

**ANALYSIS OF
DOPPLER WAVEFORMS FROM
THE CEREBRAL CIRCULATION**

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Dedicated with love to my parents

Walter and Mary

and

to my husband, Rupert

Abstract

Doppler ultrasound is currently used in nearly every medical discipline for the evaluation of blood flow. The cerebral circulation is of particular interest; but is one of the most difficult areas for Doppler ultrasound assessment due to the limitations of the cranium, and the complex haemodynamics of the brain's blood flow. However, further development of the technique of Transcranial Doppler ultrasound (TCD) could have important clinical and cost-saving benefits.

This thesis described the development and testing of a novel method for acquiring and analysing TCD blood flow velocity waveforms, in conjunction with other physiological data. Custom-designed waveform analysis software allowed for a range of waveform shape parameters and indices (in addition to those in current use) to be measured. This software may facilitate the tracking of changes in the cerebral circulation over time, during physiological or pharmaceutical interventions, or between subjects. Data can be reviewed in numerical format, 2-D (waveform shape), or 3-D rendering.

We performed a repeatability and reproducibility study for all waveform shape parameters and indices in five subjects during vasoreactivity testing. Our results showed the mean ranked score of all parameters for each testing segment is: Baseline 4.60, Hypercapnia 4.34, and Hypocapnia 4.00; showing Baseline measurements were more easily reproduced than measurements during an intervention, particularly Hypocapnia. Individual parameters with the best reproducibility over all three testing segments were: RI (Resistance Index) 19.02; Mean Resistance (*mean blood pressure/ mean velocity*) 10.64; Umin (end-diastolic velocity) 9.84; Umaxdias (velocity rise immediately after aortic valve closure) 9.83; DuDtdmax (systolic acceleration) 8.54. We discussed why some

parameters were more reliable than others in TCD studies, and how the cyclical variations in the cerebral circulation affected reproducibility.

In addition, we established a set of 'normal values' for waveform shape parameters and indices obtained from a group of 35 healthy subjects (17 males/18 females), mean age 35.8 ± 11.3 (range 22-63 years). Doppler waveform shape changes are evaluated during vasoreactivity testing using 6% CO₂ and during controlled hyperventilation.

Our study showed that Doppler waveforms were encoded with physiological information, and that each individual has a distinctive cerebral waveform shape, or 'cerebral print'. During changes in cerebral resistance (vasoreactivity testing), these 'cerebral prints' underwent measurable and reproducible shape changes which are indicative of cerebral vasodilatation or vasoconstriction. Ddttmin1 (first deceleration after peak velocity) was identified as an indicator of downstream cerebral resistance. A reduction of this parameter has been linked with a drop in resistance, whereas a rise in the value has been associated with increased distal resistance. Identification of key changes in the cerebral waveform shape may prove useful to the clinician in the assessment of patients with head injury or stroke

This thesis also explored the relationship between Doppler mean blood flow velocity and cerebral resistance changes during vasoreactivity testing. Mean Resistance Index (*mean arterial blood pressure/mean flow velocity*) was used as a surrogate for tracking changes in CVR (cerebrovascular resistance). Our results showed that for the group overall, Hypercapnia produced a 39.3% +/- 19.9 increase in mean flow velocity, however this resulted in only a 21.9% +/- 9.9 decrease in Mean Resistance Index. Whereas during Hypocapnia, a 32.4% +/- 9.3 decrease in velocity produced a much larger increase in Mean Resistance Index (48.9% +/- 22.2). Young women had the greatest capacity to

vasodilate, showing a $26.1\% \pm 9.2$ decrease in Mean Resistance ($46.0\% \pm 14.6$ increase in velocity). However, young men showed the largest change during vasoconstriction; a $59.5\% \pm 31.6$ increase in Mean Resistance ($35.3\% \pm 9.5$ decrease in velocity). This study showed that velocity changes are **not** directly proportional to changes in resistance (Mean Resistance Index). Calculation of Mean Resistance Index is a more clinically relevant measurement to report in VMR (vasomotor reserve) studies than velocity alone, and we believe it should be incorporated into TCD studies in the future. However, it is important to note that our work was based on the assumption that it is the small arterioles which are largely responsible for regulation of cerebral resistance changes, and that the middle cerebral artery does not change in diameter during the moment to moment regulation of cerebral blood flow.

The final concept we introduced was 'Cerebrovascular set-point theory'. This theory simply stated that every individual has a 'set-point' or resting level of tone in the cerebral resistance vessels. This 'set-point' is on a scale between maximal vasodilatation and maximal vasoconstriction, but *within the zone of normal autoregulation*. We assumed at the beginning of our work, that if there were a 'set-point', it would likely be in the middle between the two extremes (a maximal vasodilatation and maximal vasoconstriction). Our data has suggested that the resting level (arteriolar dilatation) of cerebral resistance vessels at Baseline, **do not** reside in the centre of the physiological VMR range for our subjects. In fact, the arterioles are normally in a state of vasodilatation, therefore their capacity to *further* vasodilate is somewhat restricted. However, this theory did suggest that the cerebral circulation has a larger capacity to vasoconstrict (than dilate), from its normal resting state. We speculated that this is because rapid rises in blood pressure and heart rate (forcing cerebral vasoconstriction) are more likely to occur in everyday life, than sudden falls in blood pressure (requiring vasodilatation). We do not fully

understand how the ‘set-point’ is determined by the cerebral circulation or what may force it to change (perhaps chronic hypertension, or arterial obstruction).

This thesis has built on the technical, practical, and theoretical foundations of Doppler ultrasound for the cerebral circulation, and has demonstrated how innovative, yet inexpensive techniques have the potential to provide a diverse range of clinically useful information.

Conference presentations

Meeting for Vascular Technology of Great Britain and Ireland 12th Annual Meeting, November 24, 2004, Leeds, UK, "Analysis of Doppler Waveforms of the Cerebral Circulation" J. M. Boyd, A. Hughes, J. A. Thomas, K. H. Parker

16th Meeting of the European Society of Neuroimaging and Cerebral Hemodynamics, May 14-16, 2006, Düsseldorf, Germany, "A New Method of Transcranial Doppler Waveform Analysis" J. M. Boyd, A. Hughes, J. A. Thomas, K. H. Parker (abstract in *Cerebrovascular Disease*, 2006 Volume 21, Supp. 3)

Cerebral Blood Flow and Brain Metabolism Imaging in Clinical Practice 2nd International Meeting, July 11-16, 2005, Cambridge, UK, "Are Doppler Waveform Features Indicators of Cerebrovascular Flow?" J. M. Boyd, A. Hughes, J. A. Thomas, K. H. Parker (abstract in *British Journal of Neurology*)

Meeting for Vascular Ultrasound 35th Anniversary Congress, June 7-9, 2007, Baltimore, Maryland, "New Transcranial Doppler (TCD) Waveform Shape Parameters: A Feasibility/Reproducibility Study" K. Boyd-Rapson, A. Hughes, J. A. Thomas, K. H. Parker (abstract in *Abstracts submitted for Vascular Ultrasound*)

Declaration of originality

The material presented in this thesis is the original work of the author, and has not been submitted for a higher degree at any other institution. The conference presentations and journal publications are derived from the research contained in this thesis. (N.b. all conference presentations and publications are cited under S. M. Byrd, maiden name, for continuity with other published material.)

Conference presentations

Society for Vascular Technology of Great Britain and Ireland 13th Annual Meeting, November 24, 2004, Leeds, UK, "Analysis of Doppler Waveforms of the Cerebral Circulation" S. M. Byrd, A Hughes, S. A. Thom, K. H. Parker.

The 11th Meeting of the European Society of Neurosonology and Cerebral Haemodynamics, May 14-16, 2006, Dusseldorf, Germany, "A New Method of Transcranial Doppler Waveform Analysis"(poster presentation) S. M. Byrd, A. Hughes, S. A. Thom, K. H. Parker (abstract in: Cerebrovascular Diseases 2006 Volume 21, Sup. 3).

Cerebral Blood Flow and Brain Metabolic Imaging in Clinical Practise 8th International Meeting, July 11-14, 2006, Cambridge, UK., "Are Doppler Waveform Contours Indicators of Cerebrovascular Tone?" S. M. Byrd, A. Hughes, S. A. Thom, K. H. Parker (abstract in British Journal of Neurosurgery).

Society for Vascular Ultrasound 30th Anniversary Conference, June 7-9th, 2007, Baltimore, Maryland, "New Transcranial Doppler (TCD) Waveform Shape Parameters- A Repeatability/ Reproducibility Study", S. Byrd-Raynor, A. Hughes, S. A. Thom, K. H. Parker (Manuscript submitted- Journal for Vascular Ultrasound).

Society for Vascular Ultrasound 30th Anniversary Conference, June 7-9th, 2007, Baltimore, Maryland, "The Relationship Between Velocity And Cerebral Resistance During Vasomotor Reactivity Testing. Should We Report A Different Measurement?", S. Byrd-Raynor, J. Alastruey, A. Hughes, S. A. Thom, K. H. Parker (Manuscript submitted- Journal for Vascular Ultrasound).

Winner of the Dr. DE Strandness Award [2007] for scientific research in vascular technology.

The following aspects of the thesis are considered to be original contributions:

Technical

- Development of Doppler waveform shape analysis software for the cerebral circulation that presents the data in numerical format, as well as a visual representation in 2-D or 3-D.
- Analysis software includes a waveform shape comparison tool to allow for tracking of changes over time; during physiological or pharmaceutical interventions; or between subjects.
- Software will analyse both antegrade and retrograde flow in the cerebral circulation, therefore both the anterior and posterior circulations can be assessed.
- Software will measure 12 additional waveform shape parameters and 4 indices (to those provided by commercial equipment), from a single ensemble-averaged Doppler waveform; potentially giving additional information about the cerebral circulation.

Practical

- Results of repeatability and reproducibility of waveform shape parameters provided.
- Establishment of 'normal values' for parameters and indices.
- Establishment of parameter values, and indices during vasoreactivity testing.

Theoretical

- The relationship between Doppler blood flow velocity, VMR, and cerebral resistance changes during vasoreactivity testing.
- DuD_{tmin1} as a potential indicator of cerebral resistance changes.
- Cerebrovascular set-point theory.

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Contents

Chapter 1

Introduction

- 1.1 Historical perspective**
- 1.2 Blood flow in arteries**
- 1.3 Anatomy of the cerebral circulation**
- 1.4 Cerebral blood flow (CBF) techniques including TCD**
 - 1.4.1 Cerebral autoregulation
 - 1.4.2 Carbon dioxide reactivity
- 1.5 Doppler waveform analysis**
- 1.6 Aims of the thesis**

Chapter 2

A system for acquiring and analysing cerebral Doppler velocity waveform shapes

- 2.1 System architecture - hardware**
 - 2.1.1 Personal computer
 - 2.1.2 Transcranial Doppler
 - 2.1.3 External hard drive
 - 2.1.4 Splitter/Connector block
 - 2.1.5 Auxiliary equipment - ECG monitor
 - 2.1.6 Auxiliary equipment - End-tidal CO₂ monitor
 - 2.1.7 Auxiliary equipment - Phonocardiograph

- 2.1.8 Auxiliary equipment - Oxygen saturation monitor
- 2.1.9 Auxiliary equipment - Blood pressure device
- 2.1.10 System operation and synchronisation
- 2.2 System architecture- analysis software design**
 - 2.2.1 Filtering/smoothing
 - 2.2.2 Waveform ensemble-averaging
 - 2.2.3 Using the contour analysis software
 - 2.2.4 Waveform indices
 - 2.2.5 Waveform comparison software
- 2.3 System summary**

Chapter 3

Methods, repeatability and reproducibility

- 3.1 Overview**
 - 3.1.1 History
 - 3.1.2 Accuracy
 - 3.1.3 Repeatability
 - 3.1.4 Reproducibility
- 3.2 Methods**
 - 3.2.1 Equipment set-up
- 3.3 Repeatability study (short timeframe)**
 - 3.3.1 Operator and velocity repeatability results
 - 3.3.2 Special considerations
 - 3.3.3 Waveform shape repeatability results
- 3.4 Reproducibility study (long timeframe)**
 - 3.4.1 Baseline

- 3.4.2 Summary
- 3.5 Cerebral vasomotor reactivity testing**
 - 3.5.1 Overview
 - 3.5.2 Methods and techniques
- 3.6 Vasoreactivity reproducibility study results**
 - 3.6.1 Hypercapnia
 - 3.6.2 Hypocapnia
- 3.7 Summary**
 - 3.7.1 Ranking and discussion
 - 3.7.2 Waveform shape changes during vasomotor reactivity testing
 - 3.7.3 Synopsis

Chapter 4

Results

- 4.1 Introduction**
 - 4.1.1 Subjects
 - 4.1.2 Methods
- 4.2 Results -parameter measurements**
 - 4.2.1 Relationship with age
- 4.3 Doppler waveform shape results**
- 4.4 Derived results**
 - 4.4.1 % Change from Baseline per mmCO₂
 - 4.4.2 Velocity and resistance
 - 4.4.3 Non-dimensional parameter results

Chapter 5

Discussion and conclusions

5.1 Overview

5.2 Discussion of results from Chapter 4

5.3 Conclusions

5.3.1 The language of Doppler waveform shape

5.3.2 Cerebral blood flow velocity and blood volume flow

5.3.3 Mean resistance index

5.3.4 Cerebrovascular set-point theory

5.4 Summary

List of figures

(Please note: the figures, followed by the tables, are organised at the back of each chapter)

Chapter 1

- 1.1 Schematic of human physiology according to Galen of Pergamus (130-201 A.D.)
- 1.2 A portion of engraving by Sir Christopher Wren of ‘fourfold chariot of the Arteries’ in *Cerebri Anatome*
- 1.3 Lumped-parameter diagram model of the arterial system, and Windkessel model diagram
- 1.4 Diagram of internal diameter, wall thickness, and relative amount of principal components of arterial vessel walls
- 1.5 Schematic of the pressure drop across the vascular system
- 1.6 Depiction of the cerebral anatomy of the brain
- 1.7 Doppler velocity waveforms from various arteries, from the heart to the brain

Chapter 2

- 2.1 Hardware architecture of the acquisition system
- 2.2 PMD 100 transcranial Doppler machine
- 2.3 Original painting of cranium and cerebral vessels
- 2.4 MARC 600 head fixation device
- 2.5 TCD peak velocity envelope depiction
- 2.6 ECG monitor and extracted trace
- 2.7 End-tidal CO₂ monitor and extracted trace
- 2.8 TCD velocity and phonocardiogram trace

- 2.9 Photograph of system hardware components
- 2.10 Savitzky-Golay smoothing filters
- 2.11 Over-smoothed Doppler waveform
- 2.12 Ensemble-averaging by various methods
- 2.13 Results display examples
- 2.14 Cardiac cycle selection
- 2.15 Extracted and synchronised signal traces
- 2.16 Common TCD waveform representations
- 2.17 Peak velocity envelope and standard deviation
- 2.18 Velocity minima example
- 2.19 Velocity maxima example
- 2.20 Flow waves, pressure waves, and velocity wave shape
- 2.21 Variations in U_{max1}
- 2.22 Velocity acceleration/deceleration
- 2.23 Cerebral angiogram of left anterior circulation
- 2.24 Depiction of τ measurement
- 2.25 Cerebral systole and diastole
- 2.26 Rise time and U_{pulse} examples
- 2.27 Measurements of time
- 2.28 Numerical display of ensemble-averaged data
- 2.29 3-D graphical display of selected cardiac cycles
- 2.30 Visual representation new indices
- 2.31 Waveform comparisons examples
- 2.32 Waveform comparisons with/without rescaling (vasoreactivity testing)
- 2.33 Waveform comparison with/without rescaling (different ages of subjects)

Chapter 3

- 3.1 Ultrasound transducer on left temporal window of a subject and anatomical diagram of the cerebral vessels
- 3.2 Comparisons of right and left MCA ensemble-averaged waveforms in four subjects
- 3.3 Arterial anatomy from the heart to the brain, and the MCA during microsurgery
- 3.4 Dependence of Doppler measured velocity on Doppler angle, as compared with MCA anatomy
- 3.5 Optimal Doppler spectrogram and sample volume placement for the study
- 3.6 Mean velocity variations over 16 seconds
- 3.7 Peak velocity variations over 16 seconds
- 3.8 End-diastolic velocity variations over 16 seconds
- 3.9 Comparison of 6 tests, of 5-minute velocity recordings
- 3.10 Individual velocity variations 16 seconds-15 minutes
- 3.11 Fast Fourier transform showing B waves, M waves and respiratory waves
- 3.12 Doppler waveform shape repeatability (Subject A)
- 3.13 Doppler waveform shape repeatability (Subject B)
- 3.14 BASELINE - waveform parameter reproducibility
- 3.15 BASELINE - waveform shape reproducibility
- 3.16 CBF relationship with PaCO_2 ; subject during Hypercapnia using a Rudolph valve for gas delivery
- 3.17 Blood pressure changes during maximal hyperventilation
- 3.18 Maximal versus controlled hyperventilation

- 3.19 HYPERCAPNIA - waveform parameter reproducibility
- 3.20 HYPERCAPNIA - waveform shape reproducibility
- 3.21 HYPOCAPNIA - waveform parameter reproducibility
- 3.22 HYPOCAPNIA - waveform shape reproducibility
- 3.23 Graphical comparison of reproducibility (ranked) scores, and scores by distribution

Chapter 4

- 4.1 Doppler waveform shape changes during vasoreactivity testing - male subjects
- 4.2 Doppler waveform shape changes during vasoreactivity testing - female subjects
- 4.3 Pressure, flow and resistance schematic
- 4.4 Physiological testing range during vasoreactivity - all subjects
- 4.5 Physiological testing range during vasoreactivity - by test
- 4.6 Physiological testing range during vasoreactivity - by gender
- 4.7 Physiological testing range during vasoreactivity - by test and gender
- 4.8 Sample plots of non-dimensional data

Chapter 5

- 5.1 3-D representation of Shape Index 1
- 5.2 3-D representation of Shape Index 2
- 5.3 3-D representation of Velocity Rise Index
- 5.4 Doppler waveform shapes changes between two Baseline tests in a young female subject
- 5.5 Graphical depiction of cerebrovascular set-point theory

- 5.6 Physiological testing range and cerebrovascular set-point
- 5.7 Cerebrovascular set-points from study groups and individuals

List of tables

(Please note: the figures, followed by the tables, are organised at the back of each chapter)

Chapter 1

Not applicable

Chapter 2

- 2.1 A description of each parameter in the output file

Chapter 3

- 3.1 Summary of 5 minutes of peak velocity data on 3 subjects
- 3.2 Summary of 16 seconds of peak velocity data on 3 subjects
- 3.3 TCD repeatability study comparison
- 3.4 Summary of waves which produce variation in cerebral blood flow velocity
- 3.5 TCD reproducibility study comparisons
- 3.6 Reproducibility (ranked) scores by parameter

Chapter 4

- 4.1 Parameter results during vasoreactivity testing - Traditional TCD Parameters
- 4.2 Parameter results during vasoreactivity testing - Velocity Minima
- 4.3 Parameter results during vasoreactivity testing - Velocity Maxima
- 4.4 Parameter results during vasoreactivity testing - Acceleration/Deceleration
- 4.5 Parameter results during vasoreactivity testing - Miscellaneous

- 4.6 Parameter results during vasoreactivity testing - Time
Measurements
- 4.7 Parameter results during vasoreactivity testing - Indices
- 4.8 Pearson correlation coefficients for age
- 4.9 % change from BASELINE per mmCO₂ results - Traditional
TCD Parameters
- 4.10 % change from BASELINE per mmCO₂ results - Velocity
Minima
- 4.11 % change from BASELINE per mmCO₂ results - Velocity
Maxima
- 4.12 % change from BASELINE per mmCO₂ results -
Acceleration/Deceleration
- 4.13 % change from BASELINE per mmCO₂ results - Miscellaneous
- 4.14 % change from BASELINE per mmCO₂ results - Time
Measurements
- 4.15 % change from BASELINE per mmCO₂ results - Indices
- 4.16 Relationship of mean velocity to mean resistance index during
HYPERCAPNIA
- 4.17 Relationship of mean velocity to mean resistance index during
HYPOCAPNIA
- 4.18 Relationship of mean velocity to mean resistance index -
Vasomotor Reserve
- 4.19 Comparison of in-vivo data and computer model simulations -
subject #98
- 4.20 Comparison of in-vivo data and computer model simulations -
subject #73
- 4.21 Non-dimensional data- means $\pm$ SD by parameter

- 4.22 Summary table of absolute mean differences
- 4.23 Results of Pearson correlation and ANOVA - Hypercapnia
- 4.24 Results of Pearson correlation and ANOVA – Hypocapnia

Chapter 5

- 5.1 Comparison of percentage change per mmCO₂ in CBF, and new Doppler waveform parameters

List of abbreviations

ACA	Anterior cerebral artery
ANOVA	Analysis of variance
ASL	Arterial spin labelling
AU	Arbitrary unit
CBF	Cerebral blood flow
CBFV	Cerebral blood flow velocity
CBV	Cerebral blood flow volume
CO ₂	Carbon dioxide
CPP	Cerebral perfusion pressure
CSF	Cerebral spinal fluid
CT	Computed tomography
CV	Coefficient of variation
DSC	MRI dynamic susceptibility contrast
DuDtmax	Maximum acceleration
DuDtmin1	Deceleration 1
DuDtmin2	Deceleration 2
ECG	Electrocardiogram
ET CO ₂	End-tidal CO ₂
ICA	Internal carotid artery
ICP	Intracranial pressure
MATLAB	Matrix Laboratory programmable software
MCA	Middle cerebral artery
mSv	Millisievert
Nbeats	Number of cardiac cycles

P	Pressure
PC	Personal computer
PCA	Posterior cerebral artery
PCT	Dynamic perfusion computed tomography
PET	Positive emission tomography
rCBF	Regional cerebral blood flow
rCMRO2	Regional glucose metabolism
rOEF	Regional oxygen extraction fraction
SPECT	Single photon emission computed tomography
StdDeviat	Standard deviation (also SD)
Tau	Time constant (τ)
TCD	Transcranial Doppler
Tmin	Time from peak of the R wave to systolic upstroke
Tmin2	Time from peak of the R wave to aortic valve closure
Trise	Rise time
U	Velocity
Umax dias	Maximum velocity diastole
Umax	Maximum velocity
Umax1	Maximum velocity 1
Umean	Mean velocity
Umin	Minimum velocity
Umin1	Minimum velocity 1
Umin2	Minimum velocity 2
Upulse	Velocity pulse
VEL	Velocity
VMR	Vasomotor reserve
XeCT	Xenon-enhanced computed tomography

*"The Doppler waveform never lies. It's our inability to understand
its language that is the problem."*

Dr. Merrill P. Spencer, 1988
Institute of Applied Physiology and Medicine
Seattle, Washington

Chapter 1

Introduction

This Chapter introduces a fascinating and complex subject, the cerebral circulation. It provides the background and basic concepts of cerebral blood flow, necessary for understanding this thesis. We begin with a historical perspective on the understanding of cerebral vessels and blood flow. We examine the physiology of blood flow in arteries. The arterial anatomy of the brain is briefly described. We review the present day techniques for measurement of cerebral blood flow, including the Transcranial Doppler (TCD), the method used in this study. We also look back at previous methods of waveform analysis and the difficulties encountered in describing and measuring Doppler waveforms. We conclude with an outline of the aims of this thesis. (Subsequent chapters will contain additional background material where required to provide a context to the specific ideas being presented.)

Note: Figures and Tables are found at the end of each Chapter in this thesis.

