. They play a role in long term neuro-humoral control of cardiovascular function and fluid-electrolyte balance. Cardiopulmonary circuitry is also implicated in short-term cardiovascular regulation (Low 2008).

Receptors are sited at the atrio-caval junction, the atria and ventricular walls of the heart, the coronary vessels and in pulmonary vasculature, with afferent fibres travelling as part of vagal afferents with synapses in medullary vasomotor brainstem regions. Typical cardiopulmonary responses are similar to baroreflex responses i.e. decrease sympathetic outflow and increase vagal activity thus modulating vessel capacitance, resistance and cardiac output.

However specific receptors such as 'atrial volume' receptors give rise to tachycardia only through the Bainbridge reflex (Malik 1998). Chemo sensitive cells in ventricular walls result in profound bradycardia and vasodilatation through the Bezold-Jarish reflex and may be elicited by noxious chemicals entering the heart through the coronary circulation (Malik 1998). Cardiopulmonary activation also allows fluid-electrolyte balance modulation through alterations in vasopressin and atrial natriuretic peptide (ANP) release.

1.3 Cardiac Control

Oxygen and essential nutrients are transported by the blood throughout the body, driven by the rhythmically pumping heart. Mechanical pumping is precisely co-ordinated by waves of electrical activity originating in the sinoatrial (SA) node, a portion of tissue (8mm long, 2mm deep) located near the junction of the right atrium with the superior vena cava (Ganong, 2005). The electrical and mechanical events responsible for driving the blood around the circulatory system are now detailed.

1.3.1 Electrical Control

The SA node is normally the most rapid pacemaker. However, the SA node is actually the integrated activity of pacemaker cells (P) in a compact region of the right atrium. These several thousand cells depolarize and produce action potentials almost synchronously, influencing each other through cell-to-cell entrainment. The location of the primary pacemaker may move among groups of cells within the region of the SA node. It is estimated that only about 1% of the cells in the SA node act as the leading pacemaker. Perinodal cells, sometimes called transitional or (T) cells, transmit the electrical impulse from the SA node to the right atrium. Thus, SA nodal dysfunction can result from abnormalities in impulse generation by the P cells or in conduction across the T cells (Arnsdorf 2009). SA node cells exhibit self-sustained oscillations in transmembrane potential. Currents flowing in across the cardiac muscle cells give rise to a wave of depolarisation spreading throughout a specialised conduction network of cells, travelling at approximately 0.8ms^{-1} . About 0.04 seconds after it has left the SA node, the wave enters very thin fibres of the atrio-ventricular node (AVN), where the conduction velocity drops to 0.02 to 0.05ms^{-1} (Guyton and Hall 1996)

The AVN consists of three subsections: the AN region (merging zone between atria and AV node), the N region (mid-portion) and the NH region (transition zone where fibres merge with the bundle of His) (See Figure 1.8). The AVN serves to impose a delay of about 0.1 seconds between contraction of the atria and the beginning of ventricular repolarisation and hence contraction which allows sufficient time for priming of ventricular pumps. At about

0.12 seconds the wave has penetrated the left AVN, travelling through the bundle of His (at 1.5ms^{-1}) and finally out over fast pathways of the Purkinje fibres, and then throughout the whole ventricular mass within 0.2 seconds (Guyton and Hall 1996).

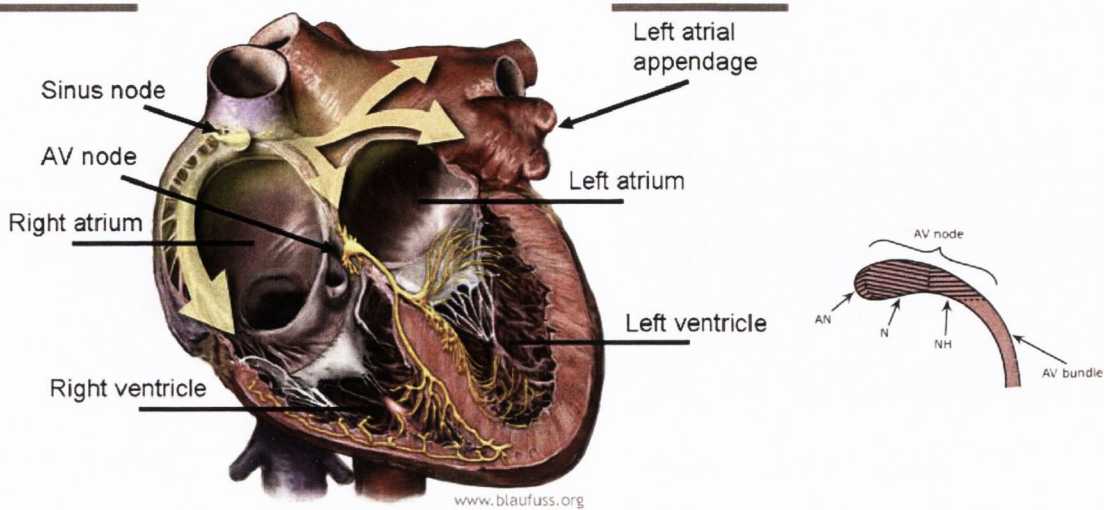


Figure 1.8: Basic conduction pathways of the heart. Inset: AVN. Waves of depolarisation normally originating at the SA node, travel across the walls of the atria, converging at the AV node. Following a brief delay, the wave of depolarisation travels down through bundle of His, into the Purkinje fibres, and subsequently spreads throughout the walls of the ventricular myocardium

As mentioned the SA node oscillates in isolation intrinsically at approximately 60 beats per minute (bpm). Under normal resting conditions the SA node is the dominant pacemaker, however AVN or Purkinje fibres are capable of assuming the dominant pacemaker role should the SA node rate drop below the rate of the others due to some external influence. Owing to tonic parasympathetic modulation of SA node activity, a resting heart rate of 70 bpm results, with the AVN and Purkinje fibres beating at rates of 50 bpm and 30 bpm respectively.

SA node pacemaker activity arises due to a transmembrane leakage current which causes a progressive depolarisation in cell membrane potential. This in turn generates an action potential and a rapid cell repolarisation once a cell-specific threshold is reached. This process continues to repeat itself in a periodic manner (Ganong 2005) (See Figure 1.9).

Autonomic control of the SA node and other pacemaker cells is governed by three basic mechanisms including threshold potential variations, altered slope of diastolic depolarisation, and changing diastolic resting potential (Ganong 2005) (See Figure 8).

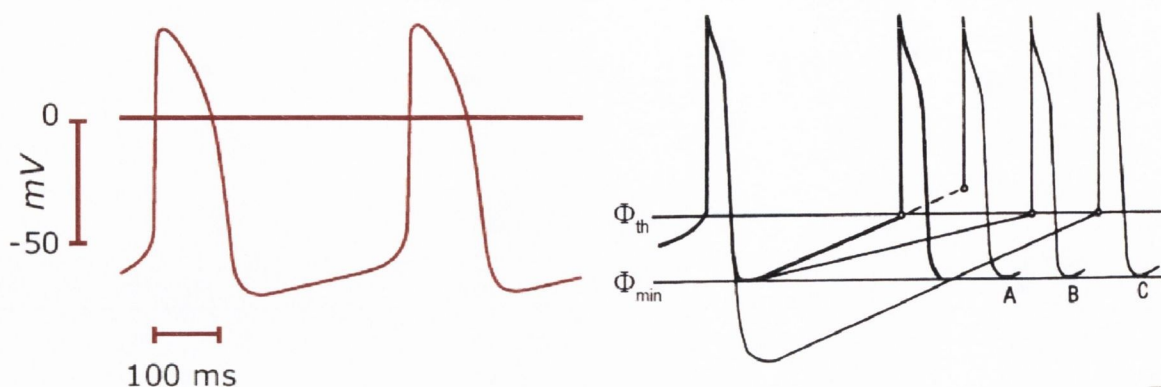


Figure 1.9: SA node spontaneous depolarisation (left). Influence of parasympathetic activation on SA node control of depolarisation through slope and recovery alterations (right)

1.3.2. Electro-Mechanical Coupling

The synchronisation of mechanical and electrical events is driven according to the following event sequence. A wave of cardiac depolarisation triggers calcium outflow from the muscle cell sarcoplasmic reticulum. Calcium influx initiates muscle fibre shortening and active muscle contraction through a well-described cross-bridge filament mechanism. The force produced by this mechanism is a parabolic function of the degree of overlap between thick and thin filaments (actin and myosin) and hence muscle length. Termination of contraction and muscle relaxation occurs through removal of calcium via an active ion channel pump (Ganong 2005).

1.3.2.1 Cardiac Cycle

At a macroscopic level the heart operates in the intact circulation as a dual mechanical pump with a periodic time evolution. The pump preload is determined by the atrial pressures and its afterload is determined by aortic and pulmonary artery pressures (Guyton and Hall 1996). The complete cardiac cycle of pressures and volumes is summarised in Figure 9.

During diastole, the ventricle fills to 120-150ml (End Diastolic Volume (EDV) along the diastolic curve (the passive pressure-volume characteristic of the heart muscle), with the end diastolic pressure equivalent to the preload (Point 1 Figure 9). Systole i.e. isovolumetric contraction of the ventricle is triggered by a ventricle depolarisation wave, increasing internal cardiac pressure rapidly. Once intraventricular pressure exceeds external aortic pressure i.e. the afterload, the aortic valve opens and ejection of stroke volume occurs

(Point 2 Figure 9). The maximum pressure reached during contraction is known as the systolic blood pressure (SBP) (Point 3 Figure 9). At the end of contraction and ejection the End Systolic Volume (ESV) is reduced to approximately 50ml, on the systolic pressure volume curve (Point 4 Figure 9). Subsequently isovolumetric relaxation occurs, allowing pressure within the ventricle to fall, driving chamber refilling (Point 5 Figure 9). In steady-state the amount of blood entering is also the amount of blood ejected during systole (stroke volume (SV) = EDV-ESV). This occurs as a direct consequence of Starling's law which states "the energy of contraction is a function of the length of the muscle fibre" i.e. the more blood entering the heart the harder the heart contracts to expel this volume (Starling and Visscher 1927).

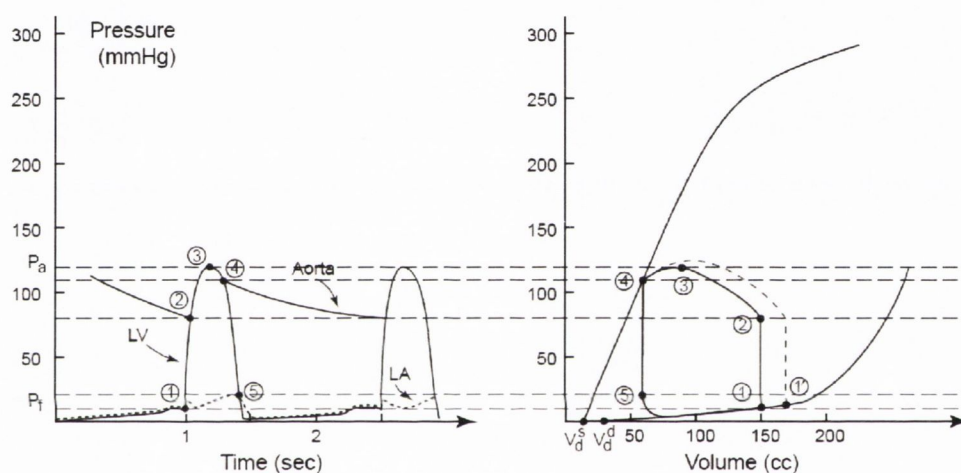


Figure 1.10: Modified Wiggers Diagram (Wiggers, 1951). Time course of pressures in the aorta, left ventricle and left atrium throughout a single cardiac cycle (left). P-V characteristic of the left ventricle, with superimposed end diastolic and end systolic curves (right).

The mechanical performance of the heart can be conveniently summarised through use of the cardiac Pressure-Volume (P-V) characteristic (Figure 9). The amount of work done by the heart can be calculated by the enclosed area of the P-V loop. Cardiac output heart related changes tend to be attributed to externally driven changes in heart contractility by increasing the slope of end-systolic function curve through sympathetic stimulation. Other important determinants of cardiac output include: heart rate, mean systemic pressure, blood volume, venous capacitance, venous unstressed filling volume, intrathoracic pressure, right ventricular diastolic capacitance, arterial resistance, arterial capacitance, and venous resistance.

1.4 Cerebral Autoregulation

Blood flows to the brain mainly through the internal carotid and vertebral arteries and returns via the jugular veins. The brain consumes about 20% of the total body oxygen (O_2) and glucose consumption when generating adenosine triphosphate (ATP). An understanding of the macro structure of the vessels supplying the brain is an important step in understanding the mechanisms of hypoperfusion experienced in syncope.

Syncope has been defined by the European Society of Cardiology as *“a symptom, defined as a transient, self-limited loss of consciousness, usually leading to falling. The onset of syncope is relatively rapid, and the subsequent recovery is spontaneous, complete, and usually prompt. The underlying mechanism is a transient global cerebral hypoperfusion.”* (Moya, Sutton et al. 2009).

Within the skull the ICA branches into a number of arteries including: the ophthalmic artery supplying the eye and other orbital structures, the posterior communicating artery which joins the posterior cerebral artery, the choroidal artery, the anterior cerebral artery (note each anterior cerebral artery is joined by the anterior communicating artery), which supplies the medial surfaces of the cortex and the “leg area” of the precentral gyrus, and finally the middle cerebral artery supplying the entire lateral surface of the cortex. The vertebral arteries in normal conditions supply blood to medullary areas. Both arteries join to form the basilar artery and divides again at the upper level of the pons to form the two posterior cerebral arteries. The Circle of Willis is an especially important structure connecting all major cerebral arteries together in such a way that blood flow through either internal carotid or vertebral arteries can supply any portion of the brain (Bannister and Mathias 1993) (See Figure 1.11).

In conjunction with global cardiovascular control, blood flow to each capillary bed can be self-regulated locally to meet metabolic demand of specific tissues. This process is known as autoregulation and is the predominant blood flow regulatory mechanism in the brain. It is thought to be governed by two principal mechanisms, the local release of vasoactive substances and a myogenic response (Bannister and Mathias 1993).

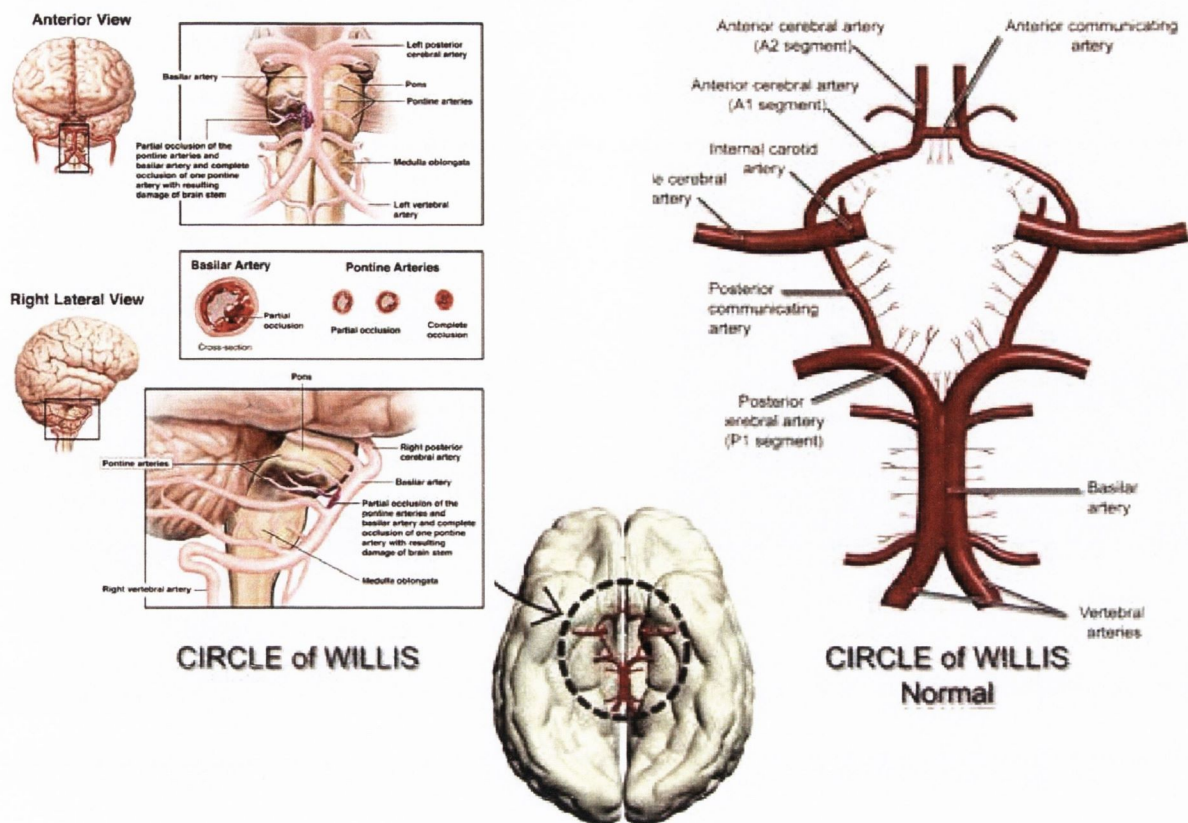


Figure 1.11: Brain blood vessel anatomy, with focus on brainstem areas and the Circle of Willis

Ultimately autoregulation achieves its effects on global blood flow to the brain through positive feedback i.e. by decreasing cerebral vascular resistance when the arterial pressures declines, and raising resistance when the pressure increases. The static pressure-flow curve governing autoregulation is shown in Figure 1.12.

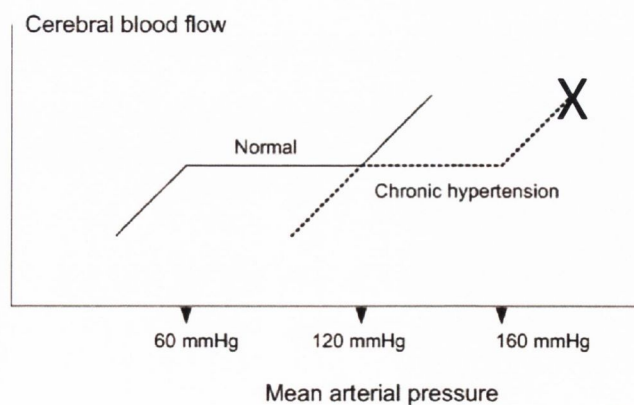


Figure 1.12: Cerebral Autoregulation

Vasoactive factors are released by several cell types e.g. white blood cells, platelets, smooth muscle fibers, macrophages, endothelial cells. These chemicals regulate dilatation of arterioles and relaxation of precapillary sphincters promoting increased/decreased blood flow as the tissue demands (Bannister and Mathias 1993).

Cerebral autoregulation is typically governed by the biochemical mechanism driven by local O_2 , carbon dioxide (CO_2) and hydrogen ion (H^+) concentrations and other metabolic by-products. Arterial PCO_2 ($PaCO_2$) is a strong vasodilator of the cerebral vasculature because it is able to increase cerebral blood flow (CBF) by 100% during severe hypercapnia. Factors released by metabolic processes include K^+ , H^+ , lactic acid, and adenosine (derived from ATP). The vessel endothelium, through a cascade of biochemical pathways releases nitric oxide (NO), a potent vasodilator (Vogel 2008). The walls of systemic vessels dilate in response to increasing CO_2 and H^+ ion concentration and lowering O_2 concentration levels and constrict when the opposite occurs.

In addition smooth muscle in arterial walls exhibits a myogenic response i.e. it contracts more forcefully when it is stretched and relaxes when stretching reduces. If flow decreases, stretching decreases and the vessel dilates producing increased flow (Bannister and Mathias 1993).

Changes in cerebral perfusion pressures also may have a serious impact on intracranial pressure (ICP) via nonlinear relationships. Cerebral circulation occurs within a closed space and so alterations in cerebral blood volume (CBV) can modify ICP. CBF variations also modulate the cerebrospinal fluid (CSF) production rate and ICP through changes in intracranial capillary pressure (Ter Minassian, Dube et al. 2002).

Global cerebral blood flow and hence consciousness is maintained at approximately 50-60ml/100g/per minute (about 15% of cardiac output (CO)), over a wide range of systemic pressures (50-150mmHg). This range is particularly relevant in syncope and probably varies across individuals. During syncope, peripheral and cerebral factors result in 5-10 second interruptions in cerebral blood supply to reticular activating areas of the brainstem (at pressures <80-90mmHg) resulting in symptoms of hypoxia such as dizziness, confusion and loss of consciousness.

In syncope the limits of cerebral autoregulation are often reduced with ageing, with pathophysiological changes impairing autoregulatory mechanisms, thereby increasing the risk of transient hypoperfusion. In chronic hypertension, the steady state cerebral pressure-

flow curve is thought to shift to higher pressures, thus cerebral blood flow declines when mean arterial pressure drops below 120mmHg (Reed and Devous 1985).

Autonomic innervation and sensory innervation of the cranium can influence cerebral blood flow and plays a role in headaches, including cluster headaches and migraine. Sympathetic outflow causes 5-10 % reductions in CBF. However during severe hypercapnia, sympathetic stimulation causes a profound decrease in cerebral blood flow. A series-resistance hypothesis between extra- and intra- parenchymal vessels is thought to be responsible for this. Sympathetic activation also causes a shift in the cerebral autoregulation curve, which is especially protective against surges in cerebral perfusion pressure (CPP) (Bannister and Mathias 1993).

Anatomical and stimulation studies of neural pathways within the brain indicate the presence of parasympathetic neurons capable of increasing cerebral blood flow upon stimulation. Under normal physiological conditions their role in blood flow control is questionable. However in situations where cerebral blood flow is reduced parasympathetic control is thought to play a role in counteracting this reduced blood flow. Thus increased cerebral parasympathetic denervation could be of importance in conditions with associated cerebral hypoperfusion (Bannister and Mathias 1993).

1.5 Central Autonomic Nervous System (CAN)

The central neural circuitry controlling arterial blood pressure, heart rate (HR), and renal function are found at all levels of the autonomic neuroaxis. These circuits have a complex neurochemical organization and are highly interconnected. Regions within the CAN integrate central and peripheral commands to maintain a continuous level of activity of cardiovascular effectors; prevent wide variations of BP through compensatory reflexes; and initiate integrated adaptive cardiovascular response to external stimuli or during different behaviours (Benarroch 1993).

As mentioned, communication within the autonomic CNS is governed by fast, point-to-point neurotransmission, which is globally modulated by slower acting amino acids, acetylcholine, monoamines, neuropeptides, purines, NO and steroids.

Neuroanatomical areas involved in autonomic regulation include the insular, anterior cingulate and ventromedial prefrontal cortices, the central nucleus of the amygdala (CNA)/bed nucleus of the stria terminalis complex (bnst), the paraventricular (PVN) and other nuclei of the hypothalamus, the periaqueductal grey matter (PAG), the parabrachial nucleus,

the nucleus of the solitary tract (NTS), the ventrolateral (VLM) and ventromedial medulla and the lateral tegmental field (LTF). As mentioned, the outputs of this circuitry include:

- (1) sympathetic preganglionic neurons (SPNs) of the intermediolateral (IML) cell column
- (2) cardiovagal neurons of the nucleus ambiguus (NA)
- (3) arginine vasopressin (AVP) secreting magnocellular neurons of the hypothalamus

The insular cortex is the primary viscerosensory cortex and receives inputs from taste and general visceral afferents. The prefrontal and anterior cingulate form the 'premotor' autonomic nuclei, while the CNA/bnst complex integrates emotional responses. The PAG is a site of integration of autonomic, behavioural and antinocioceptive responses. The NTS is the first relay station for visceral afferent information and is particularly important in central baroreflex control.

The RVLM sends taste inputs to the hypothalamus, intermediate regions receive topographically organized general visceral afferents and mediates a variety of medullary reflexes, while the caudal region is a site of convergence of viscerosensory inputs and relay of visceral information to the forebrain. The RVLM contains neurons that project to the IML cell column and tonically activate the sympathetic preganglionic neurons (SPNs) controlling cardiovascular effectors. RVLM neurons mediate reflex and behavioural responses controlling sympathetic activity including responses to hypoxia. On the other hand, the CVLM is a site of integration of medullary depressor reflexes. Both the rostral and caudal VLM relay viscerosensory information to the hypothalamus. The ventromedial medulla, including the caudal raphe nuclei, provides direct inputs to preganglionic sympathetic neurones (Low, 2008).

1.5.1 Rostro-Ventrolateral Medulla

Sympathoexcitatory neurons of the RVLM play a critical role in control of vascular tone and sympathetic activation of heart rate. RVLM neurons receive excitatory and inhibitory input from a number of areas (Low 2008).

Inhibitory inputs arise from the NTS, RN, CVL, while excitatory influences originate in the CeNa, PVN, PAG, CRG and the dorsal horn. RVLM neurons are directly excited by hypoxia and hypercapnia. Recently it has been suggested that RVLM neurons also act as pacemaker neurons helping to maintain tone. As noted they receive excitatory input from arterial chemoreceptors varying responses to vagal afferents. Often a respiratory synchronized

discharge is detected with excitation occurring during inspiration, suggesting evidence of a pulmonary stretch receptor. Areas involved in behavioural responses that are also involved in CV regulation produce profound changes in RVLM neural output (Bannister and Mathias 1993).

1.5.2 Nucleus Tractus Solitarius

It is well known that several groups of peripheral receptors contribute to reflex control of circulation including baroreceptors, chemoreceptors, intracardiac and respiratory receptors. The primary site of initial afferent integration is the NTS. Destruction of the NTS leads to fulminating hypertension with concomitant pulmonary oedema, and chronic hypertension (Seagard, Dean et al. 2001). Silva-Carvalho (Silva-Carvalho, Paton et al. 1998) note that many NTS neurons excited by baroreceptors are inhibited by chemoreceptor inputs. Ascending outputs also may play a role in these responses.

Local GABAergic mechanisms tonically inhibit NTS, CVLM, and NA neurons. Activation of local GABA receptors inhibits barosensitive neurons and results in an increase of arterial pressure and heart rate (Low 2008). Defence areas during a stress response are thought to modulate such pathways. Baroreceptor responses are facilitated in the NTS by afferent released NO, and potentiated by circulating noradrenaline, neuropeptide Y and inhibited by vasopressin. Serotonin and adenosine may excite or inhibit these neurons.

1.5.3 Nucleus Ambiguus

Vagal cardioinhibitory neurons have been shown to be located in a ventrolateral subdivision of the NA, with the ultimate effect of stimulation being bradycardia. The NA receives inputs from at least 13 different areas of the CNS including: the bed nucleus of the stria terminalis; the substantia innominate; the central nucleus of the amygdale; the paraventricular hypothalamic nucleus; the dorsomedial hypothalamic nucleus; the lateral hypothalamic area; the zone incerta; the posterior hypothalamus; the mesencephalic central grey; the mesencephalic reticular formation; the parabrachial nucleus, including the Kolliker-Fuse nucleus; the nucleus of the tractus solitarius; medullary reticular formation.

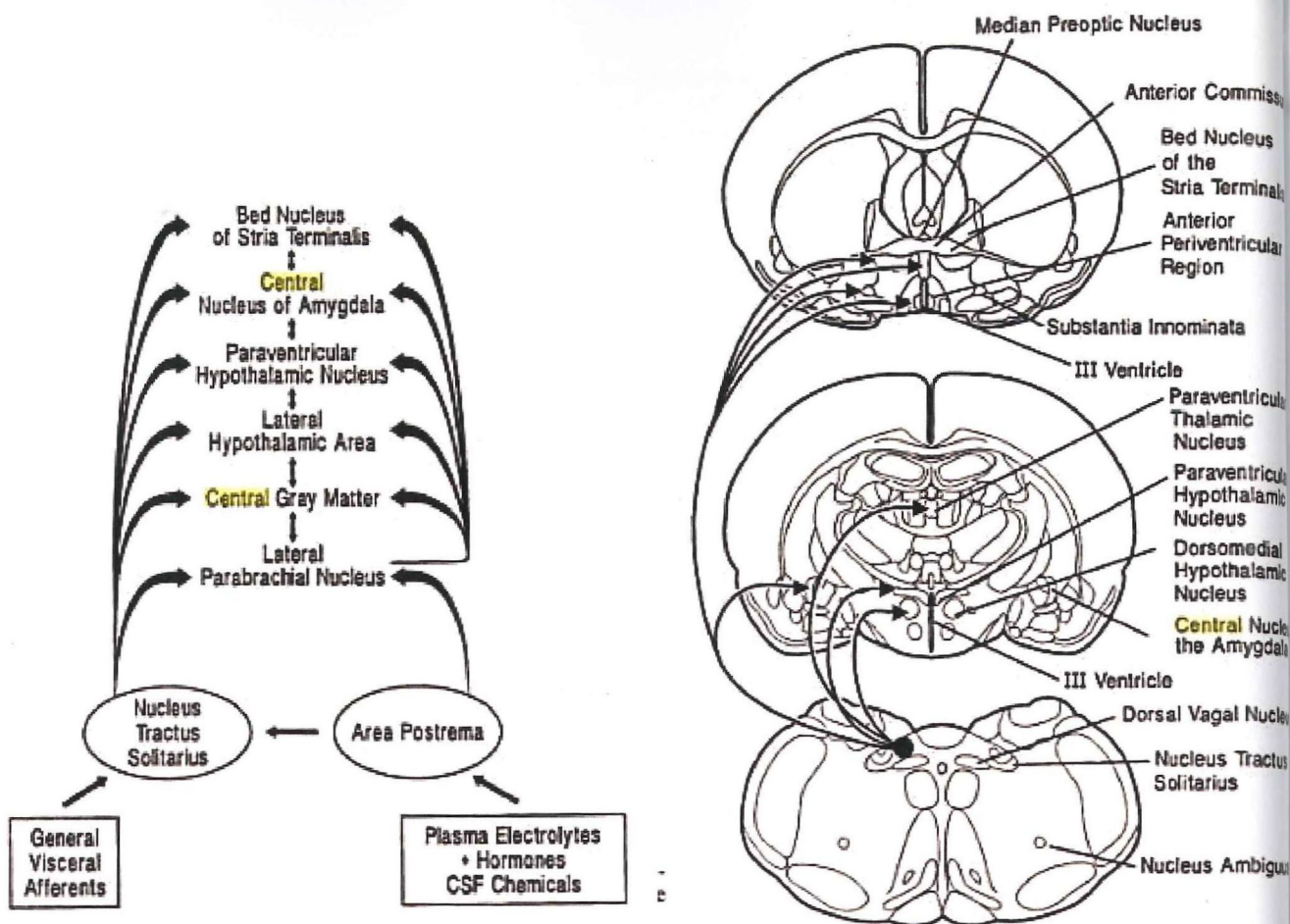


Figure 1.13: Central Autonomic Nervous System.

1.6 Carotid Sinus Hypersensitivity

As mentioned CSH is an age-related autonomic disorder characterized by exaggerated cardiac slowing (CICSH) and/or profound drops in blood pressure (VDCSH) following unilateral carotid sinus massage (McIntosh, Lawson et al. 1993). First described by Roskam in 1930 (Roskam 1930), CSH is now a well-established modifiable risk factor for syncope and unexplained falls in the elderly (Kenny, Richardson et al. 2001), responsible for symptoms in up to 30% of older patients (McIntosh, Lawson et al. 1993).

CSH is defined as asystole of greater than 3.0 seconds (CI subtype), vasodepression of greater than 50mmHg (VDCSH subtype) or a combination of the two (MXCSH subtype) in response to 5-10 seconds of longitudinal Carotid Sinus Massage (Brignole, Alboni et al. 2004). When CSH is accompanied by symptom reproduction, Carotid Sinus Syndrome (CSS) is diagnosed (Moya, Sutton et al. 2009).

Cardiac pacing reduces symptoms in those with CICSS however in VDCSS a successful treatment option remains elusive (Moore, Watts et al. 2005), which is further exacerbated by an incomplete understanding of its pathophysiology (Parry, Baptist et al. 2004).

1.6.1 History of Carotid Sinus Hypersensitivity

The word *carotid* is derived from the Greek word *karos* meaning deep sleep. It is therefore quite likely that early Greek physicians were aware of the effects of carotid massage and/or compression (Lown and Levine 1961). Although not documented, in this author's opinion it is also likely that early practitioners of acupuncture and acupressure also were familiar with the effects of carotid stimulation. Indeed modern acupuncturists are warned to avoid stimulation of neck mechanoreceptors, a practice which has historically resulted in syncope.

Shoja et al (Shoja, Tubbs et al. 2009) identify Ibn Sina (Avicenna) as the first to document Carotid Sinus Hypersensitivity around the 10th Century AD in his famous publication the Canon of Medicine. It was noted that patients who had been subjected to pressure on the carotid artery by hammam (traditional public bath staff) or masseurs, resulted in unconsciousness and falling. Avicenna noted that these drop attacks revealed disturbances of the ascending spirit of the brain. He called this condition "al-Lawa" in Arabic, translated to "Torsion" in English. He noted that patients are generally fatigued, and have excessive yawning, muscle strain and flushing and recommended drinking cold water and consuming the herb Sweet Flag (*Calamus*) or Coriander with sugar as a cure.

In western medicine Parry in 1799 (Parry 1799) made the first medical report of the heart rate slowing response to CSM. Czermak (Czermack 1866) in 1866 found pressure applied to the carotid swelling at the level of the sternocleidomastoid induced temporary bradycardia and ascribed this to mechanical stimulation of the adjoining vagus nerve. Concato (Concato 1870) noted in 1870 that only pressure applied at the bifurcation and not pressure applied to the vagus nerve alone resulted in bradycardia. This result was ignored and this method was known as the "vagus pressure test" of Czermak (Czermack 1866).

It was not until Herings meticulous investigations of the origin of this response in the 1920's did the carotid sinus finally become identified as the location of carotid stretch receptors (Hering 1923). For this work Hering received a Nobel prize. Roskam in 1930 (Roskam 1930) described the first case of carotid sinus hypersensitivity in western records, with Weiss and Baker (Weiss and Baker 1933) following up in 1933 with a series of 15 patients identified with carotid sinus hypersensitivity.

1.6.2 CSH Prevalence

The exact prevalence of CSH is still open to debate. Methodological differences in terms of study design, setting, definitions of CSH used and CSM methodology employed make this difficult (Kerr 2009). Healey et al. (Healey, Connolly et al. 2004) note that approximately 30-

40 individuals per million each year are diagnosed with CSS with CSS accounting for 1-20% of all annual pacemaker implantations per year (Brignole et al., 1990, Sutton 1989). The earliest studies by Weiss and Baker (Weiss and Baker 1933) failed to show a significant amount of responses in 50 healthy individuals, however Nathanson (NATHANSON 1946) studied 115 individuals (mean age 58.9 years, range 30 to 81) with reproducible CSH and noted 33% had symptoms of dizziness, light-headedness or weakness. Heidorn et al. (Heidorn and McNamara 1956) defining CSH as asystole following a 30 second period of CSM found cardioinhibitory responses in 23% of males aged between 25-58 years with only 4 demonstrating prolonged asystole. Franke (Franke 1963) examined over 3500 individuals with no prior history of syncope and found CSH in 8.9% of individuals, particularly in older men and those with hypertension (aged 15-92 years). CSM responses in older persons (aged 62-104 years) recruited from a long-stay geriatric ward were hypersensitive in 2% of 384 people (Mankikar and Clark 1975). The methodology in this study was quite unclear with the definition of CSH unstated and asystole defined via auscultation. In an outpatient clinic setting, Hudson et al. (Hudson, Perrins et al. 1985) examined 333 patients aged over 50 years of which 4% had asystole > 3 seconds to supine CSM. Volkman (Volkman, Schnerch et al. 1990) compared CSM responses of 210 individuals with syncope or dizziness with 163 asymptomatic individuals. It was found that CSH had a prevalence of 20% in asymptomatic individuals and 41% of symptomatic patients. Jeffreys (Jeffreys, Wood et al. 1996) also reported prevalence figures. Their study noted 4.2% of individuals exhibiting a cardioinhibitory response (aged 65-95 years). Since the advent of accurate phasic blood pressure measurements prevalence rates have increased. In a study of 25 healthy individuals McIntosh found 0% of individuals (aged 61-87 years) to have CICSH, with only 12% experiencing a reproducible vasodepressor response in the upright position (McIntosh, Lawson et al. 1994). Davies in a study examining 80 patients (mean age 77 years) attending A&E found 40% prevalence of CSH (Davies, Steen et al. 2001). Kerr in the most comprehensive study of CSH in community dwelling elders examined 340 subjects aged 65 years and over of whom 68 had contraindications (>20%). CSH was found to be present in 39% of 272 individuals (106). Of these 5.6% had CICSH, 39.6% had vasodepressor CSH, and 54.8% had mixed CSH. 29% of individuals had CSH in upright position only (Kerr 2009).

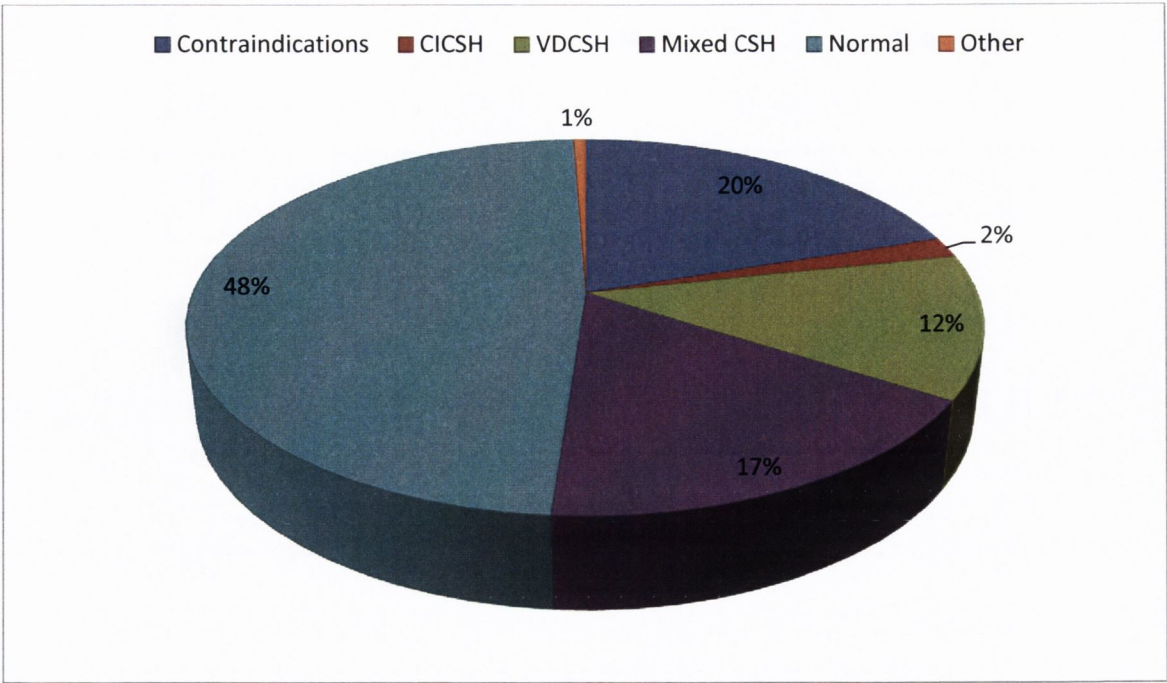


Figure 1.14: Responses to CSM in Community dwelling population according to Kerr (Kerr 2009)

1.6.3 CSH Pathophysiology

A number of hypotheses surrounding the pathophysiology of CSH have been put forward as an explanation since Roskam first described CSH (Roskam 1930). These have examined peripheral (Blanc, L'Heveder et al. 1997) and central levels (Miller, Kenny et al. 2008) of the primary cardiovascular reflex, with central hypotheses currently favoured. Other hypotheses have centred on the role of denervation of sternocleidomastoid muscle afferents as a possible causal factor (Tea, Mansourati et al. 1996).

Original evidence pointed towards peripheral abnormalities in the sinus or afferent limbs as being responsible. Weiss and Baker cited extreme carotid sinus dilatation, and evidence of neck tumours as possible sources of hypersensitivity (Weiss and Baker 1933). Others have noted the role of neck tumours in the pathophysiology of CSH, although these causes of CSH are relatively rare (Muntz and Smith 1983).

Atherosclerosis driven ischemia during massage has also been suggested as an explanation. Much of the early evidence centred around the role of atherosclerosis coupled with coronary artery disease in CSH. The severity of coronary heart disease was observed to increase the abnormality of CSM response by Sigler (Sigler 1965). Smiddy et al (Smiddy, Lewis et al. 1972) found that the abnormal response to CSM was accompanied by an abnormal ECG. Sinus node and AV node disease have also been associated with CSH,

although later studies refute this (Reiffel and Bigger 1983). Tsoufis et al. (Tsoufis, Kallikazaros et al. 2002) noticed arterial stiffening and coronary artery disease were associated with abnormal responses to CSM. Eckberg (Eckberg 1992) referring to earlier work by Brown et al (1980) noted that CSH responses can transiently occur. The incidence of CSH was found by Kallikazaros to increase in proportion to severity of carotid and coronary atherosclerosis (Kallikazaros, Stratos et al. 1997).

The manner by which CSH presents clinically and the evidence provided by research suggest that CSH by its very nature is intermittent and variable (McIntosh, Lawson et al. 1993; Richardson, Bexton et al. 2002) and has been reported to occur across a number of behavioural contexts. CSH and/or CSS commonly present as an unexplained fall, spontaneously occurring during day-to-day activities, with symptoms accompanied in 47% of cases by head movement and 73% of cases by vagal stimuli. The inherent variability in CSM responses would suggest that the autonomic milieu has a role to play. 30% of those with CSH have amnesia for loss of consciousness during CSM (Parry, Steen et al. 2005). Fascinating MRI studies have given recent biomechanical evidence which suggests head turning induces complex ICA wall stresses which could indeed be responsible for baroreflex stimulation in some individuals (Callaghan, Soellinger et al. 2009). Furthermore it may be possible that loss of consciousness may precede or follow cerebral hypoperfusion, and thus may be neurally and/or hypoperfusion driven (Miller 2009). The causes of progression from CSH to symptomatic CSH i.e. CSS are unknown.

Carotid sinus surgical denervation is also considered a possible treatment of CSH (Toorop, Scheltinga et al. 2009). Some authors have suggested that this is of limited benefit (Cheng and Norris 1973; Trout, Brown et al. 1979). Lown and Levine (Lown and Levine 1961) make an insightful suggestion, stating that because CISH and VDCSH can be produced independently, a central lesion of central origin is likely. Furthermore Kenny et al (Kenny, Lyon et al. 1987) have noted a pattern of arginine vasopressin release that is similar to normal individuals in CSH. This response requires an intact afferent limb, and again would suggest a central source of dysfunction. Hilton et al. (Hilton, Moore et al. 2000), using the pulse wave Augmentation Index (AIx) as a measure of central arterial stiffness, found no difference in those with a CSH response to CSM and those who did not. In contrast Tsoufis et al. (Tsoufis, Thomopoulos et al. 2003) in 2003 noted that the cardioinhibitory response to CSM increased with increasing local carotid stiffness in those with hypertension, suggesting this as a precursor state to CSH. This has recently been supported by work from Madden et

al. (2010) who found increased pulse wave velocity (PWV) and stiffness ($11.5 \pm 0.6 \text{ m/s}$ vs. $9.6 \pm 0.4 \text{ m/s}$) and decreased baroreflex sensitivity ($6.73 \pm 0.58 \text{ ms/mmHg}$ vs. $11.0 \pm 0.85 \text{ ms/mmHg}$) in CSH.

Measurement of neurophysiological parameters (brainstem auditory evoked potentials, somatosensory evoked potentials, blink responses, EMG of sternocleidomastoid (SCM), styloglossus and trapezius muscles) revealed an intriguing higher degree of SCM abnormality in CSH (Tea, Mansourati et al. 1996). This team subsequently found this association in CSH with no prior syncopal events. They argue that neurodegenerative disease affecting the sternocleidomastoid involves sensory proprioceptive pathways which modulate information arising from carotid baroreceptors, and that loss of this input augments CSM response. Kerr regards this as an interesting association but not causal (Kerr 2009). However in light of the findings of Iriuchijima (Iriuchijima 1972), who notes early modulation of single baroreceptor responses by simultaneous stimulation of skin and muscle afferents, this association warrants future investigation.

From an end-organ perspective the vast majority of studies have focussed on the cardioinhibitory response. Graded levels of atropine are noted to abolish the response to CSM in CSH (Kenny, McIntosh et al. 1994). No detectable end organ abnormalities in cardiac conducting tissue in CISH i.e. heart rate response to physiological abnormalities, sinus node recovery, His bundle ECG and antegrade AV periodicity (Reiffel and Bigger 1983) are seen in CSH. Sick Sinus syndrome is known to co-exist with CSH, however there is no definite evidence of a causal link (Morley and Sutton 1984). Morley and Sutton also note that sinus arrest and syncope can be stimulated by other afferents and so may not be baroreceptor specific. Volkman (Volkman, Schnerch et al. 1990) performed cardiac electrophysiological studies and CSM to examine their association, but found no significant differences in CSH. Reiffel and Bigger (Reiffel and Bigger 1983) have shown that CSM causes apparent cardiac arrest through sinoatrial exit block and not suppression of sinoatrial automaticity. SA nodal arrest and exit block may be thus due to vagal suppression of conduction across the T and other atrial cells and/or AV node. Recent results by Parry et al. (Parry, Chadwick et al. 2009) have found a 'positive' adenosine stress test, further confirming the role of AV nodal block in CSH.

In VDCSH progress has been hampered by the late development of sensitive continuous non-invasive blood pressure measurement methods. In a number of small studies the pattern of muscle nerve sympathoinhibition (as a surrogate measure of vascular sympathetic

inhibition) during CSM in CSH was noted as profound. BP responses were noted as lagging sympathoinhibition and recovery. This lag most likely accounts for response dynamics of vascular smooth muscle controlling blood vessel vasoconstriction. Whether or not effector dynamics are altered in VDCSH is unknown.

Currently opinion centres around a central medullary hypothesis at the level of the brainstem. Eckberg and Sleight (Eckberg 1992) hypothesized a central neural adaptation mechanism secondary to peripheral baroreceptor deafferentation induced by arterial compliance reduction. This was further elaborated by O'Mahony et al. (O'Mahony 1995) who suggested central upregulation of α_2 adrenoreceptors to be responsible. However in a recent study administration of Yohimbine (an α_2 receptor antagonist) did not attenuate the CSH response to patients with VDCSH (Parry, Baptist et al. 2004), thus casting doubt over the validity of this hypothesis. Polvikoski et al. (Polvikoski, Kalaria et al. 2006), found marked α -synuclein pathology in the stellate ganglia of an elderly lady with CISH, while further neuropathological studies (Miller, Kenny et al. 2008) found a small but significant increase in neurodegenerative hyperphosphorylated Tau proteins specific to brainstem nuclei, which regulate cardiovascular activity.

Attempts to detect a hypersensitive baroreflex response in CSH patients have proved inconclusive in standard tests of baroreflex sensitivity (BRS) other than CSM. Vagal baroreflex gain, as determined by blood pressure and heart rate responses to both the phenylephrine and neck suction methods, suggest baroreflex gain alterations in CSH. However studies have reported conflicting changes. Two studies (Dehn, Morley et al. 1984; Morley, Dehn et al. 1984) note significant increases in baroreflex gain, while later Morillo et al. (Morillo, Camacho et al. 1999) and Cole et al. (Cole, Zuckerman et al. 2001) report a decreased baroreflex gain. Indeed Cole et al (Cole, Zuckerman et al. 2001) suggests that the CSH is due to an "irritable carotid sinus". Differences in stimuli and protocols have been suggested as an explanation to these findings. However little focus has been directed towards the specific differences between CSM and other methods. It would be this authors opinion that a key component to elucidating the CSH response is to understand the details of CSM in depth as it is the most reliable method in provoking a hypersensitive response in man. A systematic comparison to other methods might shed further light on its underlying physiology.

Male gender is associated with CSH with the degree of positivity appearing more pronounced in males (NATHANSON 1946; Volkmann, Schnerch et al. 1990; Jeffreys, Wood et

al. 1996) CSH is also associated with age. Nathanson and others (NATHANSON 1946; Volkmann, Schnerch et al. 1990) found 70% of CSH to be over 50 years and none below 30 years. Puggioni reports 4% below 40 and 11% aged 41-50 (Puggioni, Guiducci et al. 2002). Humm et al. (Humm and Mathias 2006) found CSH to be non-existent in those aged under 50 years. Furthermore coronary artery disease and hypertension and concurrent medications are also implicated.

In one study cerebral autoregulation was also shown to be impaired in CSH (Parry, Steen et al. 2006). Cerebral autoregulatory indices differed significantly between patients with CSH and controls. Systolic, diastolic and middle cerebral arterial blood flow velocities were slower in patients with CSH and the cerebrovascular resistance index was significantly greater in patients with CSH.

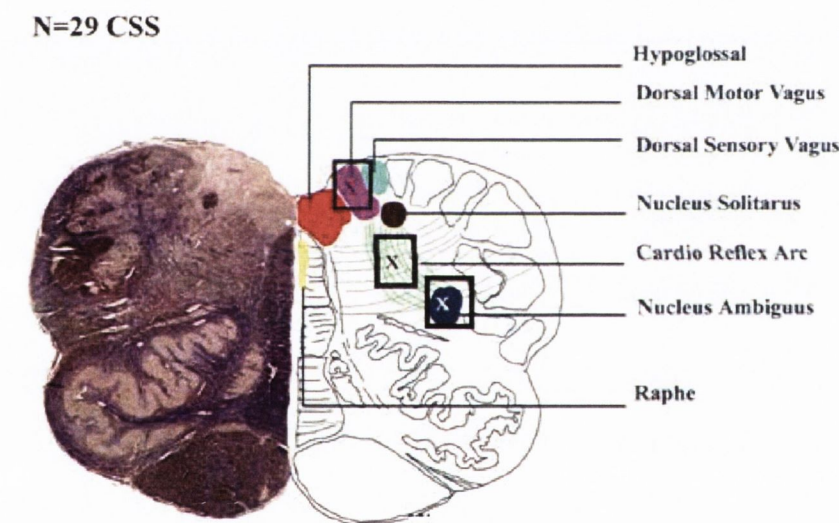


Figure 1.15: Significant increases of Central Tau pathology detected in CSH in the Nucleus Ambiguus, Cardioreflex arc, Dorsal Motor Vagus

1.6.4 CSH Diagnosis

CSH is defined as asystole of greater than 3.0 seconds (CI subtype), vasodepression of greater than 50mmHg (VD subtype) or a combination of the two (MXCSH subtype) in response to 5-10 seconds of longitudinal CSM (O'Shea, Parry et al. 2001). These diagnostic thresholds have been defined arbitrarily, with only one study giving a physiological reasoning for the selection of a 3 second cardioinhibitory cutoff (Heidorn and McNamara 1956). It was reasoned that given that heart rate rarely falls below 30/min, asystole > 2 seconds is likely

pathological. However these thresholds have been agreed and are now incorporated into recent guidelines for syncope and pacemaker implantation (Moya, Sutton et al. 2009). More recently Kerr et al. (Kerr 2009) examined responses to CSM in a large cohort of asymptomatic community dwelling individuals, and defined new CISH (7.083 seconds) and VDCSH (74mmHg) thresholds based on 95th percentile of CSM responses from a subsample of asymptomatic individuals.

Strict standardization of CSM is rare, although standardization of some elements of the method exist i.e. duration (5-10 seconds) (O'Shea, Parry et al. 2001) body position (supine/upright) (Parry, Richardson et al. 2000) and side of sinus (left or right CS)(Morillo, Camacho et al. 1999; Furlan, Diedrich et al. 2003). Right sided supine followed by left sided supine massage is performed since right CSM is more likely to give a positive cardioinhibitory response. It has been hypothesized that the right CS innervates the AV node which may be responsible for this effect (Furlan, Diedrich et al. 2003). If CSM is negative in the supine position, upright CSM is essential with one third of cases missed if supine CSM is performed only (Parry, Richardson et al. 2000). It has been found that BP responses particularly are more pronounced in the erect position. The rationale for this is unclear. One explanation may be that the assumption of upright posture increases baroreflex gain, or provides better exposure of the carotid sinus (Parry, Richardson et al. 2000).

Lack of complete standardization contributes further to the problem of defining reliable diagnostic thresholds, and the paucity of pathophysiological insight surrounding CSH. Reproducibility of responses to CSM is variable. Studies indicate a wide range of reproducibility from 41%-100% (Richardson, Bexton et al. 2002). Technique may contribute to this variability.