1.1 Historical perspective

Before the experimental studies of blood circulation by English physicians William Harvey (1578-1657) and Thomas Willis (1621-1675), the existing dogma was that all matter was composed of the four Aristotelian elements: hot and dry (*fire*); hot and moist (*air*); cold and moist (*water*); and cold and dry (*earth*). Explanations of human physiology were based on the concepts of Galen of Pergamus (130-201 A.D.) who believed the veins and arteries were separate and unconnected and that three essential 'spirits' carried by them, served as the bases of bodily functions. Figure 1.1 shows a schematic of Galen's ideas. According to his concepts, nutrients were absorbed as 'chyle' by the intestinal veins, and then refined in the liver into *natural spirits*. They were then distributed outward through the veins to nourish the body. Some venous blood was cleansed by the passage through the lungs and some seeped through the cardiac septum to be converted into *vital spirits*. The arteries distributed the *vital spirits* to generate heat and life in the body. A small portion of the blood was delivered to the brain where it was refined into *animal spirits* (from the Latin '*anima*' meaning soul or psyche). Hollow tubes in the nerves received the animal spirits, and this produced muscle contraction and motion by inflating and then flattening the muscles [Tower, 1991]. Galen also palpated the pulse and classified different pulses in terms of strength, rate, and rhythm.

William Harvey studied cardiac function and blood circulation in experimental animals and in human subjects. He was studying medicine at the University of Padua (1628) at the same time Galileo Galilei (1564-1642) was a Professor of Mathematics there.

Although Galileo is not mentioned in his work, it is believed that Harvey may have been influenced by the new quantitative teaching and reasoning that took place at the time.

He showed that the heart behaved like a muscle, and during contraction pumped blood into the arteries. Harvey was interested in the magnitude of such flow. He also noted that the blood *circulated*, and returned through the veins. He determined this by doing a simple calculation. If the human heart had a 2-ounce blood capacity and was beating 72 times a minute, the hourly output would exceed 500 pounds.

Where was all of the blood going, and where did it come from? The solution, of course, was that the body was re-using it. Although Harvey lacked a microscope to visualize the ‘connections’ between arteries and veins, he did not doubt their existence. When Harvey published these observations in 1628 in his *De Motu cordis et sanguinis* [Harvey, 1628] it dispelled the concepts of Galen involving *spirits* and made possible physiological experiments. Like many of his time, Harvey was competent in more than one field of endeavour. He was an anatomist, physiologist and eventually a personal physician to King Charles I.

It was the Oxford and London physician Thomas Willis, who along with colleagues such as Richard Lower (1631-1691) and Sir Christopher Wren (1632-1723), published *Cerebri Anatome* [Willis 1664], which was one of the first studies of the anatomy of the brain and the nerves of the cerebrum. Willis and his assistant Richard Lower examined a wide variety of animal species including man. The prominent architect, mathematician, and astronomer Sir Christopher Wren was responsible for the engraved plates from which the illustrations in Willis’ *The Anatomy of the Brain and Nerves* are derived. He also showed Willis a method for injecting agents directly into the blood stream of experimental animals using quills. Willis later exploited this idea, and used ink to delineate the cerebral vessels. One of Wren’s drawings, the ‘fourfold Chariot of the Arteries’ (Figure 1.2), showing the conjoining of the two carotid and two vertebral arteries would later be called the ‘circle of Willis’ by Albrecht von Haller (1708-1777).

Thomas Willis correlated his bedside observations with anatomical fact. He concluded that a patient could have occluded cerebral vessels, and yet be symptom-free because of blood flow through collateral vessels. Willis was fully aware of both the anatomy and the physiological importance of the circle of arteries at the base of the brain; however he was not the first to describe it. Gabrielle Fallopio (1523-1562) and Guilio Casserio (in 1627) also described or illustrated these arteries. Jahann Jakob Wepfer was the first to publish a description (but not an illustration) in his book *Apoplexy* of 1658.

and anatomy of the 17th century. It was Richard Lower (1675-1733) who

It was noted by Albrecht von Haller and Dr. Alexander Monro that very considerable quantities of blood are transmitted to the brain from the trunks that arise near the heart. They estimated that at least a tenth of the circulating mass is transmitted to the brain. It was Haller, a Swiss physiologist, along with his Scottish counterpart Robert Whytt (1714-1766), who went on to investigate electrophysiological techniques. Another of their contemporaries (Saunders, 1793) noted that the brain, although small in bulk, was an organ which received a larger quantity of blood than any other part of the body, although its function was not obvious. However, he did infer the idea that body parts must receive blood in proportion to the actions they perform.

It was the great mathematician and physicist, Sir Isaac Newton (1642-1727), who proposed the concept of fluid viscosity, which has now become central to the consideration of blood flow in arteries. The Reverend Stephen Hales (1677-1761) was the first to measure arterial pressure in an animal and to document the effect of blood loss on arterial pressure, when he published his work *Haemastaticks* (1733). He also formulated the concept of peripheral resistance and showed that the greatest resistance to blood flow resides in tiny blood vessels that are invisible to the naked eye. Hales likened the arterial system to the inverted, air-filled dome of a fire engine. This contemporary fire engine smoothed the oscillations of intermittent pumping, so that

flow through the nozzle remained nearly continuous. Hales saw the arterial system acting like a cushion and the arterioles as providing the resistance. When *Haemastaticks* was translated into German, the fire engine compression chamber was referred to as *Windkessel*, and the use of this term to describe the cushioning role of the arterial system has continued to this day.

The advances in understanding also benefited from the work of two other great mathematicians of the eighteenth century. It was Leonhard Euler (1707-1783) who established the general equations of fluid motion; and Daniel Bernoulli (1700-1782) who, among other things, is remembered for his equation linking pressure changes to interconversion of potential and kinetic energy.

During the nineteenth century, J.P Poiseuille (1799-1869) first began his research into cardiovascular physiology as a medical student, although he also had a background in physics. His major contribution was to establish a relationship between flow, the pressure gradient, and the dimensions of a capillary tube. He showed in 1840 that flow rate was related to the fourth power of the tube's internal diameter.

By the time of studies on the human cerebral circulation in the 1930s by William Lennox (1884-1960) and Frederic Gibbs (1903-1992), and by Harold Himwich (1894-1975), it was possible to quantify cerebral blood flow (CBF), and the metabolic rate of the brain for O_2 , CO_2 , and glucose ($CMRO_2$). Seymour Kety and Carl Schmidt in 1948, working at the University of Pennsylvania, made a significant contribution using inhaled nitrous oxide (N_2O) to measure cerebral blood flow. They took advantage of the Fick principle (1870) that the rate at which a diffusible substance (in this case N_2O) passes from blood into tissue, varies with the rate of blood flow through that tissue. Their experiments using hyperventilation, and 5-7% CO_2 inhalation gave quantitative evidence

of intrinsic control of the human cerebral circulation. They found that cerebral blood flow in young healthy men underwent a consistent increase, averaging about 75%, with inhalation of CO₂. There was also a marked reduction in the mean cerebrovascular resistance from 1.6 to 1.1 (mmHg/(ml/100g brain/min.))¹. Interestingly, they also noted peripheral systemic vasoconstriction, which was an effect opposite to the behaviour on the cerebral circulation. With hyperventilation, they found an average 34% decrease in cerebral blood flow, with cerebrovascular resistance increasing from 1.7 to 2.9 (mmHg/(ml/100g brain/min.)) [Kety and Schmidt 1948].

On the basis of studies on cerebral cortical slices by both K.A.C. Elliott (1903-1986) in Montreal and Henry McIlwain (1912-1992) in London, it was estimated that the majority of the oxidative metabolism of the brain is usually devoted to the support of neural conduction and transmission. It is this cellular activity that is reflected in the data from contemporary Kety-Schmidt-type studies on total brain circulation and metabolism.

From these studies it has been established that the brain stores no oxygen and has no significant stores of glycogen. Thus, failure of cerebral blood flow due to vascular occlusion, or anoxia from any other cause, will cause irreversible damage after about 8 minutes. Similar damage will occur after about 90 minutes of severe hypoglycaemia.

For the cerebral circulation, the scientific revolution of the late 20th century has principally related to methods and techniques. The introduction of CT (computerised tomography) scanning has revolutionized clinical neurological practice by providing both anatomical and pathological information on the living human brain, doing away with more invasive techniques such as cerebral angiography. Two other techniques that

¹ We are aware that this formula appears ambiguous. However, this format is often used as standard notation in the literature.

were complementary to CT also proved useful; nuclear magnetic resonance imaging (MRI) and spectroscopy, and positron emission tomography (PET).

It was once believed that the cerebral blood vessels could not dilate and constrict independently and that the cerebral circulation was entirely under the control of the systemic circulation. However, evidence accumulated over the last 100 years indicates that cerebral blood vessels are in a dynamic state. Thus the cerebral vasculature is endowed with complex regulatory systems which allow the brain to finely regulate its own blood supply.

1.2 Blood flow in arteries

Blood is a complex mixture of water, cells, proteins, lipoproteins, and ions in which nutrients and wastes are transported. About 40% of blood volume is made up of red blood cells. These semi-solid particles increase the viscosity of the blood but the viscosity is not constant at all flow rates, especially in the microcirculation. In the branches and capillaries the red blood cells can still squeeze through, and a cell-free skimming layer reduces the effective viscosity through the tube. At very low shear rates, red blood cells can clump together to form larger particles. However, in most arteries blood behaves in a Newtonian fashion and viscosity can be taken as a constant [Ku, 1997].

Blood flow and pressure are variable in time. The cyclic nature of the heart as a pump creates pulsatile conditions in the arteries. The heart ejects blood and then refills in an alternating pattern known as systole and diastole. Therefore, flow out of the heart is intermittent with flow going to zero once the aortic valve closes. The aorta acts as a compliance chamber which provides a high pressure during both systole and diastole.

Thus blood pressure is pulsatile in most arteries, yet does not go to zero during diastole. In contrast, blood flow can go to zero or even become reversed in some arteries such as the external carotid, brachial or femoral arteries. These arteries have a very high downstream resistance, which effectively creates an on/off effect with each cardiac cycle. In contrast, the internal carotid artery and the renal artery have flow that is more uniform because the downstream resistance is lower. Because the flow is variable or pulsatile in the cardiovascular system, the term 'acceleration' is used in many analyses; and the changes in pressure and flow give rise to characteristic pulsatile shapes that vary throughout the arterial system.

The entire cardiovascular system may be simplified using a 'lumped' parameter, or one-dimensional (1D) model of flow. The most well-known is the Windkessel model (Figure 1.3) which has been used to describe the rapid rise and gradual decrease of flow and pressure waveforms [McDonald, 1974]. This model describes the cardiovascular system as a compliant section followed by a resistive section. During systole it is the compliant aorta that acts like a capacitor storing blood, and discharging blood into the branches and smaller vessels during diastole. Pressure and flow waveforms given by this model are fairly close to those measured in the body, although others have produced much more elaborate models [Nichols and O'Rourke, 1990]. The lumped parameter model is useful for understanding the physiology of measured waveforms.

The large arteries such as the aorta, brachiocephalic, common carotid, subclavian and common iliac arteries have many elastic fibres but little smooth muscle in their walls and are therefore termed elastic arteries. They offer little resistance to flow, and mean pressure is only slightly less than the aorta. Their expansion and contraction cushions the sudden increase and decrease in pressure during the cardiac cycle.

Moving outward from the heart and the large elastic vessels, the arteries become smaller and are comprised of more smooth muscle and less elastic fibres. These arteries are called 'muscular arteries'. They offer a more, but still relatively small, resistance to flow. Muscular arteries include the basal cerebral vessels such as the middle cerebral, anterior cerebral, posterior cerebral and basilar arteries, which are central to this thesis. The muscular arteries give rise to even smaller arteries, which exhibit a moderate resistance to flow. It is in the smallest arteries that the resistance is largest. These arterioles can be thought of as the 'stopcocks' of the arterial system. The arterioles have the highest wall to lumen ratio in the vasculature (Figure 1.4). They regulate blood flow to a region through vasoconstriction and vasodilatation, which is often referred to as 'vascular tone'. It is in the arterioles that the pressure drop is most significant (Figure 1.5). Due to this reduction in pressure and damping effect, there is also a change from pulsatile flow to nearly steady flow. Finally, this reduced arterial pressure and steady flow reaches the venous end of the capillary bed [Aaronson and Ward, 1999].

1.3 Anatomy of the cerebral circulation

The brain has a high metabolic rate and is therefore critically dependent on the cerebral circulation. The basal cerebral arteries are conducting vessels of the circulation and are muscular by nature. Unlike the aorta which measures approximately 25mm in diameter, the cerebral vessels range between 2-4mm in diameter. Although the vessels are small and the brain represents less than 2% of the average body weight, it receives approximately 15% of the cardiac output. The brain is intolerant of ischemia because neurons do not maintain significant energy reserves. Interruption of cerebral blood flow results in loss of consciousness in as little as 5 seconds. Therefore, constant cerebral blood flow must be maintained throughout a variety of conditions. Even during circulatory crisis, maintenance of flow to the brain is considered the number one

priority. While the cardiovascular control centres are calling for widespread vasoconstriction, the cerebral regulating vessels are told to dilate.

The cerebral circulation sits within a relatively rigid structure, the cranium. The intracranial contents are incompressible, and therefore any increase in the volume of one component (brain tissue, blood or cerebral spinal fluid) must be associated with a comparable decrease in another. In contrast to many other organs, the cerebral blood flow needs to be kept within a narrow range, which averages approximately 55 ml/100 grams of brain tissue/minute.

Blood flow is delivered to the brain via four main arteries in the neck, two internal carotid arteries and two vertebral arteries. The internal carotid arteries bifurcate to form the middle cerebral and anterior cerebral arteries. These vessels form what is commonly referred to as the anterior circulation. They are responsible for delivering blood flow to the temporal, parietal, and frontal regions of the brain.

The two vertebral arteries in the neck anastomose into the basilar artery after they have entered the foramen magnum. The basilar artery courses towards the level of the anterior circulation vessels, and then divides into the right and left posterior cerebral arteries. This system is referred to as the posterior circulation, and delivers blood to the regions of the brain stem.

The anterior and posterior circulations are linked together by small connecting vessels (anterior and posterior communicating arteries), and this unique structure is termed the 'circle of Willis', as mentioned previously (Figure 1.6). These small connecting vessels create an anastomosis between separate inflow systems to the brain, and ensure back-up blood flow delivery should one or more vessels become diseased. Although the circle

of Willis appears to be a unique and effective system for delivering constant blood flow, less than half of the human population have a complete circle of Willis. Communicating arteries can be atretic or hypoplastic, thus the shunting of blood flow from one artery to another may be ineffective in time of need.

1.4 Cerebral blood flow (CBF) techniques including TCD

Numerous imaging techniques have been developed and applied to evaluate brain haemodynamics, based on the mathematical models developed in the first half of the 20th century [Stewart, 1920] [Hamilton et al., 1940] [Kety and Schmidt, 1948] [Meier and Zierler, 1954]. These include positron emission tomography (PET), single photon emission computed tomography (SPECT), Xenon-enhanced computed tomography (XeCT), dynamic perfusion computed tomography (PCT), MRI dynamic susceptibility contrast (DSC), arterial spin labelling (ASL), and Doppler ultrasound. All of these techniques give similar information in the form of cerebral blood flow (CBF) or cerebral blood volume (CBV) data, but differ in their data acquisition and processing times and whether or not they can be performed at the bedside. They also differ in their quantitative accuracy, brain coverage, and spatial resolution. This section briefly reviews each of the techniques and their advantages and disadvantages.

Positron Emission Tomography (PET)

PET uses tracers for measurement of CBF. For example, H_2^{15}O can be administered intravenously. A 1-2 minute scan is combined with arterial blood sampling measurements (used as an input function), and application of the Kety-Schmidt model leads to quantitative CBF maps [Herscovitch et al., 1983]. C^{15}O_2 is inhaled first for 8-10 minutes and the scan is performed after a steady state is reached. The same approach as

described above is used to calculate CBF maps. Successive inhalation of $^{15}\text{O}_2$, C^{15}O_2 , and C^{15}O over 60 minutes allows for measurement of rCBV (regional cerebral blood flow), rCMRO₂ (regional glucose metabolism), and rOEF which designates the fraction of the oxygen delivered to the brain (approximately 40% is extracted by the brain parenchyma and metabolised) [Frakowiak, 1980]. PET radiopharmaceuticals are cyclotron products and have a very short half-life. Whole body radiation exposure by PET examination is usually 0.5 to 2.0 mSv (millisievert) per scan, although this may differ by institutions and protocols used. The data acquisition time is generally 5-9 minutes, and the data processing time is 5-10 minutes. Interpretation of results can be visually done on the computer screen, although correlation with structural information such as CT or MRI is desirable for accuracy.

The advantage of the PET technique lies in its quantitative accuracy and reproducibility (about 5%). It covers the whole brain, and has a spatial resolution of 4-6mm [Nariai and Borbély, 2005]. The disadvantages include cost and radiation; it cannot be done at the bedside, and is not feasible in emergency settings.

Single Photon Emission CT (SPECT)

SPECT is a technique, which generates tomographic images of the 3D distribution of specific radiopharmaceuticals, and depending on their nature may reflect regional cerebral haemodynamics, dopamine, or other transporter distribution. $^{133}\text{Xenon}$ (^{133}Xe) has historically been the most important substance used for measuring brain haemodynamics, however, this produces abundant scatter and limited spatial resolution [Obrist et al., 1967]. Consequently, retention tracers such as $^{99\text{m}}\text{TC}$ -HMPAO ($^{99\text{m}}\text{TC}$ hexamethylpropylenamine oxime) are more commonly used in clinical SPECT imaging. Using retention tracers, the total scan time is about 10-15 minutes, and spatial resolution is 4-6mm. The rCBF maps from SPECT can be evaluated and compared with the

normal control data to depict regions with abnormal perfusion. Results are fairly reproducible (10%), and the radiation is 3.5-12 mSv. However, the results are not quantitative and the uptake of ^{99m}Tc -HMPAO is not linearly related to CBF and requires special correction [Lassen et al., 1988]. An exception is the ^{133}Xe SPECT technique, which uses a single detector positioned over the right lung to measure an arterial input function and to calculate quantitative CBF values. Perfusion SPECT studies are used to provide information in acute stroke with respect to complications, outcome, and treatment strategy [Nariai and Borbély, 2005]. One advantage of SPECT is that it can be used at the bedside. For instance, the tracer can be administered at the moment of a seizure and the scan can be performed later due to the retention tracer. Disadvantages are that it provides relative and not quantitative measurements and has poor spatial resolution.

Xenon-Enhanced CT (Xe-CT)

Xe-CT has been used for more than 20 years to evaluate quantitative CBF in humans [Drayer et al., 1978]. Xenon is inhaled and serves as the contrast material. The gas dissolves rapidly in the blood and crosses the lipid-rich blood-brain barrier. The concentration of Xenon in the brain is measured directly by the CT scanner, and the concentration in the arterial blood is determined indirectly from the end-tidal Xenon measurement. After acquisition of a baseline scan of the entire head, 4-6 contiguous 10mm thick slices are selected for CBF measurement. Xenon is washed out from the cerebral tissues rapidly (half-life is about 40 seconds). The average radiation dose is 3.5-10 mSv. Numerical data are superimposed on the anatomical image and yields a high-resolution map of quantitative flow data. Spatial resolution is 4mm, and examination length 10-20 minutes with data processing. Although the stability of the flow value in a single voxel is poor (10mm^3), the data re-converted to a map for visual inspection on the regions of interest can be drawn for rCBF quantitative assessment and the

reproducibility is about 12% (>100 voxels). One advantage of XeCT is the high-resolution quantitative flow data that are tightly coupled to cerebral anatomy [Sesay and Yonas, 2005]. In addition, XeCT provides accurate quantitative measurements and can assess multiple brain levels. The disadvantages include nausea and respiratory depression. One difficulty is that Xenon inhalation directly increases CBF by 20-30%, however, all of the flow data is normally acquired before this flow activation takes place (significant after 2.5 minutes of inhalation). There is a relatively long acquisition time (10 minutes), it is prone to motion artifacts, and the Xenon needs to be inhaled via a face mask which adds to patient discomfort.

Dynamic Perfusion Computed Tomography (PCT)

Dynamic PCT is a technique for measuring brain haemodynamics using first-pass tracer methodology after bolus infusion of intravenous iodinated contrast material [Eastwood et al., 2005]. Continuous cine-scanning is performed for approximately 40-45 seconds. The radiation dose involved in dynamic PCT ranges between 1.6-2.0mSv. The data processing time is about 5 minutes, and rather than the whole brain, PCT uses a 4-5cm thickness of brain. Interpretation is performed using either rate-of-upslope estimation of CBF (infusion rates above 6 ml/second), or deconvolution analysis (infusion rates 4-5 second). In areas of low perfusion, only deconvolution analysis leads to quantitatively accurate results [Wintermark et al., 2001]. Images of CBF, CBV and mean transit time are interpreted using visual assessment, and quantitative analysis of regions of interest. Reproducibility is 10-15%. One advantage is that PCT can rapidly detect the size of hypoperfused regions in the setting of acute stroke [Eastwood et al., 2002]. In addition, the equipment is widely available, including in emergency settings. The technique yields multiple perfusion parameters, and it provides accurate quantitative measurements. Disadvantages include the fact that PCT overestimates brain haemodynamics values in pixels, which include large vessels and has limited anatomic coverage. In addition, it

uses ionizing radiation and iodinated contrast media, and it cannot be used at the bedside.

Dynamic Susceptibility-Weighted Bolus-Tracking MRI (DSC)

DSC relies on the measurement of the T2 or T2* reduction during the first pass of an exogenous endovascular tracer through the capillary bed [Grandin, 2003]. The technique requires ultrafast imaging, such as echo planar imaging and the principles of echo shifting or spiral imaging. Chelate of gadolinium is the conventional tracer used. DSC does not expose patients to ionizing radiation, and intolerance to gadolinium chelates is rare. DSC relies on the application of the indicator dilution theory [Meier and Zierler, 1954]. Using commercially available software, various parameters can be calculated from the time-intensity curves measured in each pixel, allowing for reconstruction of parametric maps. Calculated parameters are: time to peak; apparent mean transit time; CBV (calculated from the area under the curve); and CBF index (CBV/apparent mean transit time) [Grandin and Pedraza, 2005]. DSC has good correlation between the CBV and CBF values in comparison with PET or XeCT [Ostergaard et al., 1998]. The advantages of DSC are that it can be combined with other imaging such as fine anatomic imaging, or MRA to provide comprehensive information and it has whole brain coverage. The disadvantages include lack of standardisation in the interpretation, and the usual contraindications for MRI such as claustrophobia. DSC is not a bedside technique.

Arterial Spin Labelling (ASL)

ASL relies on detection of magnetically labelled water. Once the magnetization of the inflowing water has been modified upstream, it induces a small MR (magnetic resonance) signal change downstream. Meanwhile, the magnetization of the perfusion tracer (the labelled water) is rapidly relaxing [Kwong et al., 1995]. Numerous ways to

measure the spin labelling have been done but the two main categories are pulsed techniques and continuous techniques. No contrast media is needed in ASL as it uses endogenous water as a tracer. Acquisition time is 5-10 minutes. Interpretation is done by a simple subtraction between the averaged control and the labelled images, which then yields a flow-weighted map [Barbier and Zaharchuk, 2005]. Various models have been proposed to convert this map into a quantitative perfusion map [Buxton et al., 1998]. ASL appears to estimate blood flow correctly in the grey matter, but numerical simulations predict an overestimation in the white matter whereas direct measurements show an underestimation. Reproducibility of quantitative perfusion maps shows a 10% change when rescanning the same subject [Parkes et al., 2004]. Perfusion maps obtained with ASL can cover the entire brain. An advantage of ASL is the ability to perform multiple repeated measurements. Disadvantages include underestimation of CBF associated with extremely delayed arterial arrival times such as those through collateral pathways.