Although CSM duration has been defined, it still allows variation to influence the outcome, with some practitioners opting for 5 seconds and others 10 seconds of CSM. Locating the carotid sinus prior to CSM is performed subjectively by anatomical landmarks, with no clear agreement on the optimum technique for this. Carotid sinus anatomy tends to be highly variable especially within elderly individuals (Thomas, Antiga et al. 2005). This greatly influences subject response to baroreflex stimulation, thus a method to accurately locate the carotid sinus is required (Querry, Smith et al. 2001). European standards (Moya, Sutton et al. 2009) explicitly suggest the anterior margin of SCM at the level of the cricoid cartilage as the optimum point, with others (O'Shea, Parry et al. 2001) suggesting the point of maximal pulsation between the angle of the mandible and the cricoid as being optimum.

Anecdotal evidence suggests that biofeedback is often used to further refine the point of massage. If a negative response is found, massage is repeated. Applied pressure and rate of massage (i.e. variation in position and pressure per second) have not been measured nor standardized previously. Owing to the dependence of baroreceptors and subtypes to the degree of vessel deformation and rate of change of deformation this would be expected to significantly affect CSM responses.

1.6.5 CSS Treatment

Three treatment approaches have been considered: pharmacological, surgical (carotid denervation) and pacing.

Pharmacological treatments have been considered in the treatment of CSS particularly in VDCSS, although studies are typically small, often non-randomized and unblinded. Anticholinergics in one case series documented 79% symptom reduction compared to a control group of 64% after a 41 month period (Sugrue, Gersh et al. 1986). Fludrocortisone was shown to have some benefits in a small case series of 11 patients (da Costa, McIntosh et al. 1993). Serotonin re-uptake inhibitors (SSRI) in a group of 3 patients reduced symptoms after 14 months (Grubb, Samoil et al. 1994; Dan, Grubb et al. 1997). Single cases reporting benefits of propranolol, ephedrine, and ergotamine in the treatment of CSS have also been documented. More recently midodrine has been shown to reduce the rate of symptoms in VDCSS with moderate success in a small randomized control trial, however the most common side effects tend to include increased mean 24 hour blood pressure (Moore, Watts et al. 2005).

Surgical denervation (bilateral or unilateral) of the CS has been employed since the 1950's with two series showing improved symptoms (Trout, Brown et al. 1979; Fachinetti, Bellocchi et al. 1998). Surgical treatment had been largely abandoned owing to the complication of altered long term cardiovascular control. However it does have the advantage of targeting both CSS subtypes. Recently there has been some renewed interest in this method. A study by Toorop et al (Toorop, Scheltinga et al. 2009) has indicated that adventitial stripping was successful in reducing CSS in 85% of 130 cases, with low complication rates when postoperative monitoring of heart rate and blood pressure is performed.

Pacing is the recommended therapeutic intervention for CICSS as per recent guidelines (Moya, Sutton et al. 2009). It has been shown to reduce syncope recurrence in CSS (Gregoratos, Cheitlin et al. 1998). Brignole et al. found positive treatment effects in the majority of paced patients with dual chamber pacing preferred to (VVI) (Brignole, Menozzi et

al. 1991). Crilley et al (Crilley, Herd et al. 1997) found reduction in syncope in 84% of patients following pacemaker implantation. Kenny found a 70% reduction in the number of injurious events following pacing in CSS (Kenny 1999; Parry, Steen et al. 2009). However in the first randomized, double-blind crossover, placebo controlled trial, permanent pacing intervention had no effect on fall rates in older patients with CSH (Parry, Chadwick et al. 2009), although authors do admit this study may have been underpowered. A recent review by Gillespie (Gillespie and Handoll 2009) advocates pacing for falls.

1.7 Carotid Sinus Massage

CSM is a convenient, simple, low cost diagnostic test used to assess baroreflex sensitivity (BRS) that can be carried out easily at the bedside in any clinic facilitated with ECG, continuous beat-to-beat blood pressure (BP) monitors and advanced emergency response equipment. The test requires little co-operation from the patient, is suitable for an elderly population and clinician training overhead is relatively low (O'Shea, Parry et al. 2001).

During CSM the patient lies supine, while firm longitudinal massage is applied for 5-10 seconds to the site of maximal pulsation at the right carotid sinus, located between the superior border of the thyroid cartilage and the angle of the mandible of the neck. This procedure is repeated on the left carotid sinus and is then replicated on both sides in a 70° head-up tilted position (O'Shea, Parry et al. 2001).

The stages of carotid sinus massage include:

- Body position: Supine and Upright Massage is essential.
- The head is typically tilted forward or backward, or to one side, until the carotid triangle is palpable.
- If neck muscles are too tight/slack it is difficult to palpate CS.
- The sinus is usually situated above the level of the thyroid cartilage.
- CS is massaged longitudinally, with the sinus being compressed against the vertebral spine typically.
- Early practioniers palpated the ipsilateral temporal artery to avoid complete occlusion of the carotid artery.

- Unilateral stimulation beginning on the right, followed by left hand side is performed.
- Massage is applied for 5 seconds producing transient blood flow and carotid artery cross sectional deformation, torsion and stretching.

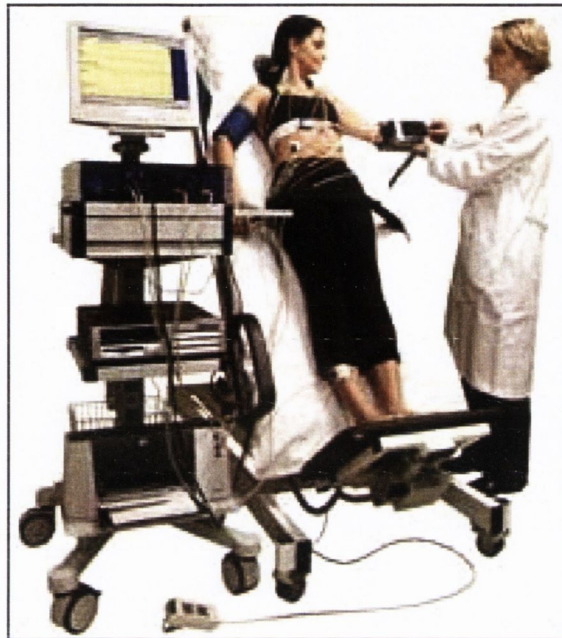


Figure 1.16: Tilt Table setup for Carotid Sinus massage

1.7.1 Neck Anatomy

The neck is bounded superiorly by the cranium, mandible and inferiorly by the clavicular bones. It is a vital structure through which major blood vessels carrying oxygenated blood and metabolic waste products pass between the head and the trunk. Major nerve fibres, lymphatic vessels and hollow conduits such as the trachea and oesophagus also pass through this relatively exposed body part. However what it loses in protection, it gains in flexibility, providing the sensory organs of the head a rotational lever to act upon.

The neck is subdivided into anatomical triangles based on surface markings provided by underlying structures, namely the sternocleidomastoid (SCM) muscle. This muscle runs obliquely from the sternum and clavicles below to the mastoid process above. In doing so, it divides the neck into an anterior triangle and a posterior triangle (Figure 1.17). The anterior triangle is further subdivided into the inferior carotid, superior carotid, submaxillary and suprahyoid triangles. The importance of such anatomical landmarks lies in their outward mapping of underlying structures. Of interest here is the location of the carotid arteries,

carotid body and carotid sinus. There are also a number of adjacent nerves, veins and lymph nodes, which may be of secondary importance in CSM and CSH.

During CSM the following structures are mechanically deformed owing to their proximity to the carotid sinus: overlying structures - skin, superficial fascia, platysma, deep fascia, SCM and carotid sheath. Within the carotid sheath, the following are encountered - carotid artery, internal jugular vein, vagus nerve, phrenic nerve, superior (recurrent) laryngeal nerve, lymph nodes and carotid body.

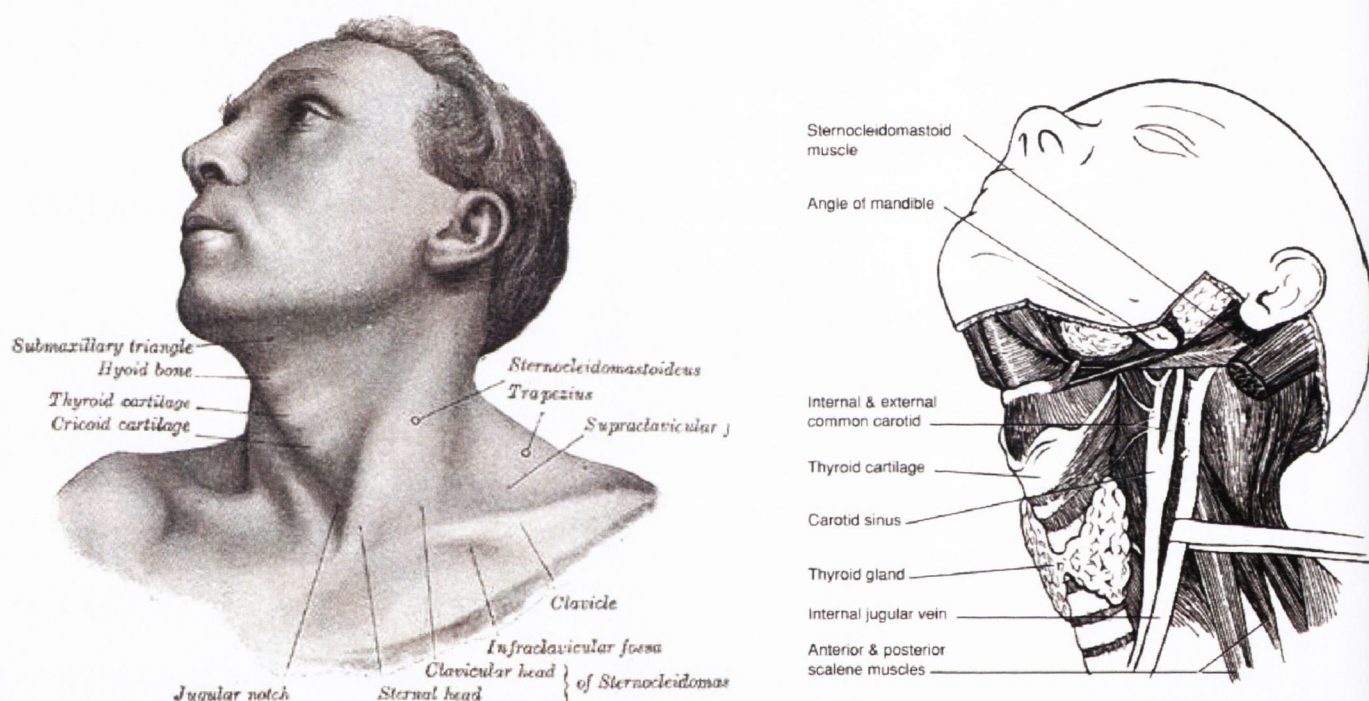


Figure 1.17: Surface (left) and Internal (right) anatomy of the neck

1.7.2 Normal Response to CSM in Man

The response to CSM in normal man results in local vascular deformation, blood flow interruptions, respiratory and cardiovascular changes. Finger pressure causes the carotid artery walls to collapse and stretch under external pressure. This process is repeated, with the carotid locally stretched and compressed in a time varying manner during massage, hence stimulating the strain sensitive baroreceptors in the neck (Lown and Levine 1961). Furthermore it is likely that partial or total carotid occlusion occurs during CSM. Local blood flow changes are known to cause transient stimulation of the carotid body, which in turn could trigger chemoreflex mediated cardiovascular and respiratory responses (Parry 1799). Brief changes in carotid blood flow transiently alter cerebral and brainstem blood supply in a

feedforward manner, potentially affecting brainstem function so as to modulate cardiovascular centres in the brainstem (Lown and Levine 1961). Indeed carotid occlusion was historically used as a test of cerebral autoregulation (Landgren and Neil 1951).

The cardiovascular effects of CSM are well documented and include: sinoatrial node changes, atrioventricular conduction alterations and blood pressure changes. Vagal changes include: sinoatrial slowing, atrial conduction defects coupled with P-wave morphology changes, sinoatrial bradycardia, prolongation of P-R interval, A-V block, sinoatrial arrest, nodal escape, asystole, and ventricular ectopic beats. No QRS complex changes have been recognized. Cohen and Lewis indicate that AV and SA node effects are mutually independent (Lown and Levine 1961) .

A depressor vasomotor reflex is also commonly evoked. Mandelstamm and Lifschitz (Mandelstamm and Lifschitz 1932) induced falls of at least 10 mmHg in SBP in 60% of a population of 335, with higher drops found in hypertension or atherosclerosis. In 106 retired workers BP fell on average by 37mmHg, but only dropped 5mmHg in 106 healthy soldiers. The vasomotor response is independent of cardiac changes.

Historically respiratory changes were recorded during CSM. Surprisingly recent CSH literature regularly omits the respiratory component of the CSM response. The reasoning for this is unclear. Hyperpnea usually follows digital pressure to the CS, with an increase in depth documented, beginning 5 to 20 seconds following CSM, and often lasting 54-90 seconds, with prolonged stimulation inducing Cheyne-Stokes respiration (Lown and Levine 1961). Galdston and co-workers have suggested that the respiratory reflex in CSM is caused by interference with the blood supply to the carotid body. This was suggested after procainization of the carotid sinus area was found to prevent the respiratory reflex, even in the presence of low concentrations of cyanide ions, which are known to stimulate carotid chemoreceptors. Furthermore when the local effects of the anaesthetic wears off, the respiratory response returns (Galdston, Goldstein et al. 1943).

1.7.3 Contraindications to CSM

The test has some limitation in relation to safety. Complications during CSM although rare do arise (Munro et al., 1994;Walsh, Clinch et al. 2006). The dangers are believed to be due to either prolonged cardiac asystole or interference with cerebral circulation. Approaching 1% of cases report complications, the majority of which are transient neurological complications, although permanent damage has been reported in single case studies

(Richardson, Bexton et al. 2000). Other complications include elevated cardiovascular or respiratory responses to CSM, such as tachycardia and ventricular fibrillation.

These risks have important practical implications for clinics performing CSM routinely; specifically patients need to provide informed consent prior to CSM and attending clinicians need to be trained in advanced resuscitation methods and aware of possible neurological implications.

As with many diagnostic tests CSM has its contraindications, including presence of a carotid bruit, recent history of stroke, myocardial infarction or ventricular tachycardia. Adherence to these exclusion criteria results in a very low complication rate of two persistent neurological defects and nine transient ischaemic events per 16,000 episodes of carotid sinus massage (Walsh, Clinch et al. 2006). Unfortunately these criteria deem a relatively large percentage of up to 20% of patients unsuitable for CSM with unexplained falls (Kerr 2009). Stratification of this group with suspected CSH and a bruit using ultrasound to determine degree of stenosis and excluding those with a stenosis >70% allowed a further 7% to safely undergo CSM (Richardson, Shaw et al. 2002).

1.8 Baroreflex Sensitivity Measurement Methods

Carotid sinus massage is the original test employed to determine baroreflex sensitivity. In CSH, CSM responses are considered hypersensitive relative to age matched controls, since blood pressure and heart rate changes in response to carotid sinus stimulation are exaggerated. Baroreflex sensitivity is thus a measure of the degree to which changes in blood pressure are sensed and modulate activity of the major cardiovascular regulating organs through the central nervous system. It can also be thought of as the slope of the regression function describing the relationship between blood pressure and measures of effector organ function i.e. heart rate, peripheral resistance, cardiac contractility and venous tone.

Since there are independent neural pathways serving each of these effectors there is thus theoretically a different baroreflex sensitivity which should be assigned to each effector organ. Quite commonly in clinical literature, this distinction between effector organ control is not made. A single baroreflex sensitivity measurement governing heart rate control is assigned as indicative of the overall baroreflex sensitivity of an individual. This occurs since few methods have been described to measure the sensitivity of other limbs of the baroreflex.

This point is particularly relevant to CSH since all four baroreflex control pathways may be involved in its pathophysiology given the various subtypes effecting heart rate, and peripheral resistance control. In fact no literature to date has discussed the possibility of a subtype purely involving venous control or conductivity of heart cells.

In this section we provide a brief overview of the vast body of literature describing the most commonly used baroreflex sensitivity measurement methods. For the interested reader refer to the excellent monograph of Eckberg et al. (Eckberg 1992) and a more recent review by Parati et al. (Parati, Di Rienzo et al. 2000). This we feel will inform selection of a suitable measurement method to aid Carotid Sinus Hypersensitivity diagnosis in older adults. Where available we highlight results of the application of those methods to Carotid Sinus Hypersensitivity.

The methods described are tabulated in Table 1.1. Two groups of methods exist, invasive and non-invasive measures. We will initially deal with the “classical” invasive laboratory measures and then discuss the more modern so called spontaneous non-invasive methods. CSM although tabulated will not be discussed in this section (Refer to section 1.7 for details of CSM).

1.8.1 Laboratory Methods

Typically these methods rely on evaluation under strict controlled laboratory environment and constitute a once off check of baroreflex sensitivity. A number of early methods e.g. carotid occlusion and electrical stimulation of carotid sinus nerve, have fallen from favour for reasons including poor reproducibility, levels of invasiveness and subject risk. We consider the more modern replacements.

1.8.1.1 Valsalva Maneuvre

Constant expiratory pressures of 40mmHg maintained for 15-20 seconds, induce reflex changes in heart rate in response to resultant changes in blood pressure (Malik 1998). Typically bradycardia is brought about by an increase in blood pressure to straining. On release of strain blood pressure drops and reflex tachycardia ensues. The slope of beat-to-beat blood pressure versus heart rate changes can be used to derive estimates of baroreflex sensitivity. This method is simple and non-invasive, but requires active cooperation from the patient, and is non-specific to carotid baroreceptors, is likely to involve chemoreceptors, and cardiopulmonary receptors amongst others. One study considered the Valsalva maneuvre in CSH, reporting a normal Valsalva ratio in CISH (Kenny, Allen et al. 1993).

18.1.2 Neck Chamber Method

This method consists of a rigid chamber sealed around the patients' neck. The chamber pressure can be increased or reduced to vary transmural pressures in the carotid and thus alter the degree of baroreceptor stimulation. Both HR and peripheral resistance limbs of the baroreflex can be tested. Furthermore the complete baroreflex characteristic including saturation can be evaluated (Parati, Di Rienzo et al. 2000). Quoted disadvantages include patient discomfort, the test is specific to carotid only, and complete pressures are not always transmitted to the carotid. A number of studies have used the neck chamber method to examine baroreflex sensitivity in CSH, with conflicting results. Dehn et al. (Dehn, Morley et al. 1984) reported an increased heart rate baroreflex sensitivity (3.61 ± 0.6 ms/mmHg versus 11.64 ± 2.51 ms/mmHg), while Cole et al. (Cole, Zuckerman et al. 2001) measured a reduced baroreflex sensitivity in CSH (3.0 ± 2.1 ms/mmHg versus 2.2 ± 3.0 ms/mmHg). Results were accounted for by subtle protocol differences.

1.8.1.3 Pharmacological Method

Smyth et al. (Smyth, Sleight et al. 1969) described a pharmacological method, which is still the most commonly used method for assessing baroreflex sensitivity in man. Intravenous pressor and/or depressor agents are administered and the effect of induced blood pressure changes on heart rate i.e. the baroreflex sensitivity is characterised by the regression function between blood pressure and heart rate changes. This method allows complete characterisation of the baroreflex sigmoid but is restricted to heart rate responses only and the administration of such pharmacological agents may be contraindicated in certain individuals. Again this method has been used to compare CSH individuals with controls. Measurements reported in one study indicate a decreased reflex sensitivity (Morillo, Camacho et al. 1999), while Morley et al. (Morley, Dehn et al. 1984) suggest increased baroreflex sensitivity in CSH. Methodology mismatches were suggested as an explanation for these result disagreements.

1.8.1.4 Tilt Testing and Lower Body Negative Pressure

Cardiovascular adjustments to head up tilting can be used as a surrogate measure of baroreflex sensitivity (Malik 1998). Head up tilting is clearly advantageous as it focuses on the bodies responses to gravity alone but typically it does not engage muscle pump activity. Both reflex adjustments in heart rate and peripheral resistance can be measured. Unfortunately this method also produces vestibular and cardiopulmonary stimulation and thus has limited specificity. Lower body negative pressure chambers can be employed to overcome vestibular pressure variations. A large sealed chamber is secured around the

lower body extremities, while pressure within the chamber is reduced, causing blood pooling within the lower limbs. However this method has the disadvantage of involving cardiopulmonary receptors since venous return is reduced significantly and hence venous pressures.

1.8.2 Spontaneous Measures of Baroreflex Sensitivity

All spontaneous measures of baroreflex sensitivity have been made possible by advances and cost reductions in electronics and digital signal processing. The basic protocol for measurement of baroreflex sensitivity using these methods is the same. Natural daily variations in continuous blood pressure about a mean arterial pressure induce heart rate changes via baroreflex pathways. Various processing algorithms inspired by system identification theory, and linear systems analysis are employed to extract baroreflex sensitivity from these two signals. Methods differ only in the proposed algorithms used to extract baroreflex sensitivity. These methods have a number of advantages. They are non-invasive, require little patient cooperation, can be performed in both laboratory and ambulatory conditions. However they cannot characterise the full sigmoidal characteristic of the baroreflex and only one method to date has claimed to measure sensitivity of the total peripheral resistance baroreflex. A brief discussion of the various algorithms exploited now follows.

1.8.2.1 Sequence Method

The 'sequence method' (Bertinieri, di Rienzo et al. 1985), identifies parallel increases or decreases of systolic pressures and R-R intervals lasting 3 or more beats. Pressures increasing or decreasing by at least 1 mmHg, and R-R intervals lengthening or shortening by at least 5ms per beat are required for a valid sequence.

A linear regression analysis is applied to each sequence. Only slope values yielding a correlation coefficient ≥ 0.85 , are accepted as an index of baroreflex sensitivity.

1.8.2.2 Spectral Method

Power spectra of systolic pressure and R-R intervals are integrated within low frequency (LF) and high frequency (HF) bands (Pagani, Somers et al. 1988). Baroreflex sensitivity is considered to be the square root of the ratio between R-R interval and systolic pressure integrated spectra. LF and HF bands are defined as per Heart Rate Variability Task Force report (Malik 1996).

1.8.2.3 Parametric Spectral Method

This method is very similar to the previous spectral method, in this case the R-R and SBP series are assumed to be an autoregressive (AR) processes and spectra are estimated via parametric methods. Baroreflex sensitivity is considered to be the square root of the ratio between R-R interval and systolic pressure integrated spectra within LF and HF bands.

Method	Author	Invasive	Risk	Sigmoidal/ Linear	Reflex Limbs	CSH S
Invasive						
Carotid Sinus Massage	Parry et al. (1799)	Semi	Med	NA	HR/TPR/Venous	Yes
Valsalva Manoeuvre	Valsalva (1704)	Semi	Low	Linear	HR	Yes
Neck Chamber	Ernsting et al. (1957)	Semi	Med	Nonlinear	HR/TPR/Venous	Yes
Pharmacological Method	Smyth et al. (1969)	Yes	Med	Nonlinear	HR	Yes
Lower Body Negative Pressure	Mancia et al. (1983)	Semi	Low	Linear	HR/TPR/Venous	No
Non Invasive						
Sequence	Bertinieri et al. (1985)	No	None	Linear	HR	No
Spectral	Pagani et al. (1988)	No	None	Linear	HR	No
Transfer Function	Robbe et al. (1987)	No	None	Linear	HR	No
Parametric Models Simple	Porta et al. (2000)	No	None	Linear	HR	No
xBRS	Westerhof et al. (2004)	No	None	Linear	HR/Latency	No
Parametric Models Complex	Mukamala et al. (2003)	No	None	Linear	HR/TPR/CPR	No

Table 1.1: Baroreflex Sensitivity Measures Applied to Carotid Sinus Hypersensitivity

1.8.2.4 Transfer Function

The baroreflex sensitivity is taken as the modulus of the transfer function between RR and SBP powers in the LF and HF bands, i.e. the magnitude of the cross-spectrum of the two signals divided by the power spectrum of SBP. Only components where the coherence between signals is greater than > 0.5 is considered (Robbe, Mulder et al. 1987).

1.8.2.5 xBRS

The xBRS method is calculated according to the method recently described by Westerhof *al.* (Westerhof, Gisolf et al. 2004). Using this method cross-correlation and regression between cubic spline interpolated (1 Hz sampling) systolic blood pressure and R-R interval are

computed over 10 second sliding windows. A time delay in the pulse interval series in the range 0-5 seconds is employed to account for differences in baroreflex conduction velocity. For each of the time delay values a cross-correlation value is calculated. The delay giving the maximum cross-correlation coefficient is selected and the corresponding positive regression coefficient ($P<0.01$) is taken as the representative BRS value for this time window. The geometric mean of all the values calculated over a 10 minute period is taken as xBRS value for each individual.

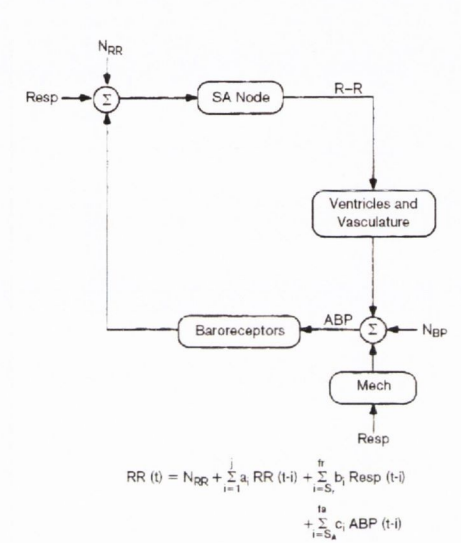


Figure 1.18: Linear Transfer Function Model of Cardiovascular System for System Identification

1.8.2.6 Parametric Modeling Methods

In these methods, a system identification procedure is taken. Parametric models of the Box-Jenkins linear transfer function form are fitted to the measured heart rate and blood pressure time series. The set of free model parameters are estimated via a least mean squares (LMS) algorithm. The models differ only in the assumed structure of model and the measured signals used. In some cases external signals such as respiration are used as exogenous inputs to account for respiratory influences on baroreflex sensitivity. A pre-requisite is the use of paced random-interval breathing, which requires patient cooperation. Parati et al. (Parati, Di Rienzo et al. 2000) describes a structure shown in Figure 1.18 to account for external influences of respiration, while more recently Mukkamala et al. (Mukkamala, Toska et al. 2003) describe a system identification method to measure the total peripheral resistance and cardiopulmonary loop gains. In this case measurement of cardiac output is essential.

1.9 Insilico Modelling of Neurocardiovascular System

Having described thoroughly the physiological and pathophysiological medical background to CSH and its diagnosis, what now follows is a review of relevant mathematical modelling work. As stated our problem requires a generic and flexible cardiovascular model which is capable of simulating the short-term (<5 minutes) closed-loop cardiovascular and cerebrovascular effects of unilateral baroreceptor stimulation i.e. CSM. For modelling purposes we consider CSM as a high magnitude, time varying strain stimulus exerted on carotid arterial walls, coupled with localised partial carotid occlusion, the degree of which is proportional to stimulus magnitude.

Capabilities of our model should also extend if possible to other commonly used tests in NCVI literature including transient and steady-state effects of orthostatic challenges i.e. HUT and intrathoracic pressure changes i.e. DB and VM (Malik 1998). CV effects of respiratory parameters should also be considered. No previously described models satisfy all these requirements. Surprisingly no models have yet to describe the effects of CSM in specific detail. This is even more unexpected given this test was the original impetus for Hering's discovery of the baroreflex (Hering 1923). A number of comprehensive models do exist which reproduce specific components which we desire i.e. generic baroreceptor stimulation, carotid occlusion and will be now examined in fuller detail.

1.9.1 Cardiovascular Models

Capturing the essence of Neurocardiovascular Instability insilico is a non-trivial task as outlined in earlier sections. Fortunately work in the field of cardiovascular modelling has been ongoing since the pioneering efforts of William Harvey (1578-1657), who in exploring the circulatory role of the heart, was the first in Western medicine to study biology quantitatively (Harvey 1889). Moens and Koertweg (Nichols and O'Rourke, 1998) utilizing the interchangeable relationship existing between mathematical descriptions of electrical and fluidic systems, provided an early transmission-line description of the circulatory system. This approach accounted for the distributed nature of the cardiovascular system allowing wave propagation and reflection phenomena to be investigated. Twenty years later in 1898 Otto Frank introduced the simple first order lumped parameter electrical equivalent model known as the Windkessel (Frank 1899), providing descriptions of average and pulsatile blood pressure and flows. Both approaches i.e. distributed and lumped parameter models and their derivatives are still in use today, often with little or no refinement. Advances in the modern era in modelling began with Womersley's classic work in 1957 on the analysis of blood flow in elastic vessels (Womersley 1957), which was closely followed in 1959 by

Grodin's (Grodins 1959) first compartmental model of the complete cardiovascular system. With the advent of the modern digital computer numerous, mathematical models of the human cardiovascular system have appeared in applications literature and have incrementally improved over the years.

The complexity of modern computational models varies widely, is dependent on the intended application with the modelling focus typically aimed at either arterial hemodynamic or neural control (Attinger and Anne 1966; Avolio 1980). Model structures range from simple one or two element lumped parameter models (Tsitlik, Halperin et al. 1992) to large multi-compartmental models of the cardiovascular tree (Liang and Liu 2006). Others have recently explored novel fractal (Jayalalitha, Shanthoshini Deviha et al. 2008) and energy based models. More elaborate approaches include the application of computational fluid dynamics methods to analysing flow in clinically significant vascular segments e.g. carotid or coronary artery with the aid of finite element analysis (F.E.M.) (Moore, David et al. 2006). Guyton's model of overall circulation provides an extremely comprehensive model of circulatory control in a model governed by more than 100 differential equations (Guyton, Coleman et al. 1971). Multiscale models i.e. those which incorporate details from cells to organisms, have recently emerged in physiological modelling literature with proposed applications in anti-arrhythmic drug testing and discovery (Shim, Jun et al. 2008). Such models are the long term focus of European and Global initiatives such as the Physiome Project (Rose 2007) with an ambitious aim of defining a quantitative description from genome to organism of a species individual. Cardiovascular models have found applications in a broad number of areas including clinician and patient education (Giannessi, Ursino et al. 2008), hypothesis generation and testing support (Heldt, Shim et al. 2002), diagnostics (Moore, David et al. 2006), therapy discovery and refinement (Banks, Holm et al. 2009), physiological measurement and signal processing optimization (Mukkamala, Toska et al. 2003).

An extensive literature exists in the area of biophysical analysis of the cardiovascular system. Many models having been produced to examine the responses to orthostatic challenges. For reviews of earlier work the reader is directed to the book by Noordergraaf et al. (Noordergraaf 1978). More recently comprehensive monographs by Ottesen (Ottesen, Olufsen et al. 2004), and Batzel et al. (Batzel, Kappel et al. 2006) and review paper by Melchior et al. (Melchior, Srinivasan et al. 1992) cover advances in this area.

Although there are a number of models which take into account distributed nature of the system, for our purposes we are interested only in lumped parameter compartmental models since the frequencies of interest are typically below the mean heart rate. With this structure each compartment represents the average behaviour of a particular segment of the physiological system, and is not capable of representing distributed characteristics such as wave reflections. The majority of comprehensive models developed are an extension of the lumped parameter model of Grodins (Grodins 1959) which consists of four compartments. Two circuits were connected in series i.e. the systemic and pulmonary circuits, which were connected through two pumps representing the function of the right and left ventricles. Grodins model also included basic regulatory mechanisms including local metabolic changes in resistance, and an empirically derived baroreflex sensitivity relationship.

Both pulsatile and non-pulsatile models have been explored by a number of authors. Non pulsatile models have been described by Grodin's (Grodins 1959), (Moller, Provic et al. 1983) each of which examines the steady state dependencies of parameter means. Ursino et al. (Ursino, Fiorenzi et al. 1996) have shown the effect of pulsatility in baroreflex control of the cardiovascular system noting that baroreflex sensitivity tends to be linearized by a pulsatile input. The model structure used includes standard mass balance equations, cardiac pump based on Sunagawa's (Sunagawa and Sagawa 1982) time-varying elastance model, as well as sympathetic and parasympathetic control of heart rate, peripheral resistance and systemic unstressed volume. Simulations have shown pulsatility to contribute to lower/higher effective mean cardiovascular variables when the mean intra sinus pressure operating point is located near major non-linear portions of the baroreflex sigmoid. Recent work by Alletti et al (Aletti, Lanzarone et al. 2009), who built upon the original vascular model of Lanzerone at al. (Lanzarone, Liani et al. 2007) noted that systemic pulsatility served to decrease apparent total peripheral resistance. Particularly important details of this model include an active peripheral resistance component which takes into account metabolic control of venules, myogenic control of arterioles, effects of capillary filtration, and a coronary network component.

DeBoer, Karemaker and Stracke (deBoer, Karemaker et al. 1987) describe a beat-to-beat model including baroreflex control of parasympathetic and sympathetic activity, heart rate contractility and the mechanical effects of respiration using a discrete difference equation

model. This model amongst others established the possible role of baroreflex feedback delay in Mayer wave production.

Ottesen (Ottesen 1997), Cavalcanti (Cavalcanti 2000) studied changing stability with increasing time delay in a simple mathematical model of short-term blood pressure control. More recently de Paor et al (de Paor and Ringwood 2006) have investigated the application of non-linear describing function stability analysis in establishing analytical solutions to the existence of Mayer waves using non-pulsatile models.

Kappel and Peer (Kappel and Peer 1993) have adapted the Grodins model to study the transition from rest to exercise, which included relationships between O_2 concentration and systemic resistance. The control element of this model is particularly important which emphasises optimal control as a fundamental concept by minimizing blood pressure variability in concert with minimizing energy expenditure. The control structure used here was of the linear quadratic form. Mutsaers et al (Mutsaers, Bachar et al. 2008) explored the use of a receding horizon controller as an alternative structure to the linear quadratic regulator (LQR) approach in conjunction with the Kappel-Peer model. It was found to be a feasible alternative to LQR for cardiovascular control.

Boyers and co-workers (Boyers, Cuthbertson et al. 1972) have simulated the hemodynamic response to changes in posture, by implementing a seven-compartment steady-state model of the cardiovascular system connected to models of the arterial baroreflex and the cardiopulmonary baroreflex. Croston and Fitzjerrell (CROSTON 1974) have devised a 28-compartment lumped parameter model to include arterial, venous, and cardiac elements. An elaborate control model including total metabolites, oxygen debt and arterial pressure was included.

Melchior and co-workers (Melchior, Srinivasan et al. 1992) have simulated the hemodynamic response to LBNP using a steady-state model. Subsequent extensions of this work (Melchior, Srinivasan et al. 1993) included a pelvic venous compartment and a Windkessel model of the systemic circulation.

Heldt et al. (Heldt, Shim et al. 2002), developed a comprehensive short term blood pressure regulatory model to examine the hypotheses surrounding the causes of orthostatic intolerance in astronauts during tilt table testing. The model includes twelve compartments including a pulsatile heart modelled via a time-varying capacitance model, which drives a detailed vascular model which includes systemic and pulmonary circuits and non-linear

pressure-volume relationships of vessels. Vascular components have the ability to reflect postural related changes in pressure, with a pulmonary model which includes a Starling resistor model to account for vessel collapse. Heldt's model also includes carotid and aortic baroreceptors and cardiopulmonary reflex models. Model parameters are largely based on literature values. Model verification was performed by comparing the simulation output under baseline conditions and at different levels of orthostatic stress to sets of population averaged hemodynamic data reported in the literature. Transient response characteristics of heart rate to tilt also compare well with reported data. Later Heldt reduced the complexity and simulation time of this model by performing classical parameter sensitivity analysis and model order reduction.

Karemaker in 2006 (van Heusden, Gisolf et al. 2006) focussed on examining the blood pressure response of the Heldt model (Heldt, Shim et al. 2002) noting that there were some important discrepancies in the models response to HUT and standing. The simulated BP response shows a major BP dip in the first 10–20 seconds after HUT. It was noted that this resembles active standing, rather than passive HUT. A baroreflex model combined with a lumped parameter model of the circulation, including viscoelastic stress-relaxation of the systemic veins was included to compensate for these discrepancies. Cardiac contraction was modeled using the varying-elasticity concept. In accordance with the experimental results, model simulations do not show a BP dip on HUT; the tilt-back response is also realistic. The direct effect of gravity on the pulmonary circulation influences the BP response in the first 5 seconds after HUT and tilt back.

More recently Ursino (Ursino and Magosso 2006) reviews his comprehensive work over the past twenty years in cardiorespiratory modelling. This has led to the development of an integrated model of short-term cardiovascular regulation which includes the non-linear interaction among several control mechanisms, including baroreceptors, peripheral chemoreceptors, lung-stretch receptors, a direct CNS response to hypoxia and hypercapnia, and local vessel response to changes in blood gas content. Examples of system response are discussed during various acute cardiovascular perturbations (pressure changes, changes in blood gas content, dynamic exercise) and model results compared with existing data in the literature. Giannessi et al (Giannessi, Ursino et al. 2008) have extended this model further to include respiratory mechanics and metabolic exchange and explored the use of this model further in various ICU applications including simulation of obstructive and cardiogenic shock. Others have based simulation models of the cardiovascular system on the structure

proposed by Ursino et al (Ursino and Magosso 2006). For example Liang (Liang and Liu 2006) constructed a large closed-loop electric analog circuit for the CVS, consisting of 42 compartments that respectively represent the main cardiovascular components in a human body extracted from details of a vascular MRI coupled with control loops described by Ursino and Magosso and a cerebral autoregulation component comprising a low-pass first-order dynamic equation, a linear equation with a pure latency, and a sigmoidal equation.

Both Smith et al (Smith, Chase et al. 2004) and Heldt et al (Heldt and Chernyak 2006) have recently advocated the use of minimal cardiovascular models in terms of real-time performance, clinical interpretability and usability. Smith in a series of studies has remarked that models found in the literature simulate specific areas of the CVS with limited direct usefulness to medical staff. They have since explored a stable minimal model of the human cardiovascular system with the ultimate aim of assisting medical staff in rapid, on site modelling to assist diagnosis and treatment. This approach uses a model with a minimal number of governing equations with the goal of capturing trends in dynamics. The model has been shown subsequently to simulate trends in left and right ventricular pressures and volumes, septum deflection and arterial flow rates. The initial model has been later developed to include a model of ANS activation to simulate hemodynamic effects of increased cardiac output in septic shock, elevated pulmonary artery pressure in left ventricular infarction, and elevated filling pressures in pericardial tamponade. A cardiovascular system model and parameter identification method has been validated for porcine experiments of induced pulmonary embolism and positive end expiratory pressure (PEEP) titrations, accurately tracking all the main hemodynamic trends (Starfinger, Chase et al. 2008).

Continuing this line of minimal modelling, Heldt derives analytical solutions to the short-term (intra-beat) and long-term (inter- beat) evolution of a minimal cardiovascular model. The model approximates is shown to turn a non-linear, periodically varying model into one that is periodically-varying and linear for physiologically reasonable initial conditions (Heldt and Chernyak 2006).

Shim et al. have (Shim, Jun et al. 2008) created a multiscale model of the cardiovascular system coupling cell, hemodynamics and autonomic nerve control function to simulate the physiological events from membrane excitation of a cardiac cell to contraction of the human heart and systemic blood circulation. This model was created using a combination of lumped parameter vasculature models, the baroreflex model described by Heldt (Heldt, Shim et al.

2002), and a cellular model describing the cellular mechanisms of heart muscle contraction, cross bridge dynamics which influence macro level tensions of the heart chambers. The recent study by Banks et al. is worth a particular mention (Banks, Holm et al. 2009). Presented is an interesting pharmaceutical industry use of cardiovascular modelling i.e. a preliminary first-pass dynamic model for delivery of drug compounds to the lungs and heart using a compartmental mass-balance approach to develop a system of nonlinear differential equations for mass accumulated in the heart as a result of intravenous injection. This model is used to predict an optimal dosing strategy that maximizes accumulation of the drug in the lungs, while minimizing accumulation in the cardiac tissue. The ultimate aim is to reduce time and costs of the drug discovery process.

Olufsen et al (Olufsen, Nadim et al. 2002; Olufsen, Ottesen et al. 2005; Olufsen, Tran et al. 2006) present a series of particularly relevant models recently which have provided quite succinct simulations of cardiovascular response to standing and tilting. Similar to previous studies the model includes systemic and venous components. Comprehensive models of baroreceptor control of heart rate and vasculature, and cerebral autoregulation are included for predicting blood flow velocity in the middle cerebral artery. Novel aspects include a detailed baroreceptor model without a set-point, and central nervous system integration of a vestibulo-sympathetic reflex to account for pre-emptive heart rate rises which occur prior to standing. Accurate blood flow velocity estimates were also acquired in a small subset of individuals.

1.9.2 Models of Baroreceptor Function

A succinct review of baroreceptor models developed prior to 1988, has been provided by Taher et al. (Taher, Cecchini et al. 1988) in the development of his own mathematical model. We initially discuss these models in brief and refer the interested reader to Taher et al. (Taher, Cecchini et al. 1988) for further details and references. More recent efforts in this area are then described.

Based on his early experimental work on baroreceptor function Landgren et al (Landgren 1952; Landgren 1952) proposed a exponentially decaying model to describe the adaptation process of single fibre baroreceptors found during a step pressure change in input pressures given by the form

$$n - n_o = k_1 e^{-t/\tau} \quad (1)$$

where k is a positive scaling constant, T describes the time constant of adaptation and n_a is the new adapted firing frequency. Sleight et al. (Sleight, Robinson et al. 1977) extended this model to include a sum of two such exponential terms with different time constants. Note these models were essentially fitting functions of the experimentally recorded data and did not exhibit saturation or threshold phenomena.

Warner et al. (Warner 1957; Warner 1958) incorporated input pressures, threshold and sensitivity to changing pressures into his model such that firing frequency, n , is described by

$$n = k_1(p - p_0) + k_2(dp/dt) \quad (2)$$

where p is input pressure, p_0 is threshold pressure, and k_1 and k_2 are scaling constants. Warner et al. (Warner 1965) later included unidirectional rate control into the model to account for dynamic hysteresis of his model. Scher and Young (Scher and Young 1963) later built upon this model to include adaptation into the model by deriving the dynamic equations of baroreceptor firing frequency according to

$$k_3 dn/dt = k_1(p - p_0) + k_2(dp/dt) - n \quad (3)$$

where k_3 is an additional constant. According to Taher et al. (Taher, Cecchini et al. 1988) a number of authors included higher order derivative terms to improve experimental fit of model

Srinivasan and Nudelman (Srinivasan and Nudelman 1972) proposed a model of two nonlinear differential equations which describes both mechanical relationship between pressure and strain of carotid fibres and the mechano-electrical transduction process governing the coupling of baroreceptors to the carotid artery. The model summarises the essential features of baroreceptor function i.e. adaptation, threshold, asymmetry and saturation.

Taher et al. (Taher, Cecchini et al. 1988) modified a version of Sleight and Robinson's single fibre model (Sleight, Robinson et al. 1977) to describe the change in baroreceptor output for a given step change in pressure input in terms of the sum of three decaying functions, scaled by a sine function and seven constants. Known baroreceptor behaviour is replicated by this model quite convincingly using one succinct equation. Noteworthy is the fact that Taher and colleagues (Taher, Cecchini et al. 1988) exclude the existence of a set point pressure in the model instead including large time constants relatively to duration of measurement. Thus baroreceptor operation resets to prevailing mean arterial pressure after a sufficiently long

period. Ottesen and coworkers (Olufsen, Tran et al. 2006) generalizes this work by Taher et al. (1988), producing a set of three coupled nonlinear differential equations to describe the output of the carotid sinus nerve. These seminal models and their derivatives, have appeared in literature in various forms and applications particularly in global models of cardiovascular control such as those proposed in (Heldt, Shim et al. 2002; Olufsen, Tran et al. 2006; Ursino and Magosso 2006). More recently the model of van Heusden et al. (van Heusden, Gisolf et al. 2006) incorporates an interesting approach include lesser known physiological effects into a model to account for the influences of stroke volume on baroreflex output.

1.9.3 Models of Cerebral Autoregulation

A brief review of some models of cerebral autoregulation is detailed here. Work in modelling cerebrovascular function began with work by authors such as Matakas, et al. (Matakas, Von Waechter et al. 1975), Hakim, S., J. G. et al. (Hakim, Venegas et al. 1976) and Greenberg, J., A. (Greenberg, Reivich et al. 1978) who examined intra-cerebral perfusion pressures (ICPP), parameters which influence intracranial pressures (ICP) and dynamics and early models of cerebral autoregulation respectively. Hudetz (Hudetz, Halsey et al. 1982) presented a computer model to examine middle cerebral artery (MCA) occlusion and a steady state model of blood flow distributions in the cerebral arterial system. The model included the Circle of Willis, pial arterial anastomoses, and a simplified form of autoregulation. Rosner et al. (Rosner and Becker 1984) examined the evolution of oscillatory plateau waves occurring in cerebral intracranial pressures using a model of cerebral autoregulation and variations in cerebral perfusion pressures. Bishop et al. (Bishop, Powell et al. 1986) modelled results obtained from blood flow velocity measurements in individuals with partially occluded carotid arteries. Hoffman (Hoffmann 1987) presents a comprehensive model, integrating a model of cerebral autoregulation, with a peripheral circulatory model including a heart, peripheral vasculature and baroreflex. Of note is the inclusion of brainstem blood flow and its effect on baroreflex function. Ursino and colleagues have explored a wide range of models over the past two decades. Models which describe cerebral autoregulatory and hemodynamic phenomena with a view to explaining changes in Transcranial Doppler indices (Ursino 1990; Ursino, Giulioni et al. 1998), evolution of plateau waves (Ursino and Di Giammarco 1991; Ursino and Lodi 1997), modulation of intracranial pressure in acute brain injury and its measurement (Ursino et al., 1995; Ursino et al., 1997) (Ursino, Iezzi et al. 1995; Ursino, Lodi et al. 1997), effects of CO₂, ischemia and systemic arterial pressure variations on cerebral autoregulation (Ursino and Magosso 2000; Ursino, Ter Minassian et al. 2000;

Magosso and Ursino 2001; Ursino and Magosso 2001), and clinical simulation for education purposes (Giannessi, Ursino et al. 2008) have all been developed. Cassot et al. (Cassot, Vergeur et al. 1995) notes in a model that anterior communicating artery (ACoA) diameter strongly modulates the effects of ICA lesions on cerebral haemodynamics. Cirovic, et al. (Cirovic, Walsh et al. 2003) describes the role of the cerebral venous bed in the cranial volume-pressure test. It was found that the cranial volume-pressure curve can be explained by collapse and/or distension of venous bed. Lu et al. (Lu, Clark et al. 2004) introduced a comprehensive model of peripheral cardiopulmonary circulation and cerebral autoregulation including gas exchange for the study of variations in O_2 concentrations. Moorhead et al. (Moorhead, Moore et al. 2004) identifies at risk Circle of Willis geometries using a cerebral autoregulatory model and a 1-D vascular model. More recently the authors from the same team have combined magnetic resonance imaging data with computer aided design software to examine flows in 3D models of the Circle of Willis (Moore, David et al. 2006) and have also extended their model of cerebral autoregulation to include O_2 concentration (Moorhead, Chase et al. 2006). Alastruey et al., (Alastruey, Parker et al. 2007) have noted the effects of carotid occlusion and Circle of Willis anatomy on cerebral blood flow noting that absence of an anterior cerebral artery combined with contralateral carotid artery occlusion results in the largest drops in cerebral blood flow.

1.9.4 Models Summary

On the basis of modelling literature over the past half-century, we are now at the point where models are moving from the purely academic to the medical applications literature. The details of the models have increased incrementally over time, and are now at a position where they can contribute to the field of neurocardiovascular instability. Although no models to date have incorporated the full complement of systems to enable proper simulation of CSM, CSH, and other NCVI's in one compact representation, there have been developments which will assist this goal. Particularly relevant to this thesis are the detailed baroreceptor models of Ottesen and Taher. Building upon Grodin's approach, simulations by Croston, Heldt, Smith, Ursino, Peer-Kappel and Karamaker of cardio-respiratory function include relevant first order details of peripheral circulatory control. Finally cerebrovascular models of Gianessi, Lodi, Terminassen, Ursino and Olufsen now allow us to gain further insight into the downstream blood flow mechanisms of carotid sinus massage.

Conclusion

A comprehensive review of the physiology and pathophysiology surrounding carotid sinus massage and carotid sinus hypersensitivity has been presented. Gaps in knowledge surround

the action of carotid sinus massage, the pathophysiology of CSH and consequently its diagnosis and treatment. A detailed introduction to the last 50 years efforts in cardiovascular modelling have also been presented from the works of Grodin's and Guyton to current efforts by Ursino and others. It has also been established that much of the technical tools for adequately modelling the action of CSM and exploring the pathophysiology, diagnosis and treatment options for CSH have already been used in related fields and thus the field is ripe to produce a successful simulation. Chapter II will now highlight the major clinical and modelling issues to be tackled in this thesis followed by a detailed outline of future chapters.

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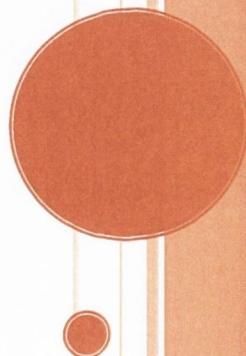
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CHAPTER 2

Carotid Sinus Hypersensitivity Issues and Thesis Structure

Following the literature review in Chapter 1, a number of pertinent clinical and modelling issues are identified in this chapter. These are highlighted as being important to advancing the field. The thesis aims and layout are then detailed.



CHAPTER 2

2.1 Introduction

Following the literature review in Chapter 1, a number of pertinent clinical and modelling issues are identified in this chapter. These issues are highlighted as being important to advancing the field. The thesis aims and layout are then detailed.

2.2 Issues in Carotid Sinus Hypersensitivity

From the review of medical literature, it is obvious that a number of gaps exist in the literature concerning:

- 1) The mechanisms of action of CSM.
- 2) The source of pathophysiology in CSH.
- 3) CSM Method.
- 4) Alternatives to CSM in CSH diagnosis.
- 5) Treatment of CSS.

2.2.1 Mechanisms of Action of CSM

Although exhaustively studied from the perspective of understanding the neuroanatomy, ultrastructure and function of baroreceptors and the baroreflex, the local effects of CSM stimulus are still not completely understood. Physiological models of CSM action quoted especially in the CSH literature describe CSM purely as a baroreceptor stimulus and can be considered essentially a test of baroreflex sensitivity.

This may be an oversimplification of the mechanisms of CSM action particularly especially considering the variety of baroreceptor subtypes, the close vicinity of major respiratory, neck muscle and laryngeal afferents and the transient effects of CSM on cerebral blood flow. We feel the following points are particularly pertinent and worth mentioning in this context.

During CSM, especially in older adults, knowledge of the biomechanical properties of the vessel wall, the distribution of wall fibre types and the relative distribution and recruitment of baroreceptors is essential to give a true reflection of afferent activity. The temporal pattern of carotid wall stresses and strains i.e. the true baroreceptor stimulus during CSM have not been well-documented. Furthermore the influence of age and disease related vascular changes on these patterns have not being investigated.

Since baroreceptors respond directly to strain, it is vital that this information is quantified to truly understand the baroreceptor stimulus and its effects on baroreceptor recruitment and function. We would predict that local strains would be particularly high during periods of high external transmural pressure, when local fibre curvature would be at its highest. The dynamics of strain during baroreceptors stimulation are also of importance to predict baroreceptor and CSM outcome, and require further quantification. Current models do not describe the relative influences of specific baroreceptor subtypes on afferent activity, and stimulus outcome. For instance some irregularly responding baroreceptors are known to have profound effects on heart rate at very high pressures. It is not unreasonable to suggest that these baroreceptors could be recruited during CSM (Eckberg 1992).

Deformation of the ICA, will ultimately result in local blood flow alterations, and downstream effects on cerebral blood flow. These effects have not been well-characterised in CSM. However it is known that chemoreceptor stimulation occurs concurrently with baroreceptor activation, resulting in increased depth of breathing.

The downstream effects of CSM on cerebral blood flow are comparable to those seen in the unilateral occlusion test of cerebral autoregulation and thus would be expected to result in relative vasodilation of cerebral vessels in the absence of any other concurrent and conflicting stimuli. Muscle afferent activation may also be involved in the response to CSM. Of particular pertinence, Iriuchijima (1972) notes that early modulation of single baroreceptor responses occurs at the level of the first few synapses, whereby simultaneously stimulated skin and muscle afferents block baroreceptor responses. Finally it is recommended, that to get highest diagnostic yield, CSM should be performed in supine and upright positions. The reasons why CSM responses are increased in the erect position are unknown. However two plausible hypotheses have been suggested to explain this finding i.e. increased baroreflex sensitivity and increased carotid sinus exposure. The role of gravity has not been distinctly focussed upon but obviously would be important especially in VDCSH.

An understanding of the relative importance of each of these factors on the CSM response and sensitivity to age related changes would contribute to the design of optimum diagnostic approaches for CSH, open up new treatment avenues for CSS, and contribute to understanding of CSH pathophysiology.

2.2.2 Source of Pathology in CSH

The uncertainty surrounding the definite effects of CSM, although rarely articulated in CSH pathophysiology literature, undoubtedly contribute to the lack of agreement surrounding the source of pathology in CSH. As mentioned in the last chapter, current opinion has identified three possible sources with current favour focussed towards the central NTS hypothesis and the muscle deafferentation theory.

Another unidentified possibility in the context of CSH and CSM is the integration of all these reflexes with cardiorespiratory activity. This is particularly surprising since cardiovascular and cardiorespiratory functions are tightly coupled systems. Furthermore, CSM is known to cause respiratory changes due to induced flow variations at the carotid bulb, a fact that is altogether ignored by CSH literature. Recent evidence provided by Hainsworth et al (2006) further strengthens this argument. It was shown that some individuals predisposed to vasovagal syncope had over reactive vasoactive responses to hypocapnia. In this authors opinion cardiorespiratory activity should also be taken into account as both systems symbiotically contribute to meeting metabolic demand, are involved in cardiovascular regulation and are directly (peripheral chemoreceptor) and indirectly (downstream central brainstem chemoreceptors) affected by CSM.

2.2.3 CSM Method

The diagnosis of CSH currently requires CSM. As a method, CSM characteristics are currently only partially standardised, in terms of body position and duration of stimulus. Improvements could be made in standardizing the localisation of the CS prior to stimulation, the magnitude and time course of pressure delivered and the degree of blood flow reduction occurring during stimulation.

Furthermore concerns surrounding CSM safety are often voiced in literature. Standardization of CSM pressures while maintaining diagnostic power such that cerebral perfusion is minimally affected should in turn minimize cerebral risks. The origin of underlying cardiac complications of CSM are not well understood, and should be explored further. Contraindications to CSM employed to minimize risks of complication, rule out 20% of individuals for CSM.

A non-invasive alternative which has the same sensitivity/specificity of CSM, with improved reliability and reduced contraindications would be preferable.

2.2.4 Alternatives to CSM

A number of alternatives to CSM have been investigated in CSH. The context of these studies has often focussed on pathophysiology and not diagnostics.

To date non-invasive vagal manoeuvres such as the Valsalva method, deep breathing, ocular pressure, neck suction chambers and other autonomic function and electrophysiology tests have been examined. The results are often significantly different between CSH and controls, however the sensitivity and specificity for these tests is low. Invasive baroreflex tests consisting of bolus injection or slow infusions of vasoactive drugs such as nitroprusside and phenylephrine have produced conflicting results with some authors detecting a hypersensitive CS in CSH, while others have found the opposite results. The reasons for these conflicting results are unclear but are often accounted for by differences in protocols. Secondly these approaches have all been developed to characterise the heart rate baroreflex and so are only aimed at quantifying the portion of the baroreflex governing heart rate control. Examination of the vasomotor branch of the baroreflex has been omitted. The reasons for this are unclear but are likely due to unavailability of well-known approaches to detecting the sensitivity of this limb and the relatively recent development of adequate methods for the diagnosis of vasodepressor CSH.

In all these cases the analysis methods employed have not taken advantage of the plethora of advanced digital signal processing methods available in engineering literature. Non-invasive tests of cardiovascular control may be particularly relevant from this perspective and range from simple methodologies such as spectral analysis of heart rate and blood pressure variability, to more complex methodologies such as heart rate turbulence, spontaneous measures of baroreflex sensitivity, and parametric model based approaches which attempt to parameterize the whole cardiovascular control system using inverse modelling approaches.

A significant step would be the exploration of some of these approaches in CSH.

2.2.5 CSS Treatment

From a treatment perspective, pacemaker interventions have been shown to control CICSS. However use of pacemakers for the control of CSH as a cause of unexplained falls has been questioned by one recent study.

Complete remedies for the vasodepressor component are elusive. As noted the vasodepressor component is not well managed by pacemakers or medications. However recent midodrine trials would suggest that a treatment which targets peripheral resistance

vessel control is a possible option. However instead of a steady state increase in peripheral resistance seen with this treatment, an improvement in transient blood pressure control is required to avoid the side effect of chronic supine hypertension.

Although the side effects of adventitial stripping are serious, recent work does advocate this approach, indicating that it treats 80% of individuals with CSS. Furthermore with proper post surgical monitoring the serious side effects of hypertension are minimized. This further supports the notion that the optimum treatment approach for VDCSH is one which improves the transient baroreflex response only.

A thorough understanding of the effects of CSM in CSH and its underlying pathophysiology should help elucidate future avenues of treatment for CSS especially the vasodepressor component.

2.3 Issues in Modeling of Carotid Sinus Massage and Carotid Sinus Hypersensitivity

The review of the modelling literature has revealed an extensive body of work in different areas of Cardiovascular Modeling which can be readily adapted to allow us to begin modelling the cardiovascular response to Carotid Sinus Massage. The following issues have been identified as crucial to furthering our goals.

- 1) Complete Model of Local Affects of unilateral CSM requires attention.
- 2) Autonomic control of combined SA and AV Node should be included aswell as the effects of resting autonomic milieu.
- 3) Brainstem Nuclei involved in baroreflex control not modelled to date.
- 4) Global cardiovascular, cerebrovascular and cardiorespiratory effects of CSM have not been examined closely in model form.

2.3.1 Modelling Local Affects of CSM

Modeling efforts to date have not focused specifically on the response to CSM. The simplicity of the test in practice belies the complexity of the underlying transient physiological response.

However much related work has focused on modeling single and multifibre baroreceptor and baroreflex responses, often as part of larger cardiovascular control system models. To appreciate the major contributors to CSM response, the biomechanical response to CSM must be understood, particularly the strain response of the carotid artery to CSM. Secondly

since CSM is a large signal stimulus, the recruitment of high pressure unmyelinated baroreceptors is likely and thus should be incorporated. Few models have included these details to date.

Flow responses during CSM in the CSH literature are all but ignored in discussions of CSH. Local effects of blood flow changes affect chemoreceptors located in the carotid body, which are known to modulate cardiorespiratory responses. Recent modelling efforts have included chemoreceptor responses. These have been combined with baroreceptor models in some cases, although unilateral effects have to date been neglected.

2.3.2 Autonomic control of SA and AV Nodes

Although some form of SA node control is always included in comprehensive models of the cardiovascular system, the autonomic control of conduction pathways and inclusion of AV node pacemaker control is generally omitted from all-purpose models.

For most purposes not focused on arrhythmia generation this would be considered a secondary effect. However in light of clinical evidence suggesting that the cardioinhibitory form of CSH is due to sinoatrial exit block and/or AV block not sinus node depression we feel that it is important to adopt a cardiac model which includes both SA and AV node control.

2.3.3 Models of Brainstem Nuclei of the Baroreflex

The neural circuitry, the inhibitory and excitatory neurotransmitters, the specific brainstem nuclei and connections to higher level nuclei have been well described in functional neuroanatomy literature. A number of these brainstem nuclei have been implicated as pivotal in the pathogenesis of CSH by recent studies.

Models of the central nervous portion of the baroreflex tend to be reduced to a single lumped parameter model. Specific nuclei involved in baroreflex responses, and those implicated in CSH, have not been well described in modeling literature. The abundance of local GABAergic connections within brainstem nuclei and top-down inhibitory/excitatory influences by higher level mid-brain and forebrain areas maybe particularly important aspects that require inclusion in future modelling efforts.

2.3.4 Global Effects of CSM on Cardiovascular, Cerebrovascular and Cardiorespiratory systems

Global effects of CSM have not been modeled to date although cardiorespiratory and cerebrovascular models have described combined baroreflex, respiratory and cerebral autoregulatory reflexes. Application of these models shall form the initial framework to our model of CSH. By raising awareness of this clinical problem in the modeling field, we would

also hope to foster future development of CSM and CSH models and systems to aid treatment and diagnosis of CSH.

Being a transient large signal stimulus, modeling CSM demands a baroreflex model embedded in a complete CV model which is capable of simulating the non-linear properties of the baroreflex.

Of particular importance are the effects of driving one limb of the baroreflex system temporarily into saturation while all other portions remain active in the linear portion. This effect has not been considered in modeling literature to date. The relative contribution of each portion of the baroreflex is important in this regard and is required since CSM involves unilateral stimulation. Since the stimulated portion of the carotid artery is occluded and constantly driven during CSM, the corresponding portion of the baroreflex is temporarily disconnected from feedback loop during CSM and reconnected on cessation of CSM. These effects on baroreflex control have yet been described and could contribute to understanding of the underlying mechanisms of CSH and mechanisms underlying general baroreflex control and its adaptation with age.

2.4 Thesis Aims

In light of the issues identified in previous sections, the aims of this thesis are as follows:

1. Design and develop a computer model of the Cardiovascular System, for the purposes of simulating carotid sinus massage and Carotid Sinus Hypersensitivity
2. Identify non-invasive biomarkers of CSH based on digital signal processing approaches, to inform both CSH pathophysiology and future diagnostic methods. These approaches should be amenable to be applied to electrocardiogram and arterial blood pressure signals obtained during steady-state and transient cardiovascular scenarios.

2.5 Thesis Layout

This thesis is arranged as follows. Chapters 3-7 deal with tackling a number of the problems identified in the areas of Carotid Sinus Hypersensitivity. The specific details of each chapter are now described.

Chapter 3-4 deals with the development, and parameterization, and simulation of the forward model of carotid sinus massage. Chapters 5-7 focus on the application of beat to beat measures of cardiovascular control in experimental studies to further our knowledge of

CSH pathophysiology and diagnosis i.e. blood pressure variability, heart rate variability, baroreflex sensitivity in 3 studies with cumulative participation of > 150 patients. Finally Chapter 8 concludes with a conclusion of results and discussion of future directions.

CHAPTER 3

A Computer Model to Simulate the Cardiovascular Effects of Carotid Sinus Massage in Health and Disease

In this chapter we build upon published models of the cardiovascular system to develop a model capable of simulating the effects of Carotid Sinus Massage. Of note the model includes compartments describing cerebral blood flow, carotid arteries under massage, and a baroreceptor model. Model assumptions, relevant physiology and parameter selections are discussed.

CHAPTER 3

3.1 Introduction

Carotid Sinus Massage (CSM) is a simple, low cost method for stimulating the carotid sinus reflex (Parati, Di Rienzo et al. 2000). During CSM, firm longitudinal massage is applied at the point of maximal pulsation over the carotid bifurcation at the level of the crichoid cartilage (O'Shea, Parry et al. 2001). CSM was first reported in western medicine by Parry in 1799 (Parry 1799), and was the impetus for the detailed research of Hering et al (Hering 1923).

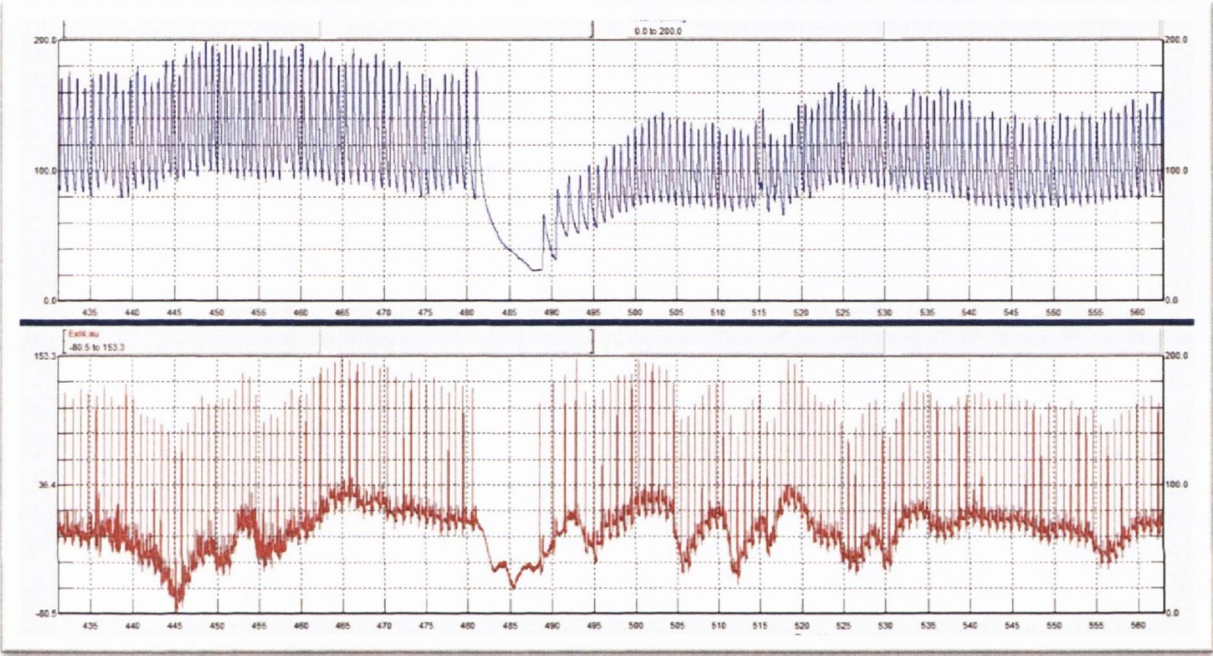


Figure 3.1: Mixed Cardioinhibitory and Vasodilatory responses to CSM

The ‘classical’ cardiovascular response to unilateral CSM provided by Hering is still well accepted by the scientific community today. Strain sensitive baroreceptors embedded in the adventitial layers of a dilated portion of the internal carotid artery (ICA) are activated by massage induced deformation of the ICA wall. Action potentials generated by increased strain are transmitted to cardiovagal and vasomotor areas of the brainstem medulla via glossopharyngeal nerves (Miller, Kenny et al. 2008). Vagal activation and sympathetic withdrawal ensues, resulting in cardioinhibition and vasodilatation, leading to bradycardia and systemic hypotension. This response is exaggerated in CSH (Figure 3.1).

The clinical importance of CSM has grown over the last number of years. CSM is the defacto choice for diagnosis of Carotid Sinus Hypersensitivity (CSH), an age related disorder, characterized by exaggerated cardioinhibitory (> 3 seconds pause) and/or vasodepressor

(>50mmHg drop in blood pressure) responses to CSM (See Figure 3.1). When CSH is accompanied by symptoms, Carotid Sinus Syndrome (CSS) is diagnosed (Moya, Sutton et al. 2009). CSH is prevalent in up to 39% of community dwelling older adults aged 65+ (Kerr 2009) and is responsible for 1% to 20% of all pacemaker implantations per year (Healey, Connolly et al. 2004). CSH is a well recognized cause of syncope and recurrent unexplained falls in the elderly (Kerr, Pearce et al. 2006) and has been associated recently with increased levels of cognitive decline (Kenny, Kalaria et al. 2002).

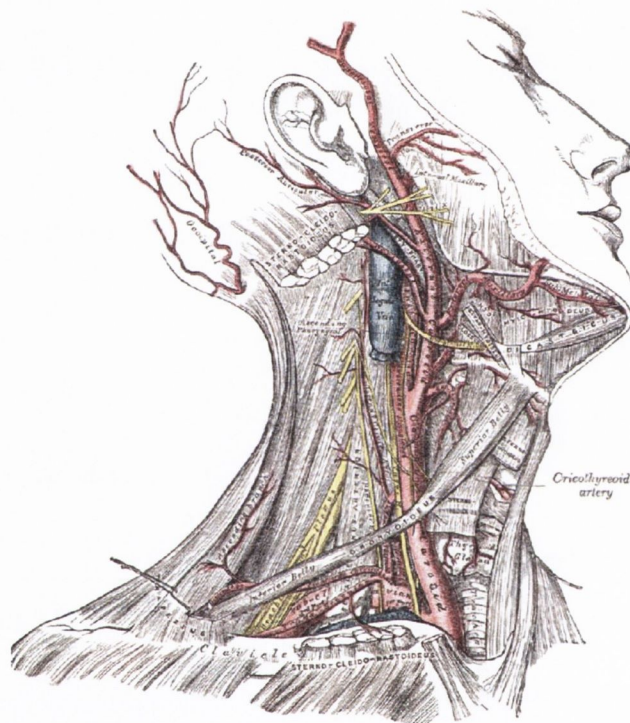


Figure 3.2: Carotid Sinus Massage performed adjacent to a number of anatomical structures i.e. carotid sinus, carotid body containing chemoreceptors, sternocleidomastoid muscle, superior recurrent laryngeal nerve, jugular vein, internal, and common carotid artery

Although the effects of CSM are reportedly well understood (i.e. the Herring inspired baroreflex mechanism) a number of facts suggest that this picture is incomplete. Firstly treatment options are inadequate, especially for the vasodepressor and mixed subtypes (Healey, Connolly et al. 2004). Secondly a number of case reports have also suggested the presence of rare, paradoxical complications of CSM which are not consistent with pure vagal stimulation i.e. tachycardia and tachyarrhythmias (Fox, Verga et al. 2008). Thirdly, much

debate still remains around the underlying pathophysiology of CSH with central (Miller, Kenny et al. 2008), peripheral (Kallikazaros, Stratos et al. 1997; Tsioufis, Kallikazaros et al. 2002; Tsioufis, Thomopoulos et al. 2003) and muscle afferent (Tea, Mansourati et al. 1996; Blanc, L'Heveder et al. 1997) hypotheses being suggested. Finally only CSM consistently detects a hypersensitive response in CSH, while other tests of baroreflex and autonomic control often suggest presence of blunted neural control in the same pathology (Kenny, Allen et al. 1993; Morillo, Camacho et al. 1999). This confusion may in part be due to the lack of understanding of the local and global effects of CSM, and of the normal age related and pathophysiological changes which occur in CSH. Greater insight into mechanisms of CSM should foster development of treatment options for CSH and a reduction in the occurrence of adverse events during testing.

The simplicity of CSM belies the possible complexity of the reflexes involved. CSM is performed at the presumed location of the carotid sinus baroreceptors, a site known to lie in close proximity to blood flow and O₂ sensitive carotid chemoreceptors (Lown and Levine 1961) (Figure 3.2). Indeed historically hyperpnea was also reported to occur in response to CSM, and was proven by Galdston et al. (Galdston, Goldstein et al. 1943) to be due to chemoreceptor stimulation. More recent neurophysiological research has indicated that chemoreceptor and baroreceptor responses are integrated at the level of the nucleus tractus solitarius (NTS) in the brainstem and modulate responses to one another (Silva-Carvalho, Paton et al. 1998). CSM not only affects blood flow locally but causes well known feedforward changes in ipsilateral and contralateral cerebral blood supply and is thus essentially a partial/complete carotid occlusion test of cerebral autoregulation (Eckard, Purdy et al. 1992). Thus the physiological model of CSM may require review. Instead of a pure baroreflex stimulus, evidence suggests that CSM could involve simultaneous local and global baroreflex, chemoreflex and cerebral autoregulatory stimulation i.e. integration of a complex array of nonlinear reflexes. This interpretation if correct may have implications for our understanding of CSH and its treatment.

As a step toward greater understanding of CSM, the approach taken in this chapter is to develop a computer based simulator of the cardiovascular system, capable of simulating a number of the proposed local and global responses to CSM. A mathematical model is a concise summary of all our physiological and clinical knowledge of a particular system (Heldt, Shim et al. 2002), and is a useful adjunct to hypothesis generation as part of the clinical research process (Heldt, Shim et al. 2002), demonstrating and explaining physiological

concepts (Giannessi, Ursino et al. 2008), supporting diagnosis especially in complex multifactorial cases and testing “what if” treatment scenarios (Smith, Chase et al. 2004; Starfinger, Chase et al. 2008). As far as we are aware no mathematical models to date have examined the response to CSM explicitly. Beginning with the compartmental model of Grodins et al. (Grodins 1959) numerous comprehensive models have been developed since the late 1950’s with some detailing baroreflex responses (Ursino, Fiorenzi et al. 1996), others chemoreflex (Batzel, Kappel et al. 2006) and others still cerebral autoregulation (Lodi, Ter Minassian et al. 1998). Individually these models don’t include the full complement of features required to examine all the questions surrounding CSM which concern us. However by aggregating relevant elements from each and with the addition of some subcomponents we develop a model capable of simulating the response to CSM.

Of particular importance to this work are recent cardiovascular models of Heldt et al (Heldt, Shim et al. 2002), van Heusden et al (van Heusden, Gisolf et al. 2006) , Ursino et al. (Ursino and Magosso 2006) and Olufsen et al. (Olufsen, Nadim et al. 2002; Olufsen, Ottesen et al. 2005; Olufsen, Tran et al. 2006; Olufsen, Alston et al. 2008; Valdez-Jasso, Haider et al. 2009). Heldt et al. (Heldt, Shim et al. 2002), developed a comprehensive short term blood pressure regulatory model to simulate causes of orthostatic intolerance in astronauts during tilt table testing. The model includes a detailed cardiovascular model with the ability to include postural related changes in blood pressure and carotid, aortic, cardiopulmonary reflex models. Van Heusden et al. (van Heusden, Gisolf et al. 2006) augmented the venous portion of the Heldt model to include viscoelastic stress relaxation properties of the systemic veins. Ursino (Ursino and Magosso 2006) recently reviews his comprehensive work over the past twenty years in cardiorespiratory modelling, which has lead to the development of an integrated model of short-term cardiovascular regulation which includes the non-linear interaction among several control mechanisms, including baroreceptors, peripheral chemoreceptors, lung-stretch receptors, a direct CNS response to hypoxia and hypercapnia and a local vessel response to changes in blood gas content. Giannessi et al. (Giannessi, Ursino et al. 2008) has recently extended this model further to include respiratory mechanics and metabolic exchange. Deformable neck artery components are included as part of an occlusion test by Lodi et al. (Lodi, Ter Minassian et al. 1998) and are particularly relevant to predicting the flow effects of CSM. Unilateral baroreflex and chemoreflex models do not exist. Olufsen et al. (Olufsen, Ottesen et al. 2005) has developed a model capable of simulating the sit-to-stand manoeuvre, and includes a simple piecewise linear model of cerebral autoregulation. The effects of pressure induced changes in vessel calibre on

pressure patterns are also investigated and shown to be important in reproducing proper pulse pressures.

Specific models of baroreceptors have been developed by Taher et al. (Taher, Cecchini et al. 1988) and Ottesen et al. (Ottesen 1997) which include dynamic properties which our model requires. These models both include representations of different fibre types characterised by different adaptation time constants. We include another aspect of baroreceptor function i.e. the inclusion of different baroreceptor fibre types with different saturation and threshold values. We feel that this nonlinearity is important in simulating the high strain conditions encountered during CSM. To achieve this as a first approximation we use a lumped sigmoid to estimate the baroreceptor population response. By varying the overall range baroreflex we can examine as a first approximation the effect of different baroreceptors with different saturation and threshold values.

In cerebrovascular research the use of mathematical models can be traced back to the work of Matakas et al. (Matakas, Von Waechter et al. 1975). These models found applications in studying intracranial pressure (ICP) response to pressure-volume tests (Cirovic, Walsh et al. 2003), the significance of ICP (Giulioni and Ursino 1996) and transcranial Doppler pulsatility indices (Ursino, Giulioni et al. 1998). The analysis and model by Ursino and colleagues is particularly pertinent here as it investigates the effects of unilateral carotid occlusion on cerebral autoregulation (Ursino, Lodi et al. 2000).

The approach taken in this chapter is as follows. Each subcomponent of the model is developed with assumptions and limitations stated. These elements are then parameterized and simulated to ensure accurate, robust and stable results. Qualitative and quantitative validation of the model is performed by examining its ability to simulate a number of common cardiovascular conditions (Smith, Chase et al. 2004).

We then use our model to probe some questions of concern which surround CSM methodology. Scientific justification for the choice of CSM clinical parameters such as magnitude, duration and rate of force applied are not readily available in contemporary clinical literature. We examine the effect of these parameters on CSM outcome variables i.e. heart rate, blood pressure and cerebral blood flow allowing us to suggest a set of optimum stimulus parameters which can inform future clinical practice.

Finally and most significantly a novel simulation of CSH is presented. Candidate physiological parameters are identified through model sensitivity analyses which most likely play a role in

the pathogenesis of CSH. This has obvious implications for CSH diagnosis and treatment. Through a trial and error simulation process the spectrum of system dynamics are examined leading to the identification of the existence of a possible novel clinical subtype of Carotid Sinus Syndrome.

3.2 Aim

The following are the aims of the chapters 3 and 4:

1. State general modelling assumptions made during model design.
2. Develop a comprehensive cardiovascular model capable of simulating the normal cardiovascular response of man to Carotid Sinus Massage to include[†]
 - a. Cardiovascular model to include a 2 chamber heart, head, combined thoracic and abdominal chamber, lower limb compartments.
 - b. Effects of orthostatic stress and intrathoracic pressure variations.
 - c. Baroreflex with left and right carotid sinus, aortic and cardiopulmonary baroreceptors.
 - d. SA and AV node control included.
3. Demonstrate that model gives normal steady state and perturbation responses.
4. Examine the effect of stimulus parameters on CSM response.
5. Simulate the CSH response and identify candidate parameters indicated in pathogenesis of CSH.
6. Simulate range of system dynamics, with a view to identifying possibly new clinical subtypes of CSM response.

3.3 Methods

The cardiovascular system is a complex distributed system of conduit vessels. Blood is pumped from the high pressure arterial side, through the microcirculation to the low pressure venous system. Each vessel is composed of a mix of elastic fibers, stiff collagen and active muscle fibers. Under certain conditions (i.e. extremes of pressure) these vessels exhibit nonlinear pressure volume relationships. Furthermore the vessels within each of the three subdivisions of vessels display widely varying physical behaviours owing to the differences in the relative mix of constituent fibres and must be parameterized accordingly. Blood itself behaves as a non-Newtonian fluid especially in smaller blood vessels. Controlling this system is a vast reciprocally connected network of autonomic nerves, with nuclei

[†] Cardiorespiratory effects of CSM induced chemoreceptor and muscle afferent activation are not included explicitly as part of this initial model. Instead we assume that they have a net inhibitory effect on baroreflex sensitivity during CSM.

residing in all areas of the central nervous system from higher order cortical areas to the lower level peripheral nerves. These serve to provide global control, direct blood cells, O_2 and nutrients throughout the body to meet the energy requirements of specific bodily organs under the demands of different behavioural contexts. Prior to developing a simplified mathematical representation of this system, we highlight the range of assumptions made.

3.3.1 General Model Assumptions

The following assumptions were made in constructing the model

- A lumped parameter pulsatile compartmental model was assumed. Distributed effects are ignored.
- Linear capacitance and resistance values for most arterial compartments are assumed.
- Inertial effects are neglected.
- Blood is assumed incompressible.
- The cardiovascular system is assumed to be a closed system.
- Interaction between topologically adjacent compartments is negligible.

A brief discussion of each assumption now follows.

3.3.1.1 Lumped Parameter Model

Although the cardiovascular system is a complex and highly distributed system, a lumped parameter model is assumed suitable for the purposes of this work with transient variations in cardiovascular parameters lasting to a maximum of 3 minutes. The model is thus incapable of modelling distributed phenomena but instead represents the average behaviour of each lump. This is justified on the basis that clinical interest in CSH (and other NCVI's except vasovagal syncope) is focused on transient changes in average pressures, volumes and flows lasting up to 3 minutes in duration following stimuli, which occur at frequencies lower than the mean heart rate. Simulation of intra cycle variations such as wave reflection effects are not of immediate interest and would come at a cost of increased model and computational complexity and can be introduced in future models if necessary (Samar et al, 2005).

3.3.1.2 Non Linear and Linear Vascular Elements

The majority of capacitances and resistances of the model can be assumed linear in the range of pressures experienced during normal steady-state supine conditions in young healthy individuals. A number of non-linearities may come into play during orthostasis and transient increases in transmural pressure experienced during CSM. The pressure-volume

relationship of vessels is characterized by a sigmoidal relationship, brought about by the initial recruitment of elastic fibres followed at higher pressures by stiff low strain collagen fibers. The relative proportion of collagen to elastic fibers brings about the wide variation in vessel behaviour and can account for changes in vessel biomechanics due to aging [See Figure 3.3].

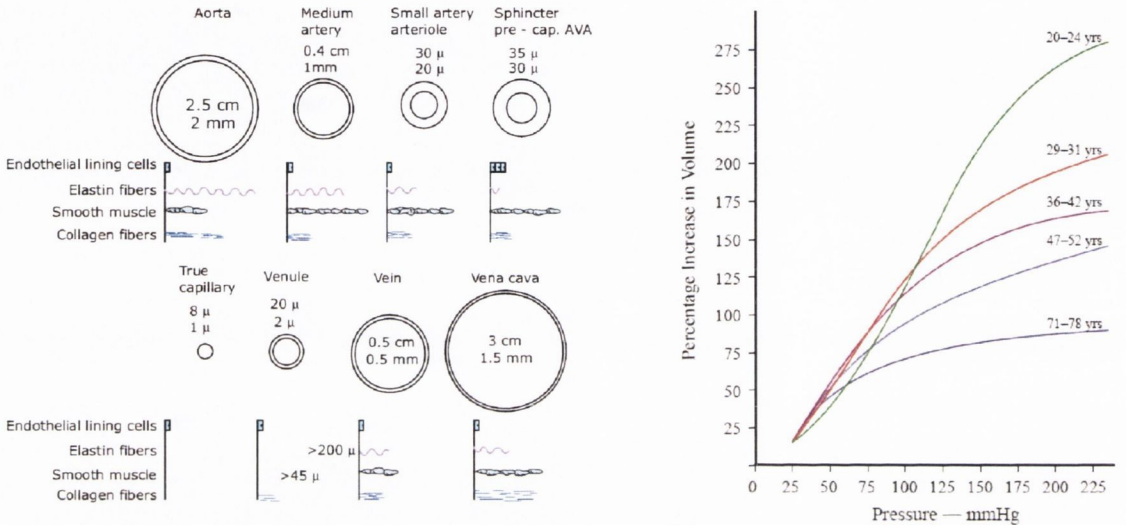


Figure 3.3: Structural composition of blood vessels (left). The effect of age on the pressure volume relationship of the aorta in man (Berne and Levy, Cardiovascular Physiology, 4th ed. (1981), p. 97.)

At normal transmural pressure changes are assumed linear and thus capacitance values of arteries are constant with pressure in this range. However at the high pressures experienced during CSM, the carotid arteries operate at least momentarily in the nonlinear saturation regime.

There is also a large variation in pressure volume characteristics through the vessels of the body (Conroy 1970). During orthostasis pressure in lower limbs increases due to hydrostatic pressure gradients. Thus lower limb vessels in this area operate in non-linear portions of the pressure-volume curve. On the other hand superiorly positioned vessels tend to operate at lower mean pressures, functioning at the linear portion of the curve. The non-linear pressure volume function is thus especially important when considering behaviour of the lower limb venous capacitance vessels (Melchior, Srinivasan et al. 1992; Melchior, Srinivasan et al. 1992; Melchior, Srinivasan et al. 1993). Van Heusden et al. (van Heusden, Gisolf et al. 2006) recently described the effects of passive viscous vessel relaxation. Delayed stretching of vessels in the lower limbs serves to aid maintenance of blood pressure and reduces initial blood pressure drops during tilt table testing and is thus important in counteracting

hypotension. Another non-linearity especially prevalent in upper body veins and pulmonary circulation is vessel collapse. This occurs when transmural pressures are negative and has the effect of reducing blood flow to zero in these vessels. These can be modeled by single or parallel arrangements of Starling resistors subject to external and internal pressure variations (Heldt, Shim et al. 2002). For simplicity we ignore these effects.

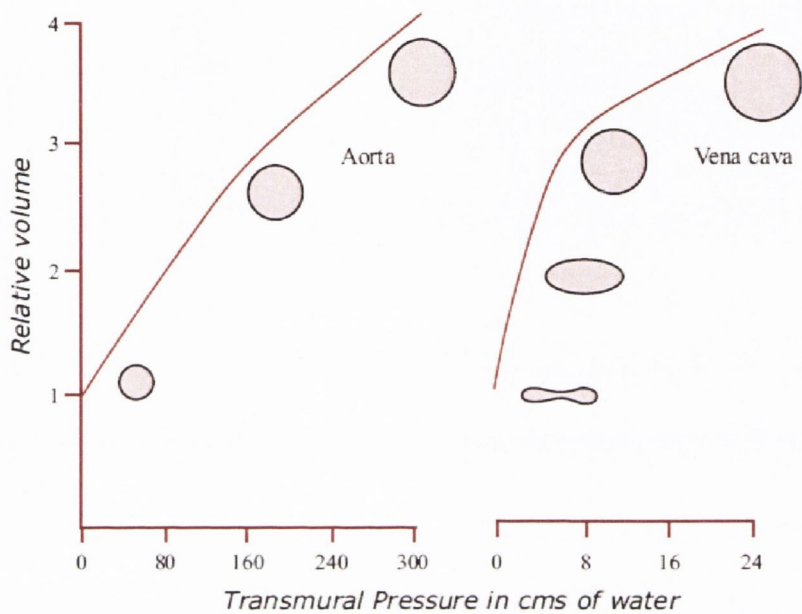


Figure 3.4: Comparison of the pressure-volume characteristic of aorta (left) versus the vena cava (right). Note collapse of the veins at low transmural pressures.

Although vessel resistance to blood flow is typically modeled as a constant parameter, pressure driven changes in lumen diameter (governed by Laplace law) are known to cause changes in apparent vessel resistance to flow. Both Aletti et al. (Aletti, Lanzarone et al. 2009) and Olufsen et al. (Olufsen, Ottesen et al. 2005) note the importance of this effect in microvasculature and large arteries respectively, detailing an apparent reduction in resistance to flow and increase in pulse pressures respectively. Again as part of our initial model these effects are ignored.

3.3.1.3 Viscous Dominated Flow

Inertial effects of blood acceleration are ignored for our purposes (Heldt, 2004). These are typically included to improve the morphology of modelled blood pressure waveforms. The contribution of inertial energy is small in both high pressure and low pressure areas relative to viscous dissipative effects and so can be ignored. Relatively high accelerations occur during valve opening and closing in the heart and aorta and are thought to be responsible for production of the dicrotic notch. Even during high accelerations experienced during

orthostasis, inertial effects were shown by Defares et al.(Defares, Osborn et al. 1963; Defares, Osborn et al. 1965; Defares 1966) to contribute to only 1% of total stroke volume and mean arterial pressure and so can be neglected for our purposes.

3.3.1.4 Anatomical Simplicity and Closed System

The complete system is assumed for our purposes to be a closed system, hence blood volume is conserved. This assumption is valid over short time periods less than 1 minute. The assumption is violated during hemorrhage, infusion of pharmacological agents and prolonged orthostasis. Initially these phenomena are not important for our consideration. Volume changes experienced are implemented through variation in total blood volume during the validation stage.

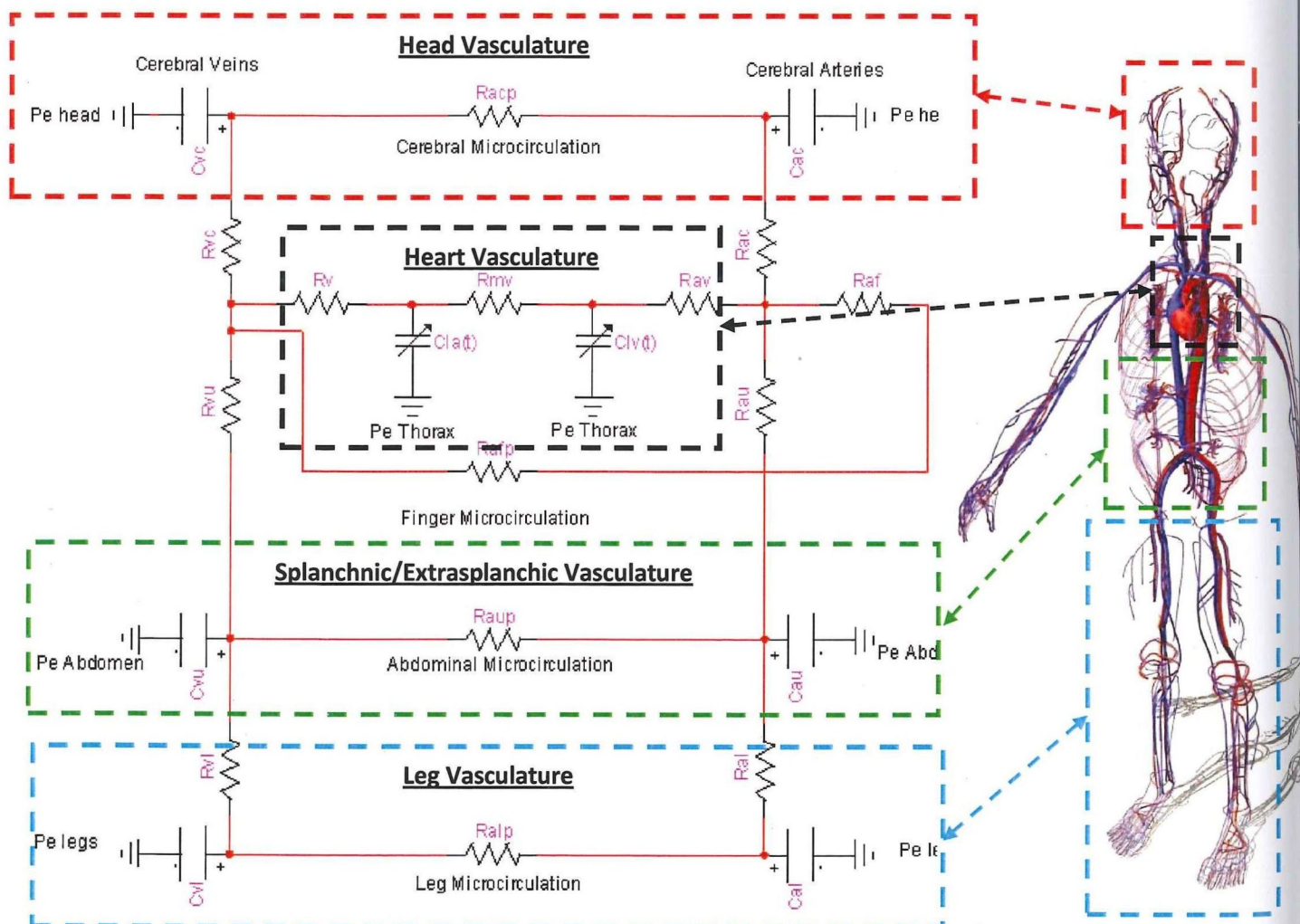


Figure 3.5: Electrical equivalent circuit of hemodynamic system (left). MRI reconstruction of anatomical areas modeled (right).

The anatomical simplicity of our model implies that interaction of adjacent structures i.e. adjacent heart chambers and adjacent blood vessels are ignored. This is not strictly correct in reality. Right and left heart chambers are separated by a flexible septal wall. Motion of this wall can cause relative changes in blood volume. Pressure variations in high pressure arteries are also known to induce pressure variations in adjacent low pressure veins (Samar, 2005).

3.3.2 Model Architecture

Our cardiovascular model is based on a framework similar to that proposed by (Heldt et al, 2002) consists of a compartmental model which predict blood pressure and volumetric blood flow in the left atrium, left ventricle, aorta, vena cava, arteries, and veins in the upper body (splanchnic and extrasplanchnic), lower body, and head (left and right cerebral arteries), as well as arteries in the finger (Fig. 3.5).

Lower and upper body arteries and veins are modelled to ensure the effect of blood pooling due to combined orthostasis and carotid sinus massage is well described. Head and neck arteries are included to examine the effects of unilateral carotid sinus massage on transient head blood flow. Finally two compartments are included to represent the left atrium and left ventricle.

Each compartment represents all vessels in the areas of similar pressure and is represented by a vascular segment building block shown in Figure 3.6. This is the electrical equivalent circuit of a compliance element (inverse elasticity) separated by resistance to flow (inflow R_i and outflow R_{i+1}), where a capacitor of capacitance C_i , is used to model the pressure-volume (V_n) relationship of the blood vessel in question. Resistance to flow is measured in P.R.U (Peripheral Resistance Units = mmHg sec ml⁻¹) and as a first approximation is related to the geometry of the vessel in question by Poiseuille's Law by the following equation:

$$R = \frac{8}{\pi} \mu \frac{l}{r^4} \tag{1}$$

where r is vessel radius, l its length and μ the viscosity of blood. As can be seen the major determining physical factor of resistance is the vessel radius. Small changes in arterial radius can bring about large changes in resistance. Since blood flowing throughout the system is inhomegenous non-Newtonian fluid, pulsatile in nature and the conduit vessels are

compliant the assumptions upon which Poiseuille's law are not strictly valid[†]. The major resistance to flow is generally located in the microcirculation at the arterioles, since large conduit vessels have a relatively small resistance to flow.

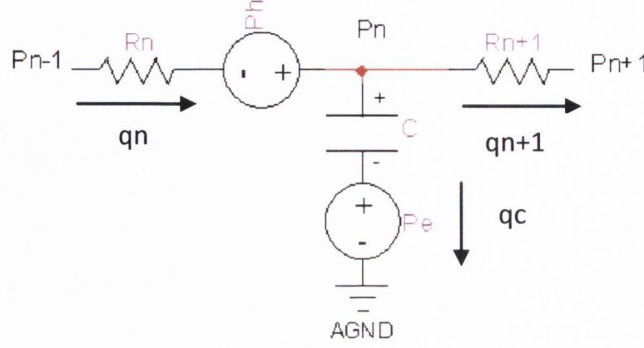


Figure 3.6: Electrical Equivalent circuit of a vascular segment compartment (Adapted from (Heldt, Shim et al. 2002))

The capacitance, C , is measured in ml/mmHg and describes the change in the volume of a vessel for a given change in transmural blood pressure ($P_n - P_e$), where P_e is the external pressure on vessel. It can be shown that C is related to the radius, r , Young's modulus, E , and vessel wall thickness, h , by the following equation:

$$C \approx \frac{2\pi r^3}{Eh} \quad (2)$$

Inertial effects are ignored here but can be included using a simple inductor if required to improve mid and high-frequency responses of model[§].

Compartmental blood pressures, P_i , are represented by voltages, while volumetric flow rate, q_i , is modelled by current. Note these are time-varying pressures and flows, where for notational convenience (t) is dropped. The pressure source P_h represents the hydrostatic gradient associated with a given vessel and P_e represents the pressure acting externally to the vessel (e.g. atmospheric, intrathoracic or negative neck pressure).

Applying conservation of mass we derive the following governing equations for a generic compartment to represent the n^{th} vascular segment

[†] Poiseuille's Law is based on assumption of steady flow of a homogenous, Newtonian fluid through a rigid tube.

[§] The inductance L of a vessel relates the rate of change of volumetric flow of blood to the induced pressure change. This can be similarly related to vessel parameters by the following equation

$$L = \frac{9\rho l}{4\pi r^2}$$

where l is length and r is radius and ρ is blood density.

$$q_n = \frac{P_{n-1} - (P_n - P_h)}{R_n} \quad (3)$$

$$q_{n+1} = \frac{P_n - (P_{n+1})}{R_{n+1}} \quad (4)$$

$$q_c = \frac{dV}{dt} = \frac{dC(P_n - P_e)}{dt} + \frac{dV_U}{dt} = C \frac{dP_n}{dt} + P_n \frac{dC}{dt} - \left(C \frac{dP_e}{dt} + P_e \frac{dC}{dt} \right) + \frac{dV_U}{dt} \quad (5)$$

$$q_n = q_{n+1} + q_c \quad (6)$$

Note V_U is the unstressed volume and $V = C(P_n - P_e) + V_U$ where V is total blood volume.

Therefore,

$$C \frac{dP_n}{dt} = \frac{P_{n-1} - (P_n - P_h)}{R_n} - \frac{P_{n+1} - (P_n)}{R_{n+1}(t)} - P_n \frac{dC}{dt} - \frac{dV_U}{dt} + \left(C \frac{dP_e}{dt} + P_e \frac{dC}{dt} \right) \quad (7)$$

In general this can be simplified to

$$C \frac{dP_n}{dt} = \frac{P_{n-1} - (P_n - P_h)}{R_n} - \frac{P_{n+1} - (P_n)}{R_{n+1}} \quad (8)$$

assuming the capacitance, unstressed volume and external pressures are constant^{**}. Thus our model consists of a set of n first order differential equations with pressures chosen as the state variable of interest. In some cases it is advantageous (or just a more natural choice!) to take chamber volume as the state variable from a numerical stability point of view. This point will be highlighted as necessary in the implementation section of this chapter.

3.3.3 Systemic Circulation

In this and following sections of this chapter we describe the selection of physical parameters for each of the compartments of the hemodynamic system. The selected values are guided where possible by human physiology and clinical literature or where necessary extrapolated from animal models. Finally we resort to estimation and an iterative refinement process through simulation where no available data exists on physical parameters of interest. The initial focus of this work is to understand the cardiovascular system response to carotid sinus massage in healthy adults. The parameters in this chapter

^{**} The first order differential terms removed in this step become important in cardiac compartments during rapid heart chamber contraction, reflex induced changes in venous tone and changes in external pressures such as lower body negative pressure.

are described as such and are representative of a 169cm, 70kg male subject with a total blood volume of 5100ml and cardiac output of 4813 ml/min.

Each compartment within the systemic system is described by

- A height value i.e. vertical distance of vessel to a hydrostatic indifference point (point where pressure does not change during body movement) used to calculate hydrostatic pressure experienced by each compartment during orthostasis.
- Input and output resistances to flow.
- Capacitance value obtained from reported pressure-volume characteristics of individual vessel segments.
- External pressure used to vary blood volume distribution in vascular beds in response to gravitational challenges.

The origin of these values is now described briefly.

3.3.3.1 Vascular Resistances

To assign parameters we adopted an approach used by Mark, Heldt and co-workers (Heldt et al., 2004). Most of the blood pressure gradient drops occur on the arterial side of the circulation with over 68% of total peripheral resistance residing in the microcirculation (arterioles and capillaries^{††}). Peripheral resistance estimates were derived from the approximate distribution of cardiac output (CO) to the circulatory branches modelled i.e. head and upper body 23% of CO, kidney and splanchnic circulation 52% of CO and lower body 25% of CO (Leggett and Williams 1995). We modeled microcirculatory resistance values to produce a total peripheral resistance of 0.933PRU. The upper body, R_{acp} , abdominal organs, R_{aup} , and legs, R_{alp} , were modelled as resistances of 6.196PRU, 2.01PRU, 4.5PRU respectively resulting in a parallel equivalent resistance of 0.933PRU^{††}.

Estimates of cerebral artery resistances, R_{ac} , by both Heldt et al. (Heldt, 2004) and Olufsen et al. (Olufsen, Ottesen et al. 2005) vary quite widely in their values from 0.015PRU to 0.409PRU respectively. An intermediate value of 0.11PRU was chosen as this produces values closer to typical blood pressure drops over vessels with a relatively large caliber (i.e. 2-3mmHg drop with 23% CO).

The abdominal compartment lumps together estimates of the effective parallel resistance of arteries serving the kidneys and splanchnic regions (0.041 PRU) (Heldt, Shim et al. 2002) with

^{††} 25% and 7% of resistance is posed by the remaining arteries and veins respectively.

^{††} Peripheral resistance of the arm and fingers values suggested by Olufsen et al. [] i.e 20 PRU were used and included in this calculation

estimates of thoracic and lower abdominal aortic resistance (0.01 PRU + 0.011 PRU) (O'Rourke 1982) assuming a 2mmHg drop in BP between abdominal aorta and abdominal microcirculation. We thus arrive at a value of 0.062 PRU for the upper body compartment resistance, R_{au} , a value close to that of 0.072 PRU suggested by Olufsen et al (Olufsen, Ottesen et al. 2005). Finally leg resistance, R_{al} , values of 0.087 PRU were used based on estimates provided by both Heldt 0.09PRU (Heldt, Shim et al. 2002) and Olufsen 0.087PRU (Olufsen, Nadim et al. 2002).

On the venous side, a relatively low resistance to blood flow is typically found (in absence of vessel collapse). Low values of resistance of 0.033PRU, 0.001PRU, 0.05 PRU and 0.11PRU were assigned to the vena cava, R_{vc} , upper body (thorax and abdomen), R_{vu} , leg, R_{vl} , and head veins, R_{vc} , respectively based on pressure measurements in inferior/superior vena cava and leg arteries described by (Wood 1958) and (Arnoldi and Linderholm 1969) respectively.

These resistance values are summarised in Table 3.1.

Symbol	Vessel Resistance	Value	Reference
	Arterioles and Microcirculation		
Racp	Cerebral peripheral resistance	6.196PRU	(Heldt, 2004) (Leggett and Williams 1995)
Raup	Abdominal Organs (Splanchnic and Extrasplanchnic)	2.01PRU	(Heldt, 2004) (Leggett and Williams 1995)
Ralp	Legs	4.5PRU	(Heldt, 2004) (Leggett and Williams 1995)
Rafp	Finger	20PRU	(Olufsen, Ottesen et al. 2005)
	Arteries		
Rac	Cerebral artery	0.212PRU	Intermediate (O'Rourke 1982) (Olufsen, Ottesen et al. 2005)
Rau	Arteries serving abdominal organs (Splanchnic and Extrasplanchnic)	0.062PRU	(Heldt, 2004) (O'Rourke 1982)
Ral	Leg arteries	0.087PRU	(Olufsen, Ottesen et al. 2005)
Raf	Finger/Arm arteries	0.183PRU	(Olufsen, Ottesen et al. 2005)
	Veins		
Rv	Vena cava	0.033PRU	(Olufsen, Ottesen et al. 2005)
Rvu	Upper body	0.001PRU	(Olufsen, Ottesen et al. 2005)
Rvl	Leg	0.05PRU	(Heldt, 2004) (O'Rourke 1982)
Rvc	Cerebral	0.11 PRU	(Heldt, 2004) (Arnoldi and Linderholm 1969)

Table 3.1: Vessel Resistances

3.3.3.2 Vascular Capacitance

As noted earlier blood vessels behave like distensible tubes, with a nonlinear pressure-volume curve, characterized by a soft-limiter sigmoidal function. Additionally an unstressed volume parameter is included when total blood volume is considered.

Many estimates of arterial capacitance have been made experimentally (de Simone, Roman et al. 1997; Balmain, Padmanabhan et al. 2007). Under conditions considered here arterial pressures can be assumed to operate in the linear region of the pressure-volume curve. When choosing appropriate parameter assignments we must be cognisant of parameters quoted in literature and the resultant time constant of approximately 1.9s which characterizes flow dynamics from arterial to venous system (Heldt, Shim et al. 2002).

On the arterial side total capacitance values for the aorta, C_a , upper body, C_{au} , finger, C_{af} , legs, C_{al} , and head, C_{ac} , were assigned values of 0.28 ml/mmHg (Remington and Hamilton 1945), 0.63 ml/mmHg (Heldt 2004), 0.1ml/mmHg (Olufsen, Ottesen, et al. 2005), 0.42 ml/mmHg (Heldt 2004), 0.42 ml/mmHg (Heldt 2004) respectively resulting in a total lumped capacitance of 1.85ml/mmHg^{§§} and an overall time constant of 1.72 seconds. Total stressed volume in the arterial system at a MAP of 92mmHg is thus 170.2ml. Similarly unstressed volumes for the same compartments were derived from estimates by the same authors (Remington and Hamilton 1945; Heldt 2004).

Capacitance on the venous side of the circulatory system plays a vital role in blood volume storage. During orthostasis the pressure in the lower limb and abdominal vessels increases significantly since a significant portion of blood is transferred to the lower abdomen and limbs. Thus the pressure-volume curve suggested by (Heldt et al, 2004) is assumed to be non-linear in these vessels according to Equation 9

$$V_t(\Delta P) = V_0 + \frac{2V_{max}}{\pi} \cdot \arctan\left(\frac{\pi C_0}{2V_{max}} \Delta P\right) \quad (9)$$

where C_0 is the compliance at zero transmural pressure, V_0 is the vessel unstressed volume, and V_{max} is the limit of the distending volume. For lower limbs and inferior vena cava the pressure-volume relationships functions were derived by fitting data described by Henry (Henry 1951) (See Figure 3.7) resulting in C_0 of 20ml/mmHg and V_{max} of 1200ml. Total blood volume in legs, pelvis, buttocks is 1112ml volume (Leggett and Williams 1995). Assuming 160ml and 36 ml of distending volume for the venous and the arterial vessels, respectively,

^{§§} Finger capacitance of 0.1 after Olufsen et al. 2005 was also included.

suggests a total unstressed volume of 916 ml, 200 ml of this assigned to the arterial compartment and the remaining 716 ml to the venous side.