Doppler Ultrasound for Blood Flow Volume Measurement in the internal carotid arteries (ICAs)

This technique, although implemented in most commercial Duplex machines since the 1990s, has not gained widespread acceptance due to its inaccuracy. There are inherent errors involved in the technique such as the impact of angle dependency on measured flow velocity and the changing vessel diameter due to pulsatile flow [Steinman et al., 2001] [Ho and Metreweli, 2000]. More recently, improvements in BFV measurement have been achieved by a combination of digital Doppler ultrasound and angle-independent dual-beam flow technology (Quantix-ND system, Cardiosonix, Israel) [Schebesch et al., 2004]. BFV measurements in the ICA can be used for assessment of hemispheric or global CBF. This technique shows a close and linear correlation with CBF in the corresponding hemisphere measured with the $^{133}\text{Xenon}$ clearance technique

[Rothoerl et al., 2003] [Solustiel et al., 2003]. However, hemispheric CBF is not actually measured but rather estimated by BFV in the corresponding ICA based on the correlation between the two parameters. Averaged CBF should not be confused with global blood flow because the BFV in the vertebrobasilar system is not taken into consideration with this technique. Reproducibility of this technique has proved satisfactory (2.7-5.2%), if careful attention is paid to user-related variations and errors. Doppler ultrasound blood flow volume measurements can easily be done at the patient's bedside in about 20 minutes, and requires no radiation or contrast agents. Disadvantages include the limited spatial resolution because BFV measurements performed on each ICA are related to the hemispheric CBF, thus allowing only for side-to-side difference comparisons, and operator dependence.

Summary

Imaging techniques dedicated to analysing brain perfusion address the same types of pathological conditions, such as acute and chronic cerebrovascular disorders, trauma, vasospasm, and brain tumours. Each technique has its own advantages and drawbacks. For instance, PET is quantitatively accurate but feasible only in specific settings. XeCT is reproducible, quantitative and more easily used than PET, but is not always available. To a certain extent, SPECT can be used at the bedside (the radiopharmaceutical administered at the moment of the actual event), with scanning done later. Doppler ultrasound and ASL do not use any contrast medium and do not require radiation; thus can be repeated as often as necessary. Although Doppler ultrasound is the easiest to perform, it does not provide a value for each brain region but only a single value for each hemisphere. PCT is a technique which can be performed on any conventional CT scanner and therefore is a good technique for stroke and head trauma patients. DSC can be combined with other MRI sequences such as anatomic imaging, diffusion

weighted imaging, and spectroscopy; therefore it provides comprehensive information in one examination.

Transcranial Doppler (TCD)

The clinical introduction of transcranial Doppler ultrasonography by Rune Aaslid in 1982 provided a new way to study cerebral blood flow velocities and haemodynamics non-invasively. This technique utilises a 2 MHz pulsed, range-gated Doppler with bidirectional capabilities. The ultrasound signal is displayed as a spectral waveform obtained from a fast Fourier transformation. It requires a low frequency ultrasound transducer in order to penetrate the thick bone of the cranium. Even then, less than 10% of the ultrasound reaches the brain, while the remainder is reflected back by the skull. Doppler signals are only available from the basal cerebral vessels in the circle of Willis due to the limitations of the cranium allowing only a few windows for TCD. Hence, the status of the smaller arteries and arterioles (regulating vessels) can only be inferred from analysis of larger artery waveforms. Even then, Doppler signals can be severely attenuated due to the poor ultrasound penetration, and hence the acquisition of clear and precise waveform shapes can be difficult. Simple clinical measurements are used to quantify cerebral Doppler waveforms, and determine the interpretation.

However, the advantages of having an inexpensive, portable and non-invasive technique to study cerebral haemodynamics at the bedside, is well worth the continued effort.

TCD has been successfully used for evaluation of vasospasm, head injury, and carotid artery disease [Newell and Winn, 1990] [Radanovic and Scaff, 2001] [Telman et al., 2006] [Markus and MacKinnon, 2005] [Moreno et al., 2000].

Along with the technique's many advantages, there are other difficulties apart from the skull. In young healthy subjects, cerebral blood flow velocities measured by TCD correlate well with simultaneously measured CBF values using SPECT but findings have been mixed for individuals with cerebrovascular disease [Demolis et al., 1996]. This may be because other brain imaging techniques measure *regional* or whole brain blood flow. The results of these studies focus on overall brain perfusion. Although CBF studies are sometimes used as the gold-standard for TCD, these techniques in fact ultimately measure two different parameters. Where CBF techniques measure blood flow volume or perfusion, TCD measures blood flow *velocities* and from this an interpretation is made about the adequacy of blood flow to a region. TCD measures flow velocities in each arterial conduit that is evaluated, and therefore can trace the source of the blood flow, or identify the reason for the lack thereof. It is not meant to infer perfusion, but rather adequacy or inadequacy of inflow into each brain territory. The sum total of the inflow results in territorial perfusion. CBF techniques do not specify the arterial conduits from which the blood flow arrives, therefore may not be as useful in terms of surgical planning.

However, the interpretation of TCD can be complicated and further confounded by the presence of collateral flow. The elevated flow velocities found in collateral pathways can mimic velocities found in local stenoses. This makes the results strongly operator dependent. Hence, understanding of cerebral haemodynamics and Doppler waveform analysis is critical to accurate TCD interpretation. Although TCD cannot be strictly termed a CBF imaging technique, cerebral blood flow velocities do have a linear relationship with CBF. TCD does not have the spatial resolution of SPECT, PET, or DSC but it has excellent temporal resolution. Like conventional Doppler ultrasound, examinations can be repeated frequently at the bedside, before and after interventions and there is no radiation involved. It is well tolerated by adults and children, and can be

quickly performed in an emergency room setting. The examination takes from 20-45 minutes depending on the number of arterial conduits investigated.

However, many important questions still remain unanswered. How much can TCD tell us about brain perfusion? Can this technique yield information that eludes more seemingly sophisticated brain imaging techniques? Or perhaps, is the true value of TCD still hidden in the un-interpreted information that resides in the Doppler waveform shape? Finally, where is the niche for TCD in the study of brain haemodynamics and where does it fit in with other cerebral perfusion studies? If we are to answer these questions, it is important to remember that cerebral perfusion is normally maintained through cerebral autoregulation. Therefore, any information gained about the mechanisms of cerebral autoregulation may lead us to greater understanding about how to maintain adequate cerebral perfusion in the clinical setting.

1.4.1 Cerebral autoregulation

The cerebrovascular bed is at all times subject to the combined influence of a number of physical and chemical stimuli that adjust vascular calibre, and thus the cerebrovascular resistance. The result is precise and rapid matching of local cerebral blood flow to neuronal metabolic requirements. In addition, even under conditions of stress such as arterial hypotension or hypoxemia, adequate supplies of blood, oxygen, and glucose must be maintained. If the cerebral vascular bed were a system of branching rigid pipes, cerebral pressure-flow relationships could be expressed in the same form as Ohm's law:

$$F = P / R$$

where F is flow, P is pressure and R is resistance. Resistance to flow is governed by the calibre of the tubing, its length, and the nature of the fluid that flows along it. The difficulty lies in the fact that blood is a non-Newtonian fluid; the length of the vascular bed may vary as the precapillary vessels open and close (exposing different parts of the

network to blood); the pressure is pulsatile; and the vessels are not rigid but distensible and actively contractile [Bell et al., 1985]. Nevertheless, the cerebrovascular bed still can be reasonably described by the equation. The fact that the velocity of the flow is proportional to the square of the vascular radius, and volume flow is proportional to the fourth power of the vascular radius is a constant reminder of the importance of those factors that control cerebrovascular calibre in the regulation of cerebral blood flow [Agarwal et al., 1969].

The term *autoregulation* implies that the responsible regulating mechanism lies within the central nervous system, and most theories suggest that it lies within the vascular smooth muscles in the arterial and arteriolar segment of the cerebrovascular bed [Dandona et al., 1978] [Rapela and Green, 1964]. Stretching of the smooth muscle in the vessel wall by high intravascular pressure leads directly to contraction [Bayliss, 1902]. The myogenic mechanism reduces the vessel calibre and increases the resistance to flow when the arteriolar transmural pressure is elevated. This explains the linkage of pressure autoregulation to changes in systemic blood pressure and subarachnoid venous pressure (equal to the tissue pressure and representing the external pressure exerted on the arteriole walls). A rise in blood pressure increases the transmural pressure and leads to vasoconstriction; while a rise in venous pressure, and hence tissue pressure, decreases the pressure differences and leads to vasodilatation.

Some special factors must be taken into account with the cerebral circulation. Not only are these vessels capable of both active and passive changes in calibre, but at the venous end the vessels are collapsible. The entire cerebrovascular system is enclosed within a rigid container that only has a limited degree of external venting. Extravascular pressure becomes an important factor in the cerebral circulation. The difference between intra-arterial pressure and the extravascular pressure (equivalent to the intracranial pressure) is

termed the transmural pressure. This transmural pressure acts on the wall of the cerebral arterial resistance vessels. The perfusion pressure of the brain is the difference between the intra-arterial pressure as the vessels enter the subarachnoid space and the pressure in the thin-walled veins in the subarachnoid space just prior to their entry into the more rigid dural sinuses [Bell et al., 1985]. Direct observation of pial artery window studies have shown that these vessels are collapsible, particularly just before the point of entry into a venous sinus [Johnston et al., 1974]. The pressure in these veins must therefore be maintained at a level slightly above the extravascular or intracranial pressure (ICP) in order to prevent collapse and to permit flow to continue.

Under normal physiological circumstances a moderate change in cerebral perfusion pressure between the limits of 50-130 mmHg produces little or no change in CBF [Lassen, 1959] [Rapela and Green, 1964]. Constant flow despite an increase in perfusion pressure implies an increase in vascular resistance. Conversely, reduction of intra-arterial pressure within the limits of 130 mmHg- 50 mmHg produces dilatation of the cerebral resistance vessels [Fog, 1937] [Fog, 1939][Folkow,1955]. Pial arteries of different calibre respond to different threshold levels of arterial pressure. The larger pial vessels, those over 200 μm in diameter, start to dilate when the mean arterial pressure falls to 90 mmHg, whereas the small vessels (under 70 μm) do not dilate until pressure falls below 60 mmHg [Kontos et al., 1978]. This pressure-flow regulation has a limit, however, beyond which cerebral vasodilatation or constriction cannot maintain a normal level of CBF. This occurs if the cerebral perfusion pressure falls below 40 mmHg, or similarly if the intravascular pressure exceeds 140 mmHg (when the pial vessels may show segments of distended vessels with leakage). Hence we can see that cerebral resistance vessels play a major part in cerebral autoregulation, and therefore any brain imaging technique which can provide information about the status of these vessels would be very useful in the study of cerebral haemodynamics.

1.4.2 Carbon dioxide reactivity

CBF (cerebral blood flow) changes by 2-3% for each 1 mmHg change in arterial CO_2 within the range of 20-60 mmHg [Reivich, 1964] [Grubb et al., 1974]. Flow changes induced by alterations in arterial $p\text{CO}_2$ begin within 2 minutes. At levels of arterial $p\text{CO}_2$ above 70 mmHg, maximal vasodilatation occurs with no additional rise in CBF as the $p\text{CO}_2$ increases further. Lowering the arterial $p\text{CO}_2$ produces no further decrease in blood flow once the CBF goes below the 20 ml/100 g/min threshold for normal neuronal function. Vasomotor reactivity has been used as an indirect method of assessing the cerebral autoregulation. Alterations in end-tidal CO_2 have been used to study the flow related changes produced by vasodilatation and vasoconstriction of the resistance vessels.

Cerebral autoregulation and carbon dioxide reactivity (vasomotor reactivity) studies are used to gain haemodynamic information in patients with cerebrovascular disease, or head injury, and prior to surgical intervention. Invaluable management insight can be gained in these patients by knowing whether they have intact or impaired autoregulatory responses. (Further discussion on cerebral vasoreactivity testing is found in Chapter 3).

1.5 Doppler waveform analysis

To date more effort has been expended on attempts to quantify the shape of velocity waveforms than on measuring volumetric flow with Doppler ultrasound. Firstly, this is because volumetric flow is remarkably difficult to measure with any degree of accuracy, and requires knowledge of the vessel dimensions and orientation, as well as the velocity waveform being derived under fairly stringent conditions. Secondly, the shape of the waveform can provide information that a simple measurement of mean flow cannot. An example of this is in arterial disease, where pulsatile components of a flow waveform

are affected by lesser degrees of a proximal stenosis than is mean flow [Lee, 1978].

Even if mean flow is reduced in such circumstances, it is impossible to tell whether this is a result of proximal or distal disease, but the shape of the waveform can give a clue as to where the problem lies.

Figure 1.7 shows how Doppler velocity waveforms can vary according to the arterial segment from which they are acquired. The object of course is to recognise those waveforms that are abnormal and how pattern recognition is often used in the interpretation of the shape of Doppler waveforms. The process of pattern recognition may be split into three stages: transduction (in this case the velocity waveform), feature extraction (for example, pulsatility index or spectral broadening) and classification (normal or abnormal) [Evans and McDicken, 2000a].

For the purposes of this thesis, we will focus on feature extraction and the clinical information it may provide. Feature extraction may be carried out on raw waveforms or spectra, but the quality of the input signal will affect the ultimate results [Hoskins et al., 1991]. Pre-processing strategies can be adopted to compress the data or improve its signal-to-noise ratio. For example, Greene and his colleagues [Greene et al., 1982] collected the carotid artery spectra from 10 heartbeats to eliminate the effects of cardiac arrhythmias, and formed an ensemble average using the ECG R-wave as the fiducial point. Thompson et al. [1985] performed their ensemble averaging on the maximum velocity, first moment, amplitude sum and mean velocity waveforms by aligning each individual waveform with respect to a point corresponding to the beginning of each maximum velocity waveform. They then fitted an analytical function to each ensemble average waveform using a least squares method and carried out further analysis on this function. Others, such as Loupas et al. [1995], developed an analysis technique for

automatically identifying and quantifying the 'early diastolic notch' in the sonograms recorded from uterine arteries.

Some feature extraction is done by combining individual features of the waveform, such as minimum amplitude, mean amplitude, or maximum acceleration into one or more indices; while others make use of either a model or a transformation to describe the overall waveform shape. Over the years many methods of feature extraction have been tried, but only a very limited number are in widespread use.

The human brain is remarkably adept at pattern recognition and an experienced observer can tell a great deal about blood flow simply by listening to a Doppler shift signal, or by looking at the velocity waveform. There are many characteristics that influence the judgement of the observer, some obvious and others more subtle.

Velocity waveforms vary from one part of the body to another, and what is normal for one site (such as flow reversal in the femoral artery), may be pathological in another (flow reversal in the cerebral circulation indicates brain death). Although subjective interpretations can be very powerful, they may not be able to distinguish more subtle changes in the Doppler waveform shape.

Several of the most popular feature extraction techniques are based on finding the ratio of the height of one feature of a waveform to that of another. The advantage of taking such a ratio is that both the numerator and the denominator include the cosine of the angle between the Doppler probe and the blood vessel, and the transmitted frequency, and thus the index is independent of these variables. Some of these indices include Pulsatility Index [Gosling et al., 1971], Resistance Index [Pourcelot, 1976], S/D Ratio [Stuart et al., 1980], Early Diastolic Notch Pulsatility Index [Loupas et al., 1995]. These indices dealt mainly with the height of various parts of the waveform.

Since changes in the circulation affect not only the height of the recognisable features of a waveform, but also the time relationship between those features; other indices have been developed which include time [Fronck et al., 1976]. The simplest measurements include acceleration and deceleration of the systolic peak. A height-width index was suggested by Johnston and colleagues [1984], which combines information about both the pulsatility and the time relationship within the arterial waveform.

While the indices mentioned so far have been concerned with the shape of the velocity waveform; spectral broadening indices [Bodily et al., 1980] [Woodcock et al., 1982] [Woodcock et al., 1983] [Kalman et al., 1985] are concerned with the distribution of the velocities within the ultrasound beam, which may be of diagnostic importance. In particular it has been found that the shape of the spectrum measured from the internal carotid artery at or around peak systole is influenced by quite moderate degrees of stenosis [Barnes et al., 1976] [Reneman and Spencer, 1979]. However, a particularly important problem with these indices is the impact of changes in of the sample volume size, which can alter the Doppler spectrum completely.

The feature extraction methods discussed so far have all concentrated on one particular attribute of the Doppler waveform. Another approach is to evaluate a large number of features, which may assist with the classification process, and then to select a set of these on the basis of their ability to discriminate between disease states. Rutherford et al. [1977] selected five out of nine features from a carotid artery waveform; Greene et al. [1982], Knox et al. [1982] and Langlois et al. [1984] selected two or three out of 94 features from recordings taken from four sites in the internal and common carotid arteries.

Another method of feature extraction based on a description of the shape of the entire blood velocity waveform in terms of a Laplace transformation was introduced by Skidmore and Woodcock [1978]. This was advantageous in that it allows for the effects of distal and proximal disease on the Doppler waveform to be separated, and was evaluated in studies by Baird et al. [1980], Johnston et al. [1984], and Junger et al. [1984].

Principal component analysis is another technique used to describe the shape of the entire Doppler waveform. This type of analysis has been applied to signals from the common carotid arteries [Martin et al., 1980], and the common femoral arteries [Macpherson et al., 1984].

The final stage of the pattern recognition process is classification. This deals with assigning the feature vectors, obtained during feature extraction, to a number of classes. These classes may be only two, consisting of normal or abnormal, or may include different degrees or distributions of disease. If the feature vectors are one-dimensional, such as pulsatility index, it is only necessary to define one or more thresholds which will be used to decide the class. However, if the feature vectors are 2-D or more, as in principal component analysis, then both the form and the position of the separating surfaces must be decided. Artificial neural network (ANN) analysis of Doppler velocity signals has been evaluated for classification purposes, with good success. Wright et al. [1997] used the maximum frequency envelopes derived from Doppler signals of the common carotid, common femoral and popliteal arteries for their study. The ANN had a high success rate for appropriate classification of the test vectors, and also made the decision as to which artery the maximum frequency envelope belonged.

Waveform analysis is a powerful diagnostic tool that is complementary to, rather than a substitute for, volumetric blood flow measurement. A variety of approaches have been

tried for each of the stages: transduction, feature extraction and selection, and finally classification. The best combination is influenced by the recording site and the objective of the analysis. The ultimate goal would be to have a quick on-line, but comprehensive, analysis of Doppler velocity waveforms which would lead to better understanding of the haemodynamics involved in the pathology, or even disease classification.

1.6 Aims of this thesis

The aim of this thesis is to create a comprehensive analysis of cerebral Doppler waveform shapes in normal subjects, and to attempt to 'decode' the meaning of waveform shape changes in the cerebral circulation. We use alterations in end-tidal CO_2 (ETCO_2) using 6% CO_2 and hyperventilation, much like Kety and Schmidt, to produce changes in cerebral resistance vessels. However, our goal is not to measure CBF, but rather to analyse the Doppler waveform shape changes that are linked with these known changes in CBF. Constantly changing cerebral resistance is one of the mechanisms that allows for blood flow to match metabolic demand of the brain. Achieving a non-invasive method which could track changes in cerebral vascular resistance may lead to better understanding of cerebral autoregulation, and improve the clinical management of patients.

In 1948, when Kety and Schmidt published their data on the effect of carbon dioxide and oxygen on cerebral blood flow [Kety and Schmidt, 1948], they concluded that there was 'evidence in man for a delicate control of the internal environment of the brain achieved through the intrinsic regulation of the tone of cerebral vessels'. Currently transcranial Doppler ultrasound is an important technique for the study of such delicate regulation of blood flow by the cerebral vessels. Unlike more global imaging

techniques, transcranial Doppler has the ability to finely dissect haemodynamic information about the individual arterial conduits which feed the brain, and is commonly used for assessment of brain haemodynamics in patient's with carotid artery disease.

However, we believe that the velocity waveform shapes generated by TCD may also 'encode' precise and invaluable information about the rapid adjustments made by the regulating (resistance) vessels in order to maintain constant blood flow during the changing environment of everyday life. The dilemma with TCD is that limited work has been done in the area of Doppler waveform shape analysis since its inception in 1980. Only simple measurements of the waveform shape are used, in spite of complex cerebral haemodynamics, making the interpretation of TCD difficult and sometime fraught with error. This has inevitably led to the under-use of a potentially powerful technique for the understanding of cerebral blood flow.

Our first challenge with this project begins with the fact that commercially available TCD equipment does not allow for sophisticated waveform shape analysis. Therefore, as part of this thesis, we construct a hardware set-up that will allow for acquisition of physiologically relevant information such as ECG, and ETCO_2 , to the TCD data.

Secondly, we use a MATLAB environment and custom-designed software to perform detailed *numerical* waveform shape analysis. The software also allows for Doppler waveform shape 2D and 3D *visual* comparisons (Chapter 2). Using these foundations, we are ready to begin the complex analysis of cerebral Doppler waveform shapes after first testing the repeatability and reproducibility (Chapter 3). In Chapter 4, we present the results from our studies using alterations of ETCO_2 (and hence CBF) in a group of 35 normal subjects. We evaluate Doppler waveform shape changes during alterations in cerebral vascular resistance produced by carbon dioxide reactivity (also known as

vasomotor reactivity testing). We discuss our findings, the implications and benefits of our studies, and propose future work in Chapter 5.

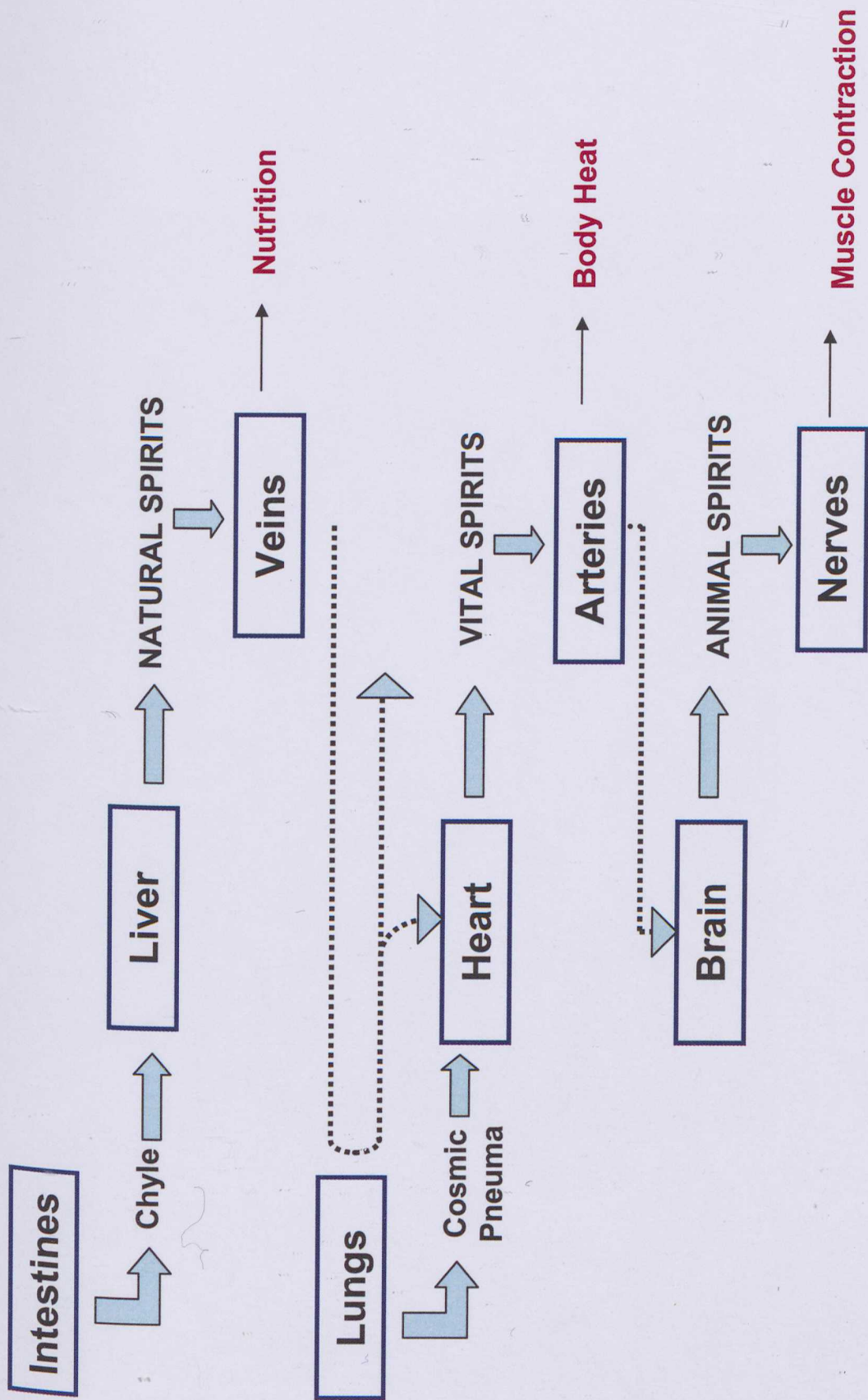


Figure 1.1 Schematic outline of the principal features of human physiology according to Galen of Pergamus (130-201 A.D.) [Tower 1991], as discussed in the text.

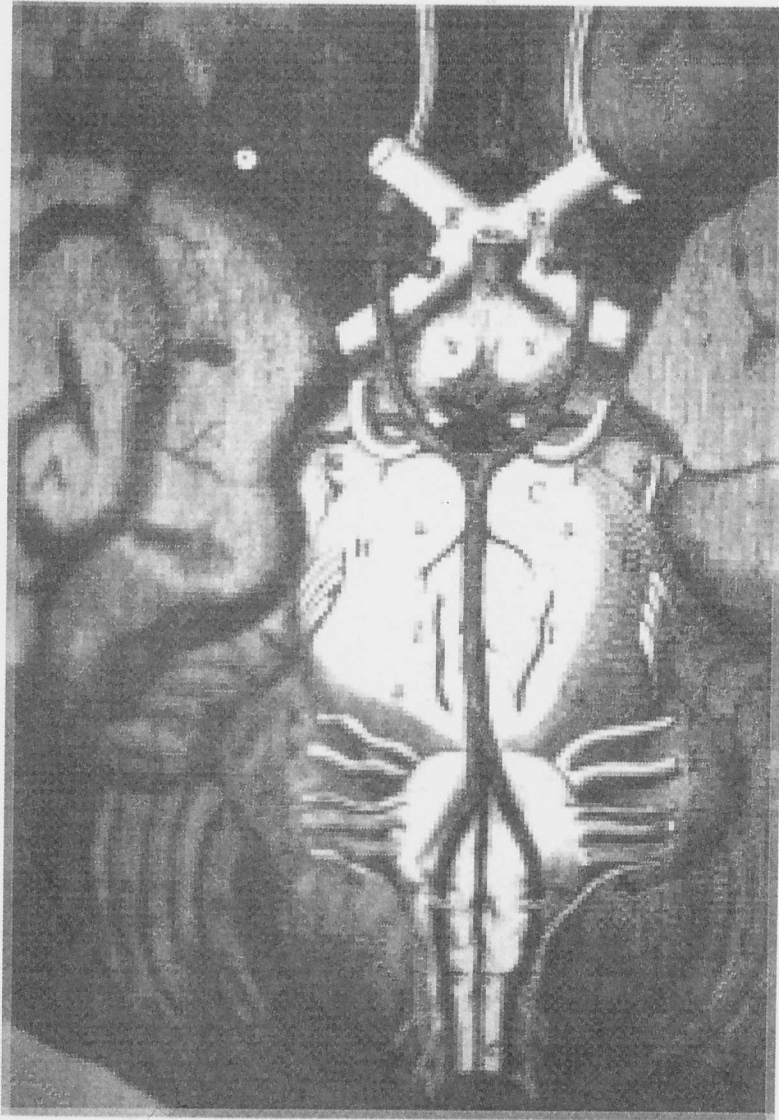


Figure 1.2 A portion of an engraving by Sir Christopher Wren's drawing from the 1664 edition of *Cerebri Anatome* by Thomas Willis depicting the "mutual conjoinings" of the two carotid arteries and the two vertebral arteries, each joined by the posterior and anterior communicating arteries to form the "fourfold chariot of the Arteries". (From Tower [1991], originally reproduced from the Tercentenary Facsimile Edition [1965] of *Cerebri Anatome*.)

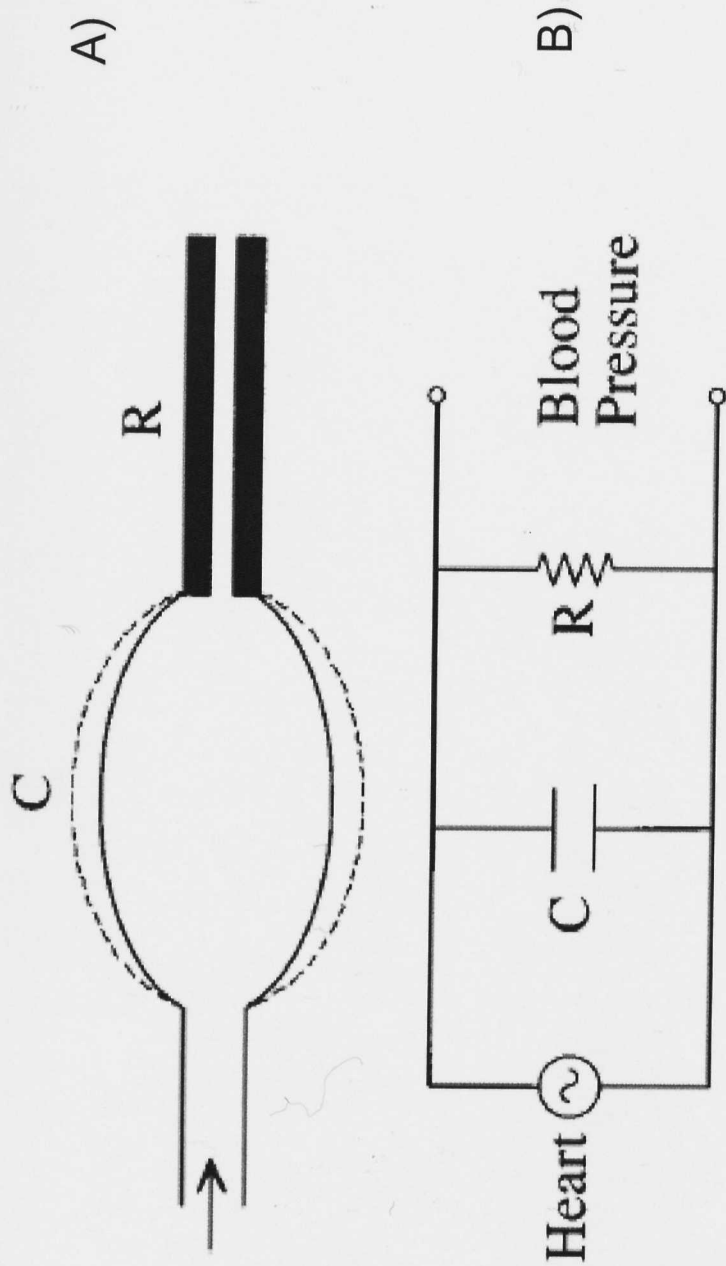


Figure 1.3 A) A lumped-parameter model of the arterial system. Fluid mechanics elements for the arterial capacitance and resistance of the elastic aorta.
 B) Conventional electrical element Windkessel model, where R is the flow resistance and C is the capacitance created by the elastic aorta [from Ku, 1997].

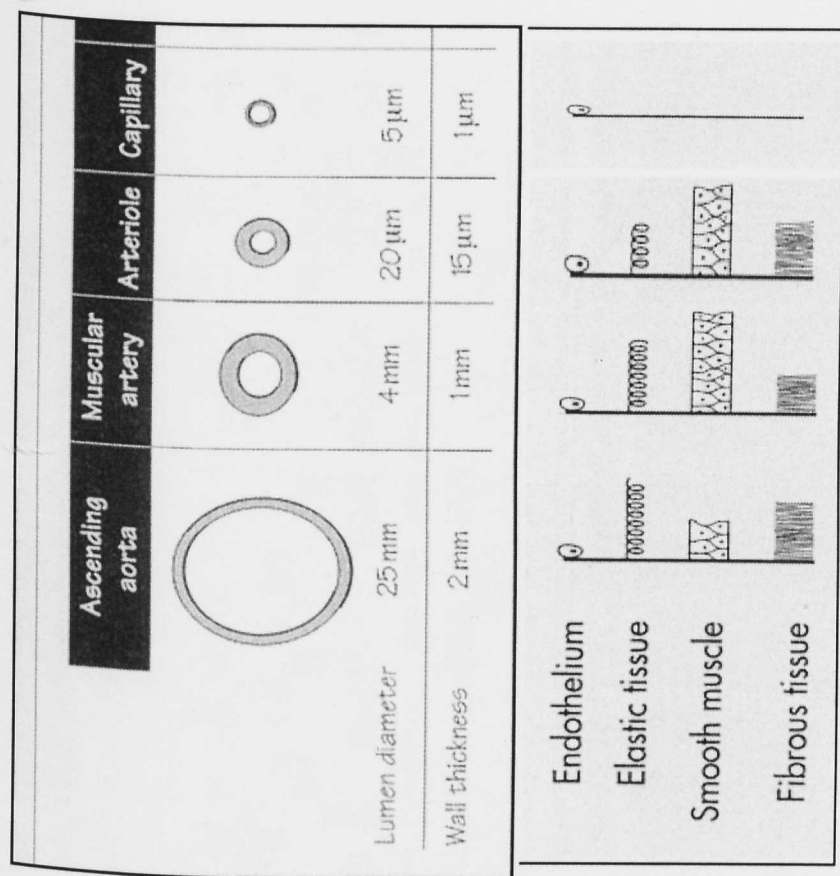


Figure 1.4 A diagram showing internal diameter, wall thickness, and relative amounts of principal components (endothelium, elastic tissue, smooth muscle, and fibrous tissue) of the vessel walls of the arteries. The middle cerebral artery is considered a muscular artery. [Redrawn from Burton, 1954]

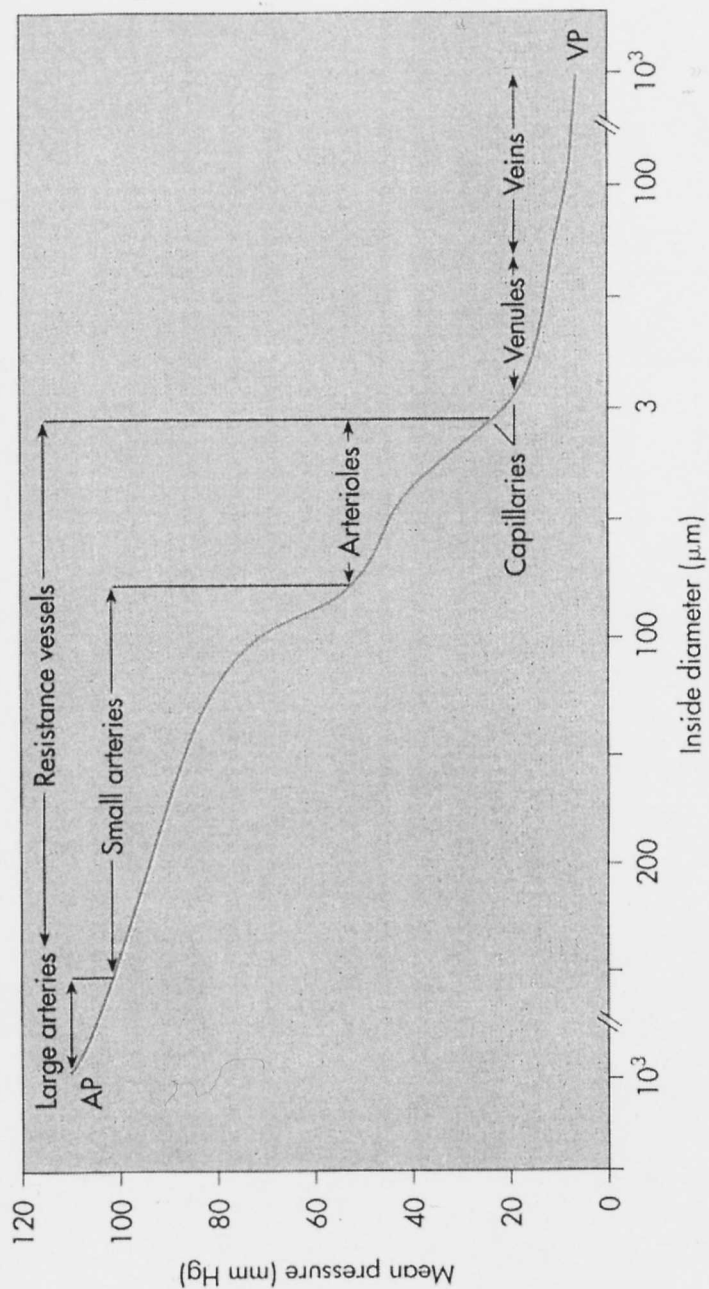


Figure 1.5 This schematic show the pressure drop across the vascular system in the hamster cheek pouch. (AP is arterial pressure, VP is venous pressure)
[Redrawn from Davis, 1986]

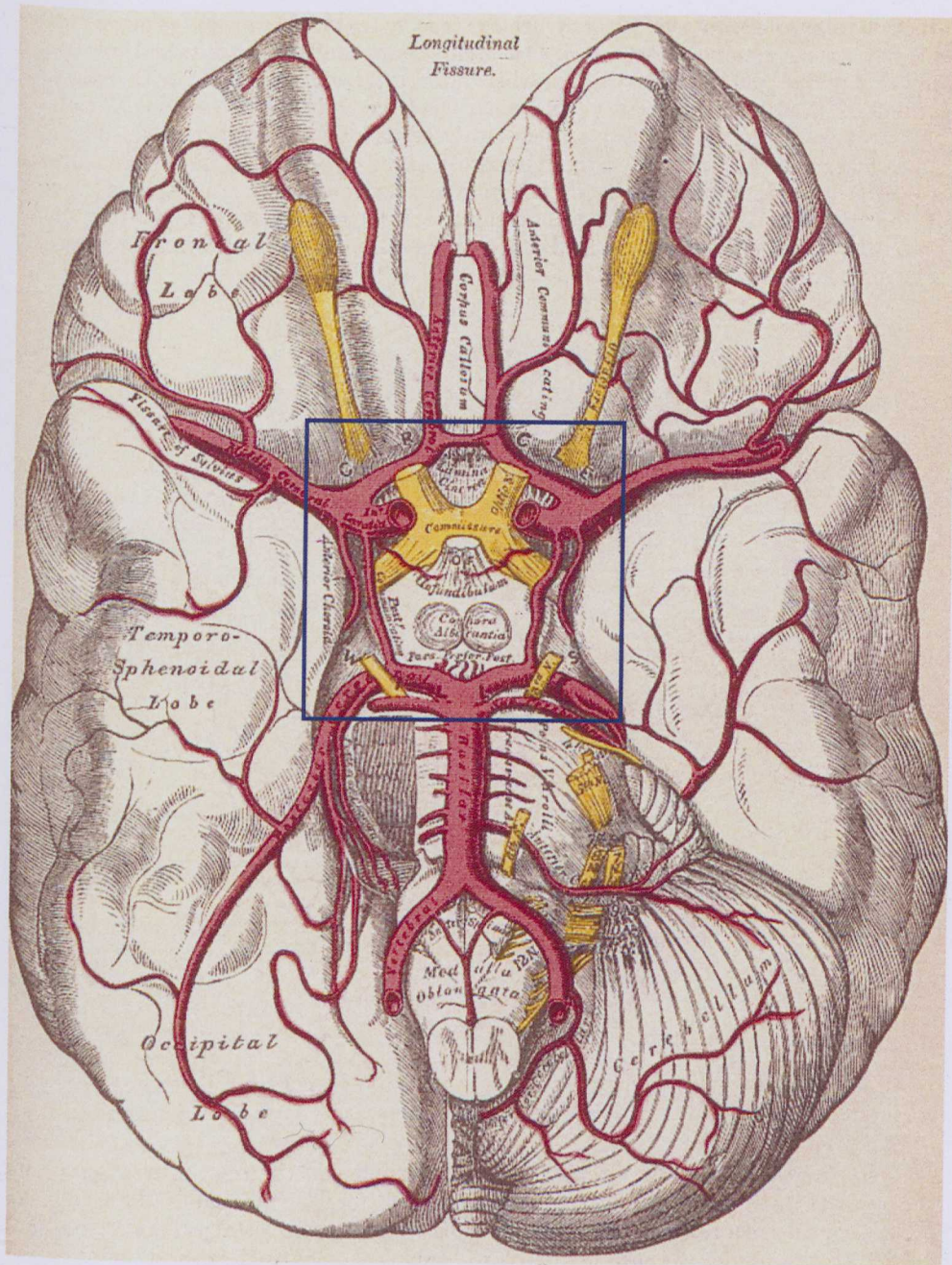


Figure 1.6 Depiction of the cerebral arterial anatomy of the brain showing the circle of Willis (boxed area) from *Anatomy, Descriptive and Surgical* [Gray, 1977].

Doppler waveforms from various arteries

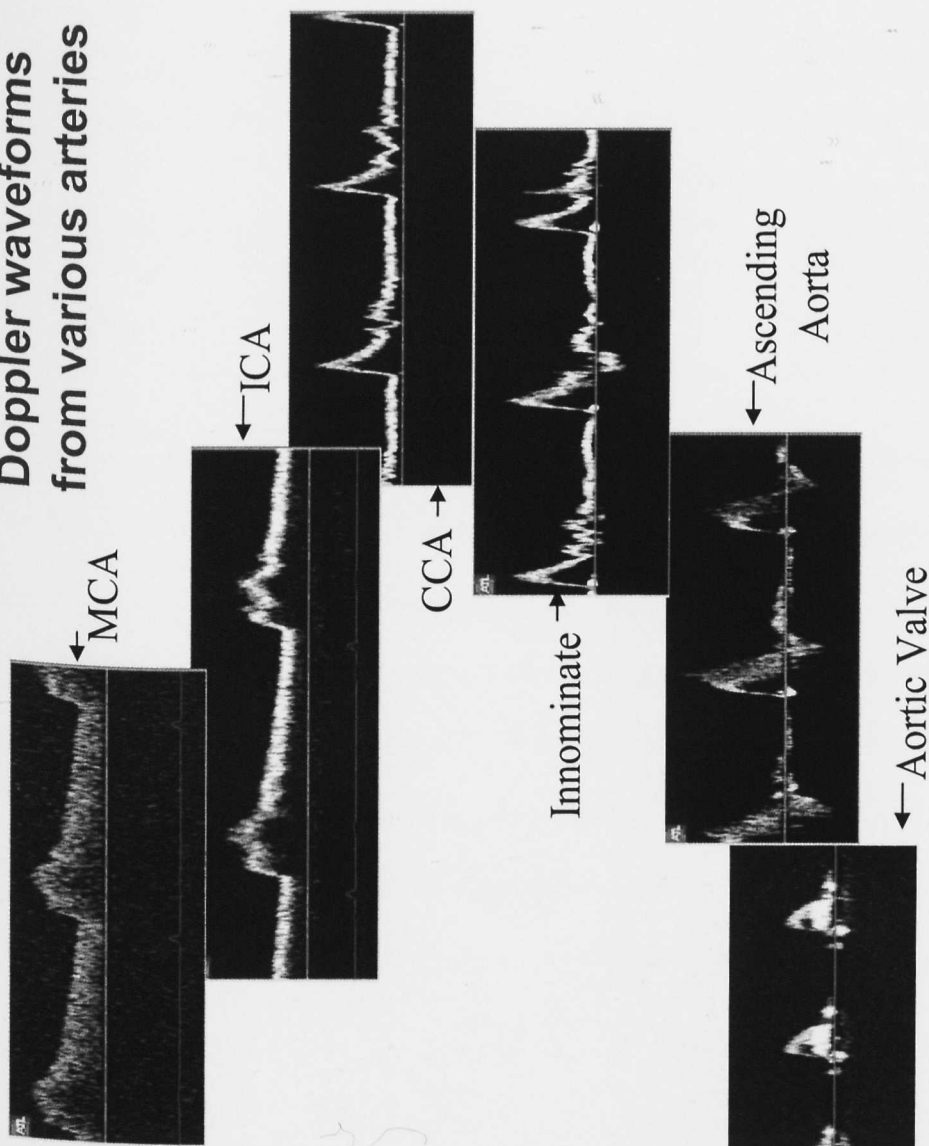


Figure 1.7 Doppler velocity waveforms from various arteries from the heart to the brain. Note how the Doppler waveform changes shape. (MCA is middle cerebral artery, ICA is internal carotid artery, CCA is common carotid artery)

Chapter 2

A system for acquiring and analysing cerebral Doppler velocity waveforms

This Chapter describes the hardware and software development behind a system for acquiring and analysing cerebral blood flow velocity waveforms. The system is based on transcranial Doppler technology currently used for clinical investigations, but with an aim to provide expanded data acquisition, synchronisation and detailed velocity waveform analysis. The first part of the chapter reviews the hardware components and system operation. This is followed by a description of the progressive development of the custom-designed analysis software program. The software architecture is centred on a MATLAB program which aligns the data from digital and analogue instruments, synchronises them, ensemble-averages the cerebral blood flow velocity waveforms, and then performs a detailed contour analysis.

2.1 System architecture - Hardware

A schematic of the acquisition system developed for this thesis is shown in Figure 2.1. The central component of the system is the PMD 100 transcranial Doppler machine (Spencer Technologies, Seattle, WA, USA) which *digitally* records the cerebral blood flow velocity signal. However, all the other data sources such as the ECG machine and end-tidal CO₂ monitor (ETCO₂) are *analogue*. As there is no common time reference between the pieces of equipment we first need a method to synchronise them. This is achieved by the generation of an audio synchronisation signal described in Section 2.1.1, which is linked to both the digital (TCD) and the analogue equipment (i.e. ECG, ETCO₂, etc). A MATLAB synchronisation program links the data together before the velocity contour analysis takes place. Further details of the system are listed under individual component sections (2.1.1-2.1.9) and a description of the software analysis program is found in Section 2.2.

2.1.1 Personal computer

The system begins with a personal computer (PC) with an Intel Pentium 1400 MHz processor, running the Windows 2000 Professional operating system. It is installed with MATLAB version 6.1. An audio synchronisation signal is generated digitally by the MATLAB software running on the PC, and output as an analogue signal through the PC's standard audio output. This filtered, randomly modulated 80 Hz audio signal is used as our synchronisation signal. If the frequency signal is too small, synchronisation accuracy may suffer as it may be outside the pass band of the microphone input. However, if the frequency is too large the PC will have to do unnecessary calculations to synchronise the data. 80 Hz is selected because it lies between these bounds.

The PC is also used to receive analogue data from the other components, such as the ECG during the experiment, through the connector block. Once the data is recorded, the PC synchronises the signals from both the digital and analogue components using the audio synchronisation signal and a specially designed MATLAB synchronisation program. The PC also houses the MATLAB velocity contour analysis software which is used *after* synchronisation and described in Section 2.2.

2.1.2 Transcranial Doppler

The synchronisation signal from the PC goes into a splitter, with one signal being sent to the transcranial Doppler machine via the microphone input jack on the remote control device. The other signal coming from the splitter is detailed in Section 2.1.4.