The splanchnic circulation is the major reservoir of blood in the body containing about (20-26)% of total blood volume (Leggett and Williams 1995). Rowell (Rowell 1993) measured vascular compliance of 2.5 ml/mmHg/kg of tissue weight for the intestines, and 25ml/mmHg/kg for the liver. When combined with their values of tissue masses for humans an human splanchnic venous compliance of approximately 50 ml/mmHg (Leggett and Williams 1995) and a total splanchnic blood volume of 1880 ml is derived. Assuming a splanchnic venous pressure of 8mmHg and arterial unstressed volume of 300 ml suggests an unstressed volume of 1142 ml for the splanchnic venous circulation in accordance with Heldt (Heldt, 2004).

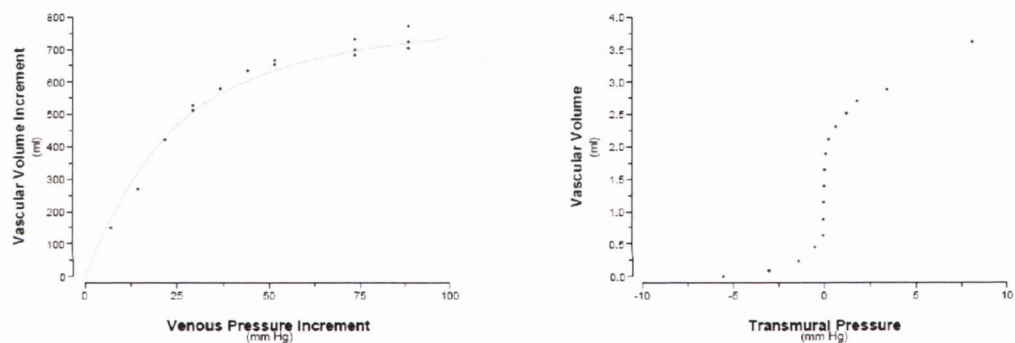


Figure 3.7: Pressure volume relationship of leg veins (left) and common iliac veins (right) (Heldt, 2004)

The circulation of the head, the neck, and the upper limbs constitute approximately 18.3 % of total blood volume, i.e. 937 ml (Rowell 1993). The arterial distending volume is approximately 38 ml, and if the assumed arterial unstressed volume is 200 ml, a remaining total venous volume of approximately 700 ml is left. A lumped venous compliance of 7 ml/mmHg is assigned to the upper body compartment, and thus the venous unstressed volume is given a value of 643 ml (Heldt, 2004).

Symbol	Vessel Compliance	Value	Reference
	Arteries		
Ca	Aortic compliance	0.28ml/mmHg	Heldt,2004; Remington and Hamilton 1945
Cau	Thoracic and Abdominal artery compliance	0.63ml/mmHg	Heldt, 2004
Cal	Leg arteries compliance	0.42ml/mmHg	Heldt 2004
Caf	Finger arteries compliance	0.1ml/mmHg	Olufsen, Ottesen, et al. 2005

Cac	Cerebral Artery compliance	0.42ml/mmHg	Heldt, 2004
	Veins		
Cvl	Leg veins compliance	20ml/mmHg	Legget, Williams, 1995; Heldt, 2004
Cvu	Thoracic and Abdominal vein compliance	50ml/mmHg	Legget, Williams, 1995; Heldt, 2004
Cv	Vena cava compliance	2.931ml/mmHg	Olufsen, Ottesen, et al., 2005
Cvc	Cerebral vein compliance	7ml/mmHg	Rowel, 1993; Heldt, 2004
	Unstressed Volumes Arteries		
Voa	Aortic unstressed volume	21ml	Heldt, 2004
Voau	Thoracic and Abdominal unstressed volume	320ml	Heldt, 2004
Voal	Leg arteries unstressed volume	200ml	Heldt, 2004
Voaf	Finger arteries unstressed volume	64ml	Olufsen, Ottesen, et al., 2005
Voac	Cerebral Artery unstressed volume	200ml	Heldt, 2004
	Unstressed Volumes Veins		
Vovl	Leg veins compliance unstressed volume	716ml	Legget, Williams, 1995; Heldt, 2004
Vovu	Thoracic and Abdominal unstressed volume	1142ml	Legget, Williams, 1995; Heldt, 2004
Vov	Vena cava unstressed volume	168.5ml	Olufsen, Ottesen, et al., 2005
Vovc	Cerebral vein unstressed volume	643ml	Heldt, 2004

Table 3.2: Vessel Compliances

3.3.3.3 Vascular Lengths

The values for the height of each vascular component about the hydrostatic pressure indifference point are based on values reported in the literature for specific vascular beds (Rowell 1993; Heldt, Shim et al. 2002; van Heusden, Gisolf et al. 2006). These values were based on life sized anatomical models, extrapolation from standard anatomical text books and from anthropomorphic studies. The heights for each of the compartments are depicted in Figure 3.8. Each height value is measured from the midpoint of each compartment in question i.e. point where the average compartment pressures and volumes are found.

Compartment	Distance	
Head	-15cm	
Right Atrium Heart	0	
Inferior Vena Cava	5cm	
Splanchnic	Liver	5cm
	Spleen	15cm
Extrasplanchnic	15cm	
Lower Limbs	65cm	

Table 3.3: Compartment heights from hydrostatic indifference point

3.3.4 Cardiac Model

For the purposes of this model, we adopted Defares's (Defares, Osborn et al. 1963) pulsatile time-varying capacitance model, which was later extended by Suga (Suga, Sagawa et al. 1973; Sunagawa and Sagawa 1982). The origins of this model are well known.

The pumping action of the heart is achieved through repetitive bouts of muscle contraction and relaxation triggered by waves of depolarization. At a macroscopic level this can be thought of as cyclical changes in the compliance of the cardiac wall. The time course of wall compliance i.e. ratio between pressure and volume was measured by Suga (Suga, Sagawa et al. 1973). It was realized that when properly normalized to systolic time interval, T_s , and peak systolic elastance, E_s , the waveform morphology from different individuals become similar and independent of heart rate, inotropic state, preload and afterload. The analogy between a mechanical time-varying compliance and electrical time-varying capacitance can be used to conveniently model the pumping action.

Van Heusden (van Heusden, Gisolf et al. 2006), Ursino (Ursino and Magosso 2006), Smith (Smith, Chase et al. 2004), Heldt (Heldt, Shim et al. 2002), and Olufsen (Olufsen, Ottesen et al. 2005) have all adopted various forms of the time varying capacitance model as the basis for their pulsatile cardiac models (See Table 3.1). The differences between models tend to be in the functional form of the end-diastolic curve, the activation function describing the time dependence of cardiac compliance, the number of chambers of the heart modelled (inclusion or exclusion of atria), valve function, the inclusion of inertial and second order effects such as interaction of chamber volumes e.g. septal wall deflection. We now discuss a number of critical points to account for the mechanical properties of cardiac muscle and relative timing between contraction events which must be assessed when considering the model structure.

It has been noted that the progression from end-diastolic (EDV) to end-systolic (ESV) curves is dependent on chamber loading conditions and a modified elastance-resistance model to account for this has been suggested (where elastance is the inverse of compliance) Suga (Suga, Sagawa et al. 1973). This is particularly important in reproduction of pressure and volume waveforms but for our qualitative examination of CSM this effect can be neglected. The EDV curve is essentially an exponential curve with positive exponent. This non-linearity becomes important at diastolic filling pressures above approximately 20mmHg when the collagen fibres limit further dilatation. Similarly, at high transmural pressures the end-systolic pressure volume relation also demonstrates saturation. Since upright and supine

CSM leads to relative hypotension and a reduction in filling pressures the assumption of a non-linear EDV and linear ESV curves is a reasonable compromise. Experimental measurements of the unstressed volume (12ml) at the end of systole indicate that they are 25% to 40% lower than the diastolic unstressed volume (30ml). This shifts the EDV curve to the right relative to the ESV curve, increasing overall stroke volume by a constant volume equal to the difference in unstressed volumes (10-15% of total stroke volume) and can be accounted for by inclusion of a simple constant. Second order effects such as motion of the atrioventricular septum (the elastic wall in which the valves are located), septal wall deflection between left and right ventricles, and the impact of the fibrous pericardium are also ignored (Smith, Chase et al., 2004). Atrioventricular septal wall deflection has been shown to have profound effects on atrial pressures at relatively high heart rates, which is not of consequence for our immediate application, although it is an interesting effect which could be included in future models. Phenomena such as septal wall deflection and pericardial effects tends to play a role in pathological situations such as genesis of cardiac tamponade and pericarditis etc and are again neglected here for our purposes (Smith, Chase et al. 2004).

Blood flow within the heart is assumed to be incompressible and devoid of mass. Thus acceleration effects of blood are ignored so too are increases in viscosity during ventricular contraction. Blood pressure waveform characteristics such as the dicrotic notch cannot be simulated by our model. The relative timing of atrial and ventricular contraction must also be calculated. Although not strictly correct, we assume that the QT interval approximates the time to ventricular systole, and PR interval corresponds to atrial systole. Bazett's formula (Bazett 1920) i.e. $K\sqrt{RR}$ (where RR is the RR-interval, and K is a scaling constant) is used to account for the changes in PR and QT interval with heart rate.

It was decided to adopt a model similar to that suggested by van Heudsen et al. (van Heudsen, Gisolf et al. 2006) i.e. a model incorporating the normalized time varying activation function, $\sigma(t)$, with a linear ESV curve and nonlinear EDV curve, described by functional form suggested by Ursino et al. (Ursino, Fiorenzi et al. 1996). The general topology of the cardiac chamber is shown in Figure 3.8. Diodes ensure unidirectional flow and are modeled by pressure dependent resistances as used by Olufsen et al. (Olufsen, Ottesen et al. 2005) where the valve (diode) resistance, R_v , is given by

$$R_v = \min(R_v + e^{10(P_a - P_v)}; 5,000) \quad (10)$$

Author	Compartments	Inertia	Valves	Pump Model	EDV Curve	ESV Curve	Other Cardiac Effects
Heusden et al. (2006)	L/R Atria L/R Ventricles	No	2 per ventricle	Normalized time-varying elastance	Nonlinear	Linear	None
Heldt et al. (2002)	L/R Ventricles	No	2 per ventricle	Normalized time-varying elastance	Linear	Linear	Inflow/Outflow ventricular resistances
Ursino et al. (1998)	L/R Atria L/R Ventricles	Yes	2 per ventricle	Time-varying elastance	Nonlinear	Linear	Viscosity increases. Passive atria
Smith et al. (2004)	L/R Ventricles	Yes	2 per ventricle	Time-varying elastance	Nonlinear	Linear	Pericardium/Septal Wall deflection
Olufsen et. al (2005)	L Atria L Ventricle	No	2 per ventricle	Time varying elastance	Nonlinear	Linear	Resistance valve model

Table 3.4: Comparison of Pulsatile Cardiac Model features included in recent cardiovascular models. PWL – Piecewise Linear.

This equation results in a large resistance (and no flow) while the valve is closed and a small resistance and (normal flow) while the valve is open. The minimum (min) value is introduced to avoid numerical problems due to large numbers.

The activation function used to describe the time-varying capacitance follows a piecewise cosine function

$$\sigma(t) = \begin{cases} 0.5 \left\{ 1 - \cos \left(\pi \cdot \frac{t}{T_s} \right) \right\} & 0 \leq t \leq T_s \\ 0.5 \left\{ 1 + \cos \left(2\pi \cdot \frac{t-T_s}{T_s} \right) \right\} & T_s \leq t \leq \frac{3}{2}T_s \\ 0 & \frac{3}{2}T_s < t \end{cases} \tag{11}$$

where Ts is the time at which peak systolic contraction occurs (minimum compliance) (Heldt, 2002).

The pressure-volume relationship during systole, P_s , is given by

$$P_s = E_s(V - V_0) \quad (12)$$

where E_s is peak systolic elastance (inverse of compliance) and V_0 is systolic unstressed volume.

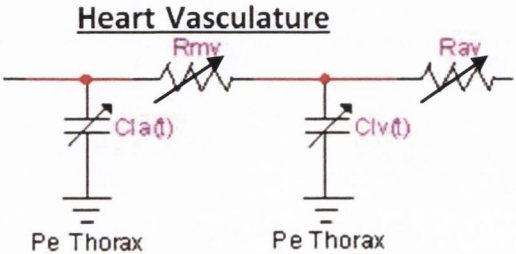


Figure 3.8: Electrical equivalent circuit of the left side of the heart.

During diastole the pressure volume curve is assumed to follow a positive exponential function

$$P_d = P_0 e^{(k_e(V - V_s) - 1)} \quad (13)$$

where P_0 and k_e are parameters describing this function and V_s is diastolic unstressed volume.

Combining these three equations gives a time dependent expression for cardiac chamber pressure $P(t)$ in terms of their active and passive pressure-volume characteristics

$$P(t) = (1 - \sigma(t)) \cdot P_d + \sigma(t) \cdot P_s \quad (14)$$

To avoid numerical differentiation of chamber capacitance as required by Eqn (7), volume is chosen as the state variable for each chamber instead of pressure with the governing differential equation for each cardiac chamber expressed in terms of input and output flows, q_i , and q_o respectively i.e.

$$\frac{dV}{dt} = q_i - q_o \quad (15)$$

3.3.4.1 Parameter Selection

In order to adequately simulate cardiac contraction a number of parameters must be estimated including chamber elastances, EDV curve parameters, P_0 and k_E , mitral and aortic valve resistances (R_{av} and R_{mv}), T_s , the fraction of the cardiac cycle spent in atrial/ventricular contraction. Finally chamber unstressed volumes are chosen.

The pressure volume relationship of the left ventricle has been the most widely studied of these chambers. As noted earlier the end systolic curve is linear over the range of normal pressures, however the end diastolic curve is more closely modeled by a positive exponential function (See Figure 3.9).

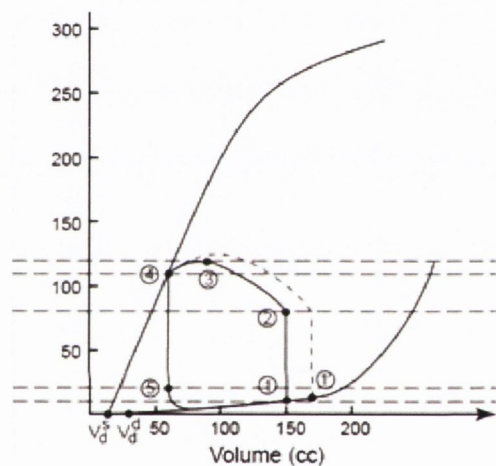


Figure 3.9: Ventricular Pressure-Volume Curve

Again the suggested approach of (Heldt et al., 2004) is taken here for chamber parameterisation. Grossman et al (Grossman, Braunwald et al. 1977), McKay (McKay, Aroesty et al. 1986) and Senzaki et al. (Senzaki, Chen et al. 1996) suggest similar values of $2.8 \pm 0.8 \text{ mmHg/ml}$, $2.5 \pm 0.6 \text{ mmHg/ml}$ and $2.0 \pm 0.7 \text{ mmHg/ml}$ for left ventricular elastance, E_{slv} , respectively. We chose the median value of 2.5 mmHg/ml as our estimate. Parameters for the non-linear EDV curve of the left ventricle are adopted from values measured by Gaasch et al. (Gaasch, Levine et al. 1976) in human subjects with $P_{OLV} = 1.5 \text{ mmHg}$ and $k_E = 0.015 \text{ ml}^{-1}$.

There is paucity of physiological data in scientific literature characterizing the left atrium in humans. Owing to this lack of data we assume linear EDV curve for the left atria. Values measured by Dernellis and colleagues (Dernellis, Stefanadis et al. 1998) report values of left

atrial end-systolic elastance $E_{sla} = 0.61 \pm 0.07 \text{ mmHg/ml}$ and end-diastolic elastance $E_{dla} = 0.5 \pm 0.07 \text{ mmHg/ml}$ in man and are adopted here.

Mitral valve and aortic valve resistances during valve opening were estimated by Olufsen et al. (Olufsen, Ottesen et al. 2005) to be $0.007 \text{ mmHg} \cdot \text{sec cm}^{-3}$ and $0.03 \text{ mmHg} \cdot \text{sec cm}^{-3}$. Heldt (Heldt, Shim et al. 2002) analyzed data presented by Firstenberg et al. (Firstenberg, Vandervoort et al. 2000) to give estimates of $0.01 \text{ mmHg} \cdot \text{sec cm}^{-3}$ for the mitral valve resistance, which compares closely to the values suggested by Olufsen et al (Olufsen, Ottesen et al. 2005).

Values for the unstressed volume for the left ventricle and atria were estimated in the van Heusden et al. (van Heusden, Gisolf et al. 2006) model to be 10ml and 0ml respectively. No differences between diastolic and systolic unstressed volumes were assumed. Ursino et al. (Ursino, Fiorenzi et al. 1996) suggests values of 16ml and 25ml. Heldt suggests a value of $25 \pm 13 \text{ ml}$ for the atria and an estimate of 50ml for the ventricles. The incongruence between parameter estimates is most likely due to the choice of either systolic or diastolic values of unstressed volume and the model structure employed. We chose a reasonable value of 30ml for ventricular unstressed volume and 25ml for atrial unstressed volume.

Timing information is gleaned from ECG parameters, which allows us to approximate the timing of atrial and ventricular contraction relative to one another, T_{s-v} , and as a fraction of total cycle time i.e. T_{sa} and T_{sv} .

Parameter Name	Annotation	Value
Left-Ventricle End Systolic Elastance	E_{slv}	2.5 mmHg/ml
Left-Ventricle End Diastolic Elastance curve scaling constant	P_{0lv}	1.5 mmHg
Left-Ventricle End Diastolic Elastance curve exponent	k_E	0.015 ml^{-1}
Left-Atrium End Systolic Elastance	E_{sla}	0.65 mmHg/ml
Left-Atrium End Diastolic Elastance	E_{dla}	0.5 mmHg/ml
ECG RR Interval	RR	900ms
Relative timing between the atrial and ventricular contraction	T_{s-v}	180ms
Atrial contraction duration	T_{sa}	230ms
Ventricular contraction duration	T_{sv}	370ms

Table 3.5: Heart Model Parameters

The ventricular systolic time interval is approximated by the Q-T-interval i.e. 370ms, while the atrial systolic time interval is approximated by a value slightly larger than the P-R-interval i.e. 230ms. Relative timing between atrial and ventricular contraction is approximated by the P-R-interval which at resting heart rates is normally 180ms (Ganong 2005). We assume that all time intervals scale with the square root of the R-R-interval according to Bazett et al. (Bazett 1920) formula. Finally, we assign a value of 900ms to the resting R-R-interval. Table 3.5 summarises the cardiac parameters.

3.3.5 Reflex Control

Two primary autonomic reflexes responsible for short term regulation of arterial blood pressure and blood flow i.e. the arterial baroreflex and cardiopulmonary reflex are included in our model, since these are thought to dominate short term physiological responses to CSM clinically. A lumped parameter control model is developed to represent the behaviour of this integrated neural control system.

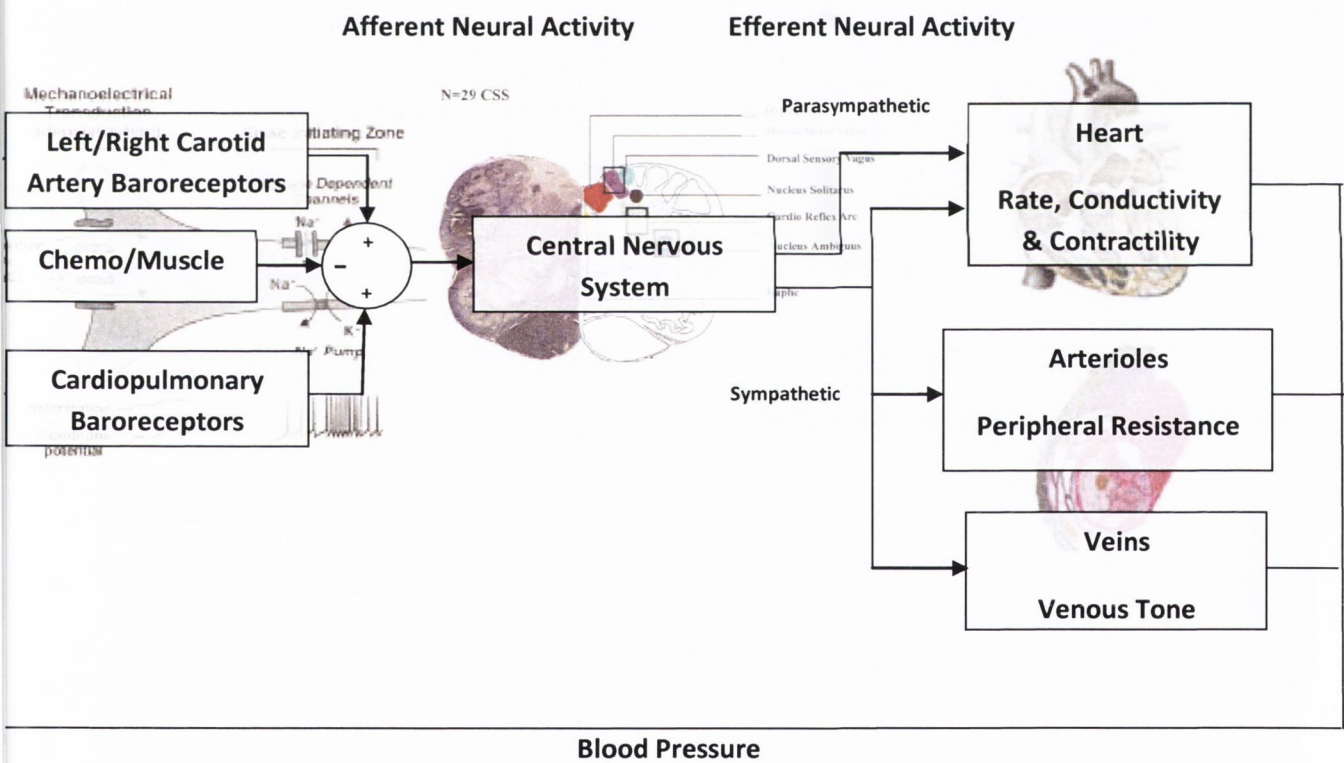


Figure 3.10: Baroreflex Model Topology

A number of novel additions to previous reflex models are incorporated in order to properly examine the effects of carotid sinus massage and further the aims stated in Chapter 2.

As noted earlier although explicit modelling of the interaction between muscle and chemoreceptor afferents and the baroreflex is not performed, the proposed net effect of

these mechanisms i.e. transient inhibition of baroreceptor outflow is included as a novel feature in our reflex model. Furthermore our baroreceptor model differentiates between left and right carotid sinus baroreceptors allowing simulation of unilateral baroreflex stimulation. Finally we include as mentioned novel attributes in our afferent receptor and efferent organ models including the representation of different baroreceptor subtypes by lumping these together into a single equivalent baroreceptor and also modelling of the effect of atrial conductivity parameters and AV node control.

3.3.5.1 Arterial Baroreflex Model

A simplified model of baroreflex physiology detailed in Chapter 1 based on a set-point non-linear negative feedback topology is adopted (See Figure 3.10 for complete control system). The general model architecture is based on control systems described by Heldt et al. (Heldt 2004) to represent the baroreflex control system dynamics. In brief mean arterial blood pressure is sensed by arterial baroreceptors located in three distinct arteries. In the face of external perturbations in blood pressure, this sensory information is used to regulate heart rate, heart muscle cell conductivity, microcirculatory peripheral resistance, venous tone, and cardiac contractility to correct and maintain consistent blood pressure and cardiac output to match metabolic demand.

Baroreceptor populations embedded in the aortic arch, left and right carotid sinuses are each represented independently in contrast to other models which often lump the activity of these separate sensory regions together. This architectural modification is included to allow simulation of unilateral and bilateral carotid stimulation.

The non-linear sigmoidal relationship between changes in mean arterial pressure and carotid sinus nerve firing frequency is typically modeled by a soft limiter function (de Paor and Ringwood 2006). However this relationship is designed to replicate only the steady-state relationship between mean input pressures and the average controlled variable. The dynamics of the afferent baroreceptors are neglected. A number of authors have produced detailed baroreceptor models. The most comprehensive of these is Ottesen et al. (Ottesen 1997), based on the earlier work of Taher et al. (Taher, Cecchini et al. 1988), which include the effects of different baroreceptors subtype adaptation rates, and a dynamic hysteresis component. Another model (van Heusden, Gisolf et al. 2006) takes an approach which is both amenable to large scale models, and is a relative compromise between these approaches, since it includes the effects of pressure pulsatility (stroke volume), mean blood pressure changes and thresholds effects. However saturation is not included. Ursino et al

(Ursino, Fiorenzi et al. 1996) augments the static non-linearity by including a rate dependent component in his baroreceptor model.

For our purposes mean aortic pressure, $\overline{P_a}$, is approximated by a first order low pass filtered version of the pulsatile aortic pressure, P_a , according to the differential equation where α is a scaling factor chosen empirically for averaging

$$\frac{d\overline{P_a}}{dt} = \alpha(P_a - \overline{P_a}) \quad (16)$$

Carotid sinus pressures are found by assuming that mean carotid sinus blood pressure is lower than aortic pressures by an amount, p_{car} , related to the pressure dropped over half the cerebral artery inflow resistance assuming 23% of the CO is flowing to head circulation (this flow is divided in two to represent equal flows to each cerebral hemisphere). Furthermore during orthostasis carotid sinus pressures are further adjusted by a hydrostatic pressure, p_{hcs} , dependent on the perpendicular distance from the regulated hydrostatic indifference point, $h_{cs} \sin \alpha(t)$, where $\alpha(t)$ is the standing angle. Thus p_{cs} sensed by each carotid sinus is calculated as

$$p_{cs} = \rho g h_{cs} \sin \alpha(t) + \overline{P_a} - p_{car} \quad (17)$$

Sensed blood pressures are then subtracted from the set-point pressure, p_{set} to give an effective error signal, e , for the control system, which is then passed through a static soft limiter non-linearity (Heldt, Shim et al. 2002) described as

$$f = 18 * \arctan(e/18) \quad (18)$$

The scaling introduced limits the error signal to approximately 28mmHg.

The effector limb of the baroreflex constitutes parasympathetic and sympathetic outflow activity which modulates four major parameters i.e. heart rate, av node conductivity, cardiac contractility, peripheral resistance, and venous tone. These are referred to as the controlled variables.

The general architecture of the efferent limb consists of a pure delay, which models the CNS delay time from affector to effector, followed by a first order low pass filter PNS or SNS block, $G_e(s)$, incorporating gain, which represents the effector dynamics in response to SNS or PNS activity. Finally the output of the effector limb is added to the baseline controlled variable, X_0 .

As is clear from our block diagram representation of the baroreflex, SNS & PNS activity only innervates the SA Node and AV Node, while the SNS activates all four controlled variables. Parameter selections for each limb are now described.

3.3.5.1.1 Heart Period

Variations in heart period require further description since they rely on the interaction between PNS and SNS activity on the SA node depolarisation potential (See Chapter 1 for an overview of relevant physiology). We model the cardiac pacemaker using an Integral Pulse Frequency Modulation (IPFM) modelling approach. In this model structure an integrator integrates an input signal $M_{SA}(t)$ until the result crosses a predetermined firing threshold, T_{SA} . When this occurs an output event is generated and the integrator is reset to zero. T_{SA} can be chosen to prescribe the mean RR interval. $M_{SA}(t)$ can be interpreted as a functional representation of the SA node transmembrane potential which depends on the cumulative contribution of autonomic activity and inherent rate of SA node cell potential since the occurrence of the previous beat. The equation for the integrator input is given by

$$m_{SA}(t) = k_0 - k_1 \left(k_2 f_p(t) - k_3 f_s(t) \right) + sp \quad (19)$$

where k_0 is intrinsic rate of rise of SA node cell potential, k_1 controls the influence of autonomic activity on the SA node, $f_s(t)$ and $f_p(t)$ are time-dependent firing frequencies of sympathetic and parasympathetic systems, sp is the tonic activity of autonomic activity at the SA node, k_2 is the weight of parasympathetic activity and k_3 is the weight of sympathetic activity. Thus this model attempts to replicate increases and decreases in the slope of the transmembrane depolarisation potential. A beat is initiated every time the function $M_{SA}(t)$ exceeds the threshold, allowing the current HR to be calculated as

$$HR = 1/(t_i - t_{i-1}) \quad (20)$$

where t_i and t_{i-1} are the times of occurrence of the current and previous beats respectively.

3.3.5.1.2 AV Node Control

For our purposes a simplified control model of AV node control is assumed. This model consists of a modification of the SA node model, since the primary effects we wish to investigate are the delaying of the occurrence of a ventricular beat and effective heart rate as measured by RR interval. We assume that PR interval dependence is proportional to

parasympathetic activity and inversely proportional to sympathetic activity. Note we also include a term for refractoriness i.e. if the time since the last beat is short then AV node is less likely to fire. The model structure is a modified integrate and fire model described by Ward et al. (2006)

$$m_{AV}(t) = k_4 - k_5 \left(k_6 f_{pav}(t) - k_7 f_{sav}(t) \right) + k_8 RP_{n-1}(t) + AT_{av} \quad (21)$$

where k_4 is the intrinsic rate of rise of AV cell resting potential, k_5 adjusts the ANS effect on the AV node, k_6 is the weight of AV parasympathetic influence, k_7 is the weight of AV sympathetic influence, k_8 is the weight of the recovery effect, $f_{pav}(t)$, $f_{sav}(t)$ is the time-varying sympathetic and parasympathetic effect on AV node, RP_{n-1} represents the previous R-to-P interval and AT_{av} is the tonic background activity. Note the integrator does not begin integrating until the SA node has fired. Once $m_{AV}(t)$ reaches a predetermined threshold, T_{av} , the ventricles are assumed to fire.

The corrected RR_c interval is initiated every time the ventricles fire, allowing the current HR to be calculated as

$$HR_C = 1/(t_{avi} - t_{avi-1}) \quad (22)$$

where t_{avi} and t_{avi-1} are the times of occurrence of the current and previous beats respectively. During simulation we also use this coupled leaky integrate-and-fire model structure to model the conductivity of the perinodal (T) cells which transmit the electrical impulse from the SA node to the right atrium.

3.3.5.1.3 Venous Tone

The details of venous tone control also warrant a brief mention. Models of venous tone modulation tend to operate through independent variations of unstressed volume of the vessel, V_o or independent variations in C (assuming total instantaneous vessel volume is constant). The effect on pressure of a change in V_o or C independently is shown in Figure 3.11 (left). As can be seen variations in C alone serve to rotate the curve around the point V_o as given by Eqn. 23. Independent changes in V_o serve to translate this curve along the V axis. A more intuitive interpretation would focus purely on increases in venous tone caused by

active contraction of venous smooth muscle which *simultaneously* decreases C and V_0 leading to a net increase in pressure (Figure 3.11).

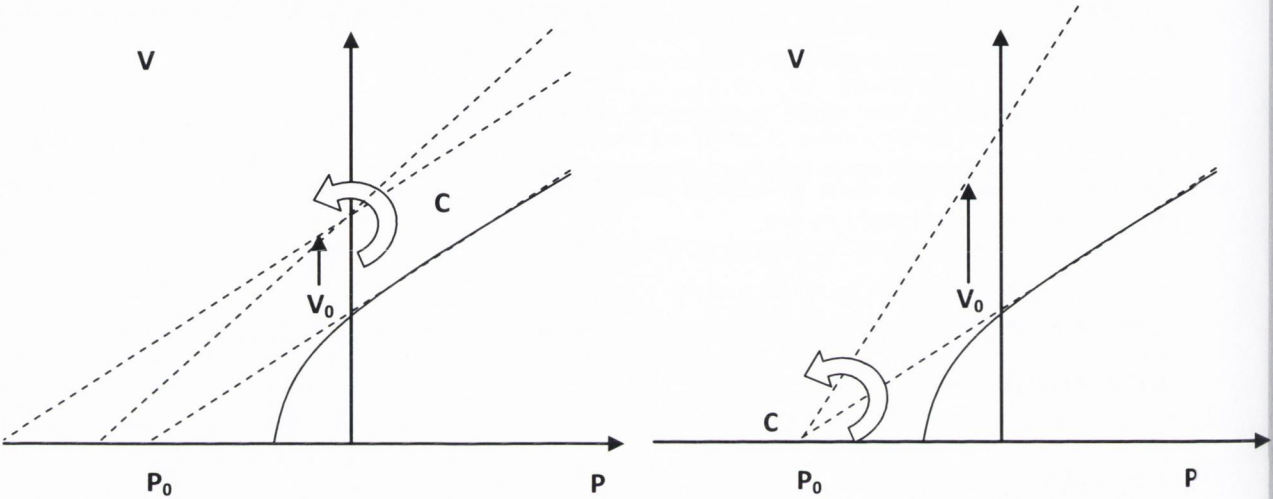


Figure 3.11: Control of Pressure-Volume Curve for typical blood vessel via sympathetic activity. (Left) Independent variation of V_0 or C (Right) Combined variation of C and V_0 about P_0

This can be achieved by recasting the equation relating vessel pressure and volume

$$V = CP + V_0 \tag{23}$$

as

$$V = C(P - P_0) \tag{24}$$

where P_0 is the intercept of the pressure-volume curve with the pressure axis. Thus by varying C , the slope of the line about the pressure axis intercept we also achieve simultaneous V_0 changes (P_0 can be calculated since values for C and V_0 are known).

3.3.5.2 Parameter Selection

As detailed previously all values for pure delays, gains and effector time constants are taken from literature where appropriate and scaled to reflect values of a 70kg individual. Both technical and ethical limitations exist in determining these parameters in humans and animals. Thus while it is desirable to determine the open-loop gains of each of the four effector mechanisms independently, determination of gain values is commonly based on the closed-loop system evaluations such as administration of phenylephrine/nitroprusside to alter blood pressure, Valsalva manoeuvres or the direct mechanical stimulation of the carotid sinus using neck chambers.

3.3.5.2.1 Afferent Parameters

The sigmoidal function's static parameters are given according to data obtained by Chapleau and Abboud (Chapleau and Abboud 1987) in non-pulsatile conditions. Furthermore it was assumed that the operating point lies at 92 mmHg. These values compare quite well with estimates made by Eckberg (Eckberg 1992), using neck chamber methods and using phenylephrine.

3.3.5.2.2 Efferent Parameters

Cardiac

A number of studies have examined the vagal latencies involved in the human arterial baroreflex. Borst et al. found a delay of 0.5s for vagally mediated heart rate changes in response to direct carotid sinus stimulation (Borst and Karemaker 1983). Eckberg et al. (Eckberg 1980) using external neck pressure stimuli found a delay of 0.44s. Note a commonly reported experimental finding is that hypotensive and hypertensive stimuli are associated with different delays. This effect is ignored here for simplicity.

Cardiac sympathetic response delay was assumed to be 2 seconds in agreement with data provided by Heldt et al. (Heldt, Shim et al. 2002) of 2.5 seconds and van Heudsen et al. (van Heudsen, Gisolf et al. 2006) of 1.5 seconds.

Impulse responses characterising the parasympathetic and sympathetic effects on heart period have been described by Berger et al. (Berger, Saul et al. 1989) and sympathetic effects only by Sato et al. (Sato, Kawada et al. 2003) in rats. We use dynamics proposed by Sato et al. for sympathetic activity i.e. time constant of 2.5 seconds and after results described by Samar et al. (Samar 2005), we neglect the parasympathetic impulse response and represent the dynamics by a pure gain.

We turn to results produced by phenylephrine and neck chamber experiments to assign values for vagal and sympathetic gains. Eckberg et al. (Eckberg 1992) suggest a value of 16ms/mmHg, while Bristow et al. (Bristow, Honour et al. 1969) measured a value of 14.8ms/mmHg. Values in previous models (deBoer, Karemaker et al. 1987; Heldt, Shim et al. 2002; van Heusden, Gisolf et al. 2006) have assumed a value of approximately 9 ms/mmHg for both limbs, resulting in a combined gain of 18ms/mmHg. A similar value is assigned here.

Contractility

Contractility control parameters are based on data reported in Suga et al. (Suga, Sagawa et al. 1973). These researchers suggest the slope of the end-systolic pressure/volume function changes to values of 210% of nominal values giving a gain of 0.007ml/mmHg². The dynamics of the contractility reflex are represented by a first-order transfer function with a time constant of 8 s and a delay of 1.5 s (van Heusden, Gisolf et al. 2006).

Peripheral Resistance

The delay of the resistance reflex is 1.5 s according to (van Heusden, Gisolf et al. 2006) 0.7 s for delay between sympathetic activity and the response of the effectors and 0.8 s for transport over the sympathetic nerves. The dynamics of the reflex are based on those presented by Sato et al. (Sato, Kawada et al. 2003) i.e. time constant of 2.5 seconds identical to that of β -sympathetic activity dynamics. These values approximate those suggested by Borst and Karemaker (Borst and Karemaker 1983). Under high orthostatic stress, the cardiovascular system is capable of doubling total peripheral resistance (Low 2008) i.e. to 2.5 PRU. This suggests a value of 0.05PRU/mmHg. Each vascular bed is assumed to contribute equally to the response.

Venous Tone

The reflexes governing unstressed volumes are considerably longer than those reported for other reflexes. There is much uncertainty surrounding these values since they are difficult to quantify. Following the reasoning of Heldt (Heldt 2004) a delay of 8 secs and time constant of 40 seconds is designated as appropriate here. Dog experiments reveal a maximum change in systemic reservoir volume of approximately 12 ml/kg, which suggest a change in venous unstressed volume of about 900 ml and a static gain value of 31 ml/mmHg. We attribute 15 ml/mmHg to the splanchnic circulation and rest to extrasplanchnic, 8 ml/mmHg to the lower body, 6 ml/mmHg to the upper body, and 2 ml/mmHg to the kidneys.

3.3.5.3 Cardiopulmonary Reflex Model

A paucity of data exists surrounding the characterization of the cardiopulmonary reflex. Essentially the CP reflex is a low pressure analog of the arterial baroreflex. In our model, the CP reflex affects both peripheral resistance and venous tone.

The general topology of the reflex model is similar to that on the high pressure side of the system. Pressure deviations sensed in the right atrium are averaged and passed through a sigmoidal function (Heldt, Shim et al. 2002)

$$g = 5 * \arctan(e/5) \quad (25)$$

The dynamics of the CP reflex are similar to the baroreflex limbs serving peripheral resistance and venous tone control. The effects of both reflexes are summed together. Heart period i.e. Bainbridge reflex and heart rate contractility control is neglected.

Pawelczyk and Raven (Pawelczyk and Raven 1989) suggest a static gain value of 0.05PRU/mmHg for the cardiopulmonary peripheral resistance limb. Heldt et al. (Heldt, Shim et al. 2002) justify the existence of a venous tone reflex on the basis that blood volume in the splanchnic system changes by 500ml in response to hemorrhage without significant changes in heart rate, cardiac output and arteriolar resistance. We thus assign the value of 100ml/mmHg to the cardiopulmonary venous tone feedback sensitivity.

3.3.6 Carotid Sinus Massage Stimulus

For our purposes we define CSM as

“A transient unilateral mechanical stimulus applied to the neck at the level of the carotid sinus which results in local time-varying deformation of the carotid artery and adjacent structures, partial or total occlusion of the common, internal and/or external carotid arteries. These local mechanical perturbations result in stimulation of carotid sinus baroreceptors, adjacent chemoreceptors, muscle afferents and partial or total interruption of carotid blood flow. Thus CSM can be considered a simultaneous baroreflex, chemoreceptor and muscle afferent and cerebral autoregulatory stimulus”

In essence CSM results in the simultaneous transient increase in carotid blood flow resistance, together with an increase in stimulation of baroreceptor, chemoreceptor, and neck muscle nerve afferents.

To model the baroreceptor stimulus at time, T_1 , we transiently decouple the carotid sinus feedback loop under stimulation, increase its input pressure, P_{cs} , to 300mmHg (equivalent to

increasing its strain) for the duration of the stimulus, while simultaneously increasing carotid resistance, R_{cs} by increasing the external carotid pressure to same value 300mmHg.

$$P_{cs}(t) = \begin{cases} p_{cs} & T_1 \geq t \geq T_2 \\ 300mmHg & T_1 < t < T_2 \end{cases} \quad (26)$$

The magnitude of force applied is coupled to resistance imposed by carotid artery under pressure. As a first order approximation we augment the stimulus model to incorporate this effect. With cessation of CSM, at time T_2 , carotid resistance is returned to its nominal value and baroreceptor input is coupled to carotid sinus pressures again. Thus the limb of the baroreflex stimulated by message is transiently decoupled during CSM.

To find the resistance of the vessel under pressure consider the following. Let A be the cross sectional area of the artery in which the baroreceptors are embedded. The instantaneous change in area can be expressed as the difference between the Laplacian tensional force, $P \cdot r$, where r is vessel radius and P is transmural pressure, and a non-linear restoring elastic force, $f(A)$

$$\frac{dA}{dt} = P \cdot r - f(A) \quad (27)$$

The choice of $f(A)$ can be informed by the known static nonlinear relationship of the pressure-volume characteristic (or area per unit length) of arteries which is known to follow a soft limiter function given by

$$A = \frac{2\alpha}{\pi} \cdot \arctan(\beta \cdot P) \quad (28)$$

where α and β are appropriate scaling factors used to fit a particular pressure-volume relationship of the artery under consideration and P is arterial transmural pressure. By assuming equilibrium conditions we find after rearranging Eqn 28 that

$$f(A) = P \cdot r = \frac{r}{\beta} \tan\left(A \frac{\pi}{2\alpha}\right) \quad (29)$$

thus

$$\frac{dA}{dt} = P(t) \cdot r - \frac{r}{\beta} \tan\left(A \frac{\pi}{2\alpha}\right) \quad \text{for } A > 0 \quad (30)$$

describes the dynamics of the arterial cross-sectional area under changing transmural pressure, P , while also retaining the static sigmoidal non-linearity. By varying P in response to changes in external pressures we can find instantaneous values for the vessel area. The resistance of the carotid under pressure is then calculated from this value according to Poiseuille's Law.

Thus local blood flows/pressures decrease and local strain increases experienced during CSM are accounted for. It is important to note that system pressures and flows are governed by the resistance change in the carotid only. The decoupled baroreceptor inputs experience an increase in strain which is modelled as an increasing pressure input but does not affect system pressures directly but indirectly as an input to the CNS.

3.3.7 Orthostatic Stress Tests

Clinical tests for gravitational stress tolerance commonly include active standing or tilt-table testing. It is also recommended clinically to perform CSM in upright position (Parry, Richardson et al. 2000). It is for this purpose we are interested in reproducing gravitational stresses on the cardiovascular system.

During tilting patients are passively tilted to a 70° angle, while monitoring major cardiovascular variables i.e. heart rate and arterial blood pressure which causes rapid shifts in blood volume resulting in relative central hypovolemia. Passive tilting in this way is designed to minimize hemodynamic influences of muscle contraction seen during active standing. Tilting is also accompanied by changes in intravascular blood volume due to alterations in oncotic pressure gradients in capillaries, arising from increases in hydrostatic pressures in lower limbs. As a first approximation we ignore this effect assuming that it occurs on a much longer time-scale than CSM related changes. However its inclusion at a later stage requires only minor adjustments to the model in order to subtract a time dependent amount of blood volume from the system.

Gravitational stresses in our model are simulated by decreasing external bias pressures, P_{bias} , in venous, splanchnic and leg compartments, such that a predetermined amount of blood pools in these regions.

In order to simulate this effect, we describe a time varying function, $\alpha(t)$, which corresponds to the time-varying tilt angle function given by

$$\alpha(t) = \begin{cases} 0 & \text{for } t < t_0 \\ \alpha_{max} \cdot \frac{1}{2}(1 - \cos(\pi \frac{t-t_0}{\Delta t})) & \text{for } t_0 \leq t \leq t_0 + \Delta t \\ \alpha_{max} & \text{for } t > t_0 + \Delta t \end{cases} \quad (31)$$

where Δt is the duration it takes to tilt from horizontal to upright position, where t_0 is the time at which tilting begins.

Each bias pressure is given by function

$$p_{bias} = p_{max} \cdot \sin(\alpha(t)) \quad (32)$$

which is used to increase the transmural pressure of each compartment, where p_{max} is hydrostatic compartmental pressure due to its vertical distance from indifference point.

3.3.8 Model Implementation

The model just described is represented by a set of coupled, non-linear time-varying first order differential equations. The state variables were initially assumed to be compartmental pressures. According to Samar (Samar 2005) significant numerical round off error can occur when simulating pressure is assumed to be the state variable since the defining equations involve numerical differentiation of time-varying compliances, unstressed volume and external bias pressures. However by recasting these equations such that the compartmental state variables under consideration are compartmental volumes we avoid the numerical differentiation step, and reduce errors accordingly.

The resulting system was implemented using the Simulink® toolbox which accompanies MATLAB®. Simulink® is an environment for simulation and model-based design of dynamical systems, which provides an interactive graphical environment and a customizable set of libraries that allow design, simulation, implementation, and testing of a variety of time-varying systems. Simulink is integrated with MATLAB®, providing access to a range of tools that allow easy algorithm, analysis and visualisation as necessary.

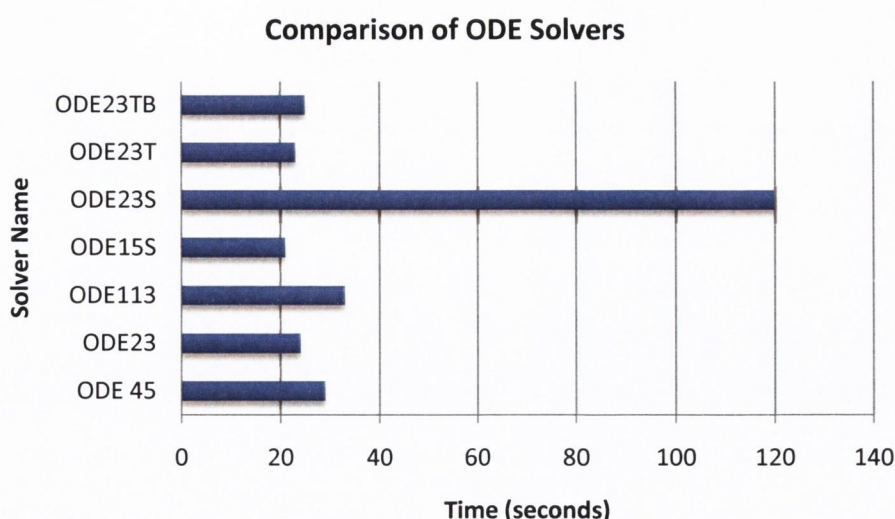


Figure 3.12: Comparison of ODE Solvers efficiency in solving equations

On initial simulations we compared each of the available MATLAB® variable step size ordinary differential equation solvers to identify the most efficient algorithm for our particular set of equations. Each simulation was run for 100 seconds. The initial maximum step size was set at 0.01 seconds.

As can be seen from Figure 3.12 the standard adaptive step size, fourth-order Runge-Kutta (ODE45) differential equation solver performed quite well on our problem. However both the numerical differentiation formula (NDF) solver (ODE15s) and the trapezoidal rule solver (ODE23t) solvers performed most efficiently. These are both designed to tackle stiff differential equation solving***.

In order to estimate the numerical errors introduced by each of the ODE solvers total blood volume (which is conserved since the system is closed and is equal to total volume at the beginning of the simulation) was monitored at each step of numerical integration procedure and compared to initial total blood volume in the system.

*** An ODE problem is stiff if the solution being sought is varying slowly, but there are nearby solutions that vary rapidly, so the numerical method must take small steps to obtain satisfactory results. Stiffness is an efficiency issue. Stiff problems typically take longer to solve using standard ODE solvers.

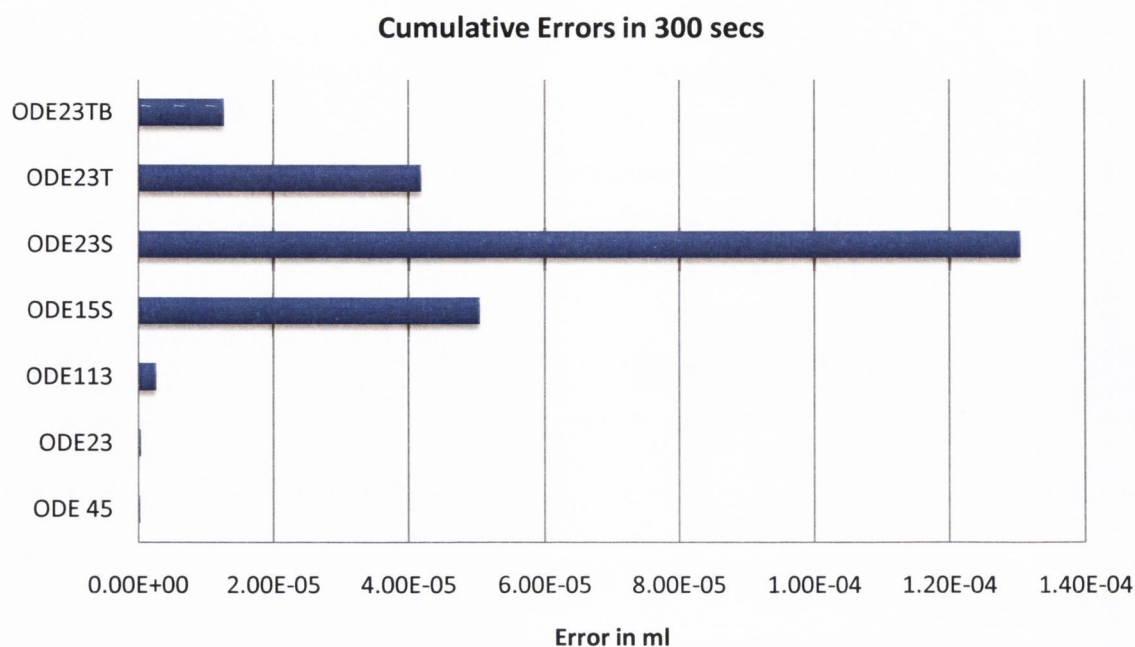


Figure 3.13: Comparison of ODE Solvers Accuracy in solving equations

Total cumulative error was calculated for each of the solvers and it was found that both Runge-Kutta algorithm of Bogacki and Shampine (ODE23) and ODE45 cumulative errors were an order of two magnitudes smaller than other approaches i.e. 2.25×10^{-7} ml. We chose ODE23 for its overall performance on both efficiency and performance. Following this selection it was found that by increasing the maximum step size to 0.1 the simulation time could be halved at the expense of increased error.

3.4 References

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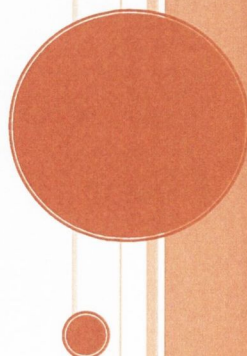
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CHAPTER 4

A Computer Model of the Cardiovascular Effects of Carotid Sinus Massage in Carotid Sinus Hypersensitivity

In this chapter we build upon the previous chapters results and provide simulation results of the system for the purposes of initial model validation. A novel simulation of Hypersensitive Carotid Sinus Syndrome is presented. Candidate physiological parameters are identified which are likely to play a role in the pathogenesis of CSH, with implications for CSH diagnosis and treatment options. The possibility of a number of “novel clinical subtypes” of CSH are discussed.



CHAPTER 4

4.1 Model Validation

In this chapter to validate the model we examined its ability to simulate a number of experimental conditions and then compare our results to available experimental data.

Initially we examined the global behaviour of the model under steady-state supine baseline conditions and compared predicted cardiovascular variables to experimental data. Performance of cardiac chambers under varying loads is also presented. A number of clinical conditions namely heart failure, aortic valve stenosis, aortic valve insufficiency, and haemorrhage are simulated to interrogate the flexibility of the model to reproduce common cardiovascular conditions and to examine the response of the reflex control system.

The transient dynamics of the global cardiovascular system are subsequently explored. In particular we examine tests typically employed to examine autonomic dysfunction i.e. the Valsalva manoeuvre, deep breathing.

Finally we test the ultimate goal of the model i.e. the response to Carotid Sinus Massage. Initially we compare our results to healthy CSM responses from literature. Following this we scrutinize the dependence of CSM outcome variables (heart rate, blood pressure, cerebral blood pressures/flows) on stimulus input parameters i.e. magnitude, rate and duration of CSM. Finally we simulate CSH and examine the sensitivity of CSM model response to parameter changes as a means of identifying novel biomarkers and potentially causal parameters which may play a role in CSH pathogenesis.

4.1.1 Steady State Simulation

Steady state cardiovascular variables obtained from a 300 second simulation are tabulated in Table 4.1, which compares predicted and experimental values obtained from a population of healthy young adults made in recumbent resting conditions. It is important to note that these measurements were made from the original parameters described in earlier sections. Since the source of this data is amalgamated from a plethora of sources with different population characteristics it would be expected that there may be significant differences between mean predicted values and clinical results.

As can be seen from Table 4.1 all variables predicted by the model are a good approximation to normal values expected in the population described with most of the variables lying within the natural limits of variation. Mean central venous pressure as estimated here is

relatively high. This is presumably as a consequence of modelling a system with only a left sided heart.

A Wiggers diagram produced by our model is shown in Figure 4.1. This clearly demonstrates the models ability to produce quite a realistic set of left ventricular, left atrium and aortic pressures waveforms. One obvious difference is the lack of a dicrotic notch and wave reflections typically noted in continuous arterial blood pressure waveforms (Nichols and O'Rourke 1998).

Cardiovascular Variables	Normal Value	Simulation
Systolic Pressure (mmHg)	90-119	117.5
Diastolic Pressure (mmHg)	60-79	81.9
Mean Arterial Pressure (mmHg)	93.33	98.5
Heart Rate (bpm)	70	67.4
Stroke Volume (ml)	80	70
Cardiac Output (l/min)	5.0	4.718
Total Blood Volume (l)	5.0	5.254
Mean Central Venous Pressure (mmHg)	2-8	9.3 ^{†††}
Ventricular Systolic Pressure (mmHg)	90-140	119.5
Ventricular Diastolic Pressure (mmHg)	5-12	5
Arterial Time Constant	1.9	1.86
Total Systemic Resistance (P.R.U)	1.0	0.93
Total Systemic Compliance (ml/mmHg)	2.0	1.92

Table 4.1: Comparison of baseline Model Predictions and Normal Values

As mentioned in our model development these effects are not reproduced owing to the exclusion of inertial and distributed effects from our model, but could be included if deemed of clinical value in the future. Towards this end, we included a series inductor to model the effects of inertia during valve closure to reproduce the expected dicrotic notch as a matter of proof of concept. The waveform morphology improvement is obviously closer to realistic values (Figure 4.1). Pressure-volume curves produced by the supine simulations also demonstrate realistic morphology as can be seen in Figure 4.2. We examine the qualitative behaviour of the left ventricle P-V loop under a number of classical scenarios.

Figure 4.2 shows the effect of varying ventricle contractility, a measure of cardiac pump function. Contractility is varied by changing the end systolic elastance (E_s). Increases in

^{†††} This value is slightly higher than normal

contractility results in increases in stroke volume assuming constant heart rate. Figure 4.2 plots a PV diagram for 3 different values of E_{es} showing the desired increase in stroke volume as contractility increases.

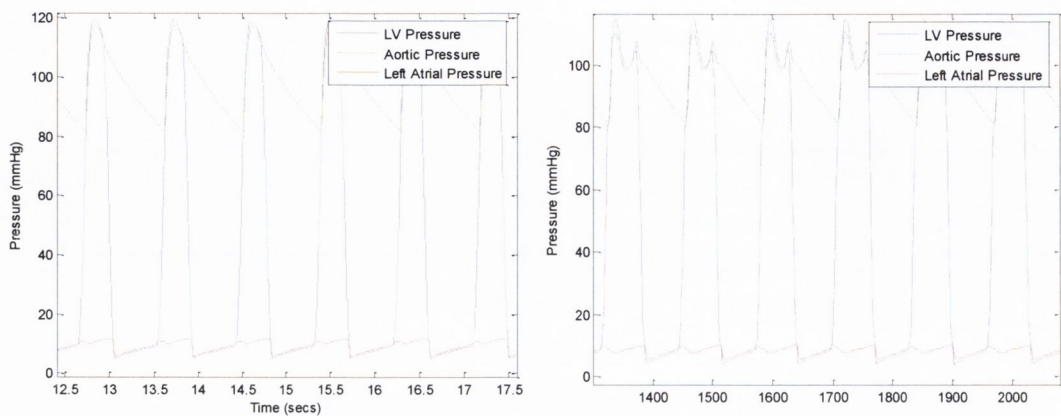


Figure 4.1: Wiggers diagram for Simulation of Cardiovascular System. (Left) Without
dicrotic notch (Right) with dicrotic notch

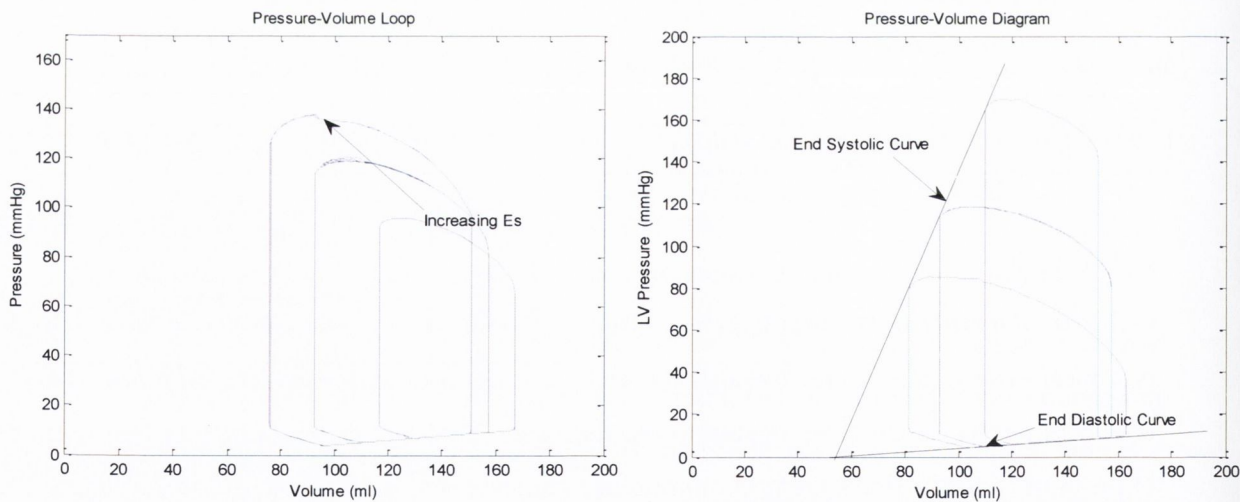


Figure 4.2: Pressure-Volume loop of Cardiovascular System. (Left) Increasing End Systolic
Elastance. (Right) Changing total peripheral resistance.

The effect of changing the systemic circulatory resistance i.e. afterload on cardiac function is also examined. Acute increases in resistance results in reduced cardiac output that varies with the magnitude of the change. Figure 4.2 shows the closed loop model output, as systemic resistance is doubled, and halved. As systemic resistance decreases, CO increases as expected stroke volume decreases while ventricular pressure decreases while increases in

systemic peripheral resistance result in the opposite trend i.e. decreased stroke volume, increased ventricular pressure.

4.1.2 Clinical Conditions and Autonomic Function Testing

The ability of the model to qualitatively simulate different types of cardiovascular pathology is investigated. Firstly different forms of cardiac disease i.e. myocardial dysfunction and valvular disorders are simulated. Secondly we investigate the cardiovascular and reflex responses to haemorrhage, and a number of autonomic function tests as examples.

Heart failure reduces the performance of the heart as a pump. One cause is diastolic dysfunction which affects the hearts ability to relax during ventricular filling and can be caused by a number of restrictive diseases including hypertrophic cardiomyopathy or infiltrative diseases such as sarcoidosis or amyloidosis. This affect can be simulated by increasing the ventricle elastance at end-diastole by a factor of 10, represented in the model by the parameter E_d . This essentially increases the mechanical stiffness of the heart walls during filling reducing end diastolic volume.

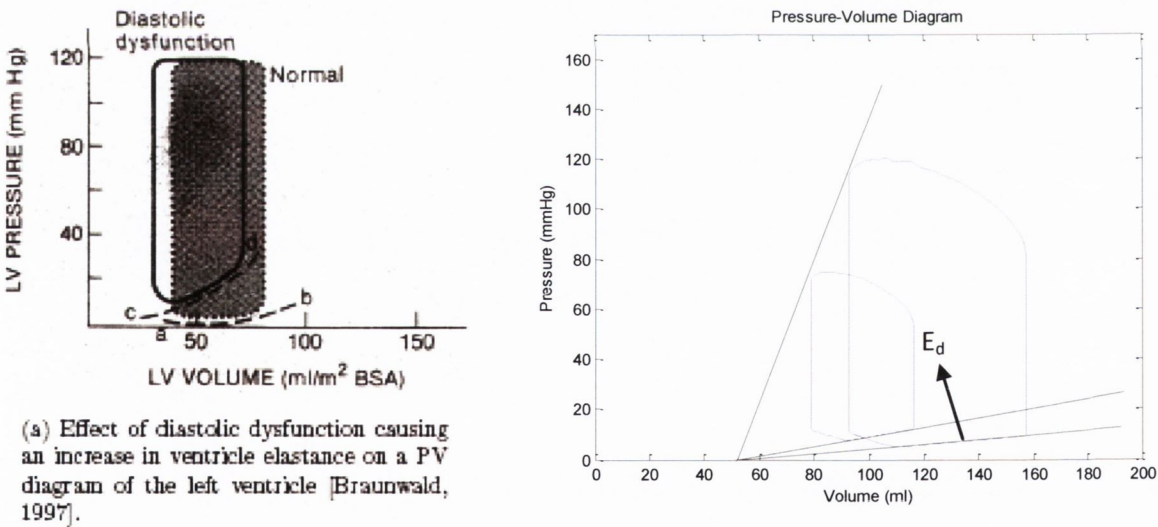


Figure 4.3: Effect of diastolic dysfunction on P-V Volume loop. Published data on effects of diastolic (left)

A PV diagram illustrating the impact of increased end diastolic elastance is shown in Figure 4.3. This is contrasted to the simulation results. Both figures show the cardiac cycle moving to the left on a PV diagram resulting in increased in ventricle filling pressure, a decrease in

ventricle volume, diminished cardiac output, and a drop in end-systolic pressure. These qualitative trends are reproduced by our model quite convincingly.

Another underlying cause of heart failure is systolic dysfunction, which impedes the hearts ability to contract during systole, thus reducing stroke volume and consequently CO. This may occur as a result of ischaemic heart disease or conditions such as dilated cardiomyopathy. Decreasing the parameter E_s by 50% allows us to simulate systolic dysfunction (Figure 4.4). Haemodynamic trends include increased ventricle preload, a rise in ventricle volume, a drop in stroke volume, and decreased systemic pressure i.e. essentially a shift of the cardiac cycle to the right. Our model again mimics these qualitative trends.

Valvular disorders are another source of cardiac pathology, which ultimately effect cardiac pump performance and can be quite reliably reproduced by our model. Two common types of aortic valve dysfunction are considered i.e. aortic stenosis and aortic insufficiency.

Aortic stenosis occurs when a heart valve does not open properly due to disease processes resulting in calcium deposition on the valve walls or age related wear and tear. This impedes blood flow leaving the heart causing a higher resistance to flow and an increased pressure gradient between ventricle and aorta during systole.

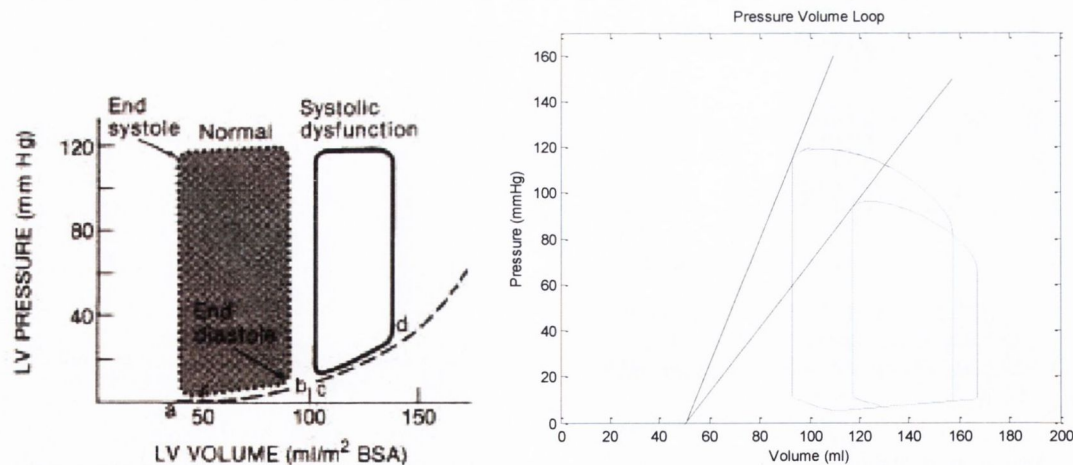


Figure 4.4: Effect of systolic dysfunction on P-V Volume loop

In these conditions the ventricle is in a pressure overloaded state. Myocardial remodelling occurs in response resulting in time with hypertrophy of muscle walls. Symptoms include dizziness, syncope and congestive heart failure. Hemodynamic consequences include

increased left ventricle systolic pressure and decreased average aortic pressure (See Figure 4.5). We simulated aortic stenosis by increasing valve resistance, which enabled us to capture the essence of pressure waveforms changes described (See Figure 4.5).

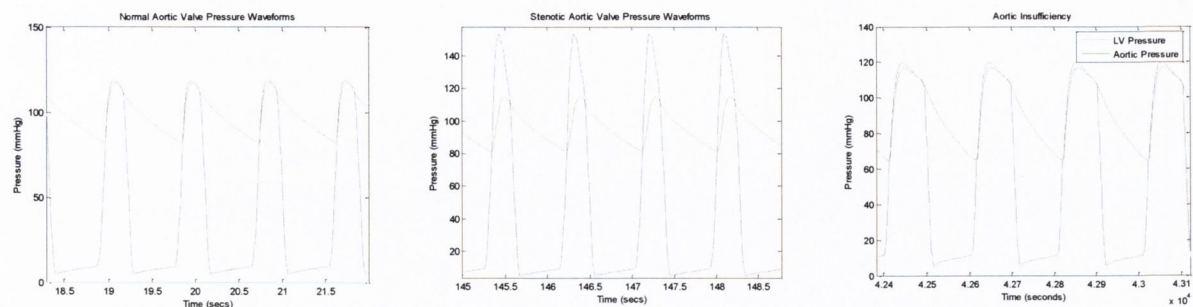


Figure 4.5: Simulations of Normal (left), Aortic Stenosis (centre), Aortic Regurgitation (right)

Aortic insufficiency on the other hand is characterised by an increase in left ventricle volume and stroke volume, and reduced aortic diastolic pressure and is caused by inadequate closing of the aortic valve. This results in backflow of blood from the aorta into the ventricle during diastole causing ventricular volume overload and reduced effective cardiac output. Causes include aortic root dilatation, aging, Marfan syndrome amongst others. Insufficiency was simulated by decreasing the closing resistance of the aortic valve thus increasing the portion of regurgitation resulting in decreased diastolic pressure and increased stroke volume. Despite stroke volume increases overall cardiac output is decreased owing to the regurgitation effect.

As a final example to validate the qualitative performance and flexibility of the controlled system in reproducing clinical scenarios we turn to simulating acute hemorrhage. Hemorrhage is the loss of blood from the circulatory system which can occur internally or externally. Typically blood loss of less than 10-15% of total blood volume can be endured without medical intervention. However Class II-IV hemorrhage i.e. 15% to 40% requires varying degrees of medical intervention from volume replacement to transfusion. Volume losses of >40% of total blood volume are critical and require immediate care. Early cardiovascular responses include baroreflex compensatory mechanisms to hypotension i.e. increased heart rate, peripheral resistance, venous tone and cardiac contractility, which typically maintain blood pressure and heart rate until the system volume falls below a critical

level. To simulate blood loss a time-varying function of volume loss was described which follows an exponential decay characteristic given by:

$$V_{loss}(t) = V_{max}(e^{-(t-t_0)/T}) \quad (30)$$

where T is the time constant of blood loss, and t_0 is the time of onset of blood loss. As can be seen from Figure 4.6, blood pressure is maintained at the beginning of haemorrhage, until a critical volume is reached. Heart rate begins to increase and blood pressure plummets as expected as hypovolemia ensues. This sequence of events is also similar to that seen in vasovagal syncope (See Figure 4.6) and thus could be taken as evidence to support the idea that the system is capable of simulating some of the important features of vasovagal syncope. Although vasovagal syncope is well known clinically, the source of the massive vasovagal response, bradycardia and vasodilation is unknown. This model indicates a possible mechanism whereby saturation of control mechanisms is partially responsible. An important omission from our model is the long term control of blood volume via the renin-aldosterone-angiotensin system (RAAS), which may serve to further buffer volume changes further prolonging time to hypotension.

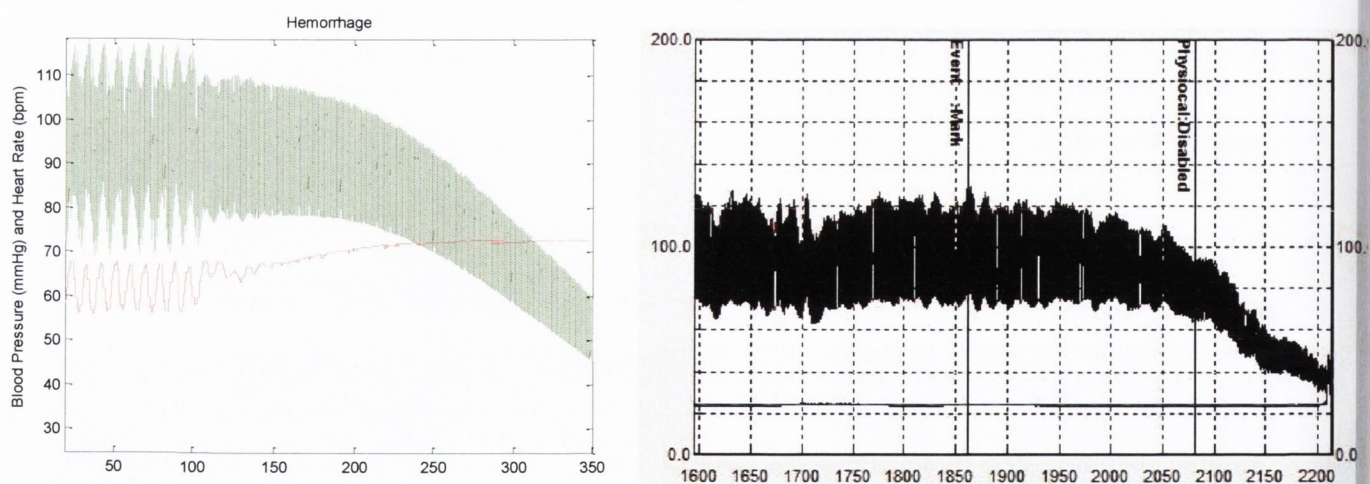


Figure 4.6: Effect of acute haemorrhage on blood pressure and baroreflex function in the model (left). Blood pressure response during an episode of vasovagal syncope. Note the similarity in responses (Right).

4.1.3 Valsalva Manoeuvre

One of the most widely used bedside tests of human autonomic function is the Valsalva manoeuvre and which is used to examine the integrity of both arterial and cardiopulmonary

reflex arcs. During this test an abrupt transient 15 second elevation of intrathoracic pressure (40mmHg) is produced by a patient blowing into the mouthpiece of a manometer. Both blood pressure and heart rate are monitored throughout. The physiological response described by Hamilton, Woodbury and Harper (Hamilton, Woodbury et al. 1944) is universally accepted and is divided into four distinct phases (See Figure 4.7). During the test intrathoracic pressure rises, venous return and stroke volume diminish and venous pressure increases. During Phase I after stimulus onset arterial pressure rises and heart rate decreases; Phase II includes a decrease in blood pressure and then recovery accompanied by speeding of heart rate while straining; on release of straining Phase III ensues with a sudden drop of arterial pressure and increase in heart rate and finally Phase IV occurs with terminal increase in blood pressure above baseline and a slowing of heart rate. The Valsalva ratio i.e. ratio of maximum RR interval after straining to minimum RR interval during straining is typically reported clinically. The Valsalva manoeuvre was simulated by increasing external bias pressures of the cardiac, venous and arterial chambers by 40mmHg for 12-15 seconds. The transition between the four phases in both heart rate and blood pressure traces of the manoeuvre is captured quite convincingly as can be seen by comparison to an actual Valsalva recording. The magnitude of blood pressure and heart rate changes do not match quantitatively as no attempt to individually tune the model to the clinical data was made. However the calculated Valsalva ratio for the simulated output was found to be 1.5 i.e. within the range of normal values for the Valsalva ratio.

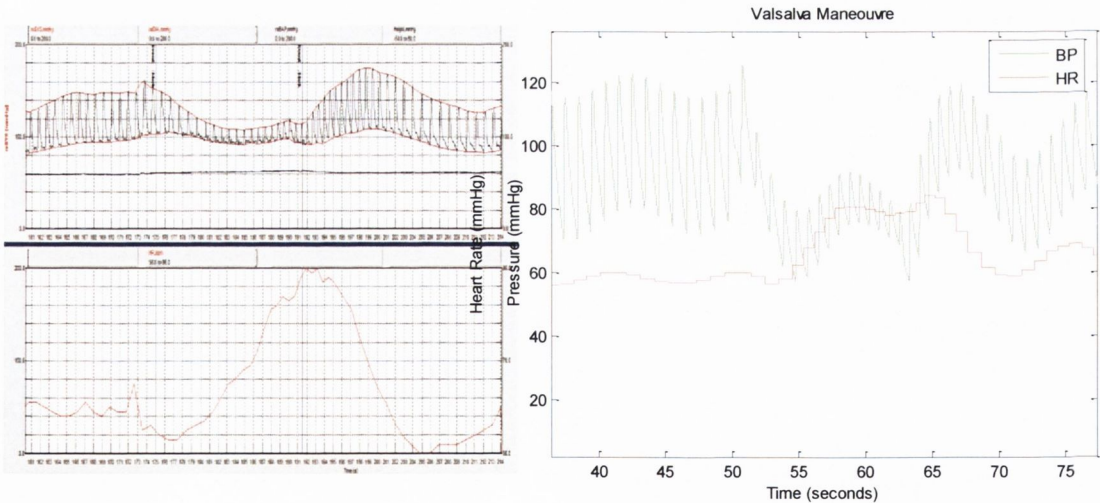


Figure 4.7: Response to Valsalva manoeuvre. Clinical response (left). Simulated response (right).

4.1.4 Deep Breathing

Controlled deep inspiration and expiration performed at a constant rate (6bpm) accentuates respiratory sinus arrhythmia and is used regularly as part of clinical autonomic nervous

system test batteries (Ewing 1981). During deep breathing heart rate is monitored, and the ratio of maximum to minimum heart rate is calculated. This is essentially a test of parasympathetic control of the heart and is an early precursor of autonomic dysfunction in diabetes mellitus (Bernardi, Rossi et al. 1989) and a valuable prognostic indicator following MI (Katz, Liberty et al. 1999).

To simulate the deep breathing test external bias pressure of the thoracic compartments were varied sinusoidally with an amplitude of 10mmHg, at a range of frequencies (0.15Hz to 0.1Hz).

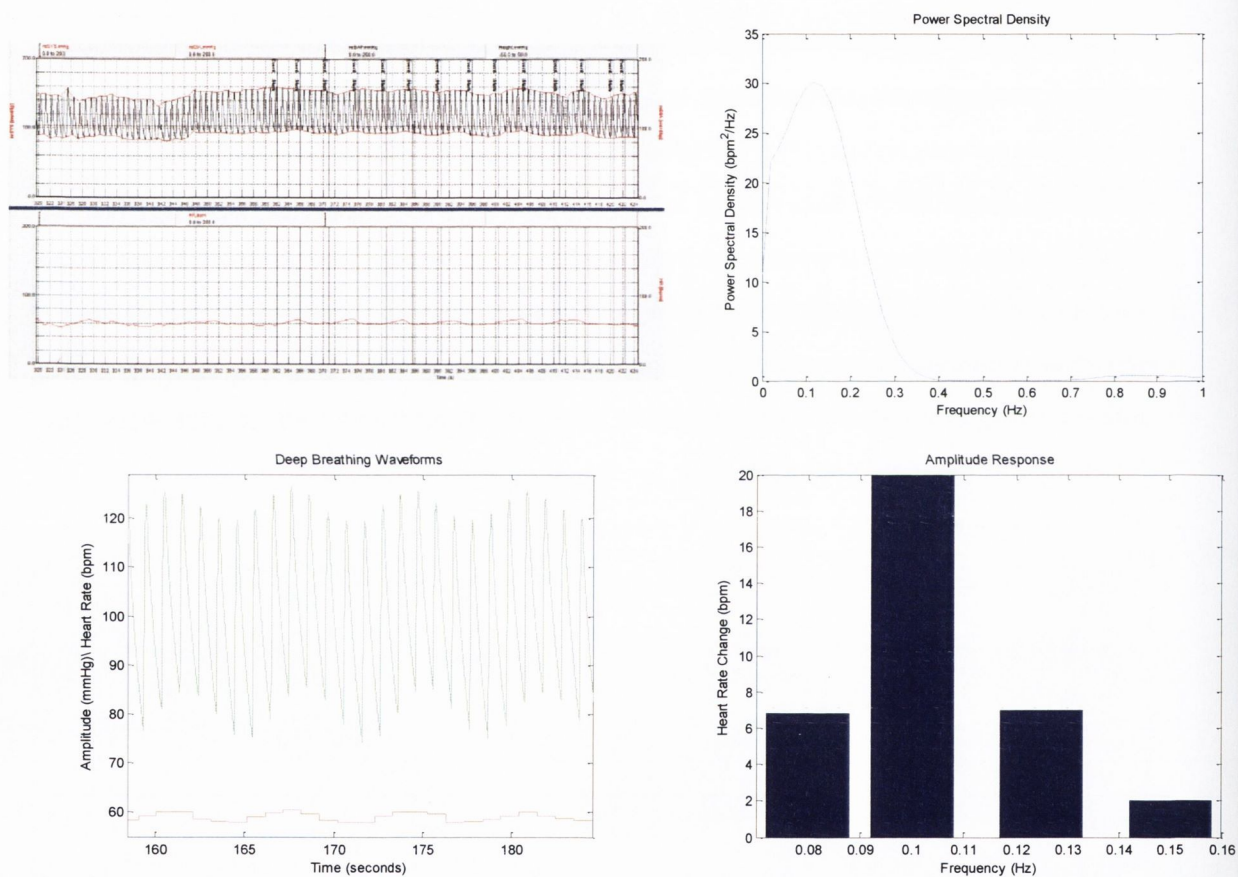


Figure 4.8: Experimental and simulation of deep breathing. Experimental data time series recording in healthy adult (Top left). Measured power spectral density of Heart rate (Top right). Simulation (Bottom left). Simulated resonance effect (Bottom right)

Figure 4.8 indicates that simulated and experimental blood pressure and heart rate are modulated at the breathing frequency as expected and the frequency spectra demonstrate this peak clearly in both scenarios. Furthermore as the breathing frequency approaches the

natural resonant frequency of the blood pressure feedback system the HR amplitude modulation increases.

4.2 Carotid Sinus Massage

Having verified the models operation in baseline, clinical and transient conditions we now proceed to examine the main goal of this Chapter, i.e. demonstrate the models ability to simulate normal and pathophysiological responses to unilateral CSM. Three points are examined in succession

- Comparison of simulation with normal response clinical data
- Examine the dependence of CSM outcome measures on stimulus parameters to inform clinical practice
- Simulation of abnormal response and comparison with CSH data with initial indication of causal parameters

4.2.1 Simulation of Carotid Sinus Massage in Healthy Man

Unilateral massage was simulated in the complete intact system. A 300mmHg equivalent stimulus was used as baroreceptor input to insure the system is driven into the saturation regime of the sigmoidal characteristic and on the basis that 300mmHg stimulus would produce a 3000msec delay system in a system with a sensitivity of 10ms/mmHg. The duration of CSM was chosen to last 5 seconds as recommended in the International Syncope Guidelines (Moya, Sutton et al. 2009).

Clinical data was obtained from control participants who were recruited prospectively from a dedicated Falls and Blackout facility. All subjects attended for a single visit between 0900 and 1300 hrs in a temperate (23°C), comfortably lit, low-noise environment. Patients had full clinical assessment including Carotid Sinus Massage (CSM) as part of routine cardiovascular assessment and the study had ethical approval from the local ethics committee.

Prior to CSM all subjects underwent a ten-minute baseline surface electrocardiogram (ECG) and continuous beat-to-beat blood pressure (TNO Finapres©) recording. Subjects were instructed to lie supine, and directed to breathe normally while measurements were taken. Following an initial 5-minute cardiovascular stabilization period Physiocal© was switched off and data was recorded for a further 5 minutes. Signals were sampled at 200Hz, filtered between 0.01-100Hz and stored digitally on a PC for further analysis. This allowed standard baseline cardiovascular variables including heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MAP) to be recorded.

Following this CSM was performed. Firm longitudinal massage was applied for 5 seconds at the point of maximal pulsation over the carotid (usually located at the level of the upper border of the crichoid cartilage) on the right and then left sides allowing a 30-second interval between stimuli. CSM was performed in both supine and upright positions (head-up tilt to 70° foot plate assisted table). Thus participants underwent a maximum of 4 episodes of CSM. In total 27 control responses were obtained measured. The results of CSM are shown in Figure 4.9, where the degree of cardioinhibition and vasodepression are plotted against one another.

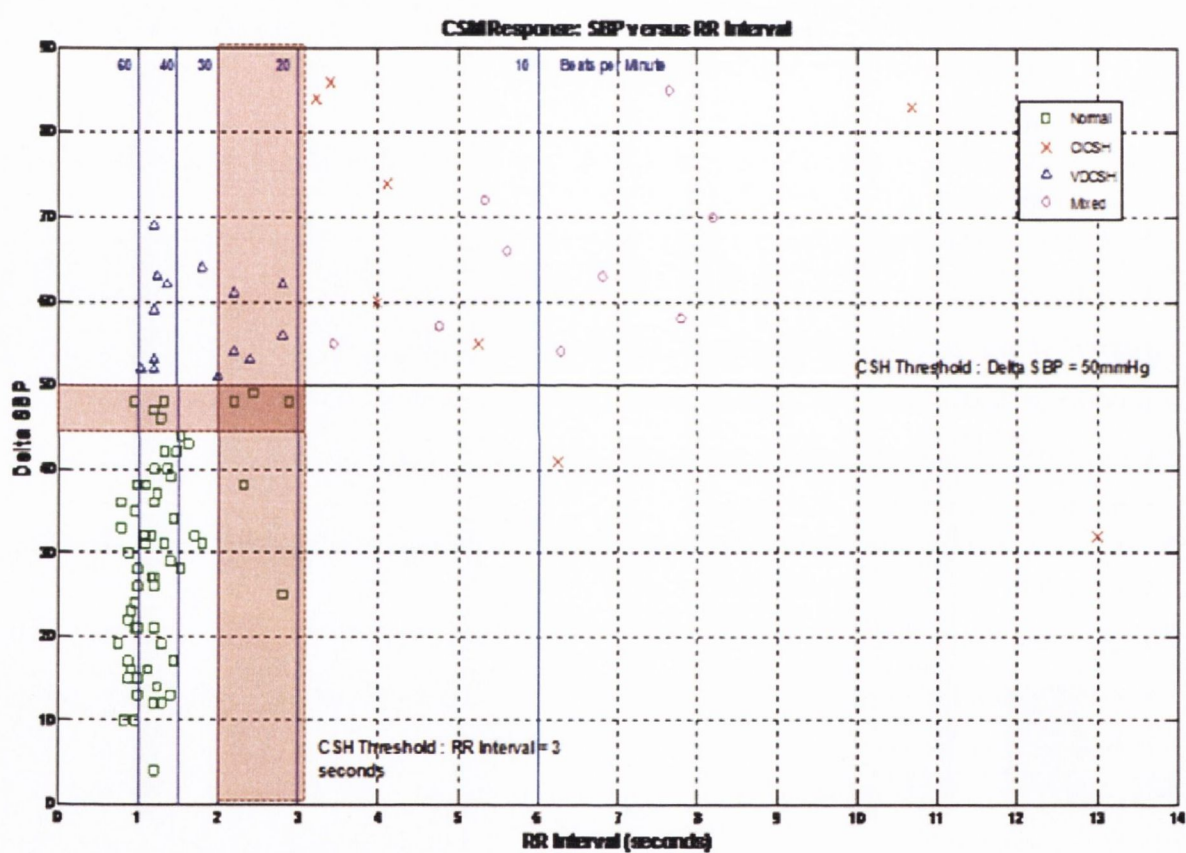


Figure 4.9: Response characteristics of clinical population to CSM where the degree of vasodepression and cardioinhibition is plotted on the y and x axes respectively.

Model prediction of maximum RR following CSM was 1.16 seconds. Drop in systolic blood pressure from baseline was 15mmHg. These compare well with normal range of values obtained experimentally where a maximum R-R interval following CSM was 1.1(0.76-1.8) seconds and maximum delta SBP was 27 (4-44mmHg).

There is however an expected difference between populations, since our model was initially designed to represent average healthy young adults, the CSM data described here is from older adults aged>50 albeit healthy. We examined heart rate and blood pressure responses for youngest group i.e. 50-60 year bracket and found clinical data to give a max RR interval of 0.96 second (0.92-1) and max drop in SBP of 18.5mmHg (10-35mmHg) . Our model is thus a relatively good match of the younger population response to CSM.

Figure 4.10 shows a comparison of one individuals R-R interval time series with model predicted values. Transient responses to CSM are similar to individual data, although there are some differences which warrant discussion. Minor tuning was performed to improve matching of data. In particular increases in resting heart rate and blood pressure set point, and increased range of baroreflex sigmoid were required. All other parameters remained fixed.

	Simulated	Actual (Total Group)	Actual (50-60 yrs)
RR Response to CSM	1.16 secs	1.1 secs (0.76-1.8)	0.96 secs (0.92-1)
SBP Response to CSM	15mmHg	27mmHg (4-44)	18.5mmHg (10-35)

Table 4.2: Normal response to CSM, comparison of simulated and actual responses

One major difference is noted in the response i.e. the marginal stability of the resultant system is evident from ringing in system responses. This overshoot is not evident in clinical response and would suggest that further model refinement is required to capture all features of the aging heart rate response to CSM. Critically the magnitude of heart rate slowing must be maintained while also minimising overshoot.

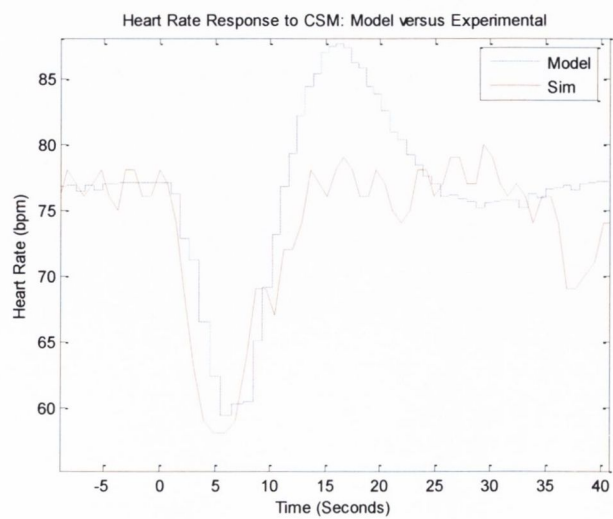


Figure 4.10: Heart rate response to CSM. Comparison of model (blue) and clinical data (red)

On further reflection it was found that this overshoot occurring in the later stages of the heart rate response results from a transient blood pressure overshoot being reflected into the heart rate control limb through the baroreflex.

To examine the role of BP in this transient separate venous and arterial alpha blockades were simulated. This was achieved by detaching baroreceptor feedback to each specific limb of the autonomic nervous system and then both as appropriate (See Figure 4.11).

As can be seen from Figure 4.11 it is actually the venous limb which is the dominant limb playing the most significant role in determining the transient heart rate overshoot i.e. when arterial resistance is blocked. Blockade of the venous limb essentially quenches this transient and the resultant HR response matches the experimental transient both quantitatively and qualitatively. Parameters of importance in matching the response include the range of sigmoid, baroreceptor sensitivity, time constant for both SNS and PNS limbs of heart rate control, and limb delays. Obviously the gain of venous and arterial limbs play a significant role in the response especially in the later portions of the response. Figure 4.12 demonstrates the models ability to also capture the transient blood pressure response quite convincingly. Salient model parameters include baroreflex range, baroreflex sensitivity, time constant for both venous and arterial resistance limbs. Of note clinical values of SBP and MAP match the model behaviour well. However the DBP blood pressure response is less well matched. This warrants further investigation in future iterations of the model.

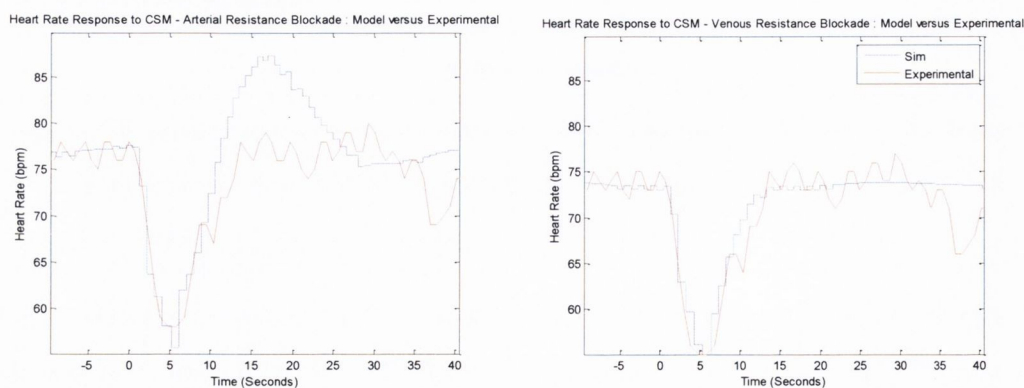


Figure 4.11: Simulation of the effect of CSM on Heart Rate. (Left) Alpha blockade of arterial resistance vessels (Right) Venous blockade of venous capacitance vessels.

Finally to further validate our model against known clinical findings. Figure 4.13 depicts results examining the effect of resting heart rate on cardioinhibitory and vasodepressor responses. Heart rate drops following CSM are directly affected by resting heart rate. This is in agreement with the results of Levy and Zieske (Levy and Zieske 1969) while blood pressure drops are practically independent of quiescent heart rate.

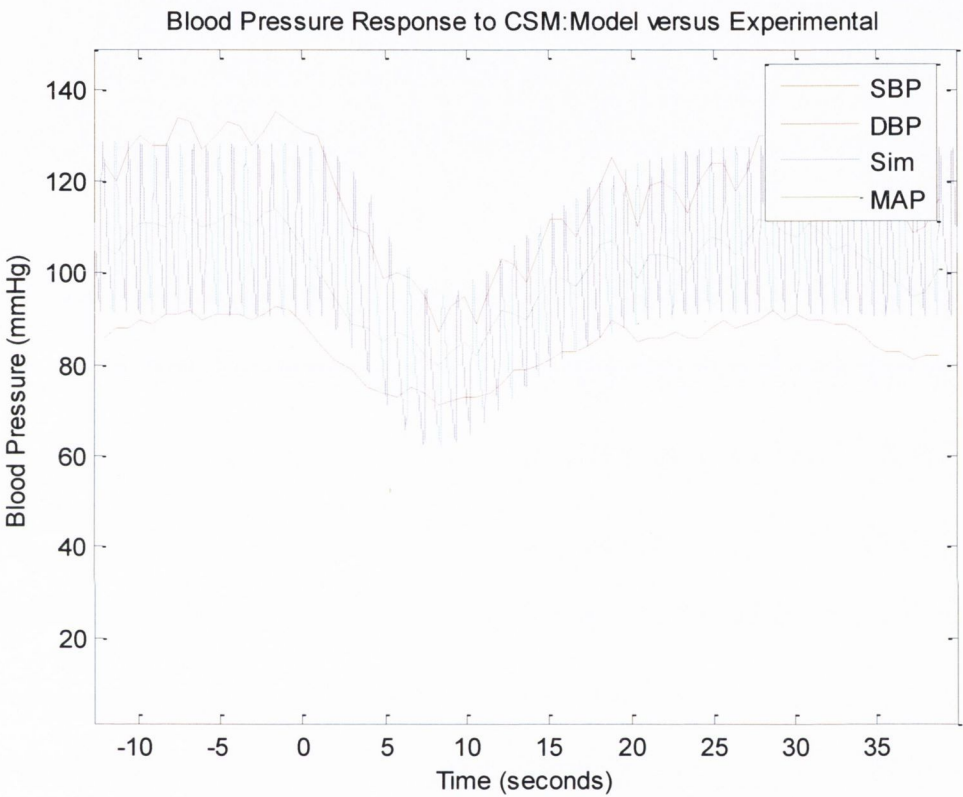


Figure 4.12: Simulation of the effect of CSM on Blood Pressure

4.2.2 Dependence on Input Stimulus Parameters of Carotid Sinus Massage

The reliability of CSM is often questioned since it is a subjective manoeuvre (O'Mahony 2001). Furthermore although rare neurological complications do arise during CSM (Richardson, Bexton et al. 2000).

In order to provide some quantitative and theoretical guidance to clinical practitioners on the optimum method for CSM from safety and reliability perspective, we examine the sensitivity of CSM outcome variables to variations in CSM parameters. In particular we focus

on the dependence on stimulus magnitude, duration and rate, parameters which can be practically varied in the clinical environment.

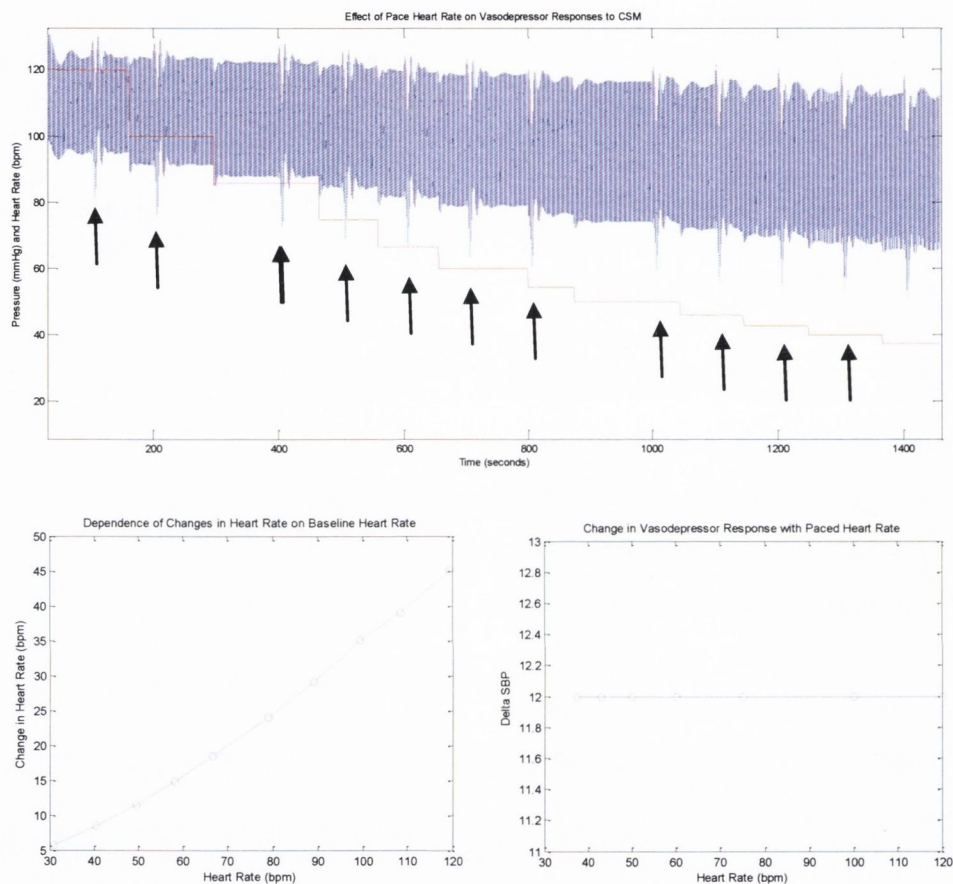


Figure 4.13: Simulation of the effect of Heart Rate on the response to CSM. Each arrow indicates a CSM event.(Top) Heart Rate (Red) and Blood Pressure simulation. Dependence of the Cardioinhibitory response on heart rate. Heart rate drops increases as heart rate increase (Bottom left). Dependence of the Vasodepressor response on heart rate. Blood pressure drops are independent of heart rate (Bottom right).

From a reliability perspective the optimum stimulus is that stimulus which produces the most reliable result or is least sensitive to changes in particular stimulus parameters. Obviously from a diagnostic perspective the stimulus must still remain capable of symptom reproduction which in the case of CSM is dizziness and/or loss of consciousness. Thus the

stimulus should be able to provoke cerebral blood flow/mean arterial pressures changes large enough to produce symptoms. Finally and importantly from a safety perspective time spent in a state of cerebral hypoperfusion should be minimized to avoid ischemic damage of neurological tissue, while still long enough to produce symptoms.

To examine the effects we increased magnitude/duration/rate independently in steps of 10% from 10% to 200% of nominal values for each parameter, where nominal values were assumed to be magnitude = 300mmHg, duration = 5 seconds, and rate = 1Hz. Maximum variation in mean, systolic, diastolic aortic pressures are examined. In the same way heart rate, cerebral pressure and blood flow changes are examined.

The contour plots in Figure 4.14. demonstrate the sensitivity of cardiovascular responses to the various combinations of stimulus parameters. As can be seen responses are most sensitive to duration of CSM between 1 to 3 seconds. Cerebral blood pressure is independent of pressure magnitude, once the carotid closing pressure is exceeded. Both heart rate and blood pressure responses are most sensitive to changes in stimulus duration below 3 and 5 seconds respectively.

An optimum stimulus of 3-5 seconds with strains brought about by an equivalent step change in pressure of 150-200mmHg, would maximize both heart rate and blood pressure responses and minimize stimulus duration. The simulation data is in agreement with Syncope Task Force recommendations (Brignole, Alboni et al. 2004) and reports by Lown and Levine (Lown and Levine 1961). Reay et al. (Reay and Holloway 1982) found minimal blood flow occurs within 6 seconds after complete compression of carotid. The absolute maximum duration of CSM should be 6 seconds if complete compression occurs.

To guide magnitude of pressures from a safety perspective, we considered the critical closing pressure of the carotid artery and the time to minimum cerebral blood flow as critical. We use range of values of arterial closing pressures defined by Sheahan et al. (Sheahan, MacMahon et al. 1993) and MacMahon et al. (Mac Mahon, Sheahan et al. 1995). Transmural pressures of 0 to -153mmHg were found to cause arterial collapse in older adults. The larger negative pressure values occurred in older adults with pseudo-hypertension. Assuming an average pressure of 93mmHg and systolic pressure of 120mmHg, would suggest that a value between 120mmHg and 273mmHg is sufficient to close the carotid arteries. An external pressure of 258mmHg was found to be sufficient for closure (Fisher's 1993), which would agree with our estimate based on Mac Mahon's study (Mac

Mahon, Sheahan et al. 1995). Aggregating these values suggest that an external pressure of 120 to 273mmHg is sufficient to close the carotid artery throughout the cardiac cycle. Thus external pressure applied during CSM should be lower than this value while giving an equivalent carotid sinus strain which would be produced by a 150-200mmHg⁺⁺⁺ pressure change.

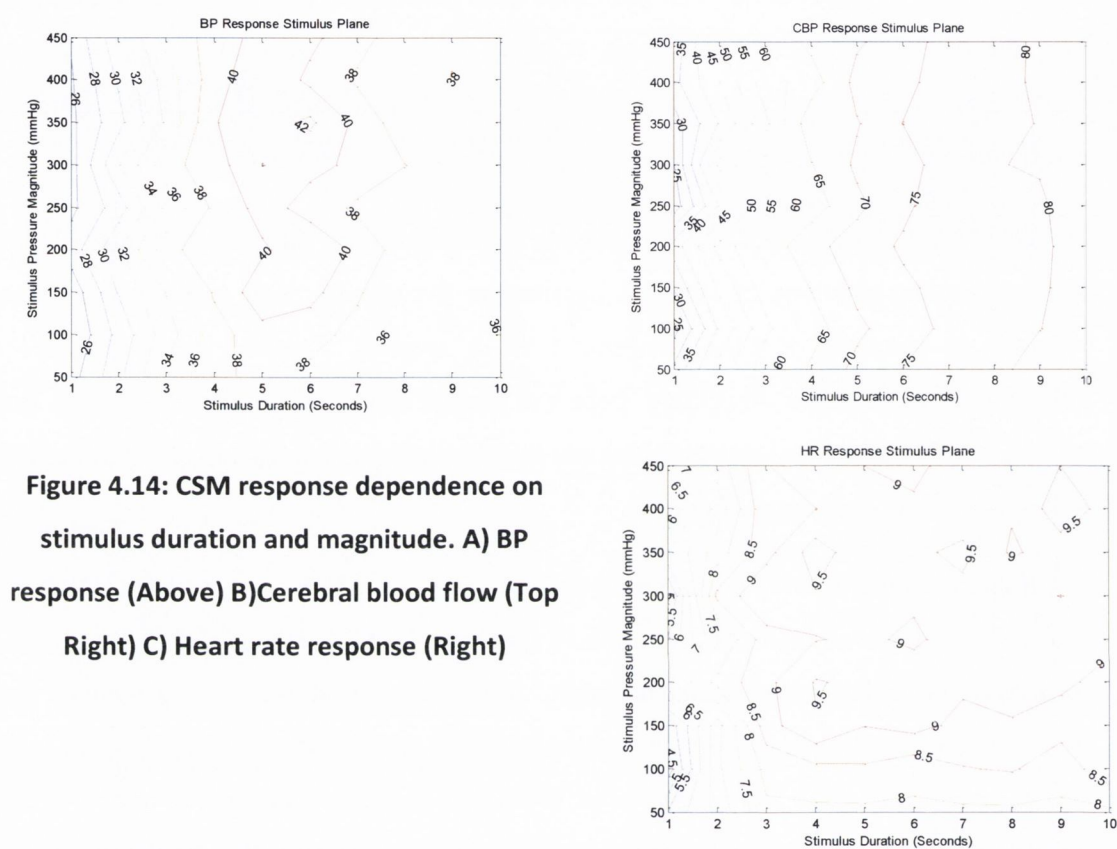


Figure 4.14: CSM response dependence on stimulus duration and magnitude. A) BP response (Above) B)Cerebral blood flow (Top Right) C) Heart rate response (Right)

4.2.3 Model Simulation of Carotid Sinus Hypersensitivity

In this section having validated our models ability to capture the cardiovascular trends seen in a normal physiological state, and selected an optimum stimulus we now examine its ability to capture both CICS_H and VDCS_H responses. By virtue of the tuning process, this also constitutes an empirical pseudo-sensitivity analysis of the parameters which identifies salient parameters governing the response to CSM.

4.2.3.1 SA Node Model of CICS_H

Our model was earlier shown to capture the normal HR response to CSM quite well. We now simulate the pathophysiological response seen in CICS_H as shown in Figure 4.15. From our modelling studies it is evident that a number of possible mechanisms could result in a CICS_H response. Two possible subtypes are identified which we term *chronotropic* and *dromotropic* CICS_H.

⁺⁺⁺ It should be noted that these pressures cannot be directly compared.

Initially to model CSH we increased the gain of the heart rate limb of the baroreflex as suggested by current models of CSH pathophysiology. It was required also to significantly increase the range of the baroreflex. Finally it was found that the relative timing between parasympathetic and sympathetic limbs was also important. Increased time delays in parasympathetic limb caused greater relative overlap of the impulse responses of each limb and increased the strength of cardioinhibition. Relative cardioinhibition was achieved using a pure SA node based model (See Figure 4.15). This model was an excellent match for the response to right sided CSM in an individual with left sided CICSH and thus explains the normal response to CSM in this individual. Note that this individual demonstrated both abnormal left sided response and a normal right sided response.