A Spencer Technologies PMD 100, non-imaging digital transcranial Doppler machine with power M mode, is used to acquire the cerebral blood flow velocity signals (Figure 2.2). Power M mode is a series of overlapping sample gates which gather information on signal intensity and flow direction over multiple depths, and then display this colour-coded information in a separate window to that of the Doppler spectrogram. Power M mode is used to facilitate temporal window location and beam angle optimisation. The Doppler spectrogram is generated by a single sample gate at a depth selected by the operator. It is the Doppler velocity spectrogram information that is used for diagnostic purposes.

A thin portion of the temporal bone is used for ultrasound penetration of the middle cerebral artery (Figure 2.3) by a 2 MHz (13mm) pulsed, range-gated ultrasound transducer. For our study, the ultrasound beam is focused on the middle cerebral artery at a depth of approximately 50mm from the outside of the skull with a sample volume of 6mm. This setting provides information from a depth of $50\text{mm} \pm 3\text{mm}$. The

location places the beam approximately midway along the course of the middle cerebral artery, before the first major branching in most adults. The Doppler transducer is attached to a head fixation device (MARC 600, Spencer Technologies) (Figure 2.4). This headband ensures stability of the ultrasound transducer during data acquisition, so the Doppler angle remains constant during the study. A complete explanation on the technique will be given in Chapter 3.

Sixteen seconds of continuous digital Doppler peak velocity envelope information is acquired from the artery of choice and saved during each recording segment. This recording length is selected as it contains a sufficient number of cardiac cycles, and also fits well with the available options on the TCD equipment. Once the recording segment is completed, the velocity file is temporarily stored on the TCD machine's internal hard drive, as it cannot be sent directly to the PC. It is the peak velocity 'envelope' data from the Doppler spectrogram which is extracted and used in recreating the waveform shape (Figure 2.5). The synchronisation signal is simultaneously recorded by the TCD and held in file with the TCD velocity data.

2.1.3 External hard drive

The transcranial Doppler velocity files along with the synchronisation signal are then exported to an external hard drive (Maxtor 3000LE). These files are later downloaded onto the PC in separate files to those from the analogue-based auxiliary equipment. Both sets of files are synchronised, via a custom designed MATLAB program, then loaded into the Doppler contour analysis program.

2.1.4 Splitter/Connector block

As discussed in Section 2.1.2, one of the synchronisation signals from the splitter goes to the TCD while the other signal is sent to a National Instruments (Austin, Texas, USA) BNC-2110 shielded connector block. The signal-labelled BNC connectors allow connection of the analogue signals from the auxiliary equipment, and allow the digital velocity and synchronisation signals from the TCD equipment to be eventually united; whilst maintaining the integrity of the measurements. The sampling rate is 200 Hz. All of the signals from the connector block are then routed back into the PC for capture and synchronisation to the TCD data. These new files are then analysed via our MATLAB program.

2.1.5 Auxiliary equipment – ECG monitor

A 3-lead ECG monitor (LifePulse 10, HME Ltd, Hertfordshire, UK) is used to provide the electrocardiogram that is used for ensemble-averaging Doppler waveforms in our MATLAB program (Section 2.2). The analogue output signal from the equipment is sent to the connector block, and then onward to the PC for capture and later synchronisation with the other data. The display screen on the device incorporates some filtering, and displays a relatively clean trace with little noise. However, the actual analogue output we use from the device provides only a raw, unfiltered version of the signal which contains more noise (Figure 2.6). We tested this by connecting an oscilloscope to the analogue output of the ECG device. However, since only the peak of the ECG R wave, which is well-defined, is needed for our software, we determined that the baseline noise was insignificant and did not require post-processing.

2.1.6 Auxiliary equipment - End-tidal CO₂ monitor (ETCO₂)

ETCO₂ is the maximal concentration of carbon dioxide (CO₂) at the end of an exhaled breath, and is expressed in mmHg. Cerebral blood flow velocities are very sensitive to changes in CO₂, so it is important to record this value during testing. We use an end-tidal CO₂ monitor (Pulse Oximeter End-Tidal Model 601, Criticare Systems, Waukesha, WI, USA) in all studies for standardisation and analysis purposes. This machine is calibrated before each testing session. The analogue signals from the ETCO₂ monitor are sent to the connector block, and then on to the PC for capture and synchronisation with the other data. (Figure 2.7)

2.1.7 Auxiliary equipment - Phonocardiograph

We built our own phonocardiograph with a computer microphone. This microphone is placed in a simple frame to attenuate any outside noise and is attached to the subject using a small suction cup device. The microphone is placed over the subject's chest in the region of the aortic valve. The sounds picked up from the device are amplified and then routed into the connector block with the other signals and later synchronised to the TCD data. The purpose of the phonocardiogram is to initially verify which portion of the waveform contour correlates with the sound of the aortic valve closure, often referred to as the 'dicotic notch' on Doppler waveforms. This is an important marker for understanding the physiology behind the waveform shape, and is also useful in developing ensemble-averaging algorithms for the Doppler waveforms. Figure 2.8 depicts the Doppler velocity waveform and the second heartbeat sound, S2 (aortic valve closure).

2.1.8 Auxiliary equipment - Oxygen saturation monitor

A Pulse Oximeter End-Tidal Model 601 was used in the early part of the study to monitor changes in oxygen saturation via a finger clip monitor. Since it was unclear what overall effects changes in O_2 saturation might have, it was included in the initial set-up and programming. This parameter was later discarded, as changes in oxygen saturation had little effect on the cerebral velocities when compared to the effect of CO_2 alterations, therefore, it was not taken further in this thesis.

2.1.9 Auxiliary equipment - Blood pressure device

An Omron 750CP (Omron Matsuska Co. Ltd, Japan) automated blood pressure device is used to take blood pressure measurements at the end of each TCD recording. It is important to acquire the blood pressure measurement immediately *after* the other recordings have been completed, as we do not want to add a stimulus (cuff inflation) but do require the subject's blood pressure to be stabilised. Changes in blood pressure can have an effect on cerebral velocities and may change during vasoreactivity, so this device is important and therefore included in the study.

2.1.10 System operation and synchronisation

Once the transcranial Doppler headband is secured on the subject and the velocity trace is optimised and stabilised the 16-second equipment recording can commence. The Doppler velocity information is recorded directly by pressing the 'save' button on the TCD remote control device. Saving of all other equipment data is accomplished via a key stroke on the PC keyboard. Immediately afterwards, the Omron blood pressure device is inflated, and the blood pressure recorded on a worksheet.

Although we acquire 16 seconds of continuous data from all instruments, the TCD velocity file with synchronisation signal remains separate and is held independently by the TCD machine's internal hard drive. When the examination finishes, this file is transferred to an external hard-drive. The external hard-drive is then connected to the PC for download. The Doppler velocity envelope data and synchronisation signal, along with the other acquired signals on the PC, are joined together through a custom designed MATLAB program. The program performs a cross-correlation to derive alignment of the data between the synchronisation signal recorded by the PC and that recorded by the TCD via the microphone input. A new file is then created. The data now consists of vectors (time, ECG, TCD, CO₂, etc). This newly synchronised, 16-second packet of data now resides in a single file and is ready for contour analysis. Figure 2.9 shows a photograph of the equipment used in the study.

2.2 System Architecture- analysis software design

Once the raw data is successfully captured and synchronised we need to reconstruct the curves of the Doppler velocity waveform and measure the contours. Due to the inherent variability in physiological data, we choose to ensemble-average the waveform data and subsequently provide a single, representative waveform for the recording period. We include a display of the standard deviation with each result, so that the inherent variance of the data which is averaged can be assessed. Once the characteristic waveform is created, the measurement software can begin to analyse the velocity maxima, minima, plateaus and acceleration/deceleration of the velocity curves. The progressive development and reasoning behind this analysis software is described in Sections 2.2.1-2.2.5.

2.2.1 Filtering/smoothing

The filtering part of the program is based on fast Fourier transforms for the ECG, and on Savitsky-Golay filtering for the velocity. Savitsky-Golay is a low pass filter that is used to visualise the relative widths and heights of spectral lines in noisy spectrometric data. Smoothing is generally used where there is a slow changing variable which may be corrupted by random noise. The Savitsky-Golay filter provides a versatile smoothing filter by using a moving window, with an n th order polynomial least-squares fitted to the points in the window. A set of polynomial coefficients is produced for each point in the window. The Savitsky-Golay filter approach also allows first derivative filters. In Figure 2.10, we can see the beneficial effects of using a Savitsky-Golay filter. Over-smoothing of data can lead to important key features of the shape being eliminated if caution is not observed. Figure 2.11 shows a waveform which has been *over-smoothed* and has nearly lost the dicrotic notch.

2.2.2 Waveform ensemble-averaging

To ensemble-average a series of Doppler waveforms it is necessary first to decide which point or points of the Doppler velocity contour are most reliable for alignment purposes. Since the ECG is a record of ventricular depolarization and repolarization, a point in the QRS complex such as the peak of the R wave can be used as a marker for waveform alignment. However, there are other methods available which we examine here. The results of various methods are tested on acquired velocity envelope data from a single representative individual, and shown in Figure 2.12, A to G. As can be seen by looking at the standard deviation (red dotted lines on either side of the blue peak velocity line) some alignment methods work better than others. For example, illustration C, the ensemble-averaged based on the diastolic points displays wider standard deviations than illustration D where the ensemble-average has been based on

the peak of the ECG R wave. After extensive testing, we chose to align the Doppler waveforms on the peak of the ECG R wave, as this proved to be a robust and simple method and had the advantage of being linked with a physiologically important time period (when the ventricles begin to contract at the start of systole).

The next important step in the software design is the results display box. At first we chose to use only the simplest display of the data because we were mainly concerned with achieving the more common Doppler waveform measurements such as peak systolic velocity (U_{max}), or end-diastolic velocity (U_{min}), seen in Figure 2.13 A.

However, as our design progressed, further waveform contour measurements were possible and this led to an expanded results display (Figure 2.13 B), and eventually to the current version as seen in Figure 2.13 C. Note that in the final version, the waveform maxima, minima, accelerations/decelerations, and other measurements such as mean velocity are listed along with the time of the event occurrence (from the peak of the ECG R wave. This time measurement is written in brackets to the right of each listed measurement). A total of 28 different variations of the program were considered and tested before the final version was selected as the most clinically useful.

2.2.3 Using the contour analysis software

2.2.3.1 Cardiac cycle selection and data overview

The analysis software works within the MATLAB environment using the synchronised data. First, the user is asked to review the cardiac cycles and corresponding cerebral waveforms before any ensemble-averaging takes place. This step allows for any irregular heartbeats, such as premature atrial or ventricular contractions, to be rejected *before* the ensemble-averaging takes place in the program, since they do not represent a 'normal' beat and would introduce erroneous information into the average (Figure 2.14). This is

done by clicking on each ECG R wave the user wishes to accept into the ensemble-averaging; the corresponding cerebral waveform will automatically be accepted at the same time. Those beats left unselected will not be included in the ensemble-average. This process keeps the ensemble-averaged waveform as accurate as possible, since only full cardiac cycles are included.

Once this is completed, the software depicts an image of all captured, synchronised data in individual windows (Figure 2.15). The purpose of this screen is to allow the user an ‘overview’ of all of the captured data, and hence have a more global picture of the physiological changes occurring during the recording period in all the haemodynamic parameters. In this screen, the user may also choose to measure information from the auxiliary equipment, such as the ETCO_2 , via a set of callipers. A description of each of the windows in Figure 2.15 is listed below.

Window A

This window displays the peak Doppler velocity envelope extracted from the TCD machine over the 16 seconds of recording time (although we drop the first second of data off this screen). Any major changes in velocity during the acquisition period will be represented in this window, such as the loss of the TCD signal due to movement, or technical problems.

Window B

The ECG trace can be seen in this window. It is used for timing purposes, and to identify cardiac arrhythmias. Since a poor ECG signal, such as that caused by low voltage, will not allow proper synchronisation, this window can alert the user to any technical problems.

Window C

In this case, the window shows the tracing from the oxygen saturation monitor. The trace remains essentially unchanged throughout the time period, and is unfiltered data.

Window D

The last window is the recording of the ETCO_2 . Note the variations in CO_2 during normal breathing and yet the TCD signal does not appear markedly affected, nor does the ECG. The maximum ETCO_2 can be measured directly from this window as shown with callipers.

To check for any gross inconsistencies in the data coming from the new system, worksheets were kept for each recording segment. Visually acquired values from the equipment monitors at a single time point were noted onto the worksheet, and checked with the computer data to ensure that there were no systematic errors in the recorded data. In addition, the measurement of the blood pressure was added to this worksheet. Throughout our testing, no gross errors were noted in the recorded values of our system.

2.2.3.2 Defining velocity waveform contours

To perform an analysis of waveform shape, it is crucial to define the key features of the waveform contour and then to measure these as precisely as possible. Since it is possible that Doppler waveform shape can give us key information about the status of the cerebral circulation at the time of the recording, then providing numerical values attached to waveform shape is important if we wish to make comparisons over time or with other individuals. It is well-established that the shape of the Doppler waveform is affected not only by local arterial factors, but also by haemodynamic factors both proximal and distal to the insonation site [Zwiebel, 2000]. Once the waveform features

are defined and measured, comparisons can be made in an individual over time, under stimuli, or amongst groups of subjects. Transcranial Doppler examination limitations have arisen from generalised testing problems, such as hyperostosis of the temporal bone window producing poor penetration of the ultrasound, but also from the equipment itself which allows only relatively crude measurements to be made of the waveform shape (e.g. peak systolic and end-diastolic velocities). Figure 2.16 is an illustration of this problem showing limited measurements available from the Doppler waveform. During routine clinical TCD examinations, velocity measurements are made both by online callipers from a frozen image (single cardiac cycle), or by a 'running' update by the equipment which averages the peak systolic and end-diastolic velocities every 3-5 cardiac cycles, and then display this averaged value on the equipment's monitor. TCD equipment can also provide derived values on screen for the user such as mean velocity, pulsatility index and resistive index. However, it is the user who decides whether to take the values from a single cardiac cycle (frozen image), or measure several cardiac cycles (the average presented on the TCD equipment display). Both methods can provide useful measurements, but they are limited in scope since the waveform carries far more physiological information than simple PSV (peak systolic velocity) or EDV (end-diastolic velocity) measurements can reflect. Therefore, we have chosen in our analysis software to concentrate on defining all the major contours of the velocity waveform shape whilst still providing traditional diagnostic parameters for the user such as 'mean velocity'.

Our analysis system allows eleven more measurements than presently available on commercial TCD equipment, and proposes new haemodynamic indices based on these new values. This will be discussed in Section 2.2.4. Using multiple measurements of waveform shape may provide further insight into the subtle changes which take place in the cerebral circulation, which were previously unnoticed due to poor visualisation of

the waveform contours on commercial TCD equipment and limited measurement capabilities.

2.2.3.3 Measured parameters and data display

The contour analysis software begins with a display of the maximum velocity envelope and the standard deviation, showing the inherent variance of the ensemble-averaged data. It also lists the number of heartbeats *selected* from the recording period for averaging (**Nbeats**), and shows the heart rate variation from chosen cardiac cycles (Figure 2.17).

Next, the system is programmed to detect all of the currently used diagnostic parameters in TCD, such as maximum velocity, minimum velocity and the mean velocity. This allows the user to have a familiar set of reference values in hand when viewing the additional new contour measurements generated by the system. The following paragraphs describe each contour we selected for measurement and the reasoning behind our choices.

The software measures three local minima of the velocity waveform, three local maxima, maximum acceleration/deceleration at various points on the velocity curve, and also detects the time from the peak of the R wave that each value occurs. In addition, parameters such as Upulse, mean velocity, T-rise and Tau are discussed later in this section, as well as the use of time measurements.

Velocity Minima

The first minimum (Figure 2.18 A) is the minimum velocity measured *prior* to the start of the systolic upstroke. It is also known by the common term ‘end diastolic velocity’.

We term this **U_{min}** (A), and it represents a time when the heart is at rest (preparing for the next cardiac ejection).

The next local minimum (Figure 2.18 B) is created by the first velocity plateau which occurs *after* peak systole. This is often termed the ‘systolic notch’, but is never measured in routine clinical TCD examinations. This first velocity plateau can be interpreted as a consequence of wave reflection [Wang, Parker, 2004]. Since our insonation site is in the middle of the MCA, this reflection may be from either the MCA bifurcation/trifurcation region or perhaps beyond, at the level of the small arterioles. This reflection is a backward wave or negative velocity, which tends to sharpen the velocity peak and then creates the first local minimum (B). We term this **U_{min1}** (B).

The third local minimum (Figure 2.18 C) is associated with closure of the aortic valve when a small amount of backflow of blood moves into the ventricles and produces this characteristic notch. This notch, often called the ‘dicrotic notch’ or ‘incisura’, can be identified in all Doppler recordings throughout the systemic circulation where both forward and backward flow is often found. However, since one of the major characteristics of the cerebral circulation is that it always has forward blood flow under normal conditions, we wanted to see if the movement of backward flow into the ventricles left its mark in the cerebral circulation waveforms. We chose to test this assumption, by checking the alignment of the aortic valve closure audio signal, and what appeared to be the dicrotic notch in the cerebral circulation waveform. Details are presented in Section 2.1.7 (Phonocardiograph) and Figure 2.8. The first heartbeat sound is known to be produced by sudden closing of the tricuspid and mitral valves due to an increase in the intraventricular pressure which begins to exceed the pressure in the atria causing the valves to close. It marks the approximate beginning of systole and this valve closure sound is often known as ‘S1’. The ventricles contract throughout systole, forcing

blood through the aorta and the pulmonary artery. When the ventricles begin to relax, the pressures within the heart become less than that in the aorta and pulmonary artery, and a brief back flow of blood causes the aortic and pulmonary valves to snap shut, producing the second heartbeat sound, S2. This marks the end of systole and the beginning of diastole. Although arteries in the peripheral arterial circulation commonly show this momentary blood backflow characteristic (Figure 2.8 D), arteries of the cerebral circulation never show reversed arterial flow, except in extreme cases of raised intracranial pressure [Hassler, 1989]. **Umin2** (C) is therefore an important marker as it indicates the end of systole.

Velocity Maxima

Three local maxima of the velocity contours are also measured in the program. The first maximum we have termed **Umax** (Figure 2.19 A). It is routinely measured in clinical TCD examinations and is better known as ‘peak-systolic velocity’. This is the maximum velocity that is reached in the cerebral circulation, due to the passage of a strong, forward moving compression wave coming from contraction of the left ventricle, which accelerates the flow and increases the pressure [Nichols, O’Rourke, 1998]. This is a very important physiological event and is measured for this reason.

Umax1 (Figure 2.19 B), the next velocity maximum which occurs *after* the velocity plateau (**Umin1**), is usually seen in the waveform morphology, however, its physiological origin is more complicated to identify. One theory is that during systole the artery expands due to the increase in pressure as the propagated wave from the heart moves through. After its passage, the artery then begins to recoil. This recoil creates a further ‘push’ of blood through the artery (forward moving compression wave), and creates a secondary acceleration in the velocity. However, it may be even more complex. It has been shown in studies of wave intensity analysis in the carotid artery that this particular

time period also corresponds to a backward moving expansion wave, or 'sucking' wave [Zambanini, 2005]. This wave may be generated from the small cerebral vessels although, as yet, we have no way to determine this. It is possible that this 'sucking' wave may be responsible for a component of this velocity increase (Figure 2.20). We discuss this issue further in Chapter 5 during our studies of vasoreactivity. Figure 2.21 depicts several variations of this unique parameter.

The last velocity maximum measured by the analysis software is termed **U_{maxdias}** (Figure 2.19 C). This refers to the peak velocity attained *after* closure of the aortic valve and during a time period referred to as diastole. This velocity rise is believed to occur because of a small forward compression wave during diastole. This wave is generated after a backward moving blood hits the closed aortic valve and then propagates forward once again.

Velocity acceleration/deceleration

As the left ventricle contracts, a rapidly moving column of blood is sent into the arterial system. Within approximately 10 milliseconds the resultant wave has reached the middle cerebral artery. The strength of the cardiac ejection can be indirectly assessed by measuring the 'systolic upstroke' of the cerebral waveform. This parameter, which is often used by cardiologists when measuring heart function, is essentially never measured in transcranial Doppler studies as the equipment does not allow for it. It is, however, an important parameter to measure since it carries information about the heart. However, since our measurement location is distant to the heart itself, any significant obstructions along the arterial path on the way to the middle cerebral artery can affect this measurement. We measure the maximum slope of the cerebral Doppler waveform, and call it **DuDt_{max}** (Figure 2.22 A).

As a consequence of wave reflection, the velocity then begins to decelerate immediately after it has reached peak velocity (U_{max}). The software measures this first deceleration slope, **DuDtmin1** (Figure 2.22 B). This deceleration measurement may be thought of as an indicator of the strength of the first reflected wave. The stronger the wave reflection the steeper this deceleration slope will become. If, however, this reflected wave is very weak, then the velocity deceleration will be slower. Figure 2.23 depicts the location of the MCA trifurcation as a possible site of wave reflection.

The last deceleration which occurs immediately before aortic valve closure, **DuDtmin2** (Figure 2.22 C), is believed to be due to a fall-off in pressure, rather than due to further wave reflections. We can see from the pressure waveform, shown at the top of Figure 2.20 A, that after the passage of a large compression wave due to ventricular systole, the pressure within the artery steadily declines.

Diastolic velocity fall-off (Tau)

After the velocity plateau created by closure of the aortic valve (U_{min2}), and following the next velocity rise from the small forward moving compression wave, there is a period of velocity fall-off. This is the result of declining pressure in the middle cerebral artery after the main cardiac compression wave has past, and the heart is refilling. In spite of this steady decline in pressure, blood continues to be propelled forward due to the elastic recoil of the arteries, the arterial Windkessel [Blez, 1995]. The software analysis program performs a best-fit exponential in this section of the waveform and calculates a time constant. This we term as Tau (τ) (Figure 2.24). If the heart rate quickens then Tau will decrease, and conversely if the heart rate slows then Tau will lengthen. Figure 2.25 shows a selection of cerebral waveforms with different heart rates. Note that a change in heart rate mainly affects the diastolic portion of the waveform (from aortic valve closure to the beginning of the next cardiac cycle).

Pulse width

Upulse (Figure 2.26 A), the pulse width, or measurement between the lowest velocity (U_{min}), and the maximum velocity (U_{max}) is calculated by the software program. This is a similar calculation to that of ‘pulse pressure’, which is a common term used in the measurement of systemic blood pressure.

Traditional transcranial Doppler parameters

The mostly widely used clinical measurement during TCD examinations is ‘mean velocity’. The majority of diagnostic criteria, such as those for cerebral vasospasm, are based on ‘mean velocity’ measurements of cerebral blood flow [Seiler, Newell, 1992]. However, the term itself may be slightly misleading since it is actually a measure of the peak velocity envelope. This reading is normally displayed on all TCD equipment, and therefore is also calculated by the software program and termed **Umean**. We have chosen also to use the peak velocity envelope (or time-averaged peak velocity) to calculate U_{mean} , so that it is consistent with industry standards and can be compared to scientific literature on TCD. In addition, we have incorporated the other commonly used parameters of peak systolic velocity (U_{max}), and end-diastolic velocity (U_{min}) as mentioned in previous paragraphs. These are the main diagnostic parameters currently used in the field, and which appear in the literature. Commonly used indices derived from these measures, such as pulsatility index (PI) and resistive index (RI), are not directly calculated by the software but derived once the data is transferred onto a spreadsheet.

Time measurements

During clinical TCD testing, the timing of various events such as aortic valve closure, or the time from cardiac contraction to peak velocity in the cerebral circulation are usually

not assessed. This is mainly due to the inadequacy of the TCD equipment to provide a method for doing so. Since all of the ensemble-averaged cerebral waveforms are aligned on the peak of the ECG R wave, this allows for the possibility of a time measurement of physiologically important events. 'Rise-time' or **Trise** (Figure 2.26 B) is often used in echocardiology studies as an indicator of the strength of the cardiac contraction. This is a measure of the time from minimum velocity (U_{min}) to maximum velocity (U_{max}). In the cerebral circulation the measurement of Trise can also be an indirect indicator of any significant obstructions between the heart and the insonation site in a cerebral vessel. For instance, a severe carotid stenosis would slow the cardiac compression wave and therefore it would take an extended period of time to reach maximum velocity in the MCA. Hence, Trise would be longer. Figure 2.26 shows an example of how Trise, Upulse and the length of systole itself are measured from the ensemble-averaged waveform. Figure 2.27 shows an example of the various time points the software also calculates which may prove useful.

Results display - numerical

Once the analysis is complete, the software generates an ensemble-averaged waveform and a results box to the right of it (Figure 2.28). This is called the *numerical* display of the data. See Table 2.1 for a complete list of results display symbols and definitions.

However, since this is 'averaged' data from a series of cardiac cycles, there is the possibility it could 'mask' some of the unique velocity contours or characteristics which are embedded in each individual cardiac cycle. In order not to lose this potentially important information, we have programmed a *visual* display of the raw velocity data to accompany the numerical display of the ensemble-averaged data. Figure 2.28 shows an example of the numerical display from 16 seconds of data, whereas Figure 2.29 depicts

the individual velocity contours of each cardiac cycle which has been included in the ensemble-averaged data.

Results display - visual representation

A three-dimensional figure of the beat-to-beat variation in velocity is generated.

Visualisation of the variations between individual cardiac cycles can provide important insight into the cerebral circulation. For example, in Figure 2.29 we can see some variation between the maximum velocity peaks (U_{max}); however, there appears to be a much greater natural variation in the second velocity peak (U_{max1}). This is mirrored by the larger standard deviation depicted in this same region in the numerical display (Figure 2.28). Although the interpretation of this is as yet unclear, it may represent the response of the cerebral circulation to small spontaneous changes in heart rate and blood pressure. Perhaps these changes force the cerebral circulation to *fine-tune*, or adjust the vascular tone of the cerebral regulating vessels, at each cardiac cycle in order to maintain constant blood flow to the brain.

We believe that within the waveform contour measurements lie key information associated with wave propagation, wave reflections and vasomotor tone. Some of these parameters have never been measured before in the cerebral circulation, and therefore normal values will need to be established and the interpretation of changes in these parameters will need to be developed.

2.2.4 Waveform indices

Defining key features and producing exact measurements of the Doppler velocity waveform contours are important. However, indices which have been derived from these measurements can also be useful and have indeed been a major part of TCD interpretation in the past. The two major historical indices: PI (pulsatility index):

$$PI = PSV - EDV / \text{mean velocity} \text{ [Gosling, King, 1974]}$$

and RI (resistance index):

$$RI = PSV - EDV / PSV \text{ [Pourcelot, 1974]}$$

are found throughout the literature on TCD [Lindegaard, 1992]. The development of these indices was originally based on the assumption of interplay between resistance and compliance of the vascular bed. The accuracy and tendency of these two indices are nearly identical in most clinical applications. Indeed both indices seem to change with alterations in vasomotor tone seen in vasomotor reserve testing; this will be discussed in Chapter 5. Since the cerebral conduit vessels, such as the MCA, are relatively stiff, we assume that the cerebral arterial compliance is practically negligible and therefore the indices must represent changes in resistance. The problem with using PI, or RI, is that changes in resistance are often small and can be overshadowed by changes in cardiovascular factors such as blood pressure. Therefore subtle changes in central factors may influence the PI or RI without the investigator being aware of such influence. We propose the use of an index we term: **mean resistance index**. This is defined by:

$$\text{Mean resistance index} = \text{mean blood pressure (mmHg)} / \text{mean blood flow velocity (cm/s)}$$

This index simply includes one of the major cardiovascular influences, the blood pressure, in conjunction with flow velocity. Although blood pressure is not often recorded during TCD examinations, it should become a more critical part of the examination as it can aid in interpretation of relative changes.

Mean resistance index should not be confused with the term ‘cerebral vascular resistance’ (CVR) which is calculated as the ratio of cerebral perfusion pressure to cerebral blood flow:

$$\text{Cerebral vascular resistance} = \text{CPP (mmHg)} / \text{CBF (ml / (100g brain / minute))}$$

where CPP equals the mean arterial blood pressure minus the intracranial pressure. This ratio *cannot* be calculated from transcranial Doppler ultrasound velocity measurements. However, the ‘mean resistance’ is an indicator of cerebral resistance which can be derived from velocity data and does consider the effects of changes in mean arterial blood pressure on the flow velocities. The usefulness of this index will be discussed in Chapter 5.

Since our interest is in Doppler waveform shape, we have developed three new indices to represent major shape changes of the waveform. These new indices are: (Figure 2.30 A-C)

$$\text{Shape Index 1} = \frac{(U_{\min 1} - U_{\min})}{(U_{\max} - U_{\min})}$$

(This index characterises the first velocity plateau produced by the first reflected wave)

$$\text{Shape Index 2} = \frac{(U_{\min 2} - U_{\min})}{(U_{\max} - U_{\min})}$$

(This index characterises the second velocity plateau associated with aortic valve closure)

$$\text{Velocity Rise Index} = \frac{(U_{\text{max}} - U_{\text{max } 1})}{(U_{\text{max}} - U_{\text{max días}})}$$

(This index characterises the velocity maxima along the waveform)

As these are newly-developed indices, their usefulness is yet to be proven. However, these are indices which are linked to changes in the waveform shape. Since we believe that the waveform shape contains a vast amount of information, these indices may prove to be shortcuts in deciphering alterations in waveform shape, especially during vasomotor reserve testing. Chapters 4 and 5 will show the results of these new indices and discuss their utility.

2.2.5 Waveform comparison software

Multiple files comparisons

Since defining and analysing waveform shape is a key to our investigations, then comparison of waveform shapes to each other is a natural extension to the software program. We developed a software feature whereby ensemble-averaged waveforms can be directly compared to one another. This feature allows for comparison of ensemble-averaged Doppler waveforms from: 1) tests done on different days, on a single individual, 2) tests done on different individuals, or 3) different arteries within the carotid or cerebral circulation (Figure 2.31 A-C). This software also allows for incorporation of TCD velocity information which was originally directed either *toward* the ultrasound transducer at the time of insonation (normally seen on TCD equipment as flow above the zero line) such as in the MCA, or with flow *away* from the transducer (generally represented as flow velocity below the zero line) as seen in the basilar artery (Figure 2.31 D). Since almost half of the cerebral velocity signals in transcranial Doppler examinations can be flowing *away* from the transducer, we wanted to ensure that the

system could work in analysing all of the cerebral waveforms which might be acquired from any point in the basal cerebral circulation regardless of the flow direction. This system also works for any artery which can be insonated with a 2 MHz transducer, such as the carotid circulation although the velocities cannot be directly applied to standard velocity criteria for stenosis.

Rescaling

When performing comparisons between the ensemble-averaged waveforms, it is useful to have two options for viewing the waveform shapes: 1) on the standard velocity/timescale to see individual amplitudes of each waveform; or 2) to view the waveforms in relation to a single key waveform or 'baseline'. This we term 'rescaling'. Figure 2.32 depicts the use of both methods. Figure 2.32 A illustrates a situation where the user wishes to compare the actual velocity measurements from a vasoreactivity test on an individual and thereby does not select the rescaling option. However, Figure 2.32 B shows a comparison of the three waveforms from the same individual with rescaling. In this instance, the user may prefer to compare the changes during CO₂ inhalation, and hyperventilation in reference to the initial baseline waveform. Hence the rescaling option is selected. Figure 2.33 shows how Doppler waveform comparisons (with and without rescaling) can be used to identify the differences in waveform shape in subjects of varying ages.

In summary, waveform comparison software could be a clinically useful tool in the future when tracking the progression/regression of pathology, evaluating treatment results of a single individual, or groups of individuals over different time points or during physiological testing.

2.3 System summary

The unique features of our acquisition system and contour analysis software are that it:

- combines commercially available hardware components to acquire and synchronise cerebral Doppler velocity information with other physiologically linked parameters such as ECG and ETCO_2 , and allows measurement of these parameters through on-line callipers;
- gives a clearer representation of waveform contours and thereby allows for more discrete contour analysis to take place;
- ensemble-averages the cerebral artery peak velocity envelope data over the acquired heartbeats during a 16-second continuous data collection, and displays the standard deviation;
- calculates from the ensemble-averaged waveform three local velocity minima, three local velocity maxima, maximum acceleration of the waveform and two deceleration points, and time values from the peak of the ECG R wave to all major velocity maxima, minima, and acceleration/deceleration measurements;
- matches the slow decrease of the last part of the averaged velocity (diastole) with an exponential decrease and gives the value of the time constant (τ) of the exponential decrease associated with the arterial Windkessel;
- plots a three-dimensional figure displaying the beat-to-beat velocity variations within the ensemble-averaged data;

- compares multiple TCD waveforms within a single subject or from multiple subjects, with or without rescaling options;
- collects common TCD diagnostic parameters (peak velocity, end-diastolic velocity and mean velocity) for user familiarity;
- calculates common TCD indices (PI, RI), and provides the data for our proposed four new cerebral indices;
- exports characteristic values into a spreadsheet.

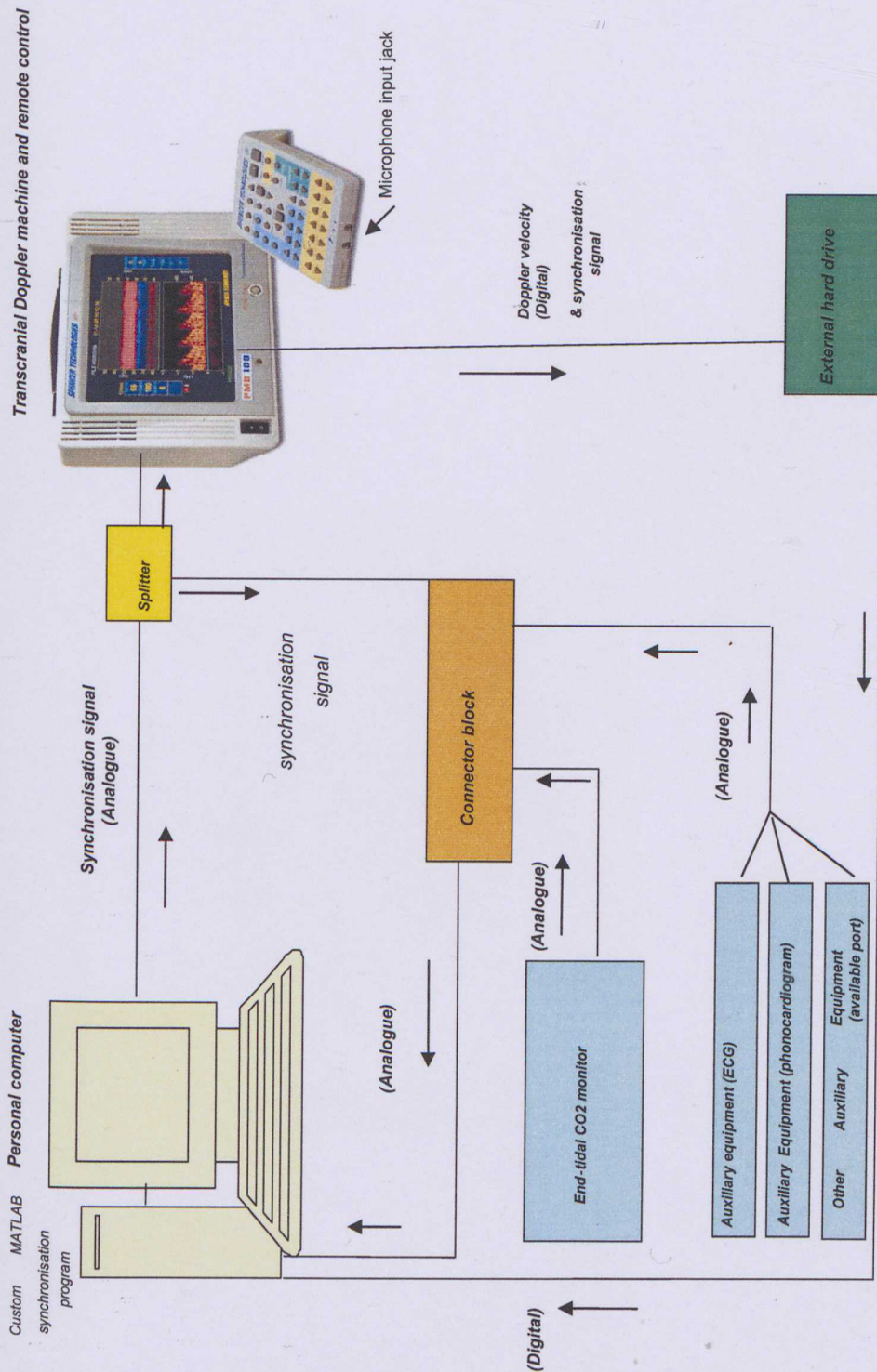


Figure 2.1 The hardware architecture of the acquisition system with the components and routing of the synchronisation signals.

Transcranial Doppler machine

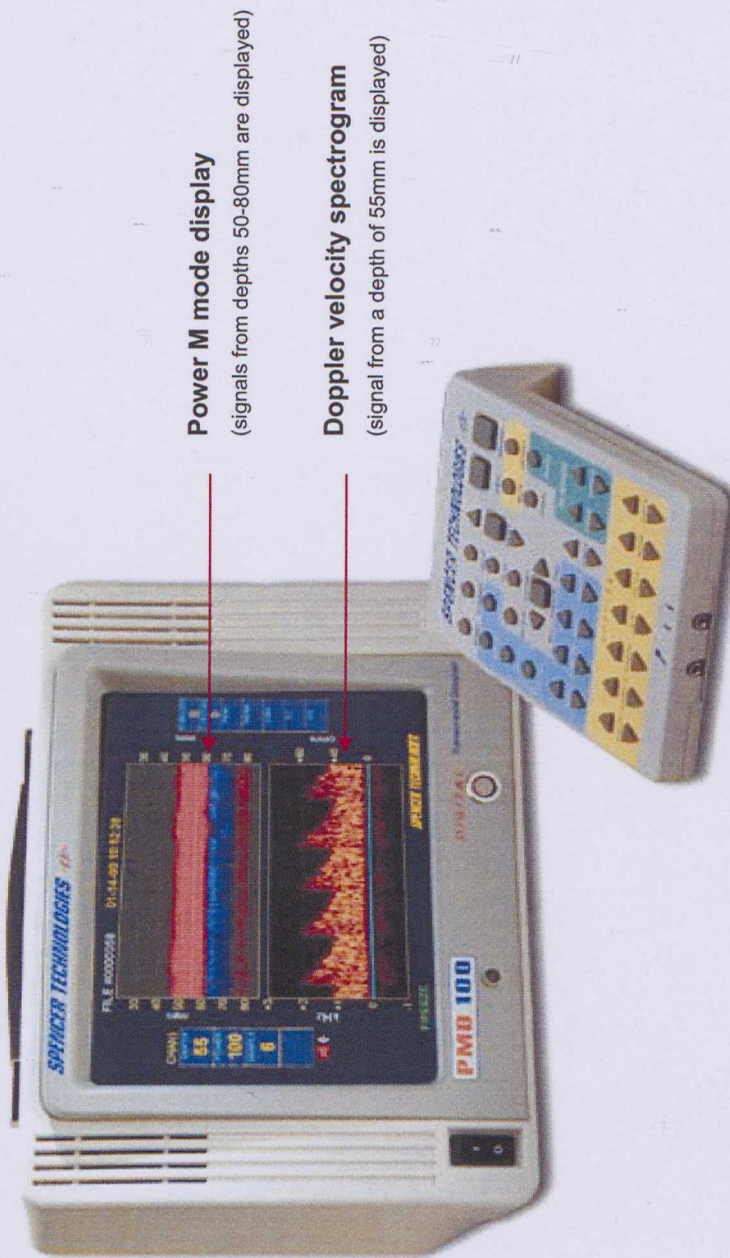


Figure 2.2 Spencer Technologies PMD 100 Transcranial Doppler machine and remote control unit. TCD screen display shows power M-mode display, and Doppler velocity spectrogram. (Photograph courtesy of Spencer Technologies)

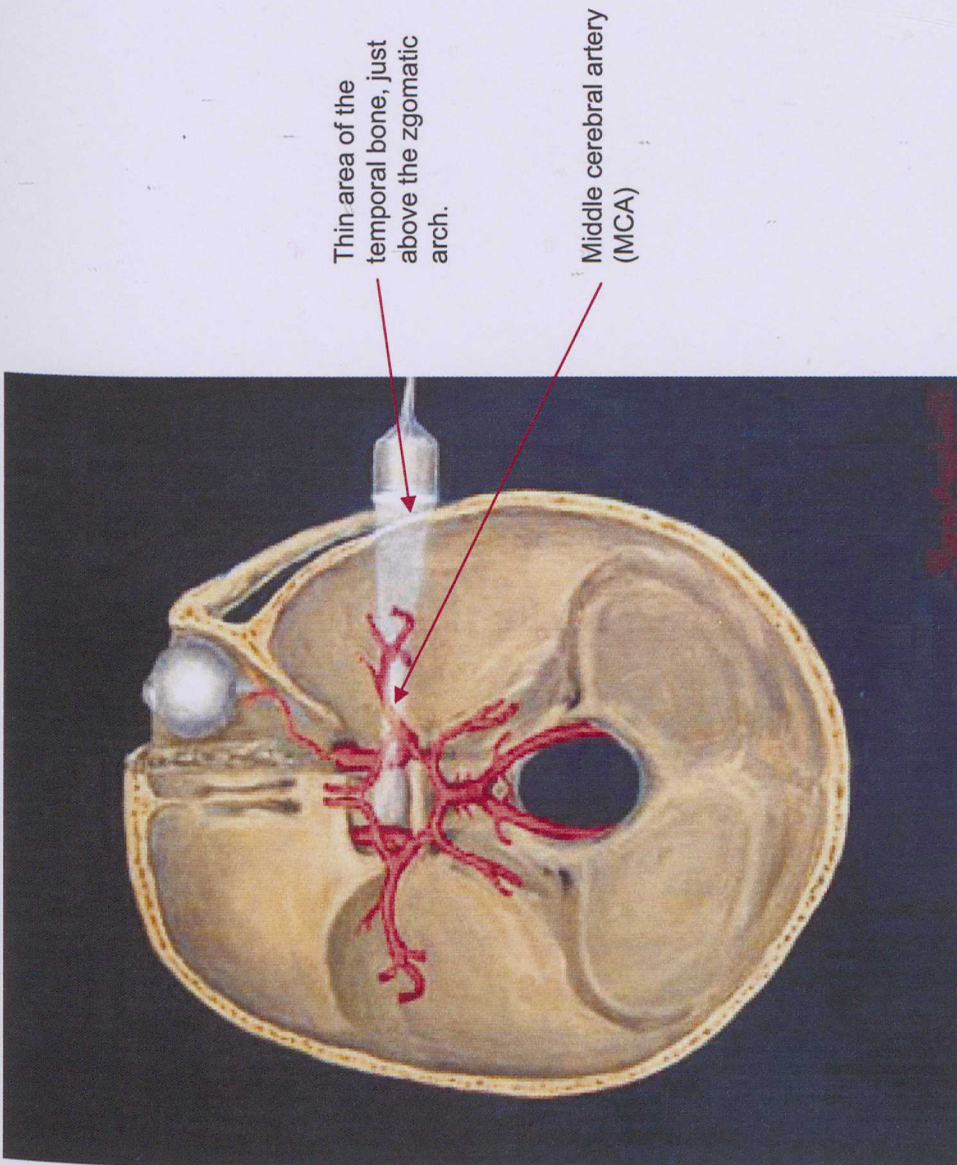


Figure 2.3 Photograph of an original painting by Rune Aaslid showing the cranium and cerebral vessels (courtesy of Rune Aaslid). A Doppler ultrasound beam illustrates the insonation of cerebral vessels through a thin portion of the temporal window.



Figure 2.4 Spencer Technologies MARC 600 head fixation device.
The red arrow points to the 2 MHz ultrasound transducer attached to the headband for stabilisation.
(Photograph courtesy of Spencer Technologies)

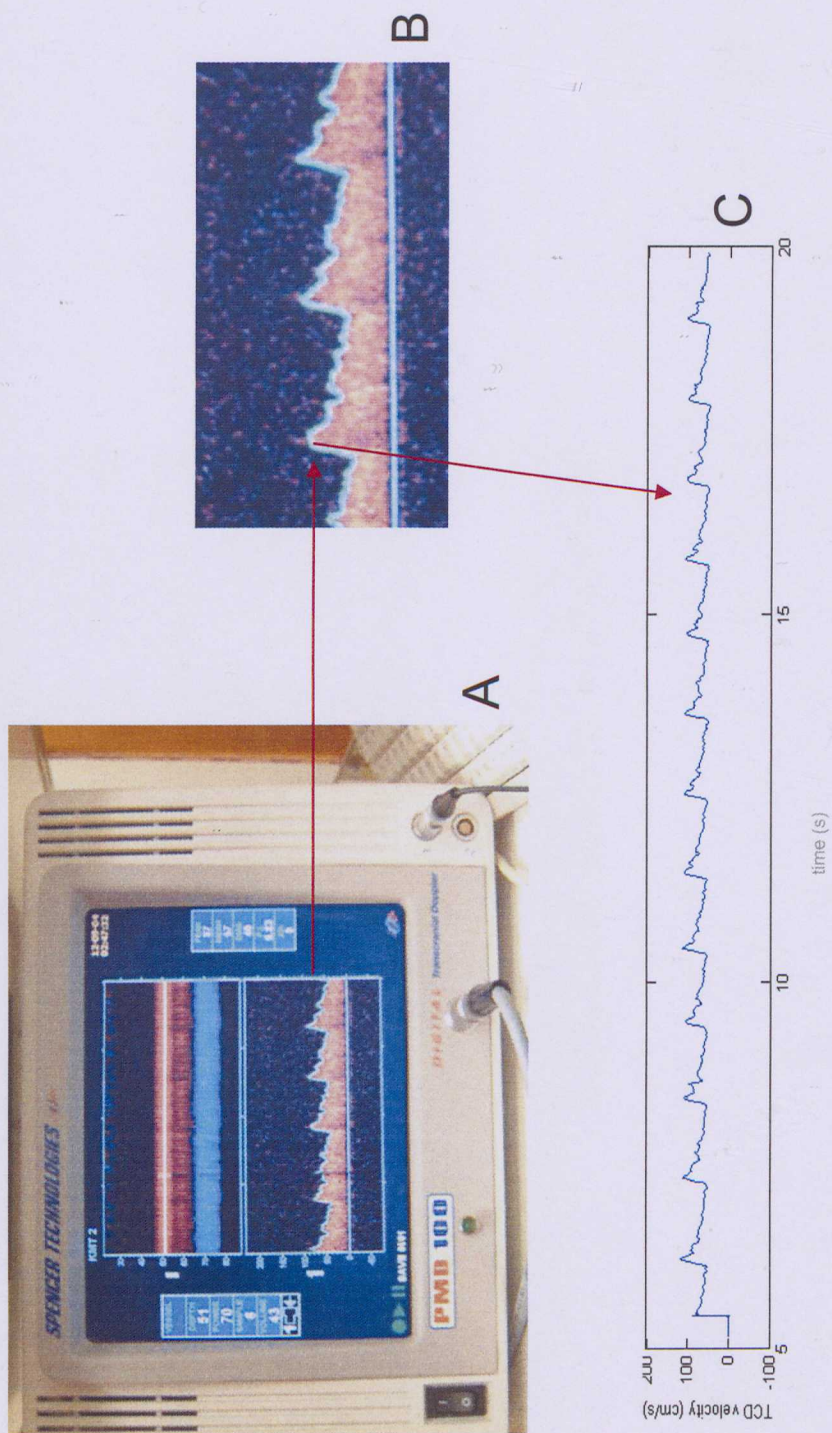


Figure 2.5 is a representation of the TCD “peak velocity envelope” data. **A)** shows the TCD recording, **B)** a zoomed image of the TCD velocity data. The light blue line is outlining the highest spectral velocities, which is termed the “peak velocity envelope”. **C)** shows the velocity outline extracted by the system over the recording period.