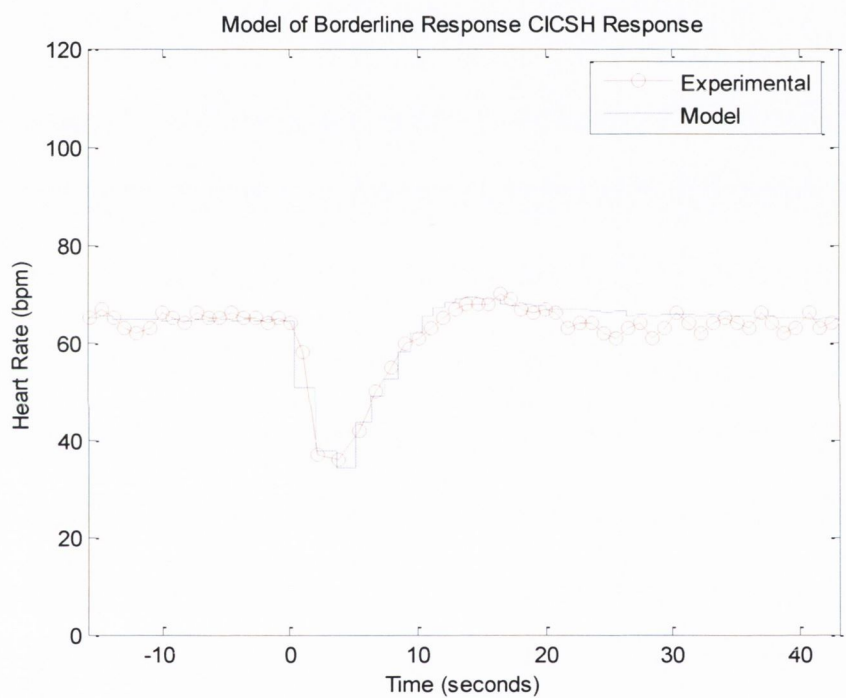


Figure 4.15: Model of right sided CSM response (normal) in an individual with left sided CSH

Matching of the pathological CICSH response in the same individual could be achieved albeit it less accurately using a pure SA node model coupled with baroreflex changes alone. Adequate slowing was difficult to achieve, although the morphology of the response was captured quite well. To achieve this result potentially unrealistic baroreflex parameter values were required (i.e. gain of >60msec/mmHg and sigmoidal range of >800mmHg, CSM stimulus of 800mmHg equivalent pressure) to obtain significant slowing (See Figure 4.16 Top and Bottom). No clinical studies to date have reported baroreflex sensitivities or range even

close to these values. Furthermore extremely high stimulus parameters were required to achieve this result. One could only speculate that during CSM these values may occur due to high levels of local carotid wall deformation and hence baroreceptor stimulation. However to date there is no record of the magnitude of strain encountered during CSM. Additionally for a response to occur spontaneously by these mechanisms in the community would require a relatively large stimulus and may not be plausible. A more detailed non-linear model of autonomic modulation of SA node control derived starting from the Hodgkin-Huxley equations could perhaps provide additional mechanisms by which we could arrive at a similar result with more realistic parameters. Inclusion of central baroreflex circuitry could only add to the complexity of this picture and array of possible behaviours. Furthermore nonlinear models of this kind have been shown to demonstrate a greater spectrum of behaviours including pulse induced pacemaker activity quenching and chaotic behaviour, which is dependent on the strength and timing of stimulus which could open up the system to nonlinear dynamic effects.

4.2.3. AV Node Model of CISH

The abrupt pause in the heart rate response in Figure 4.16 suggests another possible mechanism i.e. existence of a state change or threshold in the dynamics of heart rate control which could explain this large pause and could be modelled by a number of absent beats. From a physiological perspective this could be explained by sinoatrial exit block or AV nodal block which both have been reported to occur in CSH. Interestingly sino-atrial exit block is not detectable on the ECG and thus can present itself as impulse generation failure.

This hypothesis would be in keeping with recent results obtained during adenosine testing in CSH where a positive test result was found in 100% (n=7) of subjects with CSH (Parry et al, 2009). Furthermore CSH is a well known age-related disorder. Aging is also accompanied by senescence related fibrosis of the sinoatrial node, which is often accompanied by senescence of the atrium and conduction system of the heart and thus sinus node dysfunction (SND) i.e. sinus bradycardia, sinus pause/arrest, chronotropic incompetence, and sinoatrial exit block.

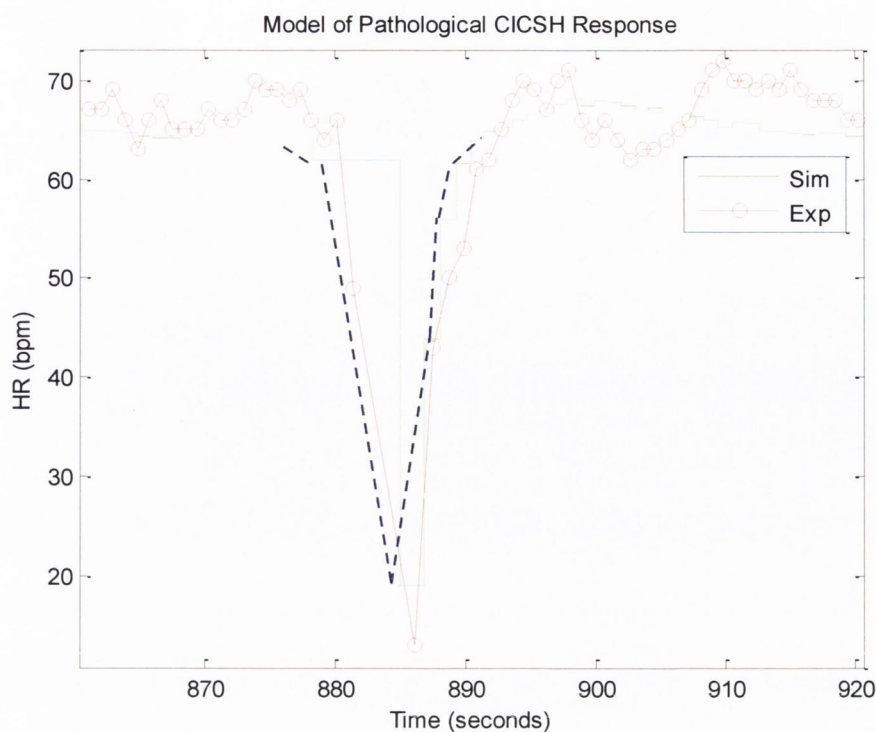


Figure 4.16: An examples of the SA Node model fit of CICSH response (abnormal) in an individual with left sided CSH. The SA node model alone has difficulty capturing this complete response accurately. Note the profile of HR simulation is a regularly sampled signal, with a new beat occurring at each step change in HR. It is this profile (dark dotted line) which must match the clinical data.

Thus CSH could be associated with increased fibrosis of the atrial conductive tissue. In tandem early EMG results document an association between CSH and sternocleidomastoid denervation thus giving further support to a role of conductive derangement in CSH.

In an attempt to improve the model accuracy we included a model of T cell (or AV node) control. The addition of this nonlinearity allows the required pauses to be reproduced without the need for very large stimuli or abnormally high baroreceptor gain and/or baroreflex range (See Figure 4.17). This model result was achieved using a realistic baroreflex gain of 5msec/mmHg, sigmoidal range of 40mmHg and CSM stimulus with amplitude > 80mmHg equivalent pressure.

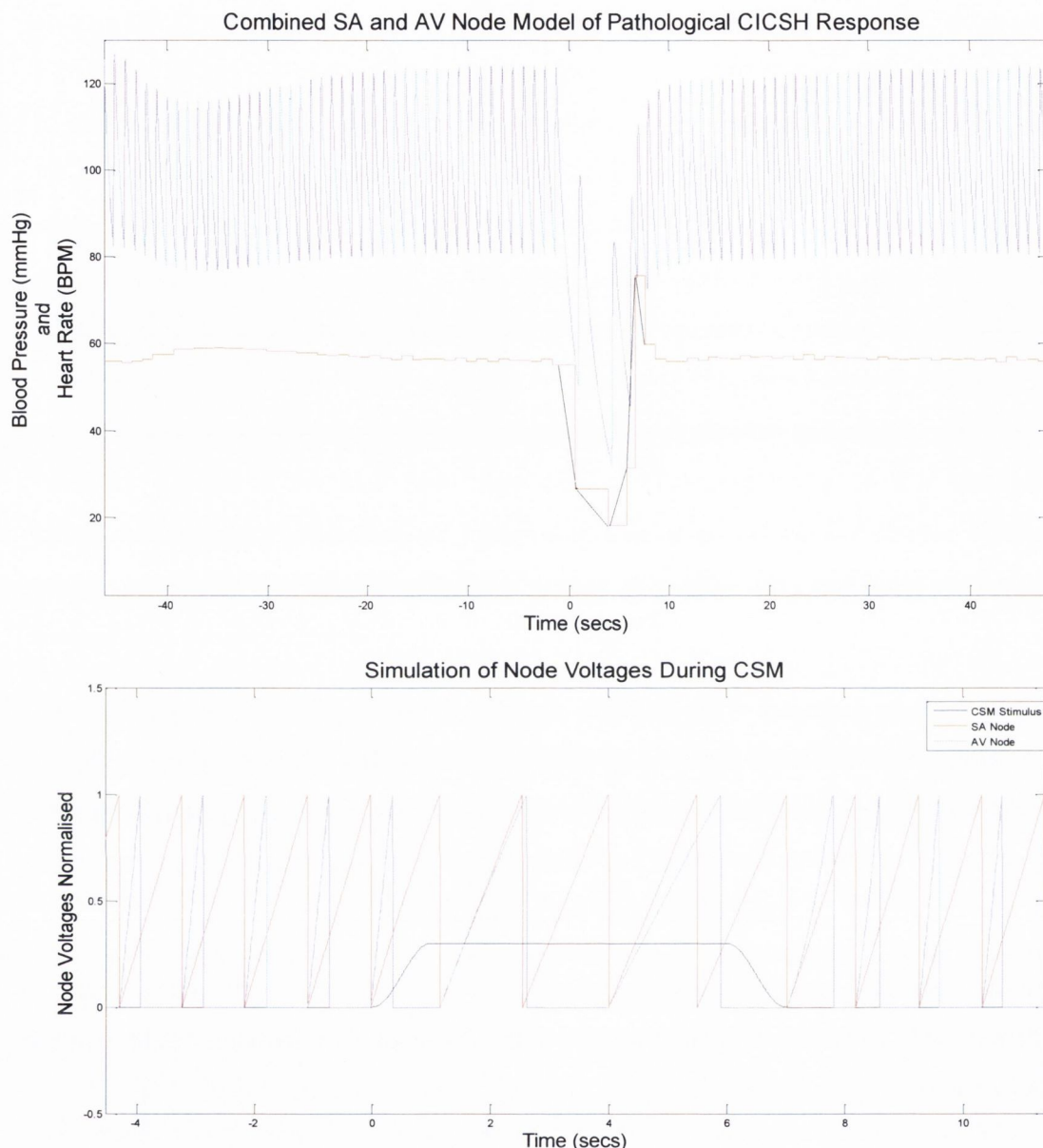


Figure 4.17: Simulation of the AV Node Model of the Cardioinhibitory response to CSM (top) and node voltages during CSM showing the skipped beat mechanism (bottom)

Furthermore to induce sinoatrial exit block the gain of autonomic limb serving T cells was higher than the SA node by a factor of 3.5. Simulation results are shown in Figure 4.17. As can be seen a pause of over 3 seconds was achieved with this model configuration. Examination of the simulation of the node voltages demonstrates the mechanism of sinoatrial exit block whereby two SA node beats are blocked by the T cells. This transition causes the heart rate to decrease by below 20bpm below the diagnostic threshold for CICSH.

4.2.3.3 Vasodepressor CSH Model

This section describes model simulations devised to mimic vasodepressor CSH. From our modelling experiments we uncovered a number of possible model configurations which could produce vasodepressor response similar to those seen clinically in CSH depending on which limb of the baroreflex is damaged. This would suggest that we have identified two potential subtypes of VDCSH i.e. arterial and venous VDCSH.

4.2.3.4 Arterial Vasodepressor CSH

This occurs when arteriole control limb is severely impaired, while venous tone is relatively intact. As you can see from the simulated response (Figure 4.18) the blood pressure drop lags the heart rate changes by 5-8 seconds and any residual arterial vasodilatation, a slow continuous drop then occurs followed by a slow recovery. A number of parameters were important in simulating the response. Firstly the venous tone gain used was 10ml/mmHg a value one third of nominal value. Again both the stimulus and range of the baroreflex were important and were raised to 800mmHg and 100 respectively. Peripheral resistance gain was reduced by a factor of 10 and similarly the heart rate response to CSM was reduced by decreasing the heart rate baroreflex sensitivity to 2ms/mmHg. Thus based on the relative system gains the venous tone loop would be expected to dominate the system response dynamics in this configuration.

The biphasic response seen in Figure 4.18 occurs due to the partial recovery brought by an impaired arteriolar response and heart rate responses. The lag is due to the inherent lag in the venous system and the rate of recovery is determined primarily by the time constant of the venous limb. As you can see this reproduces the clinical response quite well. All the relevant features i.e. initial drop (Phase I), and initial recovery (Phase II), drop (Phase III) and recovery (Phase IV) are captured.

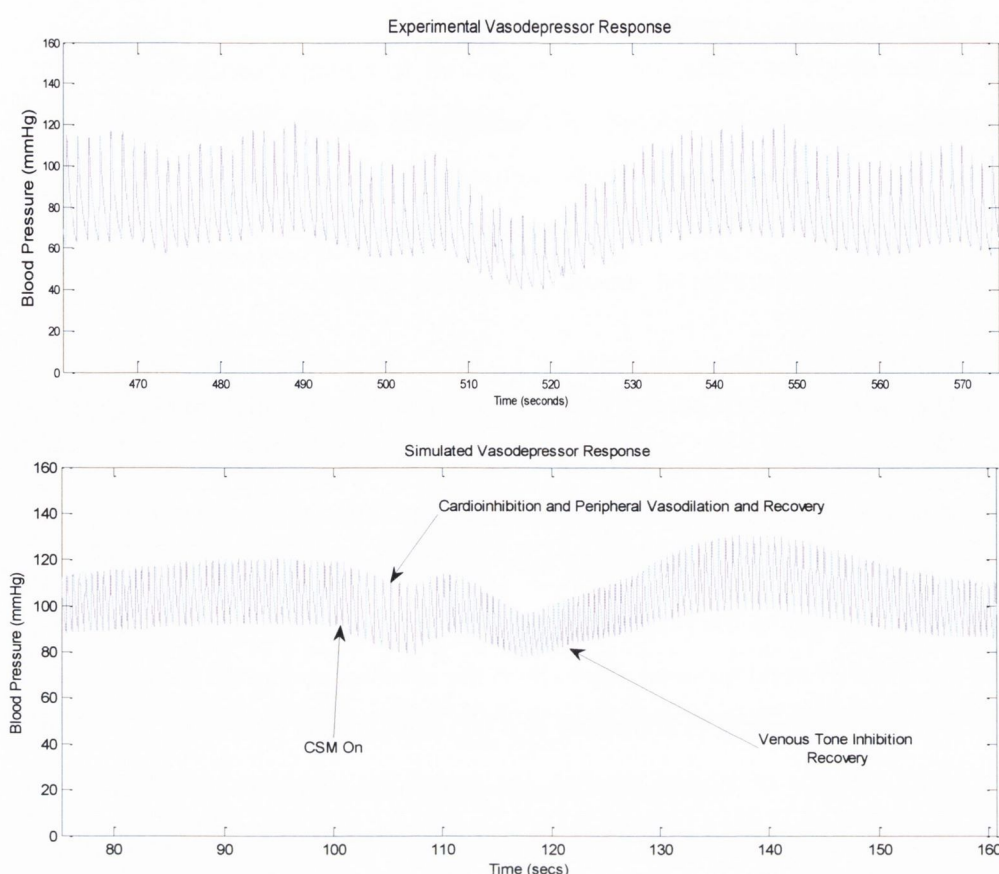


Figure 4.18: Simulated Response of Venous VDCSH (bottom) and Clinical Results (top).

4.2.3.5 Pure Venous Vasodepressor CSH

Another possible model configuration that can give rise to vasodepressor CSH was also demonstrated i.e. when the arteriole sensitivity is intact and dynamics of this limb have slowed. The venous gain maybe intact or impaired in this case. This scenario is simulated below in (Figure 4.19). As you can see in this subtype the lag phase is shorter since the lag of the dominant limb i.e. the arterial reflex is naturally shorter than the venous tone. We simulated this by increasing the time constant of the dominant limb i.e. peripheral resistance feedback to 25 seconds and maintained the venous tone gain as normal. Thus the combined response will be a summation of the two responses overlapping in time. Furthermore the CSM stimulus and range of the baroreflex was increased. The same effect can also be reproduced by changing the CNS time delay in the system such that responses overlap in time.

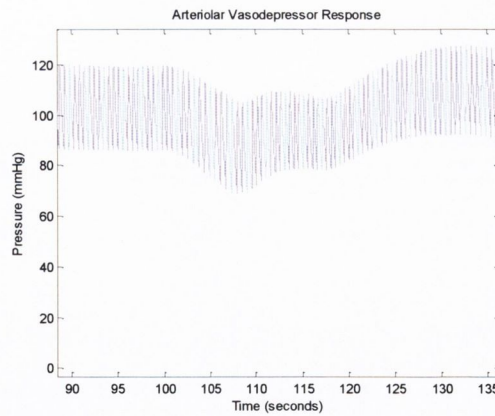


Figure 4.19: Simulated Response of Arterial VDCSH

4.2.3.6 Importance of baroreflex range and response dynamics and stimulus magnitude

To achieve heart rate and blood pressures drops seen in pathological situations i.e. CSH where pauses of the order of 2-3 seconds and blood pressure drops of $> 50\text{mmHg}$ a number of parameters were critical are thus implicated in CSH. From these simulation studies the magnitude of the initial stimulus response i.e. drop in blood pressure or heart rate to CSM was influenced by the

- magnitude of the stimulus
- the gain of the baroreflex
- the range of the baroreflex saturation curve.

Furthermore slowing of effector responses was also key in reproducing the CSH response. Finally a model which includes susceptibility to SA nodal exit block and/or AV nodal block increased the susceptibility of an exaggerated cardioinhibitory response.

4.3 Conclusion

A first model of CSM was successfully designed and developed. Simulation results compared well to experimentally recorded data. Quantitatively the model compares well to published data in its steady-state performance. The model was qualitatively validated and shown to be capable of capturing a number of tests commonly used in clinical investigation of NCVI's as well as a number of common clinical pathology states. Model predictions suggest a set of optimum parameters which should be used for clinical practice when performing CSM to both maximize safety, diagnostic power and reliability. It is recommended that future studies verify these results experimentally.

Finally and most importantly the model developed was capable of simulating Carotid Sinus Hypersensitivity. A number of novel findings were demonstrated which we feel will have important consequences for future diagnosis and treatment approaches.

Firstly our model would suggest that the possibility of a number of potentially new CISH subtypes i.e. Dromotropic and Chronotropic CSH and new VDCSH subtypes i.e. Venous CSH and Arterial CSH. Heart rate slowing is maximised when parasympathetic, and sympathetic responses overlap in time, thus cardioinhibitory CSH will be characterised by increased system delays. The relative influence of the baroreflex on pacemaker rate and conductivity of atrial tissues is also important and suggests the possibility of two CSH subtypes i.e. chronotropic and dromotropic CSH. In all cases the saturation limit of the baroreflex is also important, since it limits stimulus magnitude.

In Venous CSH arteriolar reflex is severely impaired while the venous limb is relatively intact, resulting in a lagged and prolonged drop and recovery. This would mirror the classical 'Slow Vasodepressor Response'. OH in this case is characterised by slow recovery rate. In Arterial CSH the sensitivity of arteriolar and venous limbs are relatively intact. However the relative rate of the arteriolar response is impaired. Thus both limbs vasodilate in unison to contribute to greater hypotension.

Secondly the modelling process allowed a number of parameters to be identified as paramount to the reproduction of CSH response i.e. baroreflex range, baroreflex sensitivity, stimulus magnitude and effector delays and governing time constants. Future analytical work should be aimed at formally assessing the relative sensitivity of CSM response to variation in these parameters and as a means of formalising the identification process of candidate biomarkers for CSH. We would suggest based on these modelling predictions that these parameters are likely candidates for involvement in pathogenesis of CSH. Furthermore they could potentially form a set of novel candidate biomarkers for CSH and identify future avenues for treatment regimes for CSH.

Another interesting finding is that the rate of blood pressure recovery is closely related in both CSM and active stand since similar physiological mechanisms i.e. venous and arteriolar systems are involved. Secondly the baroreflex sensitivity of these systems is important and can result in the system oscillating due to system being marginally stable or producing limit cycle behaviour. The oscillation frequency, rate of blood pressure drop and recovery following CSM and AS are directly linked and dominated by the same frequency component.

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CHAPTER 5

Mayer Wave Activity in Vasodepressor Carotid Sinus Hypersensitivity

Mayer Waves are low frequency blood pressure waves, whose modulation involves central/peripheral baroreflex pathways. VDCSH is a common hypotensive disorder, particularly in ageing. We hypothesize that VDCSH is due to impaired baroreflex function and that Mayer Wave Amplitude and oscillation frequency are therefore altered in VDCSH.

CHAPTER 5

5.0 Background

Having identified a number of candidate biomarkers of VDCSH using modelling methods in Chapter 4 namely baroreflex range, baroreflex sensitivity and the time constants governing venous and arterial reflex loops, we now proceed to examine experimentally a commonly used clinical surrogate marker of arterial and venous control i.e. blood pressure variability in VDCSH.

5.1 Introduction

Carotid Sinus Hypersensitivity (CSH) is an age-related autonomic disorder (Humm and Mathias, 2006; Kerr et al, 2006; Masson, 2006), characterized by exaggerated cardiac slowing (Cardioinhibitory Carotid Sinus Hypersensitivity) and/or profound drops in blood pressure (Vasodepressor Carotid Sinus Hypersensitivity (VDCSH)) following unilateral carotid sinus massage (Eckberg and Sleight, 1990). First described by Roskam in 1930 (Roskam, 1930), CSH is now a well-established modifiable risk factor for syncope and falls in the elderly (Kenny et al., 1991), responsible for symptoms in up to thirty percent of older patients (Mc Intosh, 1993). Cardiac pacing reduces symptoms in those with CICSS (Brignole, 1992), however in VDCSS a successful treatment option remains elusive, which is further exacerbated by an incomplete understanding of its pathophysiology. Based on experimental evidence it has been postulated (O Mahony, 1996) that CSH occurs secondary to up-regulation of α_2 adrenoreceptor induced deafferentation of the baroreflex resulting from atherosclerosis and a reduction in carotid sinus compliance. Neuropathological evidence (Miller et al, 2007) reports a small but significant increase in neurodegenerative hyperphosphorylated Tau proteins in brainstem nuclei that regulate cardiovascular activity. Polvikoski et al. (2006), found marked α -synuclein pathology in the stellate ganglia of an elderly lady with CICSH. Growing evidence thus suggests that CSH affects the baroreflex arc in central areas, however the manner in which this dysfunction leads to a hypersensitive response remains obscure. In an attempt to further understand the mechanisms contributing to VDCSH, we examine Mayer Wave activity as a non-invasive marker reflective of the state of the blood pressure regulation system. Mayer waves are low frequency (slower than respiration) arterial pressure (AP) oscillations, which exhibit a significant coherence with oscillations of sympathetic nerve activity (Julien, 2006). They are believed to result from oscillations induced in sympathetic nerve activation (SNA) of peripheral resistance vessels. Mayer waves are strongly attenuated after acute α -adrenoceptor

blockade (Japundzic N., 1990; Cevese, 2001) and sino-aortic baroreceptor denervation (Di Rienzo, 1991). These oscillations are variable in amplitude but have relatively stable intra-species frequency. In humans this frequency is age, gender and posture independent, centered typically around 0.1 Hz (Cooke, 1999). A number of authors have suggested that measurement of these oscillations may be used as a non-invasive tool for investigating underlying alterations in peripheral resistance regulatory mechanisms (de Paor and Ringwood, 2006; Ringwood and Malpas, 2001). Studies which simulate Mayer wave generation (de Paor and Ringwood, 2006; Hammer and Saul, 2005; Burgess et al.,1997) predict that Mayer wave amplitude increases with the gain and range of the baroreflex. Oscillation frequency decreases as afferent, efferent, and vascular response delays and characteristic time constants governing effector dynamics increase. This association between Mayer wave activity and baroreflex physiology provides an opportunity to study differences in baroreflex function in health and disease using non-invasive methods. Furthermore the direction of Mayer activity alterations may provide insight into the manner in which the baroreflex gain and/or range is affected. Since the generation and modulation of Mayer waves involves central baroreflex pathways common to those implicated in the pathogenesis of VDCSH, and implicitly involves gain, range and time constants of blood pressure regulation system we hypothesized that Mayer Wave activity is altered in VDCSH. The purpose of this study was to compare Mayer wave amplitude and Mayer wave frequency in VDCSH and case controls.

5.2 Methods

		Control	VDCSH	Significance
Number of cases		31/36	12/15	
Age	Median (Range)	72 (50-92)	78 (48-88)	NS
Height (cm)	mean $\pm$ SD	164.3 $\pm$ 8.9	167.8 $\pm$ 10.2	NS
Weight (kg)	mean $\pm$ SD	75.0 $\pm$ 14.4	71.2 $\pm$ 18.5	NS
SBP (mmHg)	mean $\pm$ SD	153.1 $\pm$ 17.9	159.8 $\pm$ 16.7	NS
DBP (mmHg)	mean $\pm$ SD	74.6 $\pm$ 11.0	76.7 $\pm$ 12.7	NS
MAP (mmHg)	mean $\pm$ SD	103.9 $\pm$ 11.8	108.4 $\pm$ 13.1	NS
HR (bpm)	mean $\pm$ SD	67.1 $\pm$ 12.6	71.9 $\pm$ 13.3	NS
MaxRR (msecs)	Median (Range)	882.6 (645.2 – 1308.1)	841.9 (643 – 1130.5)	NS
Nadir SBP (mmHg)	mean $\pm$ SD	124.2 $\pm$ 22.7	102.5 $\pm$ 19.7	p <0.01
Delta SBP (mmHg)	mean $\pm$ SD	27.4 $\pm$ 9.6	57.2 $\pm$ 8.2	p <0.0001

Table 5.1: Demographics and Baseline Cardiovascular Function in Normal and VDCSH groups.
MaxRR = maximum RR interval reached after CSM; Nadir SBP = Minimum SBP reached after CSM;
Delta SBP = Maximum change in SBP from baseline after CSM

5.2.1 Participants

Participants were recruited prospectively from a dedicated Fall's and Blackout facility in a large teaching hospital. All subjects attended for a single visit between 0900 and 1300 hrs in a temperate (23°C), comfortably lit, low-noise environment (Malik, 1998). Consecutive patients (aged > 50) with a history of recurrent syncope or unexplained falls in the previous year were recruited. All patients had full clinical assessment including Carotid Sinus Massage (CSM) as part of routine cardiovascular assessment. The study had ethical approval from the local ethics committee.

5.2.2 Carotid Sinus Massage

Prior to CSM all subjects underwent a ten-minute baseline surface electrocardiogram (ECG) and continuous beat-to-beat blood pressure (TNO Finapres©) recording. Subjects were instructed to lie supine, and directed to breathe normally while measurements were taken. Following an initial 5-minute cardiovascular stabilization period Physiocal© was switched off and data was recorded for a further 5 minutes. Signals were sampled at 200Hz, filtered between 0.01-100Hz and stored digitally on a PC for further analysis. This allowed standard baseline cardiovascular variables including heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MAP) to be recorded. Mayer activity was derived from last 5 minutes of this rest period.

Following this CSM was performed. Firm longitudinal massage was applied for 5 seconds at the point of maximal pulsation over the carotid (usually located at the level of the upper border of the cricoid cartilage) on the right and then left sides allowing a 30-second interval between stimuli. CSM was performed in both supine and upright positions (head-up tilt to 70° foot plate assisted table) (Parry, 2000). Thus participants underwent a maximum of 4 episodes of CSM.

5.2.3 Definition Of CSH

VDCSH was defined as a drop of 50 mm Hg or more in SBP and less than 3 seconds of asystole. CICSCH was defined as asystole of 3 seconds or more asystole and less than 50 mmHg SBP vasodepressor response; mixed CSH was a combination of cardioinhibitory CSH and vasodepressor CSH.

5.2.4 Data Analysis

All initial data processing was performed with custom written analysis software using MATLAB 6.5^{§§§}. Subject data was separated into 4 groups according to their cardiovascular response to CSM - 1) Controls (no CSH); 2) CICH; 3) VDCSH; 4) Mixed. Only those individuals with Normal or VDCSH responses to CSM were considered for further analysis. Data records were scored for significant noise and artifact, and excluded if noise was above an empirically derived threshold. ECG data was screened for abnormal rhythms, and the presence of ectopic beats^{****}. Diastolic, systolic, mean arterial blood pressure and R-R interval data records were linearly detrended prior to subsequent spectral analysis.

To derive interval frequency spectra, 5-minute R-R interval, SBP, DBP and MAP recordings were analyzed according to the method described by Berger et al. (1984). To account for differences in intervals on the frequency axis (arising from inter-individual differences in mean pulse interval), cubic spline interpolation was applied to resample spectra from 0 – 0.5Hz in steps of 0.0025Hz. Standard time domain indices of cardiovascular variability were extracted from BP and R-R series including standard deviation, and interquartile range. Frequency domain variables were calculated by integration of spectral estimates within a number of standard pre-defined frequency bands (Malik, 1998). Standard blood pressure variability frequency bands VLF (0.003-0.04Hz), LF (Mayer Wave Band – 0.04-0.15Hz), HF (Traube-Herring Band – (0.15-0.4Hz)) were examined for differences between VDCSH and controls. A number of sub-bands were further examined in the LF band including LF₁ (0.04-0.07Hz); LF₂ (0.08-0.1Hz); LF₃ (0.1-0.12Hz). This selection was achieved via statistical procedure whereby independent t tests were applied to group ensemble averaged spectra to identify those bands, which differentiate Controls and VDCSH groups. The peak power spectral density (P_i) and frequency at which this peak (f_{p_i}) occurs was found, within bands VLF, LF₁, HF and a combined band, MF, which includes LF₂ and LF₃ bands.

5.2.5 Statistical Analysis

SPSS^{®†††} version 14 was used to process study data. All features derived in previous sections were assessed for normality using data histograms, Normal Q-Q, detrended Normal Q-Q plots, and calculating distribution skewness, kurtosis, and Kolmogorov-Smirnov test statistics. Initial group age matching was assessed using Kruskal-Wallis non-parametric

^{§§§} Mathworks Inc, Natick, MA, USA

^{****} Data was excluded if the number of ectopics >5% total number of beats

^{†††} SPSS Inc. Headquarters, 233 S. Wacker Drive, 11th Floor, Chicago, Illinois, 60606

testing; height and weight were compared by one-way analysis of variance (ANOVA). Normally distributed variables were compared using Students-T tests. Nonparametric two-tailed Mann–Whitney U-test, was used to compare non-parametric data. Significance was calculated at a level of $p < 0.05$.

5.3 Results

5.3.1 Subjects

Eighty-one patients (44 male; 37 female) were recruited. The median age of subjects was 75 (48-92) years, mean height 165.55 ± 10.27 cm, and mean weight 73.46 ± 14.26 kg.

5.3.2 CSM Response

Thirty-six (17 male, 19 female) individuals had normal CSM responses; fifteen individuals displayed VDCSH (9 male, 6 female); twenty-five subjects had CICSH (14 male, 11 female); while 5 had a mixed response (4 male 1 female). Only data from controls and VDCSH groups were considered for further analysis. A further 8 data sets (5 control; 3 VDCSH) were excluded because of artifact, and ectopic beats. Data from 31 case controls and 12 VDCSH subjects were compared. Resting SBP, DBP, HR and peak frequency were normally distributed; pulse intervals, RR interval, time domain measures of SBP, MAP, DBP, HR, RR variability and COF had non normal distributions. Age, height, weight and baseline cardiovascular variables were similar between groups (See Table 1). SBP nadir and degree of vasodepressor response following CSM were more marked in VDCSH group (See Table 1).

5.3.3 Time Domain Analysis of Cardiovascular Variability

DBP and MAP variability was significantly higher in the VDCSH compared to controls ($6.6 (1.9 - 12.9)$ mmHg vs. $4.0 (1.7 - 9.5)$ mmHg; $p < 0.05$ and 6.6 mmHg ($2.9 - 10.1$) mmHg vs. 4.6 mmHg ($2.5 - 9.1$); $p < 0.05$). A trend towards increased SBP variability was noted in VDCSH (See Figure 5.1 and Table 5.2). Differences in time domain measures of HR, PI variability were not significant (See Table 5.2).

Variable		Control	VDCSH	% Change	Significance
SBP var (mmHg)	Median (Range)	6.5 (3.5 - 14.0)	10.3 (4.2 - 16.3)	36.9%	p = 0.07
DBP var (mmHg)	Median (Range)	4.0 (1.7 – 9.5)	6.6 (1.9-12.9)	39.4%	p < 0.05
MAP var (mmHg)	Median (Range)	4.6 (2.5-9.1)	6.6 (2.9-10.1)	30.3%	p < 0.05
HR var (bpm)	Median (Range)	3.6 (1.1-20.1)	5.8 (1.3-14.4)	37.9%	NS
PI var (msecs)	Median (Range)	49.2 (15.5-221.3)	79.7 (24.3-192.4)	38.3%	NS

Table 5.2: Comparison of Time Domain Indices of CV variability. DBP var = SD of DBP; SBP var = SD of SBP; MAP var = SD of MAP; HR var = SD of HR; PI var = SD of PI.

5.3.4 Frequency Domain Analysis of Cardiovascular Variability

Standard VLF; LF; and HF bands of SBP, MAP and DBP did not differ between cases and controls. A trend towards an increase in both LF (22.6%) and HF (129.6%) bands in VDCSH compared to controls was noted.

On further inspection of the SBP, MAP, and DBP frequency spectra differences between control and VDCSH groups were obvious in narrow frequency bands within the LF and HF bands (See Figure 5.2 A, B and C). Two peaks exist in the LF Band around 0.06Hz and 0.1-0.12Hz in all 3 spectra in VDCSH but not in controls. A third peak in the HF band at 0.3Hz was also noted.

Quantitative analysis indicates significant increases in LF Mayer wave activity in MAP in VDCSH compared to controls at 0.06Hz (controls - 21.7mmHg²/Hz (IQR: 30.8); VDCSH - 31.5mmHg²/Hz (IQR: 72.0) p<0.05). At 0.1Hz differences approached significance (controls - 4.9mmHg²/Hz (IQR: 9.4); VDCSH - 11.5mmHg²/Hz (IQR: 12.9) p=0.06). No significant differences were noted in DBP and SBP spectra (See Figure 5.3).

HF respiratory related blood pressure fluctuations were significantly increased at 0.3Hz in SBP for case versus controls (17.4mmHg²/Hz (IQR: 47.9) vs. 4.1mmHg²/Hz (IQR: 10.4) p<0.05) and MAP records (32.5mmHg²/Hz (IQR: 76.9) vs. 64.6mmHg²/Hz (IQR: 59.8) p<0.01). A non-significant increase was found in DBP spectra at these frequencies (See Figure 5.3).

Blood Pressure Variability

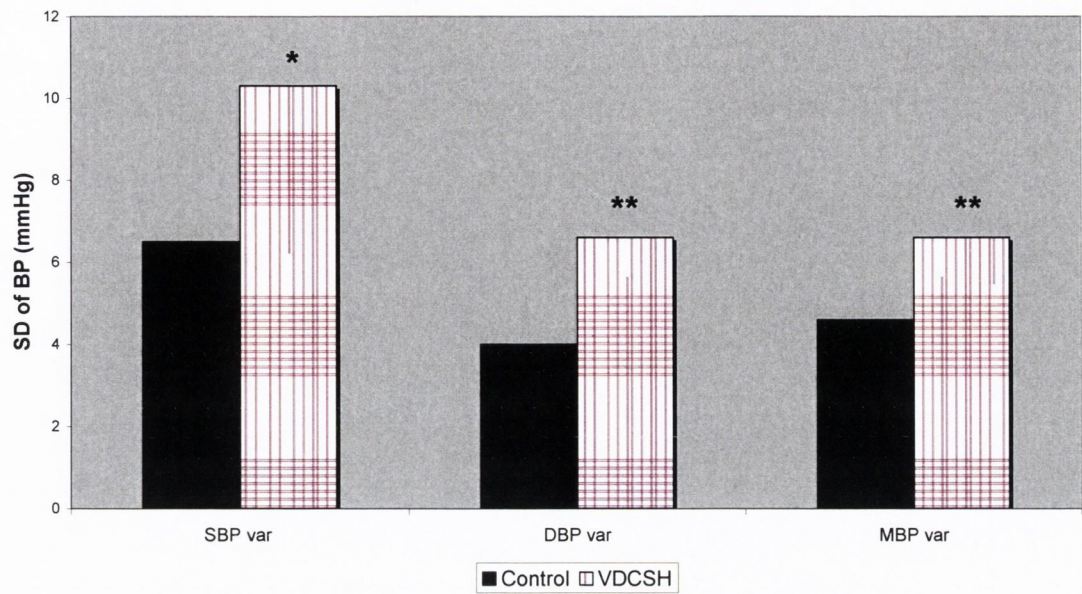


Figure 5.1: Comparison of Time Domain Indices of BP variability. DBP var = SD of DBP; SBP var = SD of SBP; MAP var = SD of MAP. (* $p < 0.1$; ** $p < 0.05$)

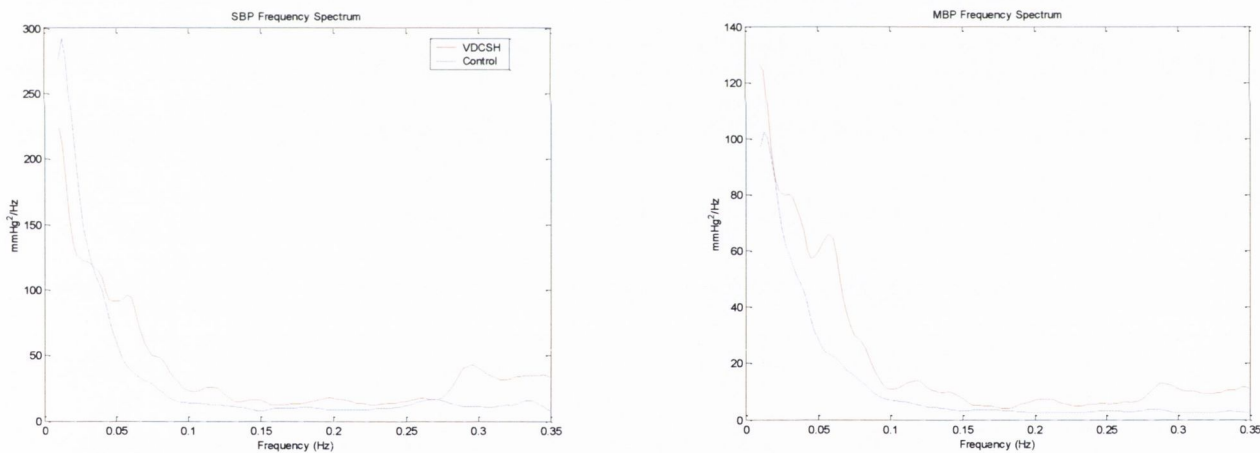
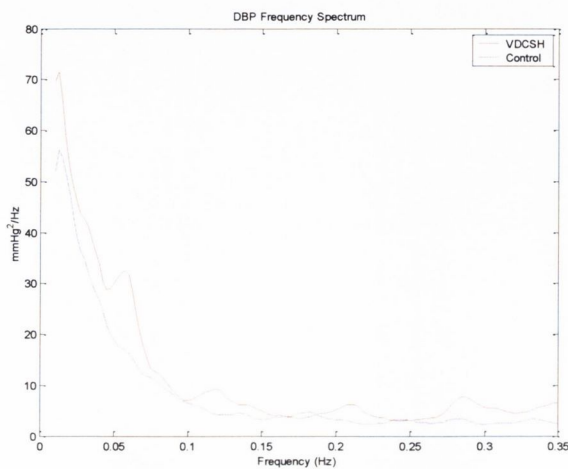
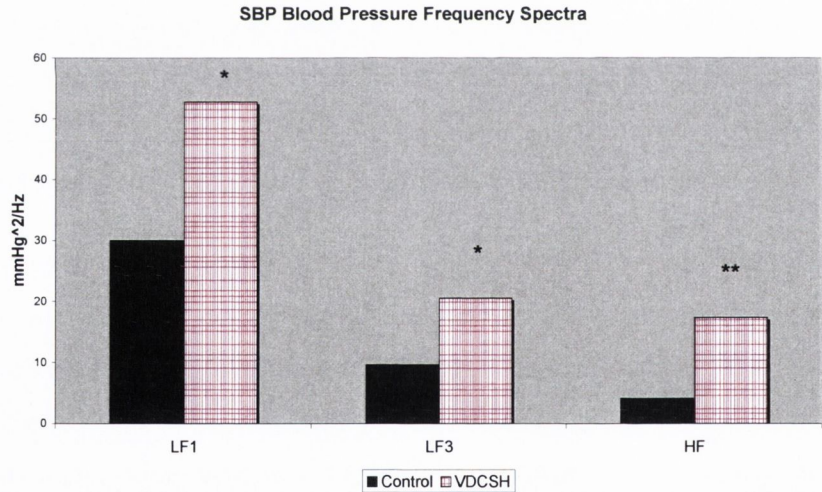


Figure 5.2A: Comparison of Ensemble Average Frequency Spectra between VDCSH and controls. A) SBP spectra (above left) B) MAP spectra (above right) C) DBP spectra (below).



Variable	Band	Control	VDCSH	% Change	Significance
SBP (mmHg²)	SBP_{VLF}	4.43 (IQR 6.36)	3.48 (IQR 6.09)	-21.4%	NS
	SBP_{LF}	3.97 (IQR 4.47)	5.24 (IQR 11.73)	32.0%	NS
	SBP_{HF}	1.58 (IQR 2.78)	2.69 (IQR 6.54)	70.3%	NS
MAP (mmHg²)	MAP_{VLF}	2.08 (IQR 4.52)	2.8 (IQR 4.51)	34.6%	NS
	MAP_{LF}	2.18 (IQR 2.12)	2.66 (IQR 7.56)	22.0%	NS
	MAP_{HF}	0.58 (IQR 1.65)	1.21 (IQR 3.93)	108.6%	NS
DBP (mmHg²)	DBP_{VLF}	1.34 (IQR 2.2)	1.74 (IQR 2.01)	29.9%	NS
	DBP_{LF}	1.55 (IQR 2.19)	1.78 (IQR 2.24)	14.8%	NS
	DBP_{HF}	0.34 (IQR 1.66)	1.06 (IQR 1.58)	211.8%	NS

Table 5.3: Comparison of Standard Frequency Domain Indices of CV variability.
Subscripts VLF; LF and HF denote standard frequency bands VLF (0.003-0.04Hz),
LF (0.04-0.15Hz), HF (0.15-0.4Hz).



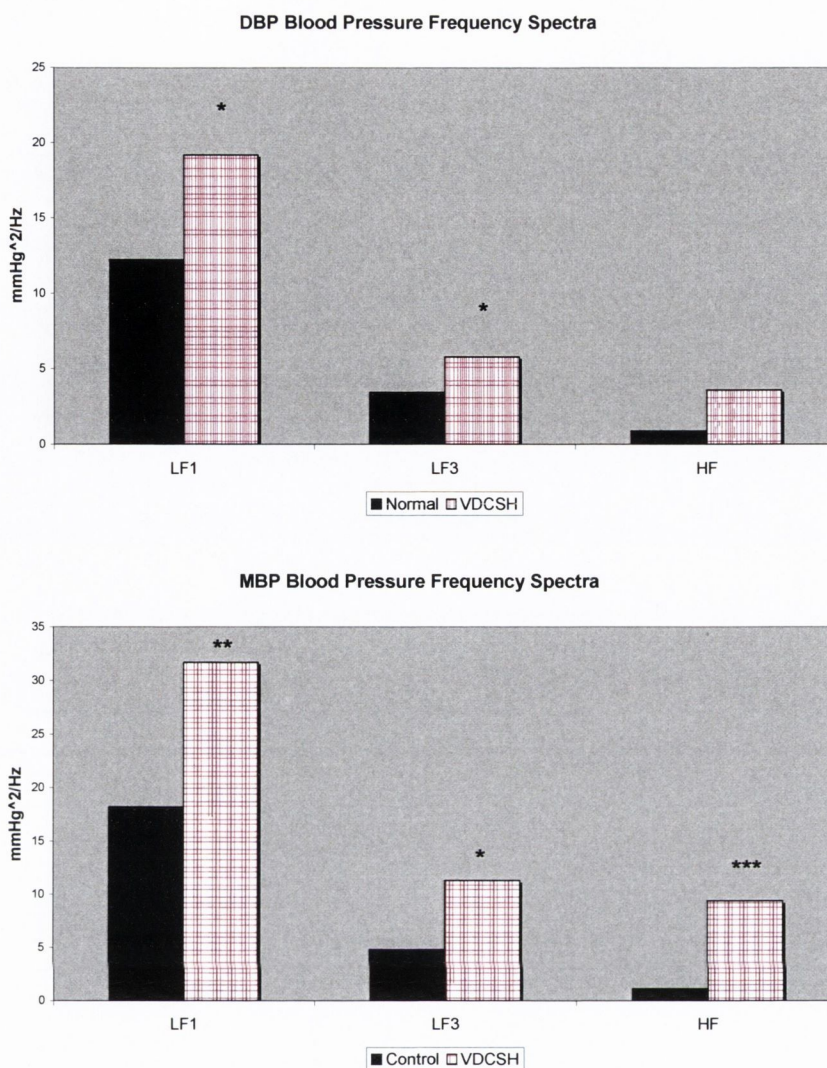


Figure 5.3: Comparison of Frequency Domain Indices of BP variability. A) SBP (Top) B) DBP (Middle) C) MAP (Bottom). (* $p < 0.1$; ** $p < 0.05$; * $p < 0.01$)**

5.3.5 Frequency of Peaks Analysis

No significant differences were found between f_p values (See Table 4), between cases and controls. For clarity only SBP figures are shown, as trends and values for DBP and MAP were almost identical.

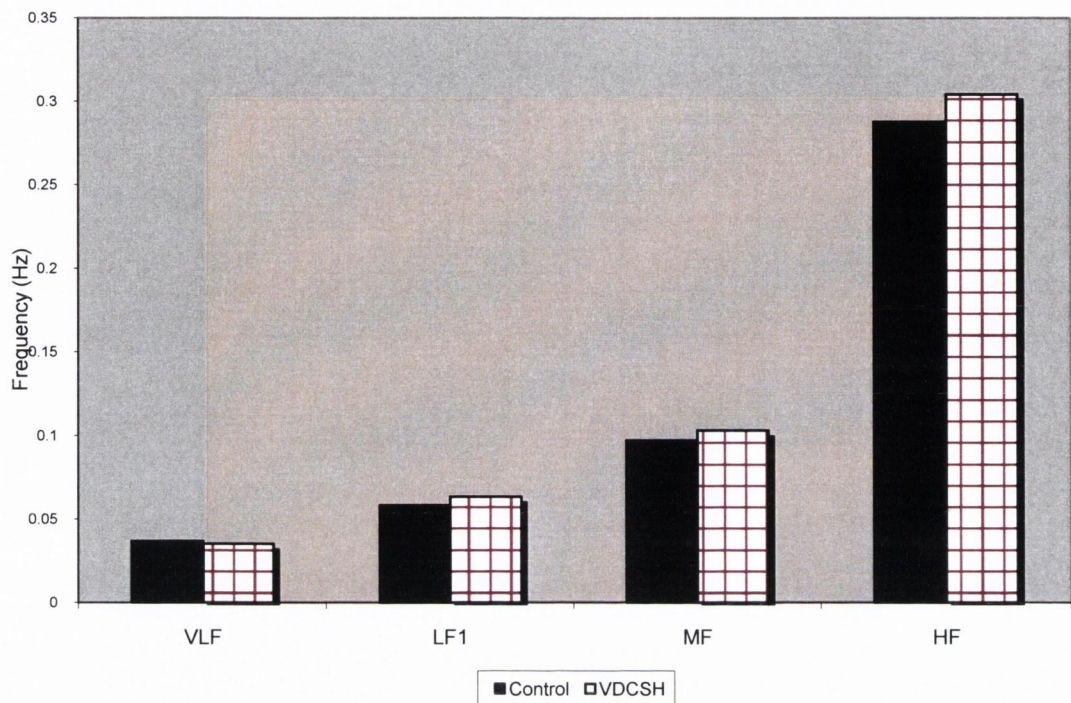


Figure 5.4: Comparison of Centre of Frequency values

Variable	Band	Control	VDCSH	% Change	Significance
SBP	F _{VLF}	0.037 ± 0.0025	0.035 ± 0.005	- 4.1%	NS
	F _{LF1}	0.0583 ± 0.0058	0.063 ± 0.006	8.8%	NS
	F _{MF}	0.097 ± 0.012	0.103 ± 0.01	6.19%	NS
	F _{HF}	0.288 ± 0.023	0.304 ± 0.043	5.7%	NS

Table 5.4: Comparison of the Frequency of Peak for SBP for the defined frequency bands VLF, LF, MF, HF

5.4 Discussion

VDCSH is associated with significant increases in short-term blood pressure variability indices. These increases occur in two frequency bands – LF Mayer band, which is influenced strongly by baroreflex control of peripheral resistance vasculature and HF Traube Herring band, primarily respiratory related activity.

As far as we are aware this is the first study investigating characteristics of short-term blood pressure fluctuations - Mayer waves in VDCSH.

A small but statistically significant increase in total DBP and MAP variability in VDCSH was detected. Increased blood pressure variability has been linked independently to end organ damage (Frattola et al., 1993; Palatini et al., 1992). Although these findings support the postulate that medullary centres maybe implicated in abnormal responses in VDCSH (Miller et al, 2006), increases in total blood pressure variability are non-specific and could arise from a number of internal and external sources, including cardiac activity (O Leary and Woodbury, 1996), respiratory activity (Alessandro Jandre et al ., 2007), hypo- or hyperactive baroreflexes (Eckberg and Sleight, 1992), cognitive activation (Middeke and Schrader, 1994) and muscle activation (Malik, 1998) amongst others. Wideband pressure fluctuations or increased blood pressure variance of this magnitude has been associated with blunted baroreflexes (Mancia et al, 1980), with aging (Cicconetti, 2000), arterial stiffness (Mancia G., 2001), in animal models with baroreflex deafferentation (Julien, 2006). In such cases increases in total blood pressure variability have been attributed to a reduced ability to modulate peripheral resistance and vascular compliance for blood pressure control in the face of internal and external disturbances.

Paradoxically increases in blood pressure variability restricted to specific Mayer wave frequency bands have been explained by an increase in the gain and/or range of the baroreflex (Hammer and Saul, 2005; de Paor and Ringwood, 2006). Experimental and theoretical evidence has been provided in support of this conclusion (Julien, 2006). It has been reasoned that a highly reactive baroreflex will impose strong focussed modulations upon any internal or external blood pressure fluctuations *only within* a narrow frequency band (Julien, 2006) typically around 0.1Hz. Furthermore the amplitude of these oscillations will be determined by the saturation and threshold properties of the baroreflex (de Paor and Ringwood, 2006). In this case a sharp resonant peak would be expected in blood pressure spectra around the natural oscillating frequency of the feedback loop.

To draw any conclusions and make inferences regarding the nature of dysfunction in VDCSH from this finding, spectral analysis was used to further interrogate the source of the variability by decomposing the pressure fluctuations into their constituent sub bands.

As hypothesized significant alterations in the LF Mayer band were detected indicated by a small peak in the LF bands. Such changes are consistent with alterations in the peripheral resistance-controlling arc of the baroreflex in VDCSH (Julien, 2006; Ringwood and Malpas, 2001), and could be considered indicative of an increased gain or range of the baroreflex. However since the frequency of this peak is at the lower end of the Mayer wave band at

0.06Hz, some doubt still remains over whether one can definitively conclude that a hypersensitive baroreflex response exists in VDCSH. This is the first study to report possible surrogate markers for baroreflex sensitivity controlling peripheral resistance in VDCSH. In CSH a hypersensitive response has only been observed reliably during CSM in comparison to other BRS measures. Other studies have examined BRS in CICSH only, and have had contradictory results when assessing BRS using methods other than CSM in cardioinhibitory CSH populations. Some have reported a paradoxical decrease in BRS (Morillo, 1999), no change in BRS (Cole et al., 2001), while others have indicated an increase in BRS (Morley et al, 1984; Dehn et al., 1984). It has been suggested that this discrepancy is due to differences in stimuli characteristics and protocol (Morillo et al, 1999). However none to date have investigated the gain of the peripheral resistance feedback loop in vasodepressor form of CSH and so no parallels can be drawn here with other studies in VDCSH.