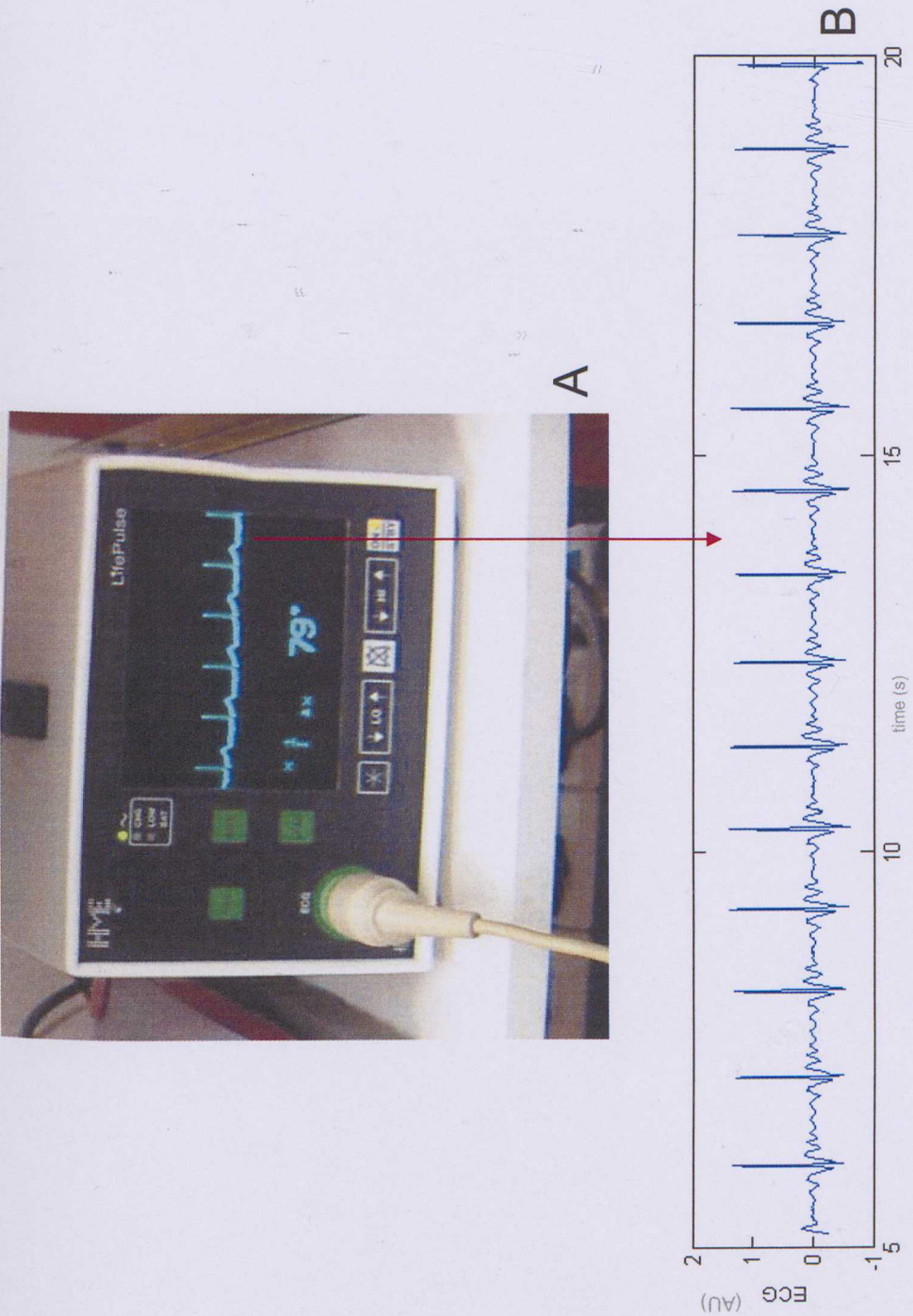


Figure 2.6 A) ECG monitor and B) ECG trace extracted by the system.



Figure 2.7 A) End-tidal CO₂ monitor, and B) extracted trace of approximately 3 respiratory cycles over the recording period, with measurement (48 mmHg)

analogdat_BK valve 2_20040701T104011_1_Synch

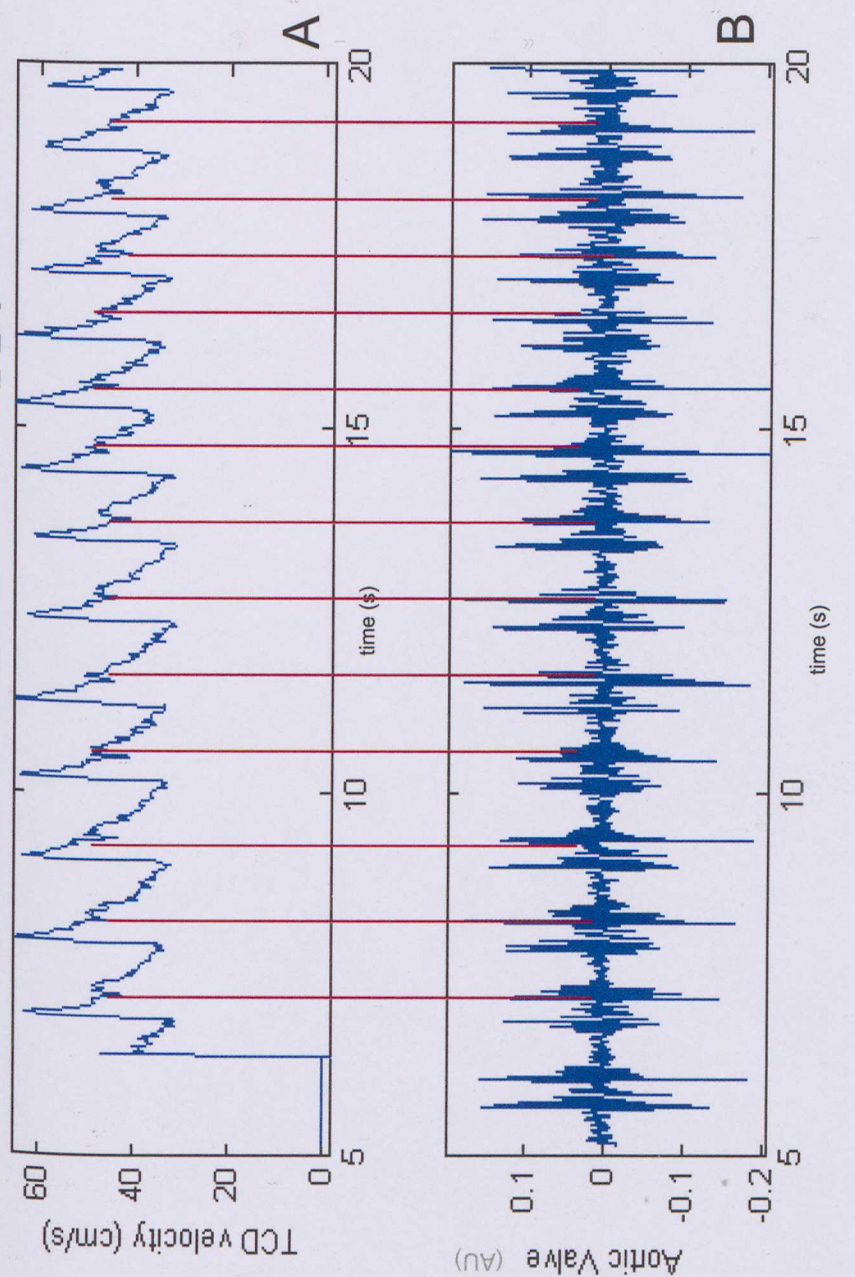


Figure 2.8 A) Measurement by TCD of the velocity envelope “dicrotic notch”, as compared to B) the second heart sound (S2) as recorded by the phonocardiogram. Red lines indicate the alignment of the notch and S2 (aortic valve closure). C) Signature of aortic valve closure on cerebral waveform. D) Red arrow points to region on peripheral arterial waveform (common femoral artery) where backflow signifies aortic valve closure. (Red vertical lines on main image have been visually defined and are an approximation of the dicrotic notch and S2).

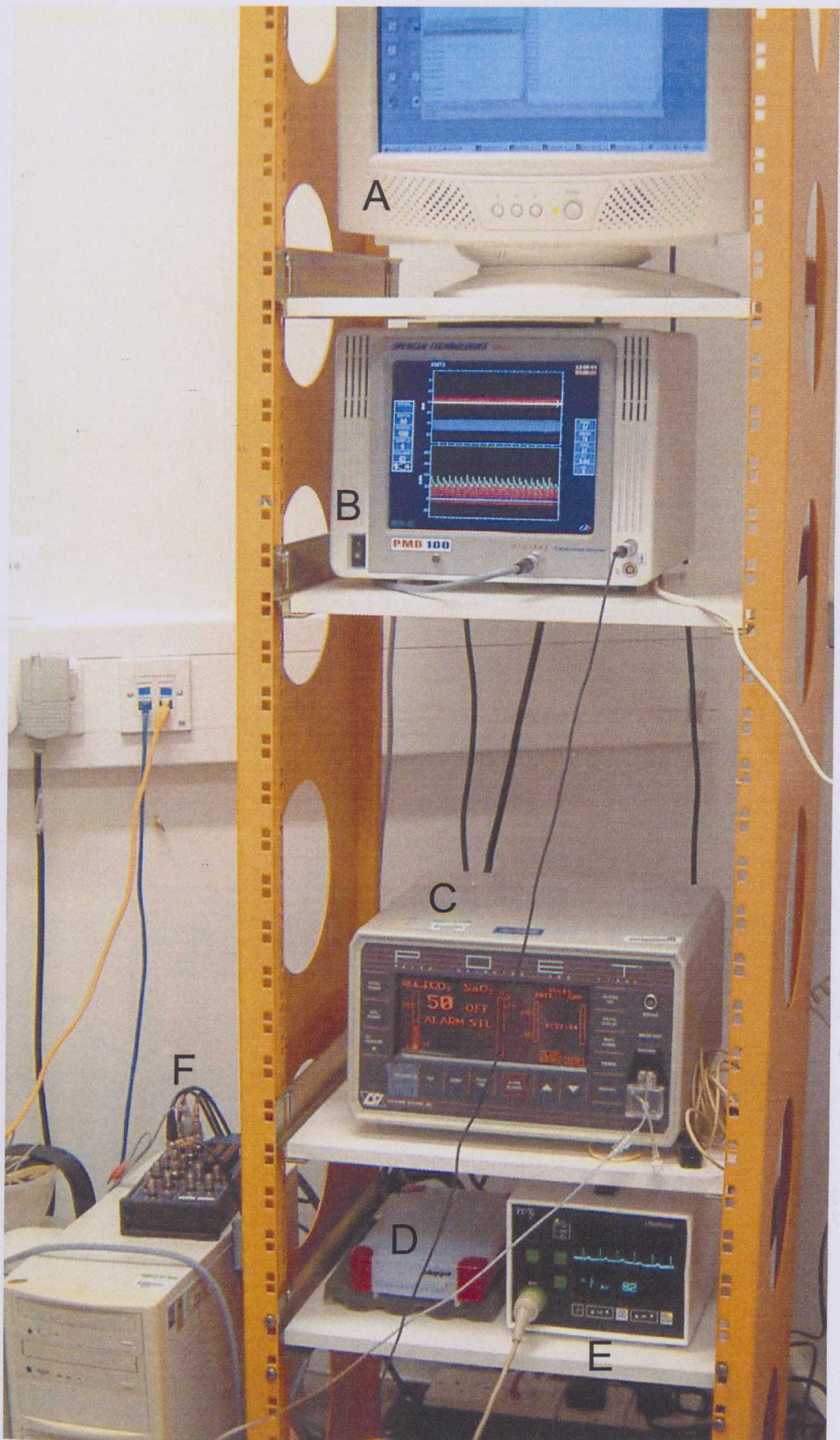


Figure 2.9 A photograph of the acquisition system hardware with the **A)** PC, **B)** TCD, **C)** ETCO₂ monitor, **D)** external hard drive, **E)** ECG, and **F)** connector block.

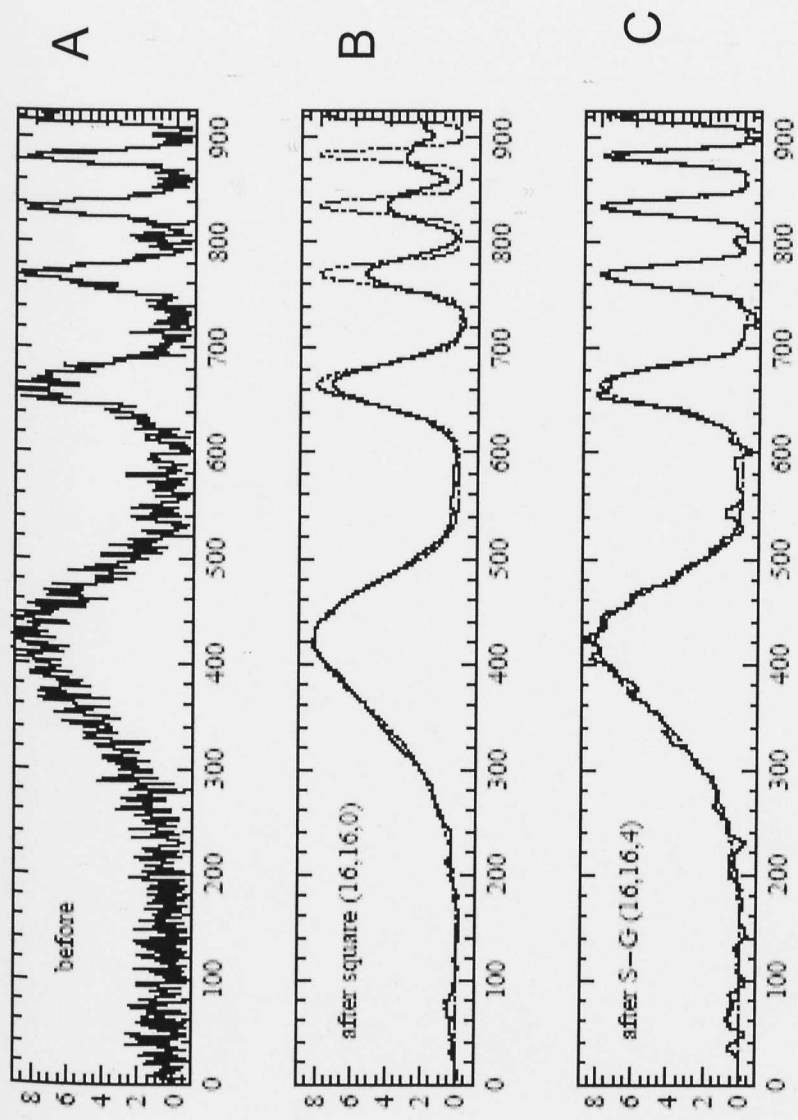


Figure 2.10 A): Synthetic noisy data consisting of a sequence of progressively narrower bumps, and additive Gaussian white noise. B) Result of smoothing the data by a simple moving window average. Note that the narrow features are broadened and suffer corresponding loss of amplitude. The dotted curve is the underlying function used to generate the synthetic data. C) Results of smoothing the data by a Savitzky-Golay smoothing filter (of degree 4) using the same 33 points. While there is less smoothing of the broadest feature, narrower features have their heights and widths preserved. (from Numerical Recipes in C: The Art of Scientific Computing, [Press et al., 1992])

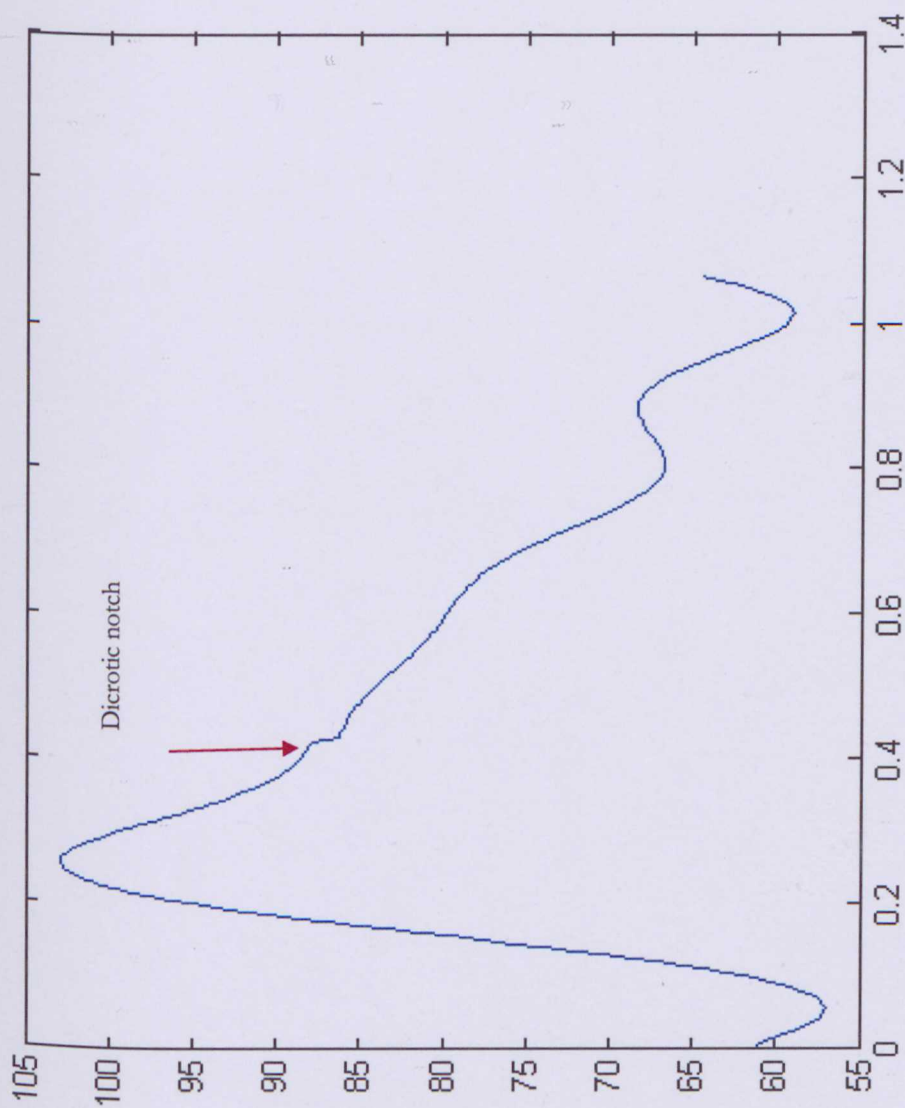


Figure 2.11 Example of a Doppler waveform which has been over-smoothed and hence lost important velocity contours. Arrow indicates the location where a dicrotic notch is normally located but is hardly noticeable in this waveform.

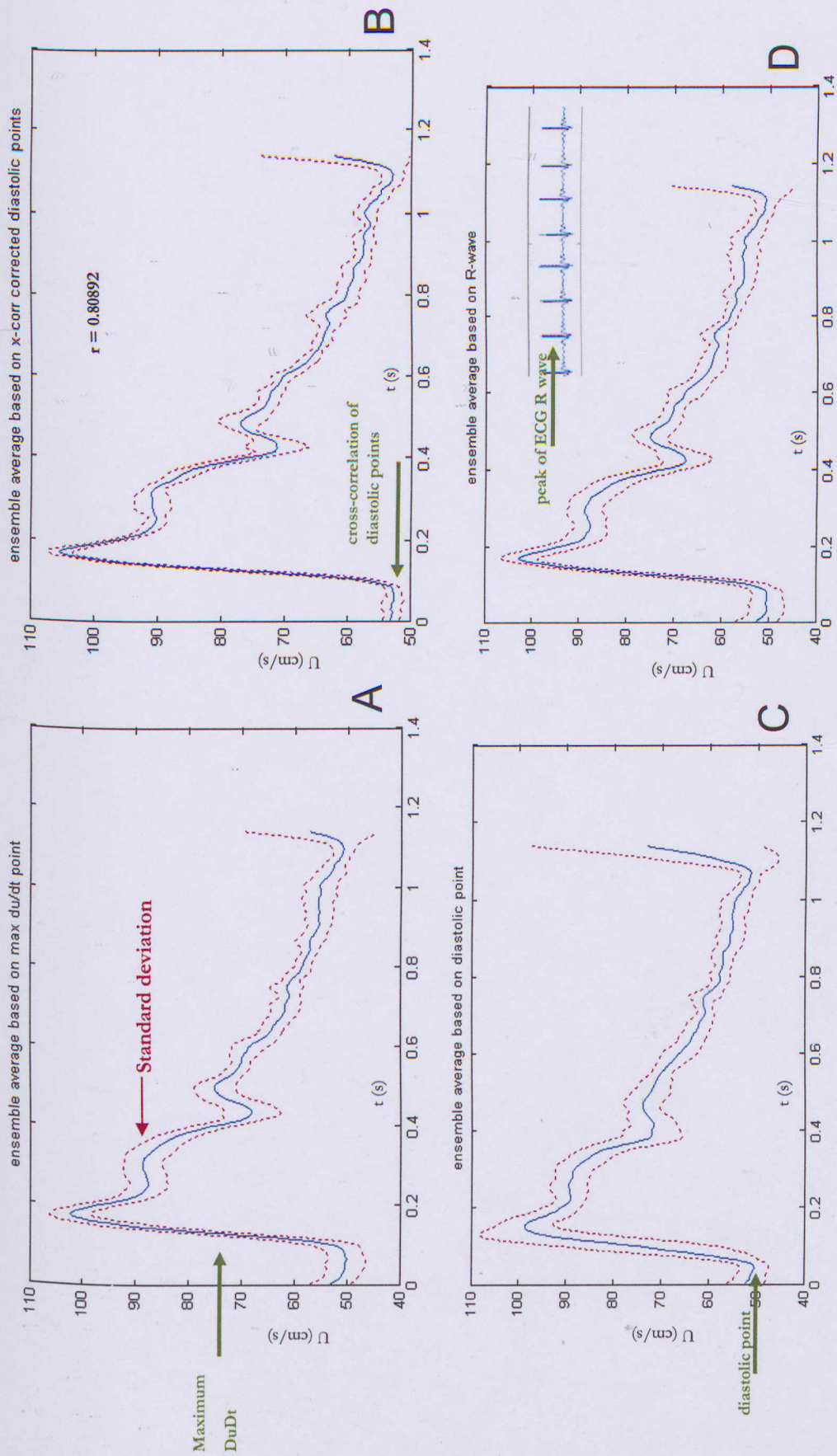


Figure 2.12 Ensemble-averaging of the same 11 cardiac cycles of Doppler velocity waveforms are depicted using 4 different methods: **A**) maximum Du/Dt ; **B**) cross-correlation of diastolic points; **C**) diastolic points alone; **D**) alignment based on the peak of the ECG R wave (dotted lines indicate standard deviation). (Continued on next page)