This finding is not in isolation. An increase in HF respiratory blood pressure waves was also detected. These results are consistent with altered respiratory drive in VDCSH resulting in increased tidal volume and therefore increased intra thoracic pressures during inspiration. Peripheral and central respiration and cardiovascular control centres are intimately linked (Janig et al., 2006) so it is plausible that respiratory centres are also affected in CSH. Increases in cardiorespiratory variables to our knowledge have not been documented in CSH, however altered respiratory parameters including tidal and minute volume have been noted in other forms of neurocardiovascular syncope (Virag, 2007; Kenny et al. 1993) noted altered cardiorespiratory coupling during deep breathing test in a small series of patients with CICSH. Galdston in 1943 (Galdston et al., 1943) reported hyperpnea in response to Carotid Sinus massage hypothesizing that blood flow to chemoreceptors was altered. Furthermore our findings would be in keeping with Doux and Yun's recent hypothesis, which suggests that carotid artery disease, induces maladaptation of chemoreceptors and baroreceptors in ischaemic stroke, which in turn may be responsible for autonomic mediated dysfunction in cerebral autoregulation (Doux and Yun, 2006).

Unfortunately a definite conclusion cannot be drawn into nature and direction of dysfunction in VDCSH based on these results alone. Further scientific investigation is hence warranted into 1) the nature of blood pressure variability in VDCSH to determine if the cause is truly a hypersensitive or hyposensitive baroreflex 2) the role cardiorespiratory activity plays in CSH pathogenesis.

5.5 Conclusion

Blood pressure variability, in particular Mayer and Traube Herring bands were increased in VDCSH. This finding is consistent with the hypothesis that baroreflex activity is altered in VDCSH, but may also implicate cardiorespiratory centres in pathogenesis of VDCSH. Blood pressure variability thus holds the potential as a novel non-invasive marker of VDCSH, which may be related to degree of dysfunction in CSH. Further research is required to confirm the underlying physiological cause and nature of this variability.

5.6 Limitations

As of any case control study, we are limited in making any statements regarding causality in relation to VDCSH and blood pressure variability. However strong, biologically plausible mechanisms have been established by which VDCSH could affect blood pressure variability [10]. These mechanisms are supported by previous studies, looking at neurogenic sources of blood pressure control in autonomic dysfunction [40]. Such levels of autonomic dysfunction have also been shown to occur in CSH by previous authors [42]. Furthermore altered circadian blood pressure control was also noted previously in CSH [45]. Another possible limitation of our study is the lack of respiratory variable measurement. This limits our ability in drawing a definite conclusion as to the source of the detected variability especially in the HF band. However since our significant findings were specifically found in the HF band of systolic and mean arterial blood pressure spectra and not in the diastolic blood pressure records, this would support our hypothesis that these differences are respiratory related. Respiratory activity is well known to affect SBP/MAP significantly.

5.7 References

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CHAPTER 6

Pathological Modulation of Baroreflex Sensitivity and Latency in Carotid Sinus Hypersensitivity

Having initially characterised the dynamics of blood pressure regulation in VDCSH resting conditions, this study aimed to improve upon the currently limited understanding of pathological changes in the baroreflex especially in CICSH using non-invasive measures of spontaneous baroreflex sensitivity and response latency in Carotid Sinus Hypersensitivity (CSH).

CHAPTER 6

6.1 Background

In the last chapter we characterised the dynamics of blood pressure regulation in VDCSH during resting conditions. In this study we aimed to improve upon the currently limited understanding of pathological changes in the baroreflex especially in CISH. Here we apply non-invasive measures of spontaneous baroreflex sensitivity and response latency to this task. Furthermore we compared the suitability of different non-invasive baroreflex sensitivity measures in a CSH population.

6.2 Introduction

As alluded to in previous chapters CSH is associated with aging, recurrent falls and syncope (Kenny et al, 2001), Dementia and Parkinson's disease (Ballard et al, 1998; Kenny et al., 2004) and is diagnosed with carotid sinus massage (CSM) (Brignole, 2001).

The pathophysiological mechanisms of CSH are poorly understood. Eckberg and Sleight (Eckberg and Sleight, 1992) hypothesized a central neural adaptation mechanism secondary to peripheral baroreceptor deafferentation induced by arterial compliance reduction. O'Mahony et. al. (1995) suggested central upregulation of $\alpha 2$ adrenoreceptors as its mechanism. However in a recent study administration of Yohimbine (an $\alpha 2$ receptor antagonist) did not attenuate the CSH response to patients with VDCSH (Parry et al, 2004), thus casting doubt over the validity of this hypothesis. Polvikoski et al. (2006), found marked α -synuclein pathology in the stellate ganglia of an elderly lady with CISH, while further neuropathological studies (Miller et al., 2007) found a small but significant increase in neurodegenerative hyperphosphorylated Tau proteins specific to brainstem nuclei, which regulate cardiovascular activity. Attempts to detect a hypersensitive baroreflex response in CSH patients have proven inconclusive in tests of baroreflex sensitivity (BRS) other than CSM. Vagal baroreflex gain, as determined by blood pressure and heart rate responses to both the phenylephrine and neck suction methods, suggest baroreflex gain alterations in CSH. However studies have reported conflicting changes. Morley (Morley et al., 1984) and Dehn (Dehn et al., 1984) note significant increases in baroreflex gain, while later Morillo (Morillo et al, 1999) and Cole (2001) report a decreased baroreflex gain. Differences in stimuli and protocols have been suggested as an explanation for these findings. On this basis current evidence suggests CSH to be characterised by altered baroreflex function located centrally and/or peripherally, resulting in measured increases or decreases in BRS depending on the methodology used. The state of baroreflex function is (Eckberg and Sleight et al.,

1992) characterised by a number of parameters including its sensitivity and latency of response (See Figure 6.1 A). BRS determines the magnitude of heart rate or vascular resistance changes induced by specific blood pressure changes, while the response latency determines the delay following the stimulus to the occurrence of maximal heart rate or vascular changes.

Surprisingly few studies to date have examined these characteristics in CSH using spontaneous non-invasive measures such as the sequence (Parati et al, 2000), alpha (Parati et al, 2000) or xBRS (Westerhof et al., 2004) methods. We hypothesized in this study that CSH is associated with altered CV regulation characterized by altered BRS and latency. The purpose of this study was to test this hypothesis in individuals with CSH (asymptomatic and symptomatic) and non-CSH controls. As part of this aim we compared different non-invasive metrics of BRS in older adults for use in CSH.

6.3 Methods

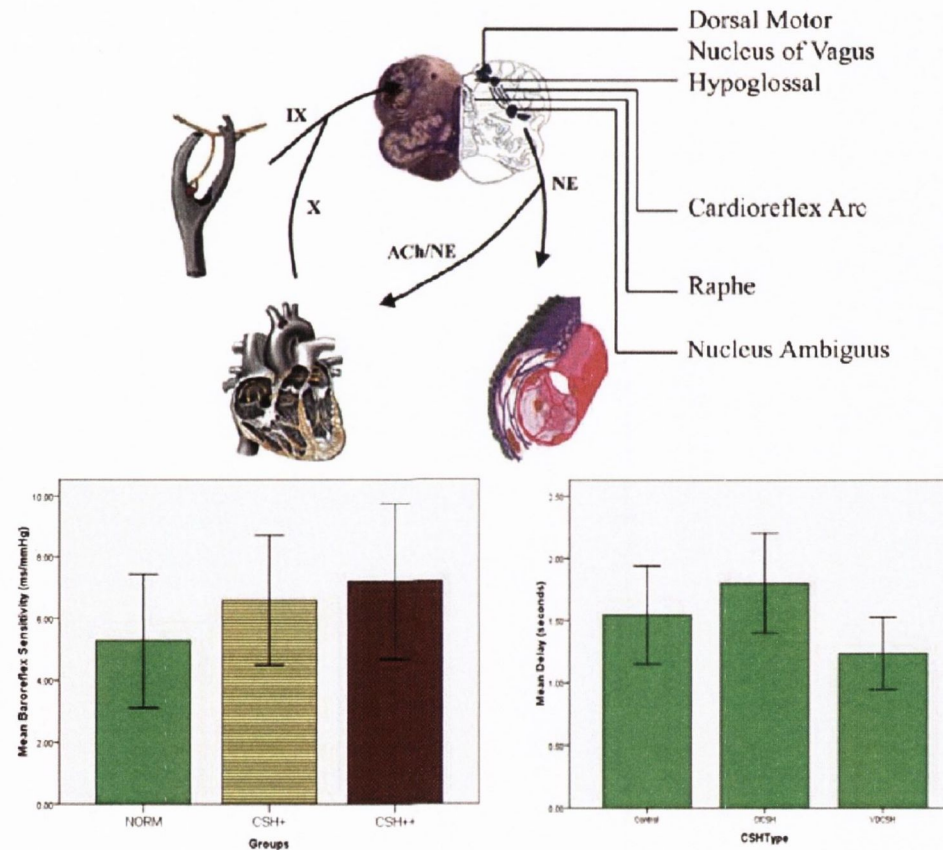
6.3.1 Participants

Participants were recruited prospectively from a dedicated syncope and falls unit in a large teaching hospital. All subjects fasted prior to attending for a single visit between 0900 and 1300 hrs in a temperate (23°C), comfortably lit, low-noise environment. Subjects abstained from alcohol and caffeine for 12 h prior to the experiments. Consecutive patients (aged > 50) with a history of recurrent syncope or unexplained falls in the previous year were recruited. All patients had full clinical assessment including Carotid Sinus Massage (CSM) as part of routine cardiovascular assessment. The study had ethical approval from the local ethics committee.

6.3.2 Protocol

Prior to CSM all subjects underwent a ten-minute baseline surface electrocardiogram (ECG) and continuous beat-to-beat blood pressure (TNO Finapres©) recording. Subjects were instructed to lie supine, and directed to breathe normally at a constant rate and comfortable tidal volume while measurements were taken. Following an initial 15-minute cardiovascular stabilization period Physiocal© was switched off and data was recorded for a further 10 minutes. Signals were sampled at 200Hz, filtered between 0.01-100Hz and stored digitally on a PC for further analysis

Figure 6.1 (A) Simple Schematic diagram of the baroreflex pathways (Adapted from Miller et al. (9). Carotid Sinus and Aortic arch baroreceptors activate the baroreflex, transmitted via Vagal (X) and Glossopharyngeal (IX) fibres to brainstem nuclei with afferent time delay T_a . Labelled brainstem nuclei then regulate efferent cardiac ganglion and peripheral resistance vessels with efferent time delays T_{ec} and T_{ev} . (B) Spontaneous BRS shows trend towards increased values in CSH. (C) Vagal baroreflex latency governing cardiac control is increased in CISH versus VDCSH and controls ($P=0.012$).



. This allowed standard baseline cardiovascular variables including heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MAP) to be recorded. BRS measures were derived from the last 10 minutes of this steady state rest period.

CSM was subsequently performed according to international guidelines (Eckberg and Sleight, 1992). Firm longitudinal massage was applied for 5 seconds at the point of maximal pulsation over the carotid (usually located at the level of the upper border of the cricoid cartilage) on the right and then left sides. CSM was performed in both supine and upright positions (head-up tilt to 70° foot plate assisted table), thus participants underwent a maximum of 4 episodes of CSM. Responses were classified as normal (NORM), borderline CSH (CSH+) and definite CSH (CSH++) according to the definition given in Table 2 with each group being further divided into specific subtypes of CSH i.e. borderline vasodepressor CSH (VDCSH+) and borderline cardioinhibitory CSH (CICSH+) and definite vasodepressor CSH (VDCSH++) and definite cardioinhibitory CSH (CICSH++).

6.3.3 Analysis

All initial data processing was performed with custom written software using MATLAB 6.5^{####}. Subject data was grouped according to CSM response. Data records were scored for significant noise and artifact, and excluded if noise was above an empirically derived threshold. Blood pressure systolic and ECG R wave detection values were corrected for errors by automatic methods and manual screening. All data was further screened for abnormal rhythms, and the presence of ectopic beats^{§§§§}.

Three BRS estimates were used and were calculated as follows. Power spectra of systolic pressure and R–R intervals were integrated within the frequency range, 0.04–0.15 Hz. The BRS was considered to be the square root of the ratio between R–R interval and systolic pressure integrated spectra (the α -coefficient (Parati et al, 2000)). We further filtered these values accepting α -coefficients only when the coherence was ≥ 0.50 and the phase was negative within this frequency range. Two representative values of BRS were derived – low frequency α -coefficient (LF_{α}) and high frequency α -coefficient (HF_{α}).

Secondly, BRS was derived according to the sequence method (Parati et al, 2000), which assumes that parallel up-going (BRS+) and down-going (BRS-) pairs of systolic pressures and R–R intervals, reflect spontaneous baroreflex physiology. Parameters derived by

Mathworks Inc, Natick, MA, USA

§§§§ Data was excluded if the number of ectopics >5% total number of beats

Rothlisberger (Rothlisberger et al., 2003), were implemented whereby valid sequences were identified as three or more consecutive pairs of systolic pressures increasing or decreasing by at least 1 mmHg, and R–R intervals lengthening or shortening by at least 5ms per beat. If linear regression analysis of three such pairs yielded a correlation coefficient ≥ 0.80 , we accepted this slope as an index of BRS. BRS+ and BRS- values were averaged to give a total value BRS_{SEQ}.

Finally the cross correlation BRS (xBRS) method was calculated according to the method recently described by Westerhof *et al.* (2004). Using this method cross-correlation and regression between cubic spline interpolated (1 Hz sampling) systolic blood pressure and R-R intervals are computed over 10 second sliding windows.

A time delay in the pulse interval series in the range 0-5 seconds is employed to account for differences in baroreflex conduction latency. For each of the time delay values a cross-correlation value is calculated. The delay giving the maximum cross-correlation coefficient is selected and the corresponding positive regression coefficient is taken as the representative BRS value for this time window. The geometric mean of all the values calculated over a 10 minute period was taken as the xBRS value for each individual.

6.3.4 Comparison of BRS Methods in CSH

Both the sequence and spectral BRS estimation methods utilize thresholds, which were derived by the original investigators to increase the reliability of the BRS estimate, and improve the likelihood that pulse interval changes were coupled to blood pressure changes and not randomly occurring events which coincide temporally. The inclusion of these thresholds thus ensures that BRS engagement is detected reliably. In individuals with very low BRS values no value is reported with these methods. However in the xBRS method no thresholds were used however a P value (<0.01) was required for a regression coefficient to be included in the BRS estimate. In addition to reporting BRS estimates between groups, we also compared different BRS methods in CSH by quantifying the % of records where an estimate was unavailable as a result of thresholding (See Table 5).

Table 6.1: Classification of Carotid Sinus Massage Responses (CSM)

General Classification		Subtype	Response to CSM
Normal (NORM)			RR interval <2sec SBP Change <40mmHg
Borderline CSH (CSH+)	CICSH+*	Pure CICSH+	RR interval >2sec and < 3sec SBP Change <40mmHg
		Mixed CSH+	RR interval >2sec and <3sec SBP Change >40mmHg and <50mmHg
	VDCSH+		RR interval <2sec SBP Change >40mmHg and <50mmHg
Definite CSH (CSH++)	CICSH++*	Pure CICSH++	RR interval >3sec SBP Change <40mmHg
		Mixed CSH++	RR interval >3sec SBP Change >40mmHg and <50mmHg
	VDCSH++		RR interval <3sec SBP Change >50mmHg

6.3.5 Statistical Analysis

SPSS^{*****} version 14 was used to process data. All features derived in previous sections were assessed for normality using data histograms, and calculating distribution skewness, kurtosis, and Kolmogorov-Smirnov test statistics. Initial group matching was assessed using Krushkall-Wallis non-parametric testing and one-way analysis of variance (ANOVA). Krushkall-Wallis testing was also used to compare unadjusted BRS values, with ANOVA used to compare latency values. Hierarchical linear regression analysis was performed to control for potential confounders of baseline heart rate, blood pressure, age, sex and medical history. All BRS values were non-normally distributed and therefore natural logarithmically transformed before regression. The B coefficient with 95% CIs were presented for both the transformed and untransformed variables. The exponential value of B for transformed variables represents the estimated ratio of the adjusted means between groups, while the B coefficient presented for untransformed variables represents the estimated difference between adjusted means. Significance was calculated at a level of $p < 0.05$. Multivariate regression analysis was performed to evaluate the independent influence of age, heart rate and pharmacological agents on each of the estimates of BRS, as a means of determining confounding variables that may mask the underlying influence of pathology on BRS values in a CSH population.

6.4 Results

6.4.1 Subjects

Ninety two patients (46 male; 46 female) mean age 71.6 (SD +/-7.6) years, mean weight 73.4 (SD $\pm$ 14.1) kg, and mean height 1.67 (SD $\pm$ 0.08) m were recruited. Twenty (9 male, 11 female) individuals remained with normal CSM responses following exclusion of those with cognitive impairment; seventeen individuals displayed CICSH++ (10 male, 7 female); eight subjects had VDCSH++ (5 male, 3 female); eleven had CICSH+ (4 male, 7 female); while ten (4 male, 6 female) individuals had VDCSH+.

6.4.2 Baseline Characteristics

The degree of group matching was assessed by comparing patient demographics, clinical characteristics, proportions of prescribed medications and baseline cardiovascular variables. On analysis groups were shown to be relatively well matched across groups (See Table 2 & Table 3).

***** SPSS Inc. Headquarters, 233 S. Wacker Drive, 11th Floor, Chicago, Illinois, 60606

6.4.3 Baroreflex Sensitivity

6.4.3.1 BRS Estimate Distributions

The Kolmogorov-Smirnov test was performed on each measure following separation into respective groups. The hypothesis that BRS+, BRS-, BRS_{SEQ}, LF _{α} , HF _{α} , xBRS are normally distributed was rejected ($P < 0.05$).

6.4.3.2 Sensitivity of Baroreflex Methods in CSH

The xBRS method provided an estimate in 98% of the cases, whilst the sequence method, and HF _{α} performed comparably providing valid estimates in 94% and 93% of cases respectively (See Table 5). The LF _{α} method identified a BRS estimates in only 66% of individuals. Furthermore when comparing results between CSH subgroups 21% of individuals with CISH had missing values, the highest of all subgroups.

Table 6.2: Subject Demographics, Comorbidities and Medications. Groups show no significant differences in demographics (P>0.05), medications (P>0.05) and comorbidities (P>0.05)

Group	<i>Physical Characteristics</i>				Comorbidities				<i>Medications</i>		
	Age (yrs)	M/F	Weight (kg)	Height (m)	CVD	DM	HTN	OH	CA	AntiHTN	Psych.
Control	67+/-7.5	9/11	75.8+/-15.8	1.66+/-0.08	19%	11%	76%	85%	42%	38%	16%
CICSH++	74+/-8.0	7/10	71.4+/-14.7	1.69+/-0.08	24%	12%	41%	87%	33%	31%	7%
VDCSH++	74+/-4.5	5/3	69.5+/-18.5	1.69+/-0.08	13%	13%	57%	100%	63%	50%	25%
CICSH+	74+/-9.1	4/6	71.4+/-7.6	1.65+/-0.07	9%	0%	64%	82%	56%	45%	33%
VDCSH+	71+/-3.3	4/6	71.9+/-11.1	1.67+/-0.07	20%	20%	50%	80%	44%	40%	11%

* P<0.01 CVD=Cardiovascular disease; DM=Diabetes Mellitus; HTN=Hypertension; OH=Orthostatic hypotension; VVS=Vasovagal syncope; AntiHTN=Antihypertensive⁺⁺⁺⁺; CA=Cardioactive⁺⁺⁺⁺; Psych.=Psychotropic^{§§§§§}

*P<0.01 RR_{MAX} = Max RR interval post CSM; ΔSBP = Change in SBP post CSM; HR=Heart rate; SBP=Systolic blood pressure; DBP=Diastolic blood pressure; MAP = Mean arterial pressure;

⁺⁺⁺⁺ ACE inhibitor, Alpha Blocker, Beta blocker, Calcium channel blocker, Thiazide diuretic

⁺⁺⁺⁺ Antianginal (nitrate), or Antiarrhythmics, Fludrocortisone or Midodrine

^{§§§§§} Typical or atypical neuroleptic, anticholinergic, anticholinergic, cholinesterase inhibitor, TCAD, SSRI, other antidepressant, antiparkinsons or other psychotropic medication

As can be seen in Table 4, 8% of the NORM group; 14.6% CICS^H+; 18% VDCS^H+; 20.6% CICS^H++ and 3.75% VDCS^H++ had missing values.

Table 6.3: Carotid Sinus Massage Responses and Baseline Cardiovascular Variables. Significant differences exist between CSM responses ($P<0.01$), while no significant differences were found between baseline cardiovascular variables

Group	CSM Response			Baseline Cardiovascular Variables		
	RR _{MAX}	ΔSBP	HR	SBP	DBP	MAP
	(secs)	(mmHg)	(bpm)	(mmHg)	(mmHg)	(mmHg)
Control	1.1+/-0.2	24.7+/-9.2	65+/-11	135+/-23	73+/-8	97+/-13
CICS ^H /Mixed	6.2+/-2.6*	64.4+/-15.4*	70+/-11	138+/-22	74+/-9	100+/-14
VDCS ^H	1.3+/-0.3	59.3+/-6.4*	61+/-6	129+/-16	65+/-11	88+/-12
Borderline	2.5+/-0.3*	49.5+/-10.5*	68+/-10	145+/-25	70+/-7	98+/-9
CICS ^H /Mixed						
Borderline VDCS ^H	1.3+/-0.2	44.0+/-3.1*	67+/-13	123+/-25	72+/-18	92+/-20

6.4.3.3 Effect of Age, Heart Rate, Pharmacological Agents on BRS values in CSH

Baseline heart rate was the only significant factor to affect any of the BRS metrics ($p<0.05$). Heart rate accounted for 13.5% of log transformed BRS_{seq} variance ($P=0.01$), 15.3% of log transformed HF_{α} ($P=0.009$). All other factors considered did not affect BRS values significantly.

6.4.3.4 Comparison of BRS Values between Groups

The unadjusted means for BRS_{seq} , BRS_+ , BRS_- , LF_{α} , HF_{α} and $xBRS$ results are given in Table 5. There was a trend in 4 out of 6 measures towards an increase in BRS in CSH. However none of these differences was significant for either CSH+ or CSH++ ($P>0.05$).

The average of all 6 BRS estimates was taken across each individual to examine this trend. Trends towards an increased BRS (See Figure 6.1 B) were found in CSH++ (7.21ms/mmHg +/- 4.2; $P=0.186$) compared to controls (5.28ms/mmHg +/- 3.91), with CSH+ having an intermediate BRS value (6.59ms/mmHg +/- 3.14; $P=0.197$), however these differences were

insignificant. Following adjustment for confounders the differences between each of the 6 BRS values remained statistically insignificant as given in Table 6.

Table 6.4: Comparison of BRS Methods and % individuals with missing BRS values

	BRS+	BRS-	BRS _{Seq}	LF α	HF α	xBRS	Mean
Control	0%	4.8%	0%	28.6%	9.5%	0%	8%
Borderline CICSH	18.2%	9.1%	9.1%	36.4%	9.1%	0%	14.6%
Borderline VDCSH	20.0%	10.0%	10.0%	40.0%	20.0%	0%	18%
CICSH	17.6%	17.6%	17.6%	47.1%	11.8%	11.8%	20.6%
VDCSH	12.5%	0.0%	0.0%	12.5%	0%	0%	3.75%
Mean Missing	14%	8%	7%	33%	10%	2%	
Mean Valid (100-Mean Missing)	86%	92%	93%	67%	90%	98%	

Table 6.5: Comparison of BRS Values and Time delay values between Groups

	Controls	CSH+	CSH++	Sig
Baroreflex Sensitivity				
BRS+ (ms/mmHg), Mean (95% CI)	5.4 (3.6-7.2)	4.4 (3.0-5.8)	4.4 (2.7-5.9)	0.460
BRS- (ms/mmHg), Mean (95% CI)	8.4 (5.33-11.4)	8.2 (4.8-11.6)	9.0 (6.5-11.5)	0.751
BRS _{SEQ} (ms/mmHg), Mean (95% CI)	7.1 (4.9-9.4)	7.2 (3.7-10.7)	7.2(5.3-9.0)	0.930
Low Frequency Alpha (ms/mmHg), Mean (95% CI)	5.4 (3.6-7.2)	6.2 (4.3-8.1)	6.8 (4.2- 9.4)	0.814
High Frequency Alpha (ms/mmHg), Mean (95% CI)	8.1 (3.8-12.5)	5.7 (4.2-7.2)	6.7 (4.5-8.8)	0.926
xBRS (ms/mmHg), Mean (95% CI)	6.0 (4.3-7.7)	8.6 (4.6-12.6)	6.6 (4.6-8.6)	0.948
Delay	Controls	CICSH	VDCSH	Sig
Time delay (seconds)	1.3 (0.9-1.7)	1.9 (1.4-2.3)	1.3 (1.0-1.6)	0.043

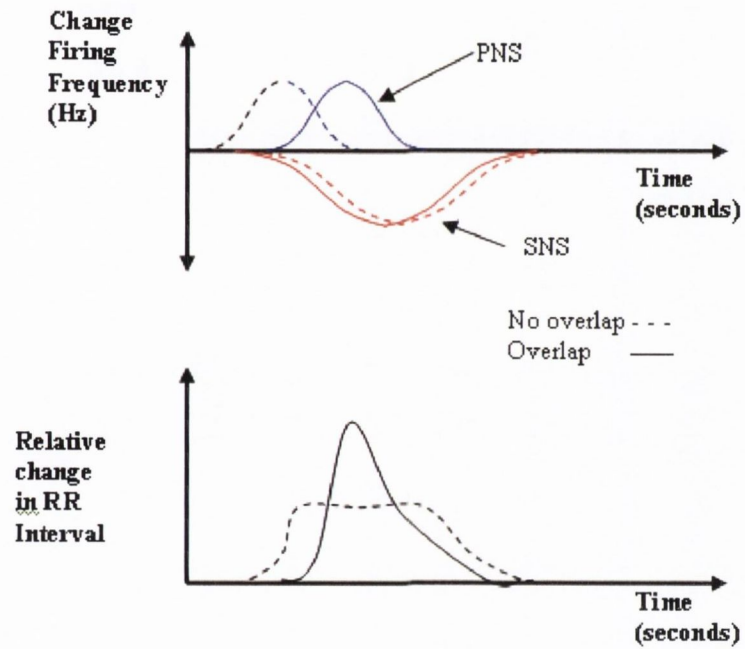
Table 6.6: Comparison of BRS Values and Time delay values between group

	Groups			
	Controls versus CSH+		Controls versus CSH++	
	B (95% CI)	Sig	e ^B or B (95%CI)	Sig
Baroreflex Slope				
Upward Slope (ms/mmHg), Mean (95% CI)	-0.139 (-0.205-0.055)	0.254	0.0 (-.149 - 0.149)	0.997
Downward Slope (ms/mmHg), Mean (95% CI)	0.096 (-0.099-0.206)	0.483	0.04 (-0.14 - 0.19)	0.762
Total Slope (ms/mmHg), Mean (95% CI)	0.04 (-0.114 -0.157)	0.157	0.051 (-0.116-0.177)	0.679
Low Frequency Alpha (ms/mmHg), Mean (95% CI)	0.068(-0.148-0.216)	0.705	0.186 (-0.09-0.298)	0.285
High Frequency Alpha (ms/mmHg), Mean (95% CI)	0.149 (-0.071-0.254)	0.261	0.104 (-0.316-0.03)	0.104
xBRS (ms/mmHg), Mean (95% CI)	-1.04 (-0.533-0.263)	0.498	0.128 (-.245-0.614)	0.392
Delay				
	Controls versus CICSH		Controls versus VDCSH	
Time delay (seconds)	0.385 (0.154-1.186)	0.012	-0.152 (-0.897-0.311)	0.334

6.3.3.5 Baroreflex Latency in CSH

Unadjusted mean delay was significantly altered in CSH ($P<0.043$). CICSH was associated with a significantly increased delay (1.9 (1.4-2.3); $P=0.043$) compared to controls (1.3secs (0.9-1.7)). Response latency in VDCSH (1.3 (1.0-1.6); $P=0.977$) was unaltered compared to controls but was significantly lower than in CICSH ($P=0.044$) (See Table 5). As before the differences were then adjusted for age and heart rate (See Table 6). Response latency in CICSH remained statistically significant ($P=0.012$) compared to controls while no differences between VDCSH and controls were detected.

Figure 6.2 Illustration of the effects of changes to relative timing between sympathetic and parasympathetic activation patterns on normalised RR interval changes



6.4 Discussion

To our knowledge this is the first study in the literature using and comparing non-invasive measures of BRS and latency in a CSH population to verify the hypothesis that CSH is associated with changes in BRS function. Our primary result indicates that BRS latency is increased in CICH, while spontaneous measures of BRS did not show a significant change in CSH. Finally xBRS provided estimates of BRS in 98% of subjects, with CICH associated with the highest levels of missing BRS estimates with over 21% of subjects with no eligible BRS values calculated.

Failure to report a BRS measurement is pertinent from a physiological perspective and may shed some light on the nature of baroreflex dysfunction. Commonly used BRS methods were examined. The xBRS approach reported more eligible BRS sequences across all patient groups compared to either the sequence or spectral methods (See Table 5). Although no comparisons can be drawn to similar studies in CSH, studies to date have explored spontaneous BRS measurements in elderly individuals and those with impaired BRS function e.g. sleep apnea (Ryan et al, 2007). It has been concluded that lower or dysfunctional BRS values will not be detected by methods which used strict threshold criteria (Ward et al, 2006; Laude et al, 2003). As expected the xBRS method reports more eligible values in this regard. This is not surprising considering it was developed to measure low BRS values and has less strict acceptance criteria for an eligible sequence i.e. a statistically significant correlation between HR and BP sequences must be found (Westerhof et al, 2004). From this perspective the spread across methods is also worth noting i.e. the LF_{α} reports a BRS value in only 67% of subjects, while xBRS reports in 98% of individuals. That different methods perform differently in this regard most likely indicates that different physiological mechanisms are being measured by each of the different BRS methods. For instance HF_{α} values are more like to be associated with parasympathetic control of baroreflex, while slower LF_{α} values are more likely to interrogate a combination of slower sympathetic and parasympathetic responses. The fact that the study group in general had low reported % eligible LF_{α} values would suggest the study population had either low or nonlinear LF portions of the baroreflex.

BRS methods on average reported an eligible BRS value in controls i.e. those without dysfunctional baroreflex control, while in the CSH population, BRS methods often failed to identify valid BRS estimates. This was particularly striking in the xBRS method, where the CICH group demonstrated failure in over 10% of individuals while all of individuals in the

other groups produced valid BRS estimates. All BRS methods considered assume that spontaneous blood pressure fluctuations are linearly coupled to heart period changes. Some employ thresholds to enforce this. Why individuals with CSH less frequently satisfy threshold criteria could either be because BRS is severely impaired in CSH and thus changes in blood pressure do not evoke sufficiently strong changes in heart period to be considered valid BRS estimates according to empirically determined thresholds or BRS is dysfunctional in CSH, with blood pressure changes being non-linearly related to changes in heart period. Thus tests based on linear correlations may fail in these cases. In CSH populations it is thus not unreasonable to speculate that that nature of baroreflex dysfunction in CSH is either low or nonlinear in nature. Further work is warranted to investigate the nature of this dysfunction further. Whatever the specific conclusion in CSH it is useful to acknowledge that failure to report a BRS is often a valuable asset of non-invasive BRS methods in interpreting the underlying physiological phenomenon.

Another important point to note is that baseline HR tended to be increased in the CSH population compared to controls (although in this group this was insignificant) especially in the cardioinhibitory form and would suggest an enhanced resting sympathetic tone exists in these individuals. Furthermore HR was noted to significantly affect BRS measures in this cohort of patients, while age, weight and height did not. This result is well known in BRS literature and agrees with other studies and serves to validate the accuracy of our results further. Both Kardos et al. (2001) and Abrahamsson et al (2003) have found a strong relationship between BRS and HR. However Kardos et al. (2001) also indicated a relationship between anthropometric measures including age, body mass index (BMI), gender, blood pressure (BP) and smoking and BRS. The reason for this inconsistency is unclear, but maybe accounted for by sample population differences. Kardos et al. (2001) investigated a large sample of 1134 healthy workers with a large age range 18 to 60 years compared to our smaller sample size and narrower age range.

The significant change in latency in heart rate responses detected in CICSH compared to controls is intriguing. We found the distribution of delays to be increased compared to controls, which could be suggestive of reduced vagal tone, increased sympathetic tone or greater overlap in time or delays in sympathetic and parasympathetic responses in CICSH. Although no parallels can be drawn between other studies investigating CSH, a number of studies have compared fainters to non-fainters and the time course of parasympathetic and sympathetic activation. Westerhof et al. (2004) and Guilli et al. (2005) detected a similar

increase in latency accounting for this by suggesting that earlier sympathetic activation and withdrawal occurs in fainters versus non-fainters. A similar reasoning could be applied in CSH, whereby the overlap in the time course of vagal activation and sympathetic withdrawal is more pronounced, resulting in greater drops in heart rate and vascular tone. As emphasised by Westerhof et al. (2004) this latency shift could also be explained by an increase in HR to greater than 77bpm, however the mean HR in CISH was 70bpm making this less likely in our study. No trends towards either enhanced or decreased BRS was found in CSH+ and CSH++ when the average of all BRS measures was taken. Small insignificant differences in means (2ms/mmHg) were found in comparison to controls and borderline cases. This result is similar to that found by Cole et al (2001), who found a non significant trend towards a slight increase in BRS using the neck suction method. Larger increases were detected in (Morley et al, 1984; Dehn et al., 1984), which may be accounted for by differences in stimuli. Non-invasive spontaneous measures of BRS do not rely on large scale pressure changes such as those seen in pharmacological/neck suction methods. Furthermore the rate of pressure changes also differs between methods – this is controllable in the neck suction method and frequency based methods. Morillo et al. (1999) used a randomly ordered administration of pressor and depressor agents compared to Morley et al. (1984). Differences exist in baroreceptor sensitivities to directional changes in pressure (Eckberg and Sleight, 1992), which may explain the detected decrease in BRS found by these researchers. Furthermore in BRS studies to date in CSH, carotid arterial stiffness has not been controlled for. Depending on the cohort under study this could potentially affect the BRS results reported and conclusions drawn. The pathophysiological implications of our results are worth discussing, although no definite conclusions can be drawn at this stage. Eckberg and Sleight (1992) and later O'Mahony et. al. (1995) hypothesized that up regulation of $\alpha 2$ adrenoreceptors secondary to peripheral baroreceptor deafferentation is responsible for CSH. These mechanisms have been recently discounted by some investigators (Parry et al, 2004; Kenny et al., 1987) and confirmed by others. Neuropathological evidence provided by Polvikoski et al. (2006), found marked α -synuclein pathology in the stellate ganglia of an elderly lady with CISH, while Miller et al. (2007) reported significant increase in neurodegenerative hyperphosphorylated Tau proteins in brainstem nuclei which regulate cardiovascular activity. The manner by which these central and peripheral pathological changes may result in exaggerated CSM responses remains unclear. General age related baroreflex alterations characterised by a slowing of governing time constants involved in sympathetic and vagal activation and withdrawal may lead to the detected increased

baroreflex latency. This delayed and overall poorly controlled heart rate combined with as yet other detected age related pathological mechanisms may become especially evident in response to large vagal disturbances such as those seen in CSH. Further confirmatory experimental work is warranted to unmask the underlying pathology responsible for CSH.

6.5 Limitations

Non invasive BRS measures tend not to provide a valid BRS estimate especially in individuals with impaired baroreflex. This can result in missing values and potentially over estimate of reported BRS values in such populations. We overcame this limitation by using the newly developed xBRS method which resulted in a significant improvement in our ability to measure baroreflex sensitivity in this population. Furthermore non invasive measures of BRS are typically limited by presence of ectopic beats, and atrial fibrillation. In our study this resulted in loss of 10% of patients. However the advantages of the non-invasive nature of the methods compared with more invasive methods of BRS assessment significantly outweighed the disadvantages especially for use in frail older patients.

6.6 Conclusion

According to our results the latency of baroreflex responses are altered in CISH. Time domain and frequency domain measures of spontaneous BRS are unchanged in those with CSH. Alterations in baroreflex function may result in weakly linear or nonlinear coupling between BP and HR resulting in lower BRS detection rates being reported in CSH. The manner by which these changes in baroreflex function combine to contribute to an exaggerated response in CSH is yet unclear. However despite this non-invasive spontaneous measures of BRS, particularly the xBRS method, may hold potential as part of a broader array of future novel non-invasive biomarkers of CSH.

6.7 Acknowledgments

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CHAPTER 7

Characteristics of Baroreflex Sensitivity Variability in Carotid Sinus Hypersensitivity

In this chapter we hypothesize that CSH is associated with increased BRS variability, particularly an increased rate of occurrence of periods of high BRS. We suggest that this places individuals at increased risk of exaggerated responses to vagal stimuli. To test this hypothesis we compared time domain and frequency domain characteristics of BRS variability in individuals with and without CSH. Secondly we hypothesize that since baroreflex sensitivity modulation is governed by predominantly central mechanisms, alterations in BRS variability if detected in CSH support the notion that CSH is principally central in origin.

CHAPTER 7

7.0 Background

Previous chapters have examined surrogate markers of baroreflex control of blood pressure and heart rate using resting measures in patients with Carotid Sinus Hypersensitivity. The techniques and approaches considered assume a static underlying neural control system. It is well known however that the baroreflex is under constant top-down central control primarily via neurons within the NTS. In this chapter we investigate emerging concepts of baroreflex modulation with a view to elucidating whether or not they have a role to play in CSH.

7.1 Introduction

Carotid Sinus Hypersensitivity (CSH) is a disorder of ageing characterised by intermittent bouts of exaggerated hypotension and/or bradycardia and is diagnosed in patients with unexplained falls or syncope, when carotid sinus massage (CSM) evokes asystole > 3seconds and/or a fall in systolic blood pressure (SBP) of more than 50mmHg (Brignole, 1998).

CSH by its nature is both intermittent and variable, presenting as unexplained falls, occurring spontaneously during day-to-day activities with symptoms accompanied in 47% of cases by head movement and 73% of cases by vagal stimuli (McIntosh et al, 1993). Reproducibility of CSH responses to CSM are also variable, with studies indicating a wide range of reproducibility from 41%-100% (Richardson et al., 2002). CSH responses are often seen in the presence of beta-blockers (Kenny and Traynor, 1991) and are attenuated in a graded manner during atropine administration (Kenny et al., 1991).

Current opinion regards CSH as central in origin, however definitive pathophysiological evidence to support this remains elusive. Eckberg and Sleight (1992) and O'Mahony et al. (1995) hypothesized that upregulation of α_2 adrenoreceptors secondary to peripheral baroreceptor deafferentation is responsible for CSH. This has been refuted by a study where α_2 receptor antagonists did not attenuate responses to CSM in patients with VDCSH (Parry et al, 2004). Pulse wave augmentation index (AIx) studies (Hilton et al., 2000) found no central arterial stiffness differences in those with a CSH response to CSM compared to controls. Miller et al (2008) noted a significant increase in neurodegenerative hyperphosphorylated Tau proteins in CSH specific to brainstem nuclei, which regulate cardiovascular activity. Finucane et al. (2010) have shown an increase in baroreflex response latency, while others have demonstrated altered baroreflex sensitivity in CSH (Morley, 1984)

(Dehn et al.,1984)(Morillo et al., 1999) (Cole et al., 2001). New concepts have recently come to the fore in the understanding of basic baroreflex physiology, which may go some way to explaining the natural variability of CSH presentation and the source of its underlying pathophysiology. Eckberg et al. (2005) and Karemaker et al (2008), both present the idea that the baroreflex is an adaptive neural controller, which even in quiet supine steady state conditions is continuously being readjusted by central mechanisms over a period of seconds. This variability is altered in the presence of pharmacological agents (i.e. beta blockers) and varying behavioural conditions (i.e. orthostasis). As can be seen from Figure 7.1, spontaneous BRS measures swing wildly over time between high and low values in supine conditions and increased variability is noted in the presence of beta-blockers. During intervals where BRS is at maximum, individuals are most prone to carotid stimuli.

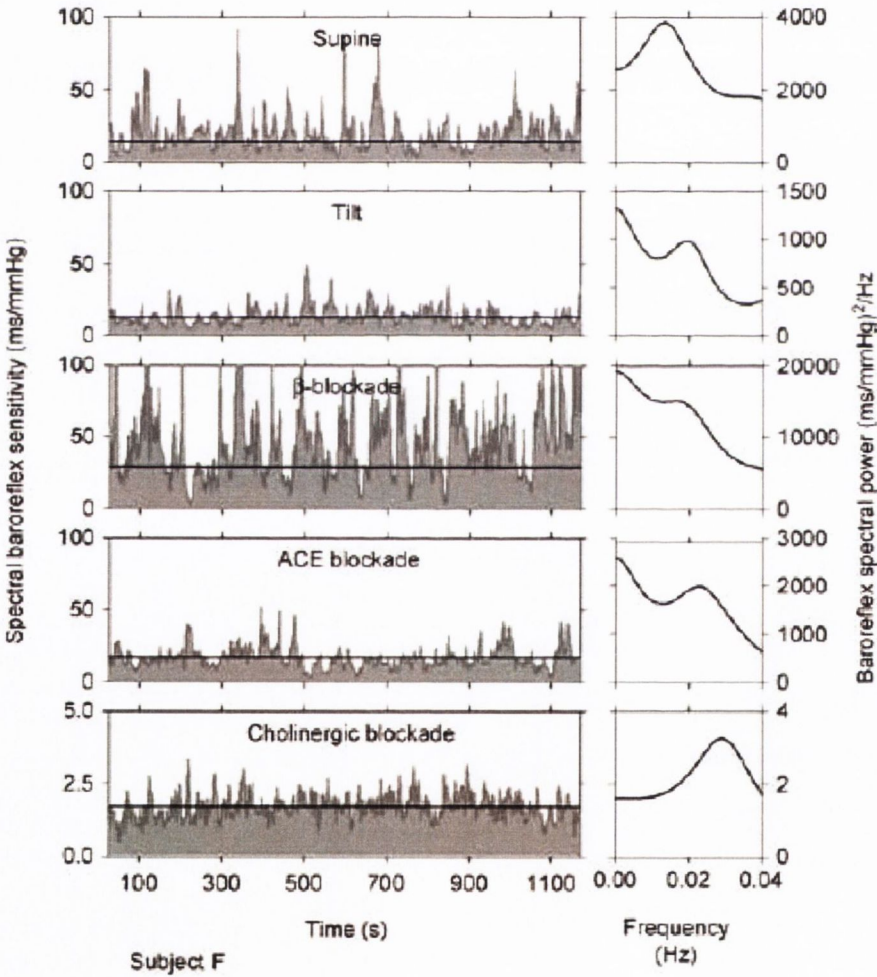


Figure 7.1: Influence of body position and pharmacological blockade on moving cross-spectral baroreflex sensitivity and spectral power (Adapted from Eckberg et al. 2005)

In the last chapter we examined spontaneous measures of BRS in CSH. In light of these new BRS findings we re-examine our results with a renewed hypothesis. We hypothesize that CSH is associated with increased BRS variability, particularly an increased rate of occurrence of periods of high BRS. We suggest that this places individuals at increased risk of exaggerated responses to vagal stimuli. To test this hypothesis we compared time domain and frequency domain characteristics of BRS variability in individuals with and without CSH. Secondly we hypothesize that since baroreflex sensitivity modulation is governed by predominantly central mechanisms, alterations in BRS variability if detected in CSH support the notion that CSH is principally central in origin.

7.2 Methods

7.2.1 Participants

Participants were recruited prospectively from a dedicated syncope unit as part of a larger study investigating autonomic and baroreflex function in CSH. All subjects fasted prior to attending for a single visit between 0900 and 1300 hrs. Subjects refrained from alcohol and caffeine for 12 hours prior to the experiments. Consecutive patients (aged > 50) with a history of recurrent syncope or unexplained falls in the previous year were recruited. All patients had full clinical assessment including Carotid Sinus Massage (CSM) as part of routine cardiovascular assessment. Ethical approval was granted by the local ethics committee.

7.2.2 Protocol

Prior to CSM all subjects underwent a ten-minute baseline surface electrocardiogram (ECG) and continuous beat-to-beat blood pressure (TNO Finapres©) recording. Subjects were instructed to lie supine and directed to breathe normally at a constant rate and comfortable tidal volume while measurements were taken. Following this Physiocal© was switched off and data was recorded for a further 10 minutes. BRS variability measures were derived from the last 10 minutes of this steady state rest period. Following this CSM was performed according to international guidelines, in both supine and upright positions (head-up tilt to 70° with foot plate assisted table). CSM responses were classified as normal (NORM), borderline CSH (CSH+) and definite CSH (CSH++) according to definitions given in Table 7.1.

7.2.3 Analysis

Data processing was performed in MATLAB 6.5^{©21}. Records were scored for significant noise and artifact, and excluded if noise was above an empirically derived threshold. Blood

²¹ Mathworks Inc, Natick, MA, USA

pressure systolic and ECG R wave detection values were corrected for errors by automatic methods and manual screening. Data was screened for abnormal rhythms, and the presence of ectopic beats²².

Table 7.1: Classification of Responses to CSM

General Classification	Subtype	Response to CSM
Normal (NORM)		RR interval <2sec SBP Change <40mmHg
Borderline CSH (CSH+)	CICSH+*	RR interval >2sec and < 3sec SBP Change <40mmHg or RR interval >2sec and <3sec SBP Change >40mmHg and <50mmHg
	VDCSH+	RR interval <2sec SBP Change >40mmHg and <50mmHg
Definite CSH (CSH++)	CICSH++*	RR interval >3sec SBP Change <40mmHg or RR interval >3sec SBP Change >40mmHg and <50mmHg
	VDCSH++	RR interval <3sec SBP Change >50mmHg

²² Data was excluded if the number of ectopics >5% total number of beats

¹ Note the distinction between cardioinhibitory and mixed responses was not made as CSM was not repeated with atropine. CICS_H refers to both CICS_H and Mixed responses

Power spectra of systolic pressure and R–R intervals were integrated within the frequency range, 0.04–0.15 Hz. BRS was considered to be the square root of the ratio between R–R interval and systolic pressure integrated spectra (the α -coefficient). We further filtered these values accepting α -coefficients, only when the coherence was ≥ 0.50 and the phase was negative within this frequency range. Two representative values of BRS were derived – low frequency α -coefficient (LF $_{\alpha}$) and high frequency α -coefficient (HF $_{\alpha}$).

To obtain time-varying estimates of BRS, we iteratively applied the α -methods to 15-second windows of overlapping data, resulting in 100 estimates of BRS from each 10 min data set (Eckberg, 2005). BRS time series were then characterised using time and frequency domain parameters including median BRS, minimum and maximum BRS and BRS interquartile range (IQR). As can be seen in Figure 7.3B, variations in BRS over time are characterized by sharp spikes which occur at varying time intervals, with differing amplitude and duration. Autoregressive parametric methods were used to determine the centre frequency (COF) of BRS oscillations to determine the dominant spectral frequencies in BRS variability. As a second quantitative measure of frequency content, the spectral power of the top 3 dominant peaks was ranked and the centre of frequency was found for each peak. We compared the centre of frequency for the 1st (F1), 2nd (F2) and 3rd (F3) ranked peaks between groups.

7.2.4 Statistical Analysis

SPSS^{®23} version 14 was used to process study data. All features derived in previous sections were assessed for normality using data histograms, calculating distribution skewness, kurtosis, and Kolmogorov-Smirnov test statistics. Initial group age matching was assessed using Kruskal-Wallis non-parametric testing; height and weight were compared by one-way analysis of variance (ANOVA). Normally distributed variables were compared using independent t tests. Nonparametric alternatives were applied where appropriate. Significance was calculated at a level of $p < 0.05$.

²³ SPSS Inc. Headquarters, 233 S. Wacker Drive, 11th Floor, Chicago, Illinois, 60606

7.3 Results

7.3.1 Subjects & Baseline Characteristics

Ninety two patients (46 male; 46 female) mean age 71.6 (SD +/-7.6) years, mean weight 73.4 (SD ± 14.1) kg, and mean height 1.67 (SD ± 0.08) m were recruited. Twenty (9 male, 11 female) individuals remained with normal CSM responses following exclusion of those with cognitive impairment; seventeen individuals displayed CICSH++ (10 male, 7 female); eight subjects had VDCSH++ (5 male, 3 female); eleven had CICSH+ (4 male, 7 female); while ten (4 male, 6 female) individuals had VDCSH+. The degree of grouping matching was assessed by comparing patient demographics, clinical characteristics, proportions of prescribed medications and baseline cardiovascular variables. On analysis groups were shown to be relatively well matched across groups (See Table 7.2).

Table 7.2: Patient Demographics, CSM Response and Baseline Cardiovascular Variables

		Group				
		Control	CICSH+	VDCSH+	CICSH++	VDCSH++
Physical Characteristics	Age (yrs)	67+/-7.5	74+/-9.1	71+/-3.3	74+/-8.0	74+/-4.5
	M/F	9/11	4/6	4/6	7/10	5/3
	Weight (kg)	75.8+/-15.8	71.4+/-7.6	71.9+/-11.1	71.4+/-14.7	69.5+/-18.5
	Height (m)	1.66+/-0.08	1.65+/-0.07	1.67+/-0.07	1.69+/-0.08	1.69+/-0.08
Comorbidities	CVD	19%	9%	20%	24%	13%
	DM	11%	0%	20%	12%	13%
	HTN	76%	64%	50%	41%	57%
	OH	85%	82%	80%	87%	100%
Medications	CA	42%	56%	44%	33%	63%
	AntiHTN	38%	45%	40%	31%	50%
	Psych.	16%	33%	11%	7%	25%
CSM Response	RR _{MAX} (secs)	1.1+/-0.2	2.5+/-0.3*	1.3+/-0.2	6.2+/-2.6*	1.3+/-0.3
	ΔSBP (mmHg)	24.7+/-9.2	49.5+/-10.5*	44.0+/-3.1*	64.4+/-15.4*	59.3+/-6.4*
Baseline Cardiovascular Status	HR (bpm)	65+/-11	68+/-10	67+/-13	70+/-11	61+/-6
	SBP (mmHg)	135+/-23	145+/-25	123+/-25	138+/-22	129+/-16
	DBP (mmHg)	73+/-8	70+/-7	72+/-18	74+/-9	65+/-11
	MAP (mmHg)	97+/-13	98+/-9	92+/-20	100+/-14	88+/-12

* P<0.01 CVD=Cardiovascular disease; DM=Diabetes Mellitus; HTN=Hypertension; OH=Orthostatic hypotension; AntiHTN=Antihypertensive²⁴; CA=Cardioactive²⁵; Psych.=Psychotropic²⁶ RR_{MAX} = Max RR interval post CSM; ΔSBP = Change in SBP post CSM; HR=Heart rate; SBP=Systolic blood pressure; DBP=Diastolic blood pressure; MAP = Mean arterial pressure

7.3.2 BRS Analysis

The unadjusted means for LF_α, HF_α are given in Table 7.3. There was a trend in LF_α towards an increase in BRS in CSH+ (P>0.05) and CSH++ (P>0.05), while a decrease in HF_α was found in CSH+ (P>0.05) and CSH++ (P>0.05). Differences between groups were not significant. Following adjustment for resting heart rate, together with beta blockers, psychotropics and age, similar trends remained. However the differences between each of the BRS values remained statistically insignificant (See Table 7.4).

Table 7.3: Time and frequency domain measures of BRS variability

		BRS Alpha		Time Domain					Frequency Domain	
Group		LF _α	HF _α	Median	IQR	Min	Max	IQR/Median	COF	FreqRank
Control		5.4 (3.6-7.2)	8.1 (3.8-12.5)	5.9+/-3.7	7.5+/-6.2	0.7+/-0.5	72.4+/-60.1	1.2 +/- 0.24	0.09 +/-0.03	0.04 +/-0.02
+	CICSH+	6.2 (4.3-8.1)	5.7 (4.2-7.2)	5.9+/-4.9	7.2+/-5.7	0.65+/-0.6	63.7+/-50.2	1.27 +/- 0.15	0.08 +/-0.03	0.04 +/-0.02
	VDCSH+			5.86+/-2.7	5.9+/-2.9	0.69+/-0.5	45.4+/-21.6	0.98 +/- 0.18 *	0.1 +/-0.04	0.05 +/-0.02
++	CICSH++	6.8 (4.2-9.4)	6.7 (4.5-8.8)	5.6+/-4.0	6.1+/-3.8	0.65+/-0.4	41.8+/-20.6	1.1 +/- 0.2	0.1 +/-0.04	0.07 0.04 *
	VDCSH++			6.0+/-4.7	7.1+/-5.5	0.66+/-0.7	60.5+/-66.5	1.2 +/-0.27	0.07 +/-0.02	0.04 +/-0.02

* P < 0.1 * P < 0.05

²⁴ ACE inhibitor, Alpha Blocker, Beta blocker, Calcium channel blocker, Thiazide diuretic
²⁵ Antianginal (nitrate), or Antiarrhythmics, Fludrocortisone or Midodrine
²⁶ Typical or atypical neuroleptic, anticholinergic, anticholinergic, cholinesterase inhibitor, TCAD, SSRI, other antidepressant, antiparkinsons or other psychotropic medication

7.3.3 Time Domain Analysis of BRS Variability

Max, min and overall BRS variability as determined by its interquartile range (IQR) was similar across all 5 groups (Figure 7.2A). Numerically this is confirmed in Table 7.3 where no significant differences were found between groups. A highly significant linear relationship ($r = 0.94$; $P<0.0001$) between IQR of BRS and median BRS was found to exist (Figure 7.2B). When we examined this relationship across groups (Table 7.3), the ratio between median BRS and BRS IQR was found to be decreased in VDCSH+ ($P<0.05$), compared to controls but was not altered in CICSH+ ($P>0.05$), CICSH++ ($P>0.05$), VDCSH++ ($P>0.05$) groups.

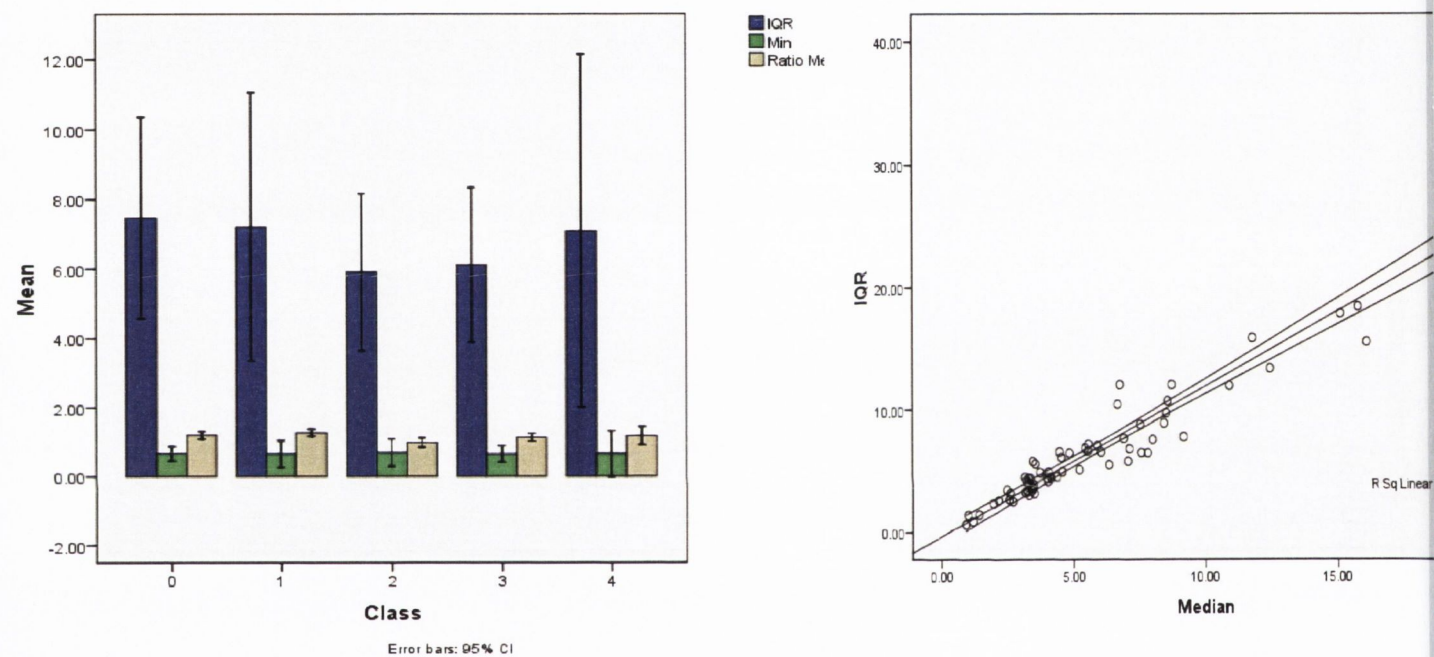


Figure 7.2A) Comparison between IQR, Min BRS, Ratio of IQR of BRS 2B) Plot of BRS IQR versus Median BRS, indicating a very strong correlation ($r = 0.94$; $P<0.0001$)

7.3.4 Frequency Domain Analysis of BRS Variability

Frequency domain parameters, which characterise the dominant spectral content of BRS changes, were found to be increased in CICSH compared to controls as can be seen in Figure 7.3C and Table 7.3. This increase was significant ($P<0.05$). Sample BRS variability plots are shown in Figure 7.3A and 7.3B. This is further emphasised in Figure 7.3B where the higher frequency information is evident in CICSH.

Correlation analysis was performed to examine the association between measures of variability and CSM response. Initial analysis indicated a strong and highly significant correlation ($p=0.44$; $P<0.001$) between RR interval following CSM and the frequency of the second peak in the BRS spectrum. Investigation of the scatterplot for this variable indicates

that this relationship was due in part to the spread pattern of values especially those highlighted in red in Figure 7.4.

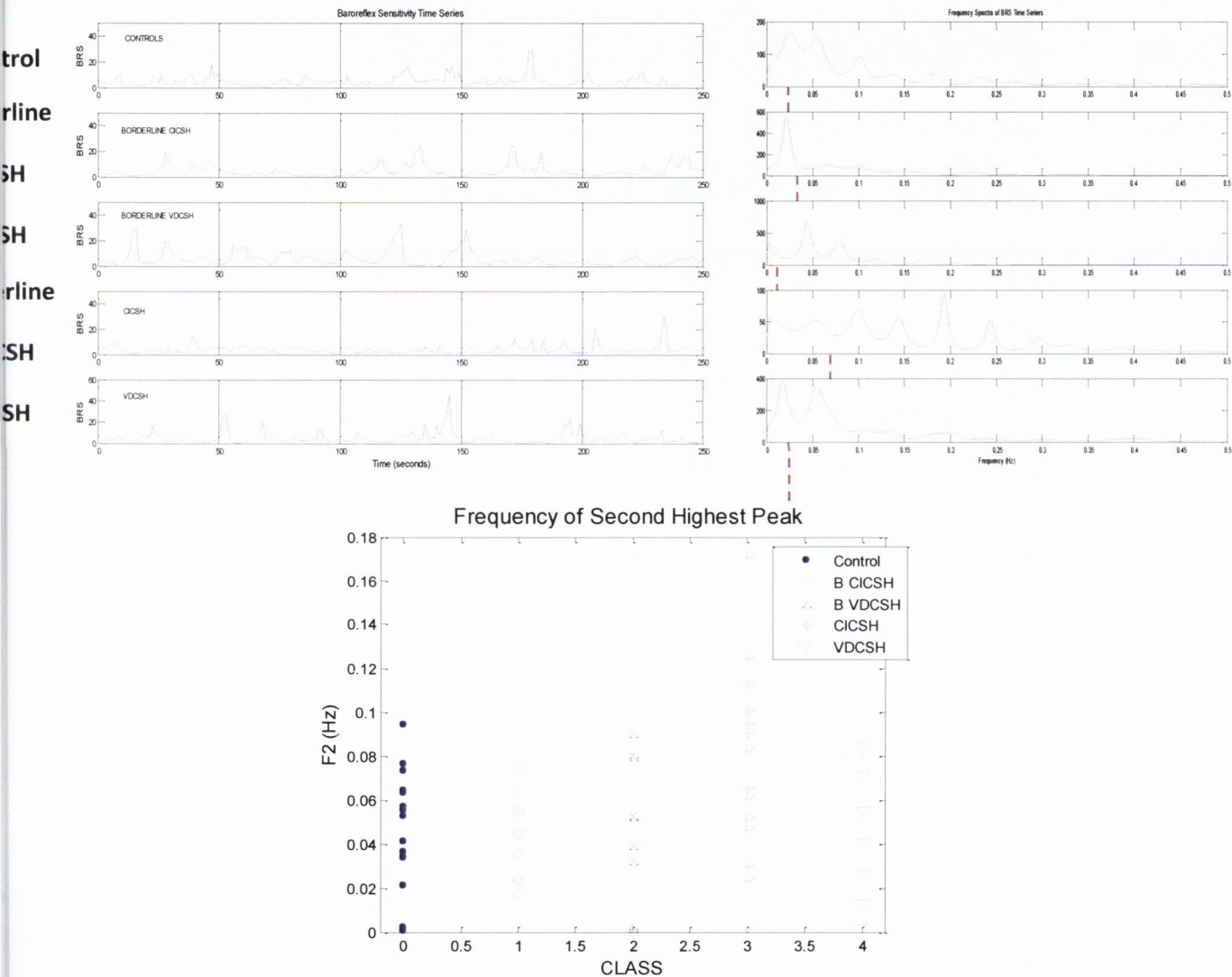


Figure 7.3A) BRS Variability time series in Controls, Borderline CICSH, Borderline VDCSH, CICSH and VDCSH B) Frequency spectra of BRS time series, frequency of second resonant peak is higher in CICSH. C) Scatterplot of frequency of second resonant peak between groups

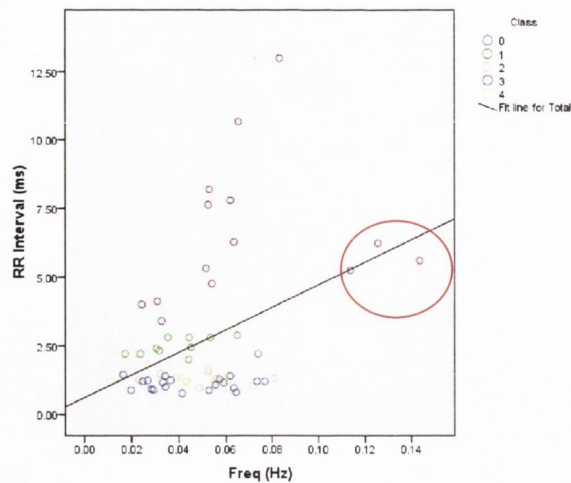


Figure 7.4A) Correlation between RR interval following CSM versus frequency of second resonant peak in BRS power spectrum ($\rho=0.44$; $P<0.001$).

7.4 Discussion & Conclusion

In this chapter we focussed on identifying characteristics of modulation of BRS variability in a CSH population using non-invasive measures of BRS. To the best of our knowledge this study is unique in this regard and is the first of its kind to show that the spectral content of BRS variability is altered in CISH.

In investigating the nature of resting BRS variability in CSH a number of findings were noted. Firstly time domain parameters of variability including amplitude, and standard deviation were similar between groups. All groups demonstrated a large amount of inherent variability with similar maximum and minimum values. This inherent variability of BRS could account for the reported variation in reproducibility results noted by Richardson et al. (2002). These results are also in agreement with both Karemaker et al. (2008) and Eckberg et al. (2005) who note that this variability is physiological in origin, arising in part from the inherent constant fluctuations in neural activity within the CNS. Furthermore the amount of variability was linearly proportional to the median BRS value in agreement with Karemaker et al. (2008). The reasons for this linear relationship are yet unknown, but this result does serve to validate the results of our analysis with previous studies (Eckberg et al., 2005).

Of particular interest is the increase in frequency of these variations in CISH and the relationship detected between HR response to CSM and the frequency of these oscillations. In agreement with (Karemaker and Wesseling, 2008) the mean frequency of oscillations lay in the region of 0.03-0.05Hz, however in CISH the shift to higher frequencies was noted and correlated linearly with CSM response in CISH. The reasons for this are unclear. If we are to

accept the conclusion that variations in BRS are of central origin, we could conclude that yet unidentified CNS mechanisms most probably circuits of the central autonomic network (CAN) (Bennarroch, 1993), centrally modulate BRS in a ongoing fashion in an analogous manner to the early attention based mechanisms of visual information processing (Kelly et al., 2008). This could serve to adapt baroreflex sensitivity as required by different behavioural situations. The shift in frequency found in CSH may indicate central dysfunction of the CAN, potentially driven by the same neurodegenerative processes responsible for the small but significant increase in neurodegenerative hyperphosphorylated Tau proteins found by Miller et al. (2007). However until a transparent link between BRS variability and the underlying structure and integration of neural circuitry governing cardiovascular and autonomic control is determined definite conclusions cannot be drawn here.

From a clinical perspective it is yet to be seen whether or not the higher frequency components in BRS corresponds to increased vulnerability to large vagal stimuli such as those experienced in CSM or other reported vagal manoeuvres as they would be more likely to occur during a time when BRS is high. From a methodological perspective the nature and underlying causes of BRS variability should be investigated further from both methodological and physiological perspectives.

Future studies in this area should focus on establishing the relationship between syncope, falls and the nature of BRS variability on the basis of these results over longer time periods. We would suggest that increased BRS variability and latency may be a potential non-invasive biomarkers for central alterations in baroreflex control seen in CSH, and hence could be useful in identifying those at risk of unexplained syncope and falls.

7.5 Limitations

We measured BRS during normal breathing rather than paced breathing. Some authorities have noted that BRS variations are influenced by breathing. Whether or not it would have influenced frequency spectra of BRS measure over time requires further confirmation. Furthermore the suitability of a paced breathing protocol for frail elderly individuals requires further investigation especially since a high level of cooperation from our subjects who also often had hearing difficulties is required.

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CONCLUSION

In this chapter conclusions of the thesis are summarised. Future directions are also discussed for this area of research.

CONCLUSION

In this thesis we explored the application of cardiovascular systems modelling and non-invasive indices of cardiovascular variability with a view to better understanding the underlying cause of this condition and developing a set of candidate non-invasive biomarkers for CSH. We observed that non-invasive markers of baroreflex sensitivity and blood pressure variability contain relevant information which can inform both future diagnostic systems and the understanding of this difficult condition. It is also clear that a deterministic biophysical modelling approach is capable of succinctly describing the dynamics of carotid sinus massage, and thus may play a role in identifying the underlying causal pathophysiology and guiding the selection of future treatment and diagnostic approaches.

In Chapter 3 a novel model of Carotid Sinus Massage was developed, indicating that realistic modelling of heart rate and blood pressure responses require a full description of baroreflex and cardiopulmonary reflexes on normal man. Model predictions identify a set of optimum parameters which we suggest once validated experimentally could be used for clinical practice when performing CSM to both maximize safety, diagnostic power and reliability. In fact these parameters are very close to those currently used clinically determined through a trial and error process.

Our model detail was successful in simulating the pathophysiological responses seen in Carotid Sinus Hypersensitivity demonstrating both cardioinhibitory and vasodepressor responses. A number of novel findings were demonstrated which we feel will have important consequences for future diagnosis and treatment options.

To achieve heart rate and blood pressures drops seen in pathological situations i.e. CSH where pauses of the order of 2-3 seconds and blood pressure drops of $> 50\text{mmHg}$ a number of parameters were critical are thus implicated in CSH. From these simulation studies the magnitude of the initial stimulus response i.e. drop in blood pressure or heart rate to CSM was influenced by the

- magnitude of the stimulus
- the gain of the baroreflex
- the range of the baroreflex saturation curve.

Furthermore slowing of effector responses was also key in reproducing the CSH response. Finally a model which includes susceptibility to SA nodal exit block and/or AV nodal block was seen to reproduce the cardioinhibitory response seen in practice

From a clinical perspective our model would suggest that the possibility of a number of potentially new CISH subtypes i.e. 'Dromotropic' and 'Chronotropic' CSH and new VDCSH subtypes i.e. 'Venous CSH' and 'Arterial CSH'. Heart rate slowing is maximised when parasympathetic, and sympathetic responses overlap in time, thus cardioinhibitory CSH will be characterised by increased system delays. The relative influence of the baroreflex on pacemaker rate and conductivity of atrial tissues is also important and suggests the possibility of two CSH subtypes i.e. chronotropic and dromotropic CSH. In all cases the saturation limit of the baroreflex is also important, since it limits stimulus magnitude.

In Venous CSH the arteriolar reflex is severely impaired while the venous limb is relatively intact, resulting in a lagged and prolonged drop and recovery. This would mirror the classical 'Slow Vasodepressor Response'. Hypotension in this case is characterised by slow recovery rate. In Arterial CSH the sensitivity of arteriolar and venous limbs are relatively intact. However the relative rate of the arteriolar response is impaired. Thus both the venous and arteriolar limbs vasodilate in unison to contribute to greater hypotension.

The model developed is quite a powerful model, and could more generally find applications in identifying underlying pathophysiology in other neurocardiovascular instabilities, longitudinal simulations, directing selection of future experimental protocols, interventions and education.

Chapters 4, 5 and 6 investigated a number of advanced digital signal processing methods for non-invasively measuring the candidate parameters identified in Chapter 3.

An association between VDCSH and increases in short-term blood pressure variability indices was found in Chapter 4. Two frequency bands were identified as important, the LF Mayer band, which is influenced strongly by baroreflex control of peripheral resistance vasculature and the HF Traube Herring band which is primarily respiratory related activity. As hypothesized, significant alterations in the LF Mayer band were detected, in VDCSH indicated by a small peak in the LF bands. Such changes are consistent with alterations in the peripheral resistance-controlling arc of the baroreflex in VDCSH, and could be considered indicative of an altered gain or range of the baroreflex. However since the frequency of this peak is at the lower end of the Mayer wave band (at 0.06Hz), some doubt still remains over

whether one can definitively conclude that a hypersensitive baroreflex response exists in VDCSH. Indeed lower frequency mechanisms such as venous tone control mechanisms could be dominant in VDCSH, which would go some way to explaining the lagged responses seen in VDCSH and also the relatively high prevalence of slow response hypotension in VDCSH. This would agree with our model simulations in Chapter 3. An increase in HF respiratory blood pressure waves was also detected and unexpected. These results are consistent with altered respiratory drive in VDCSH resulting in increased tidal volume and therefore increased intra thoracic pressures during inspiration. Peripheral and central respiration and cardiovascular control centres are intimately linked so it is plausible that respiratory centres are also affected in CSH. In fact recent results suggest other forms of syncope are accompanied by altered vascular responses to hypercapnia which cause sudden exaggerated cerebral vasoconstriction and peripheral vasodilation responses leading to an increased risk of syncope. During CSM increased depth of breathing often occurs which could in those with exaggerated vascular responses cause similar responses leading to symptoms. Cardiorespiratory influences may thus play a role in conversion of CSH to symptomatic CSH. Furthermore both frequency bands could contribute useful diagnostic information and be the basis of future biomarkers for CSH and identifying those who will convert from CSH to CSS.

Chapter 5 examined non-invasive measures of BRS and latency in a CSH population to verify the hypothesis that CSH is associated with changes in baroreflex sensitivity. Results indicate that BRS latency is increased in CSH, while spontaneous measures of BRS were not significantly different. We compared the performance of various non-invasive measures of baroreflex sensitivity in CSH. This identified a candidate method for use as a tool in CSH i.e. the xBRS method. Perhaps more interestingly, method performance and comparisons could also be pertinent from a physiological perspective. BRS methods on average performed best in controls i.e. those without dysfunctional baroreflex control, while in the CSH population, BRS methods often failed to identify valid BRS estimates. All BRS methods are based on the assumption of linearity and employ thresholds to enforce this. The reason why individuals with CSH violate these criteria maybe explained by an impaired baroreflex in CSH. Alternatively blood pressure changes may be non-linearly related to changes in heart period, thus tests based on linear correlations may fail. This may suggest that CSH causes a pathological increase in non-linearity of baroreflex function. Non-linear deterministic measurements of synchronisation (or their stochastic variants) may prove a fruitful avenue for future studies to consider.

It was surmised that general age related baroreflex alterations characterised by a slowing of governing time constants involved in sympathetic and vagal activation and withdrawal may lead to the detected increased baroreflex latency. This delayed and overall poorly controlled heart rate combined with as yet other detected age related pathological mechanisms may become especially evident in response to large vagal disturbances such as those seen in CSH.

Baseline HR also tended to be increased in the CSH population compared to controls (although in this group this was insignificant) especially in the cardioinhibitory form and would suggest an enhanced resting sympathetic tone exists in these individuals. The results of Levy and Zieske maybe relevant here, where vagal activity in the presence of increased sympathetic tone is known to enhance vagal responses leaving those individuals with increased resting heart rate more susceptible to cardioinhibition or AV block.

Finally in Chapter 6 we focussed on identifying characteristics of modulation of BRS variability in a CSH population. To the best of our knowledge this study is unique in this regard and is the first of its kind to show that the spectral content of BRS variability is altered in CISH.

In investigating the nature of resting BRS variability in CSH a number of findings were noted. Firstly time domain parameters of variability including amplitude, and standard deviation were similar between groups. All groups demonstrated a large amount of inherent variability with similar maximum and minimum values. Of particular interest is the increase in frequency of these variations in CISH and the linear relationship detected between CSM response and the frequency of these oscillations. The reasons for this are unclear. If we are to accept the conclusion that variations in BRS are of central origin, we could conclude that yet unidentified CNS mechanisms most probably circuits of the central autonomic network (CAN) centrally modulate BRS in a ongoing fashion in an analogous manner to the early attention based mechanisms of visual information processing. The shift in frequency found in CSH may indicate central dysfunction of the CAN. However until a transparent link between BRS variability and the underlying structure and integration of neural circuitry governing cardiovascular and autonomic control is determined definite conclusions cannot be drawn here.

8.2 Future directions

As in all theses much work has been done, but avenues anew have presented themselves at each juncture along the development of the thesis. We have made a number of significant advances in terms of cardiovascular modelling and experimental measurements in CSH.

A number of important questions remain unanswered in both the fields of CSH modelling and experimental physiological.

Modelling inspired non-invasive metrics of cardiovascular variability and baroreflex sensitivity are powerful tools for investigating autonomic control. In particular we noted that CSH is characterised by increased blood pressure variability in both low frequency and high frequency bands, higher sympathetic tone, altered cardiorespiratory activity and increased response latency. Our results suggest that cardiorespiratory activity, interaction between vagal and sympathetic systems and increased neural latencies may be important in developing CSH and its conversion to symptomatic CSS. These variables may also inform the development of future diagnostic biomarkers for CSH. Future work should explore more advanced system identification methods to further characterise the state of the cardiovascular control system and explore the sensitivity and specificity of these parameters in identifying individuals at risk of CSH. Nonlinear methods should also be investigated in this regard to identify whether or not CISH is associated with altered function (nonlinear) or low baroreflex sensitivity.

The nature of baroreflex variability discussed in the final chapter of this thesis warrants further exploration from both methodological and physiological perspectives. It is possible the variability noted in this and other studies maybe methodology related and could result from time varying phase relationships between blood pressure and time domain variables producing a beat like phenomenon. On the other hand the variability could indeed be a marker of central modulation of the baroreflex. If this is true further exploration of this measure should be undertaken to examine its relationship to central neuromodulation. Animal studies could be potentially rewarding in this respect.

From a modelling perspective it would be pertinent to explore the inclusion of a multifibre baroreceptor model which accounts explicitly for baroreceptor fibre types and block representation of the brainstem nuclei involved in cardiovascular control. This would allow for further exploration and design of experiments to explore possible mechanisms whereby the range of baroreceptor outputs can be increased and thus examine the factors associated with limiting baroreceptor stimulus during CSM.

Quantitative methods such as classical sensitivity and generalized sensitivity analysis should be explored to formalise future approaches to CSH biomarker identification, diagnosis and treatment. Analytical approaches such as describing function analysis would be a worthwhile

avenue to explore to further structure model behaviour analysis and potentially improve and simplify goodness-of-fit of model.

Experimentally a number of physiological measurement methods warrant development and exploration in CSH. In particular more accurate methods to non-invasively measure model state variables (CO, TPR, Blood Volume) and methods to measure individual parameters characterising the biomechanical properties of the cardiovascular system are required. MRI approaches could be investigated in this regard and would be a valuable resource for the modelling community. Beat to beat blood pressure is inherently variable and prone to noise, especially during syncopal episodes when clinically the blood pressure measurement is of upmost importance. Robust and accurate noise rejection algorithms are required in this regard.

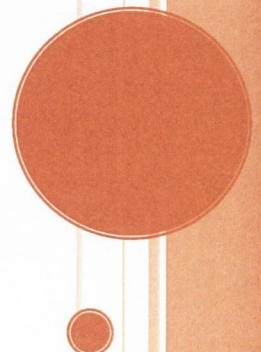
As a first step to measuring the stimulus produced by CSM, carotid deformation could be measured using ultrasound methods and ideally quasi real-time MRI studies. This could also be coupled with a study investigating the interaction between local carotid arterial stiffness and baroreflex sensitivity in CSH to untangle the role of arterial stiffness in CSH.

Finally and probably most interesting is the renewed interest in implantable baroreflex stimulators. These warrant further investigation for a number of reasons in CSH. Firstly it would offer a unique experimental opportunity to explore neural mechanisms of baroreflex control in CSH in the absence of mechanical confounders and bring us a step closer to examining the underlying pathophysiology of CSH. Secondly CSH may have impact on the long term success of such techniques and would warrant future investigation from this perspective.

APPENDIX 1.0

A.1.1 Improving Carotid Sinus Massage Reliability through the Design of Supporting Tools

The reliability of Carotid Sinus Massage is often questioned clinically as being subjective in nature. Sources of variability in CSM include the accuracy of the clinician in locating the correct point of stimulation based on anatomical landmarks, ability to standardize the manoeuvre in terms of rate, pressure and duration. In this Appendix we describe experimental work carried out to address these issues.



A.1.1 Accuracy of Anatomical Landmarks for Locating the Carotid Sinus

The major sources of variability in CSM include

- Locating Carotid Sinus accurately
- Applying the pressure in a standardized manner in terms of:
 - Magnitude
 - Rate
 - Duration

In this Appendix we describe experimental work carried out in order to quantify the error in locating the carotid sinus accurately in comparison to an ultrasound gold standard. Having provided experimental evidence that a technical system is required to improve locating the carotid sinus we describe two technical solutions based on ultrasound. Methods are designed and tested to this address this problem.

A.1.2 Accuracy of Anatomical Landmarks for Locating the Carotid Sinus

A.1.2.1 Introduction

Carotid sinus massage (CSM) is a valuable bedside test for Carotid Sinus Syndrome (CSS) a common cause of recurrent falls in the elderly. However CSM is not without its limitations being both subjective and variable in nature. In this study we sought to further examine sources of variability which influence CSM i.e. in this case the error introduced by using anatomical landmarks for locating the Carotid Sinus (CS). We compared the accuracy of this method to a gold standard ultrasound measurement in a group of patients attending for carotid artery screening.

A.1.2.2 Methods

Consecutive patients (n=20) attending the vascular laboratory for carotid artery screening were recruited prospectively. All patients had full clinical assessment including Carotid Doppler Ultrasound as part of routine vascular assessment. A point on the skin (US) overlying the CS was marked by a vascular technician. Subsequently two clinicians trained in CSM were asked to locate the CS using the anatomical landmark while blinded to the true location. The distance of these points to US was then measured using a set of callipers. All measurements derived were assessed for normality and compared using non-parametric

tests for differences in means. Spearman's rank correlation coefficient (ρ) were used to investigate Univariate relationships between variables. Significance was calculated at a level of $p \leq 0.05$.

A.1.2.3 Results

The anatomical method underestimates actual CS location by 1.5 ± 1.3 cm ($14.1 \pm 17.1\%$). Error extremes ranged from 4 cm below to 2 cm above CS using this method. Errors in locating the right CS versus left CS were significantly higher ($p=0.029$). A moderate correlation between US and anatomical landmarks was found $r=0.371$ ($p=0.031$).

A.1.2.4 Conclusion

As far as we are aware this is the first study of its kind to characterise the accuracy of standard anatomical landmarks used in CSM. Methods using anatomical landmarks alone demonstrate an average error of 14% in comparison to ultrasound methods and it is likely are suitable when carotid pulse is palpated easily. Furthermore higher errors occur when locating the right CS, which may influence detected prevalence of CSH subtypes. Based on these results it is reasonable to suggest that technological interventions may play a future role in those situations where the carotid pulse is not easily palpated during CSM.

A.1.3 Doppler Flow Method for Guiding Carotid Sinus Massage

A.1.3.1 Introduction

Carotid Sinus Massage (CSM) is a simple effective method used to diagnose Carotid Sinus Syndrome (CSS). During CSM firm longitudinal massage is performed at the point of maximal pulsation located between the thyroid cartilage and the angle of the mandible. This point is thought to be an accurate anatomical landmark of the carotid sinus and bifurcation.

Recently work in our group (Finucane et al, 2009) has shown the error of this anatomical landmark to be as large as 14% in certain individuals characterised by a difficult to palpate carotid pulse. In these cases a technological intervention is advocated to improve accuracy of CS determination and ultimately CSM reliability.

We present here a system design based on the analysis of blood flow Doppler signals which is capable of guiding a clinician to the site overlying the CS prior to CSM. Section 2 describes the technical details of the approach. Section 3 presents initial results of the method.

Section 4 finishes with a discussion of the advantages and disadvantages of this approach describing some design improvements recommended for future work.

A.1.3.2 Methods

A.1.3.2.1 Changes in Doppler Flow Signal Characteristics

A handheld Blood Flow Doppler System (8.4MHz, Huntley Medical) was used to record Doppler signals from points over the common carotid, internal and external carotid arteries i.e. above and below the carotid bifurcation (See Figure A.1). A number of differences are evident in the waveforms between those recorded above and below the carotid bifurcation i.e. frequency shifts are of higher magnitude and have increased pulsatility above the carotid bifurcation. Processing of the sonogram signal was performed to extract a number of biomarkers sensitive to waveform pattern changes experienced during traversal of the carotid bifurcation (described below).

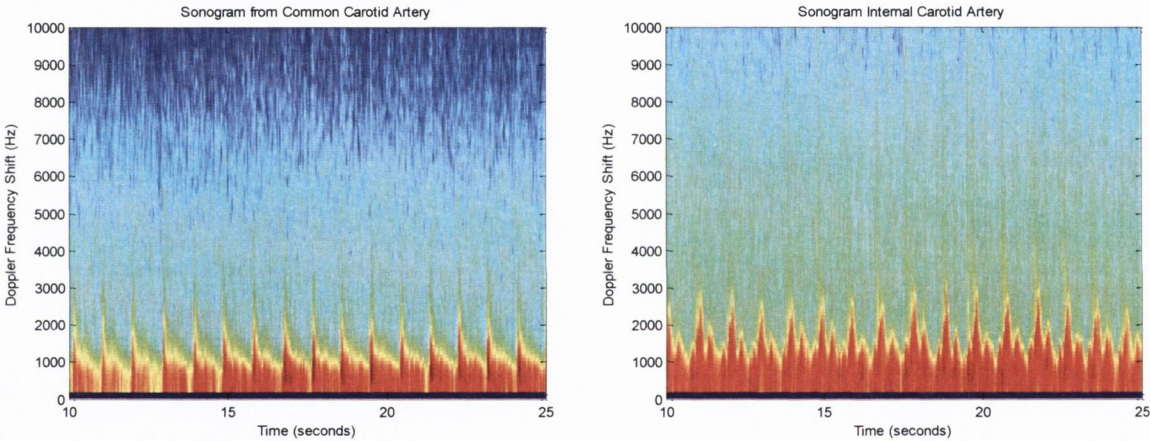


Figure A.1: Sonogram from Common Carotid Artery (left) and Internal Carotid Artery (right)

A.1.3.2.2 Doppler Signal Processing

The Doppler audio output representing flow towards and away from the transducer was connected to TOSHIBA laptop computer (processor 2.00 GHz Intel Core Duo), via a standard audio card stereo input analogue-to-digital (ADC) interface. Data was digitised at 20.05 kHz. Signals thus obtained were analyzed and displayed using custom written software coded in MATLAB®. Data was analyzed in 256 sample segments. Each segment was Hanning windowed, and then fast Fourier transformed to generate a new spectrum every 4.96 ms (a frame overlap of 57.42%). The two lowest frequency bins in each Fourier spectrum are set to zero to implement a high pass filter to reject any large signals due to tissue motion. The instantaneous intensity weighted mean (IWM) envelope (Evans and McDicken, 2000), the

instantaneous maximum frequency (MAF) envelope using the simple threshold method (Gibbons et al, 1984), and a flag indicating the start of each new cardiac cycle were derived from the resulting sonogram using the method described by Evans (Evans , 1988).

A number of standard beat to beat values were calculated from the resulting sonogram envelopes including average maximum frequency (kHz)(M), average intensity weighted mean Doppler shift frequency (kHz), maximum of maximum frequency shift envelope (kHz) (S), minimum of maximum frequency shift (D) envelope (kHz). Gosling’s pulsatility index (PI)(Gosling and King, 1974) and Pourcelot’s resistance index (RI) (Planiol and Pourcelot, 1973) were then derived from these values where

$$PI = \frac{S-D}{M} \tag{1}$$

$$RI = \frac{S-D_1}{S} \tag{2}$$

with D₁ representing the end diastolic height of sonogram envelope.

Gosling’s original Pulsatility index PI_{orig}, defined as the total oscillatory energy in the velocity waveform divided by the mean flow velocity of each cardiac cycle i.e.:

$$PI_{orig} = \frac{\sum_{n=1}^{\infty} a_n^2}{M^2} \tag{3}$$

was also calculated.

A.1.3.2.3 System Testing

N=183 beats were measured from a young healthy subject (Female, age 28) at two locations measured 2cm above and 2cm below the carotid bifurcation. Derived signal indices were compared using Wilcoxon’s sign rank test suitable for paired samples. The sensitivity, specificity and receiver operating characteristic (ROC) curve of each index was also examined to determine its effectiveness in differentiating between signals obtained from above and below the bifurcation. This approach was used as a guide to selecting the most appropriate measures to be incorporated into a final clinical feedback system.

A 1.3.3 Results

A 1.3.3.1 Index Comparisons Above and Below Carotid Bifurcation

Table 1 compares the indices derived from recordings above and below the bifurcation. Median and range are quoted for each variable. The average of maximum Doppler frequency shift envelope was significantly higher (1633.1 (1377-1849)Hz) above the bifurcation

compared to below (1289.7 (635-1746) Hz). Similarly D and S were also significantly increased (See table 1). PI was significantly decreased above the bifurcation compared to below (1.204 (0.751-5.989) vs. 0.96 (0.685-1.434)). Similarly RI was decreased (0.438 (0.257-1) vs. 0.385(0.118-0.621)). The degree of pulsatility (PI_{orig}) was noted as being consistently of significantly higher magnitude in locations superior to the bifurcation (3.14×10^8 (1.65×10^7 - 1.44×10^9)) compared to measurements made at inferior positions (4.27×10^7 (5.29×10^6 - 1.94×10^{11})).

	Below Bifurcation	Above Bifurcation	Sig.
M	1289.7 (635-1746)	1633.1 (1377-1849)	P<0.0001
D	869.9 (0-1292)	1044 (792-1240)	P<0.0001
S	2383.9 (1584-5546)	2612 (2205-3445)	P<0.0001
PI	1.204 (0.751-5.989)	0.96 (0.685-1.434)	P<0.0001
RI	0.438 (0.257-1)	0.385(0.118-0.621)	P=0.052
PI_{orig}	4.27×10^7 (5.29×10^6 - 1.94×10^{11})	3.14×10^8 (1.65×10^7 - 1.44×10^9)	P<0.0001

Table 1: Comparison of Indices Above and Below the Bifurcation. M = Average maximum frequency (kHz); S = maximum of maximum frequency shift envelope (kHz); D = minimum of maximum frequency shift envelope; PI = Gosling’s simplified pulsatility index; RI= Pourcelot’s resistance index; PI_{orig} = Gosling’s original Pulsatility index.

A 1.3.3.2 Sensitivity and Specificity of Features

As can be seen from Table 2 and the accompanying ROC curves in Figure A.2, M provides the best classification performance with an average accuracy of 87.5%. The RI index performs poorly with an accuracy of 60.2%.

	Sensitivity	Specificity	Average Accuracy	Area Under ROC Curve
M	86%	89%	87.5%	93.2%
D	100%	42.9%	71.45%	72.2%
S	81%	70%	75.5%	79.8%
PI	80%	62.8%	71.4%	76.7%
RI	87.9%	32.6%	60.2%	59.8%
PI _{orig}	74.4%	82.1%	78.25%	79.2%

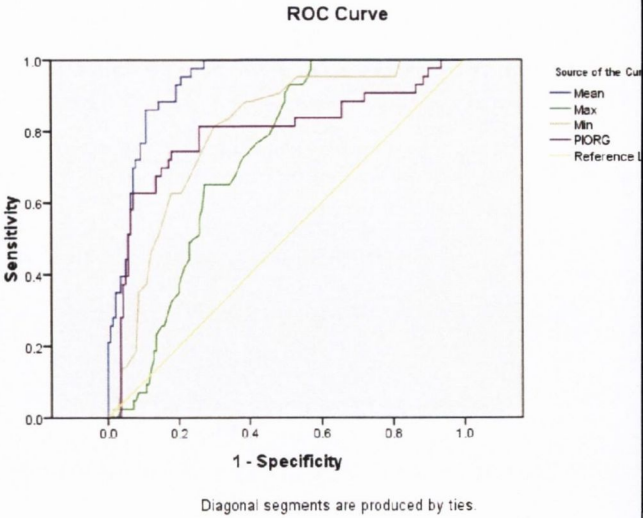


Table 2: Comparison of Detection Accuracy between Indices

FigureA.2: ROC Curve

A 1.3.3.3 Group Discrimination Linear Discriminant Analysis

Combining the 5 indices into a multidimensional feature vector serves to significantly improve the group separation of the indices, with an average classification accuracy of 98.4% achieved (100% sensitivity, 93% specificity). This is illustrated in the 2D scatterplot diagram and ROC curves of Figure A.3.

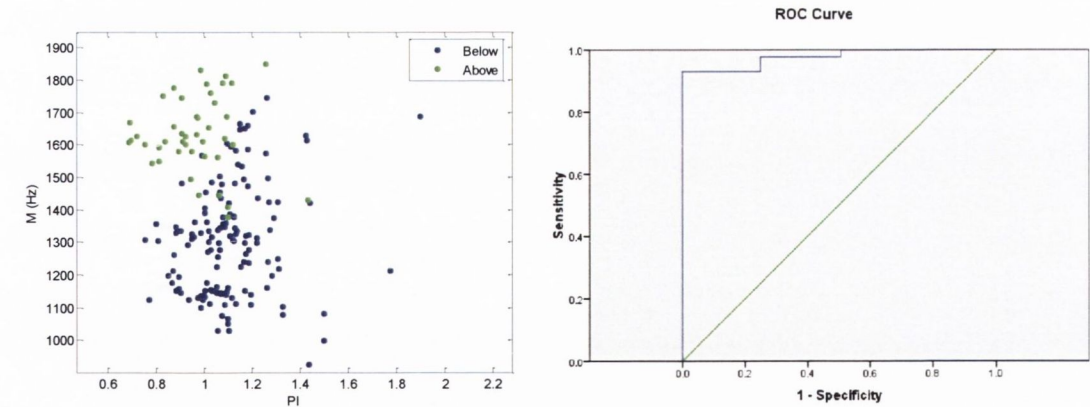


Figure A.3: Scatterplot (Left) and ROC curve for Linear Discriminant Function

A 1.3.4 Discussion & Conclusion

In this study, a system for detecting the location of the carotid bifurcation was developed. Tests of the system demonstrated that it successfully identified sonograms recorded from locations positioned superior and inferior to the carotid bifurcation with an accuracy of

98.4%, even in the face of high level noise. A combination of features proved more accurate in identifying these differences compared to use of single best feature which gave a quite respectable classification accuracy of 87.5%.

The significance of this study is that a low cost technical framework for blood vessel bifurcation location is described. By combining a low cost Flow Doppler system which is commonly available in clinical environments with advanced PC based audio signal processing, a practical system for the easy detection of carotid bifurcation is made possible removing the need for higher end costly ultrasound machines. Such a system may improve reliability and accuracy of CSM especially in those individuals where palpation of the carotid pulse is difficult. Future work should be aimed at identifying the robustness of this method in a larger patient population and comparing it with alternative approaches based on standard ultrasound methods. Importantly the effect of standardizing bifurcation location on CSM variance requires elucidation.

A 1.3.5 References

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A.1.4 Toward A Method for Ultrasound Guided Carotid Sinus Massage: An Image Processing Algorithm for Automated Carotid Bifurcation Location

A.1.4.1 Introduction

Carotid Sinus Massage (CSM) is a clinical method used to diagnose Carotid Sinus Syndrome (CSS). During CSM firm longitudinal massage is performed at the point of maximal pulsation located between the thyroid cartilage and the angle of the mandible. This point is thought to be an accurate anatomical landmark of the carotid sinus and bifurcation.

Recently work in our group (Finucane et al, 2009) has shown the error of this subjectively determined anatomical landmark to be as large as 50% in certain individuals characterised by a difficult to palpate carotid pulse. In these cases a technological intervention maybe advocated to improve accuracy of CS determination and ultimately CSM reliability.

Here we present an advanced image processing algorithm based on the analysis of high resolution B-mode ultrasound images which is capable of providing a standardized location to a clinician as to the location of the CS prior to CSM.

Section 2 describes the technical details of the approach taken. Section 3 presents initial results of the method. Section 4 finishes with a discussion of the advantages and disadvantages of this approach describing some design improvements recommended for future work.

A.1.4.2 Methods

A.1.4.2.1 Image Acquisition

A high resolution Phillips Ultrasound System was used to record images of the right common carotid (CCA), the right carotid bifurcation and right internal and external carotid arteries with a 7.5 MHz linear array transducer. Each subject was placed in a supine position with the head rotated 45° to the left and the jugular and carotid were located in the transverse view according to a modified protocol described by Beach et al. (Beach et al., 2009) . For each individual the depth of field, gain, monitor intensity setting and all other initial instrumentation settings used at baseline were maintained for all follow-up examinations. A frame digitizer was used to sample ultrasound images at 30Hz. A total for 300 frames were analyzed per individual.

1.4.2.2 Transverse Ultrasound Characteristics of the Carotid Bifurcation

Anatomically it is obvious that at the bifurcation the CCA splits into two daughter vessels (Figure A.4).

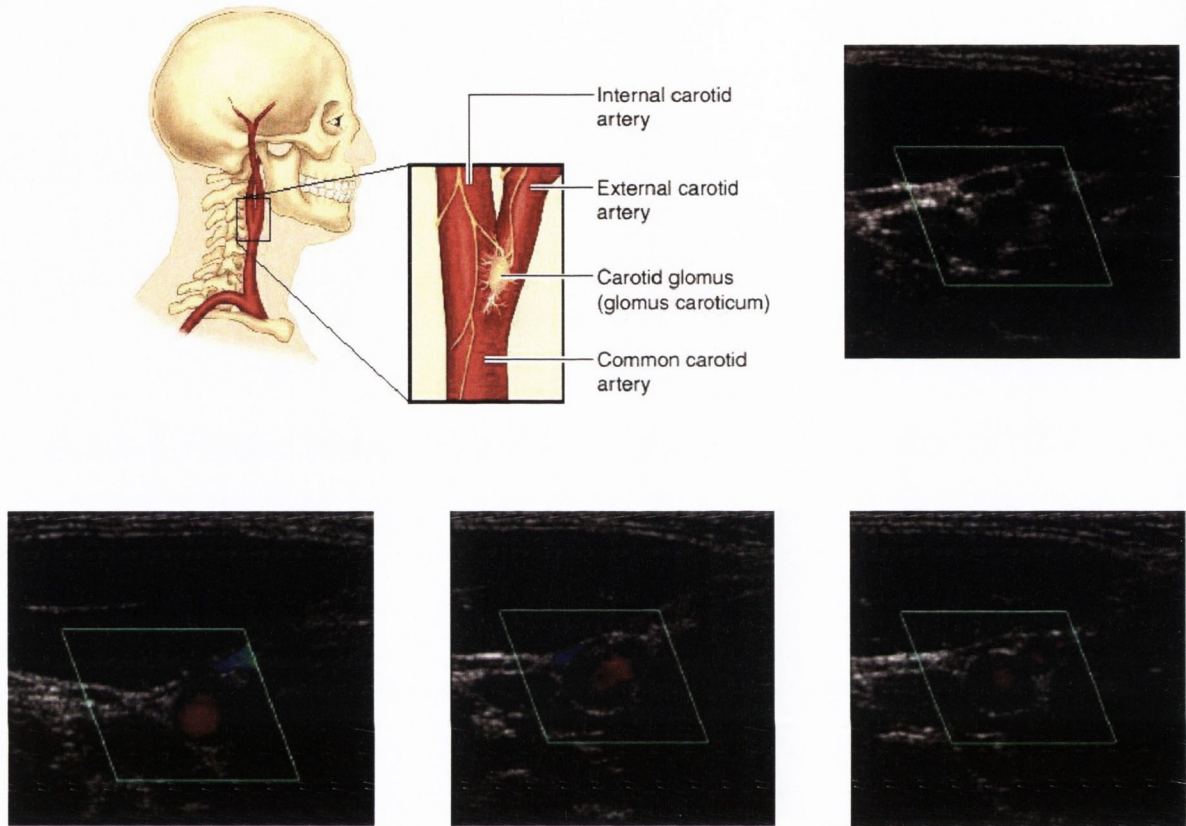


Figure A.4: Carotid Bifurcation Anatomy and Transverse Ultrasound Sections

Using transverse ultrasound imaging this transition is clearly visible, and is characterised by the point where a single cluster of ultrasound pixels approximately 1cm in diameter divides into two smaller clusters measuring almost 0.5cm in diameter each.

Our image processing problem statement can be expressed as follows:

To Identify the ultrasound image at which a single cluster of pixels splits into two distinct pixel clusters.

A.1.4.2.3 Image Processing Steps

To automate this process a number of advanced image processing steps were taken (Figure A.2).

A.1.4.2.4 Preprocessing

Initially the image was pre-processed using HSV filtering to remove Doppler colour information. The filtered red pixels were retained for a later step to identify an approximate centroid of the vessel.

A.1.4.2.5 Edge Extraction

The colour filtered image was transformed from RGB colour space to gray scale image, and horizontal and vertical Sobel filter applied (Sobel, I. and Feldman, G, 1973). Edges were automatically extracted from the first frame using a threshold based edge search algorithm. These initial edges were used as initialization parameters for rapid edge extraction from subsequent frames, which was achieved using a modified simplified snake algorithm.

A.1.4.2.6 Ellipse Fitting

The edge point cloud extracted was parameterized using an efficient direct solution to the least mean squares ellipse fitting method recently proposed by Courtney and de Paor (2004). This step gives ellipse 1 (E1). The original point cloud was further subdivided into two sets of points based on their location relative to the minor axis of this primary ellipse. These two secondary point clouds were fit again using the method described by Courtney and de Paor (2004) to give ellipse 2 (E2) and ellipse 3 (E3).

A.1.4.2.7 Feature Extraction

The following parameters were extracted using the parameterised ellipses from Section 2.2.3

- Mean squared error (MSE) between all points and E1
- Area of overlap (AOO) between E2 and E3.

Note the MSE was calculated efficiently using a matrix expression for least mean squares statement. The area of overlap was determined by numerical integration.

A.1.4.2.8 Hard Threshold Based Decision

Empirical thresholds were determined and applied to the extracted features to determine the location of the bifurcation.

A.1.4.3 Results

A.1.4.3.1 Image Processing Steps

The results from each of the major signal processing steps are depicted in Figure A.2.

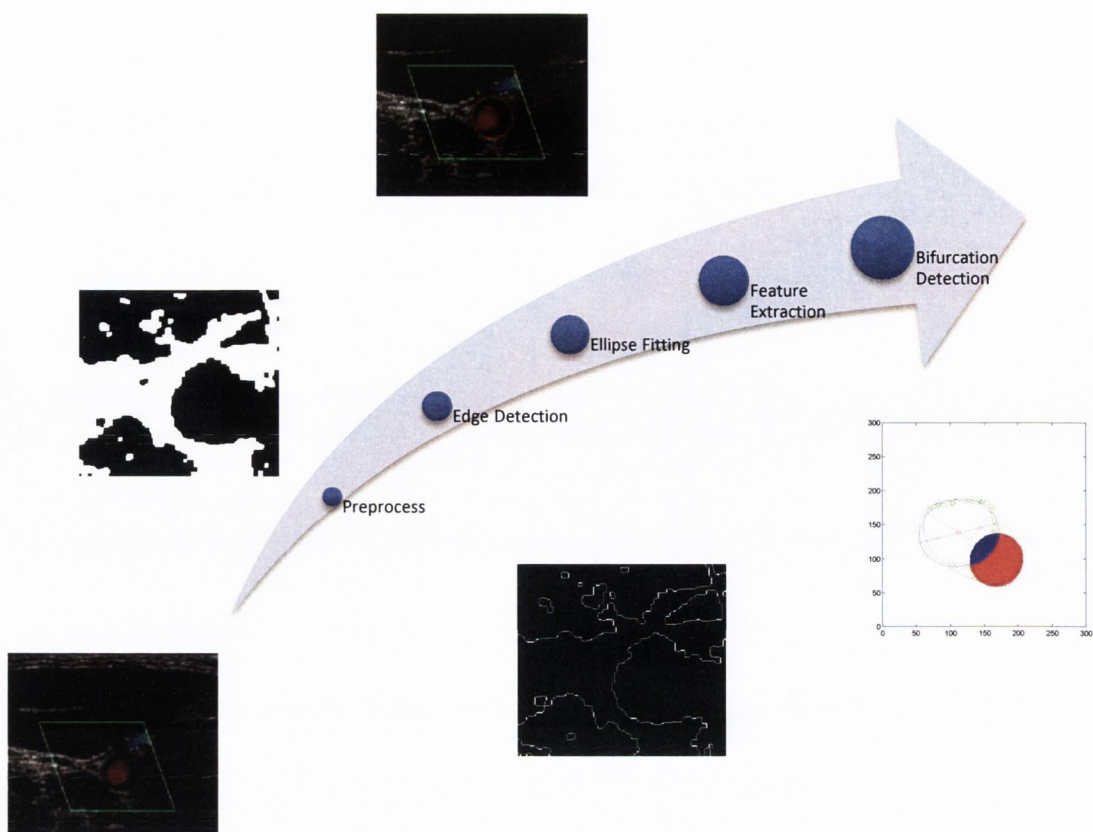
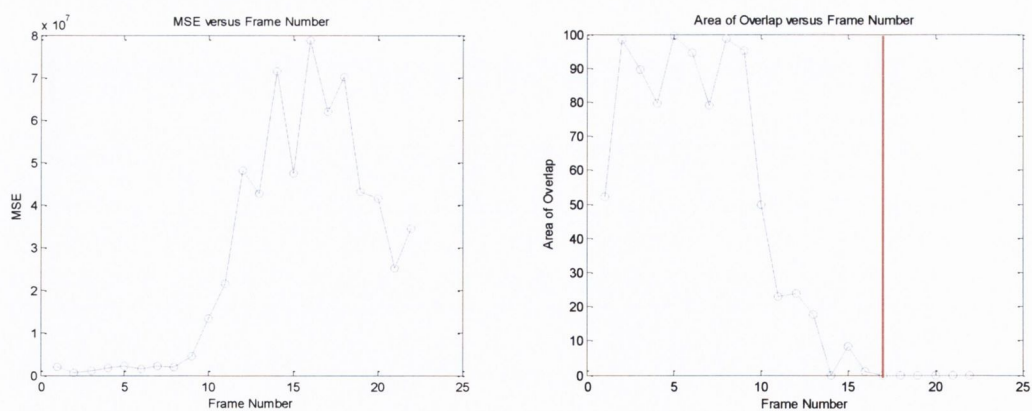


Figure A.5: Image Processing Pipeline Flowchart and Sample Results

A.1.4.3.2 Features versus Frame Number

Extracted features (AOO and MSE) were plotted versus frame number (See Figure A.3).



MSE is initialised used to detect the onset of bifurcation as the carotid diverges from elliptical shape. AOO decreases steadily to zero when bifurcation has occurred, however as is evident there is some evidence of false detection at the 14th data point instead of the decision threshold of 17.

A.1.4.4 Discussion & Conclusion

In this study, a system for detecting the location of the carotid bifurcation was developed. The features extracted i.e. MSE and AOO proved to be promising candidates for automated bifurcation detection. Initial tests of the system demonstrated that it successfully identified ultrasound image features coinciding with the location of the carotid bifurcation. Some refinement of the algorithm around the threshold is required to avoid noise related triggering of bifurcation detection.

The significance of this study is that a technical framework for blood vessel bifurcation location has been described. By combining advanced PC based image processing methods with commonly available ultrasound imaging systems, a practical solution for the detection of carotid bifurcation is made possible. Although this system is only suitable currently for high end ultrasound machines, the wider availability of lower cost portable bedside ultrasounds will make this a sustainable solution in future clinical practice. Furthermore this approach allows carotid screening in tandem to improve CSM safety. Future work should be aimed at determining the robustness of this method in a large patient population and the effect of this intervention on CSM outcome reliability. Further refinements in algorithm are also warranted to improve real-time performance. Since the bifurcation or splitting of objects occurs regularly in nature i.e. cell splitting, object coalescing we hope that this approach may have application in a wide range of scientific fields.

A.1.4.5 References

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