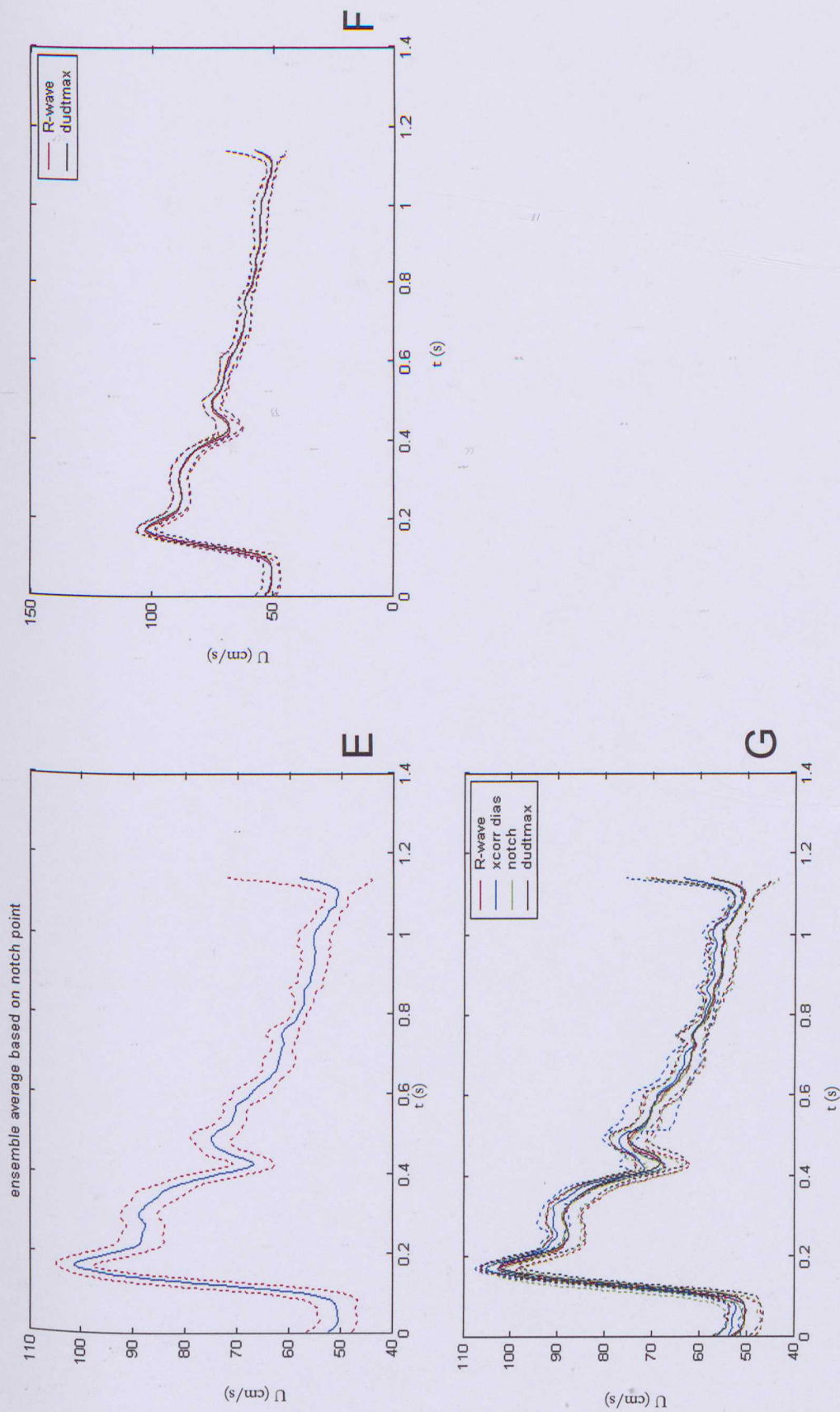


Figure 2.12 continued. E) ensemble-averaging based on the dicrotic notch point, F) results if 2 parameters are used for averaging (peak of ECG R wave and DuDmax, (note change of scale) G) if all parameters are selected. Note the differences in the standard deviation for each ensemble-averaging technique.

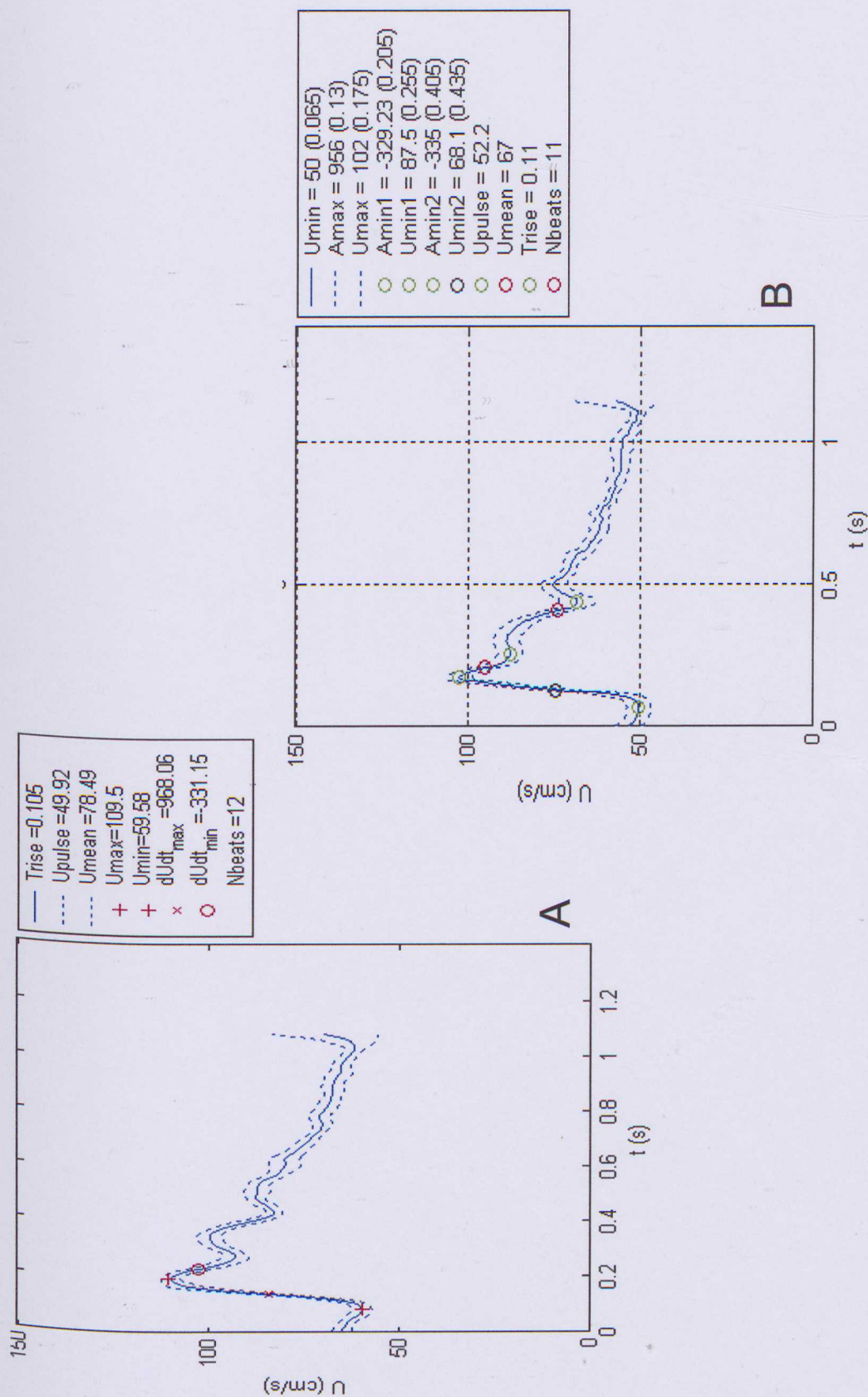
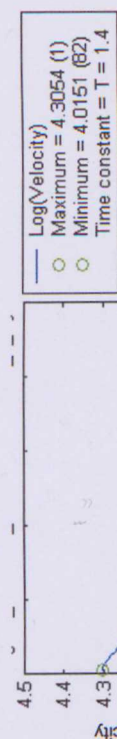
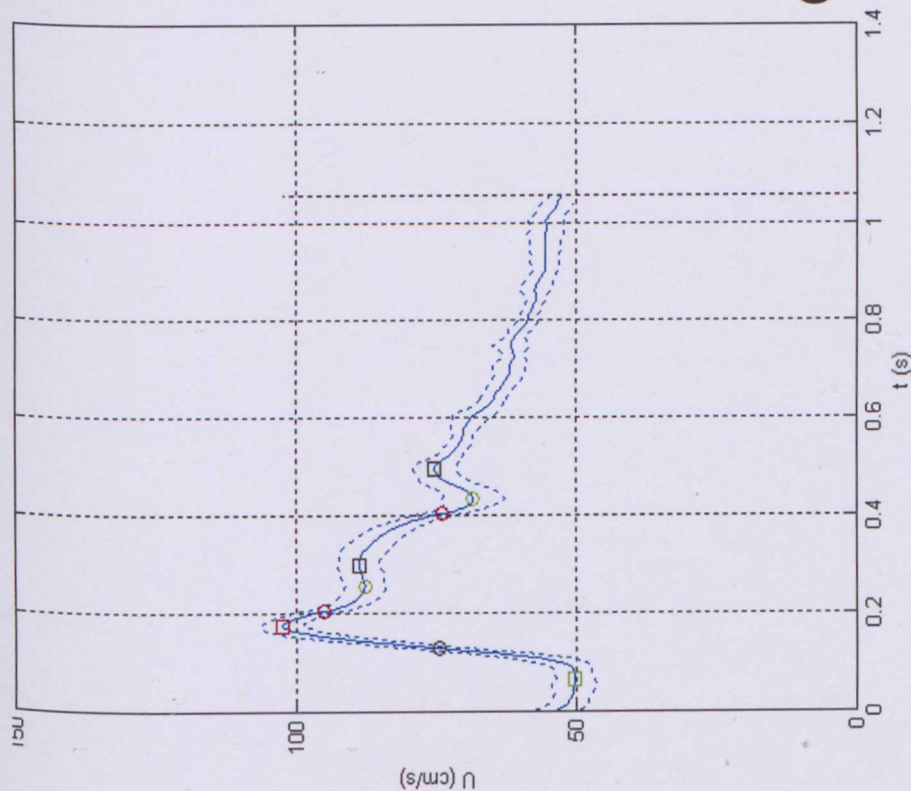


Figure 2.13 **A)** results box during early software development; **B)** further analysis and expanded results display (Continued on next page)



C

Note: this example of Tau is taken from a different subject.

Figure 2.13 continued C) final version of the results display box.

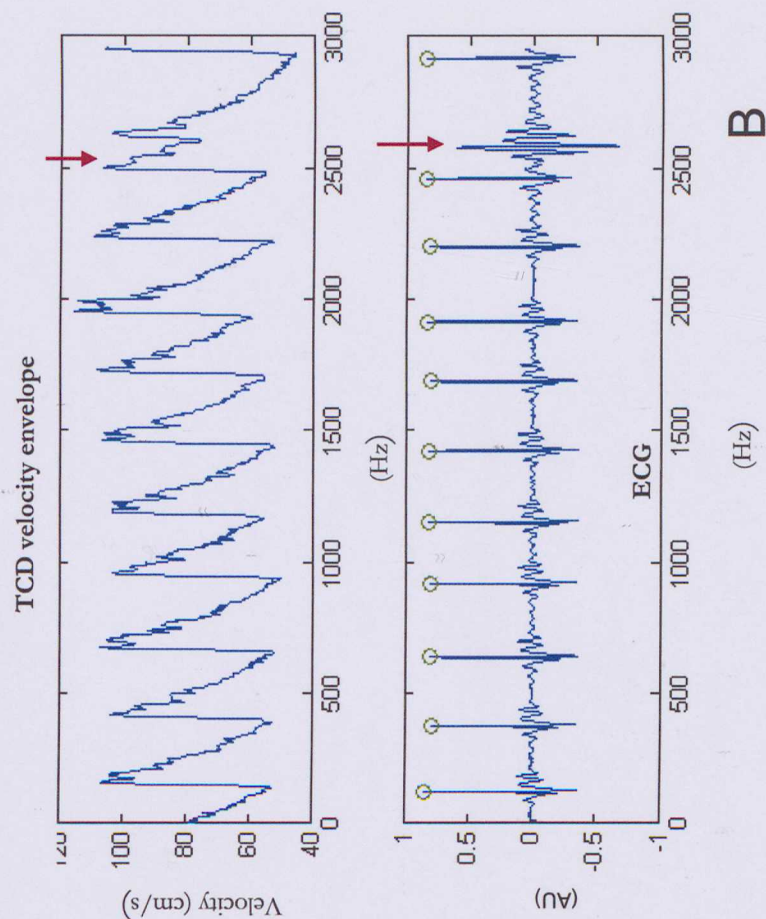
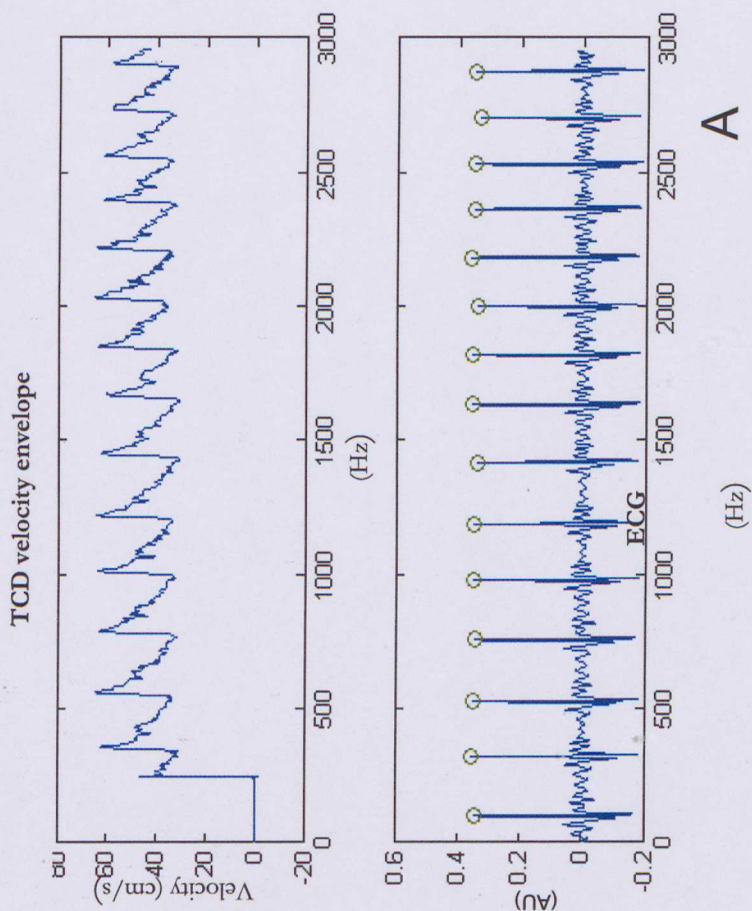


Figure 2.14 A) Normal cardiac rhythm with corresponding TCD velocity envelope. B) Displays irregular heart beats which should be de-selected before ensemble-averaging. Arrows point to an irregular heart beat which would be rejected from the ensemble-averaging process. Note its effect on the cerebral waveform.

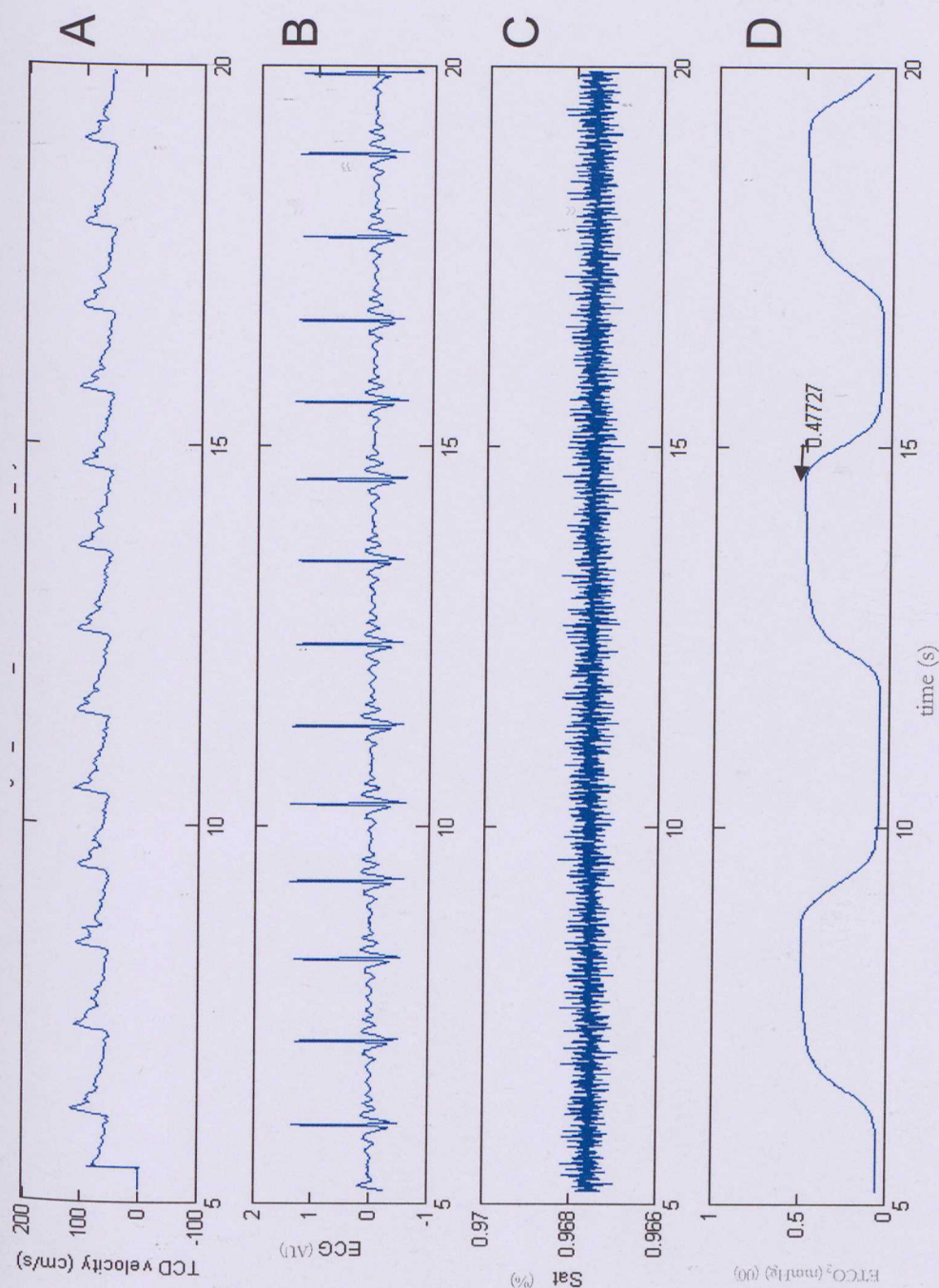
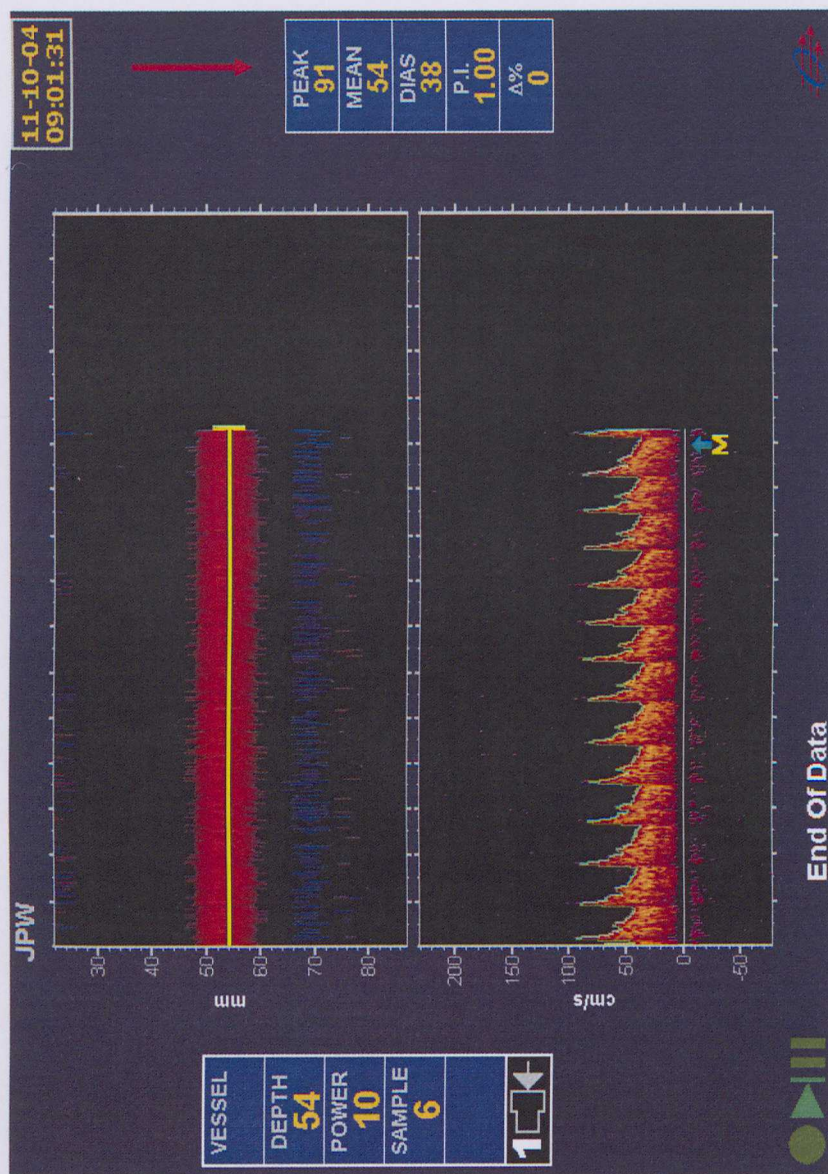
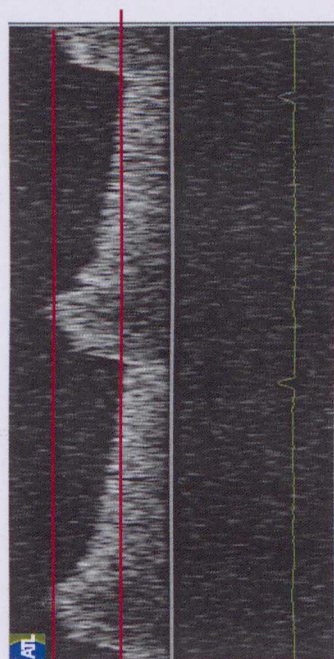


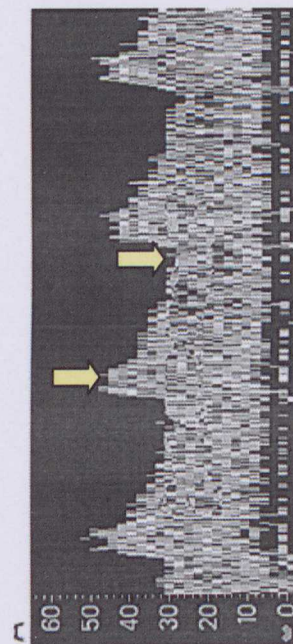
Figure 2.15 An example of extracted and synchronised traces from digital and analogue equipment for use in contour analysis software. (The arrow points to the measurement of ET/CO₂)



C



A



B

Figure 2.16 shows the transcranial Doppler waveform representations and measuring techniques of different TCD systems. A) A TCD duplex ultrasound machine with callipers, B) a non-imaging TCD machine and callipers, C) non-imaging TCD machine with "running update" values (red arrow). This box shows the average of the last 4 cardiac cycles of information. Mean velocity and PI are derived values.

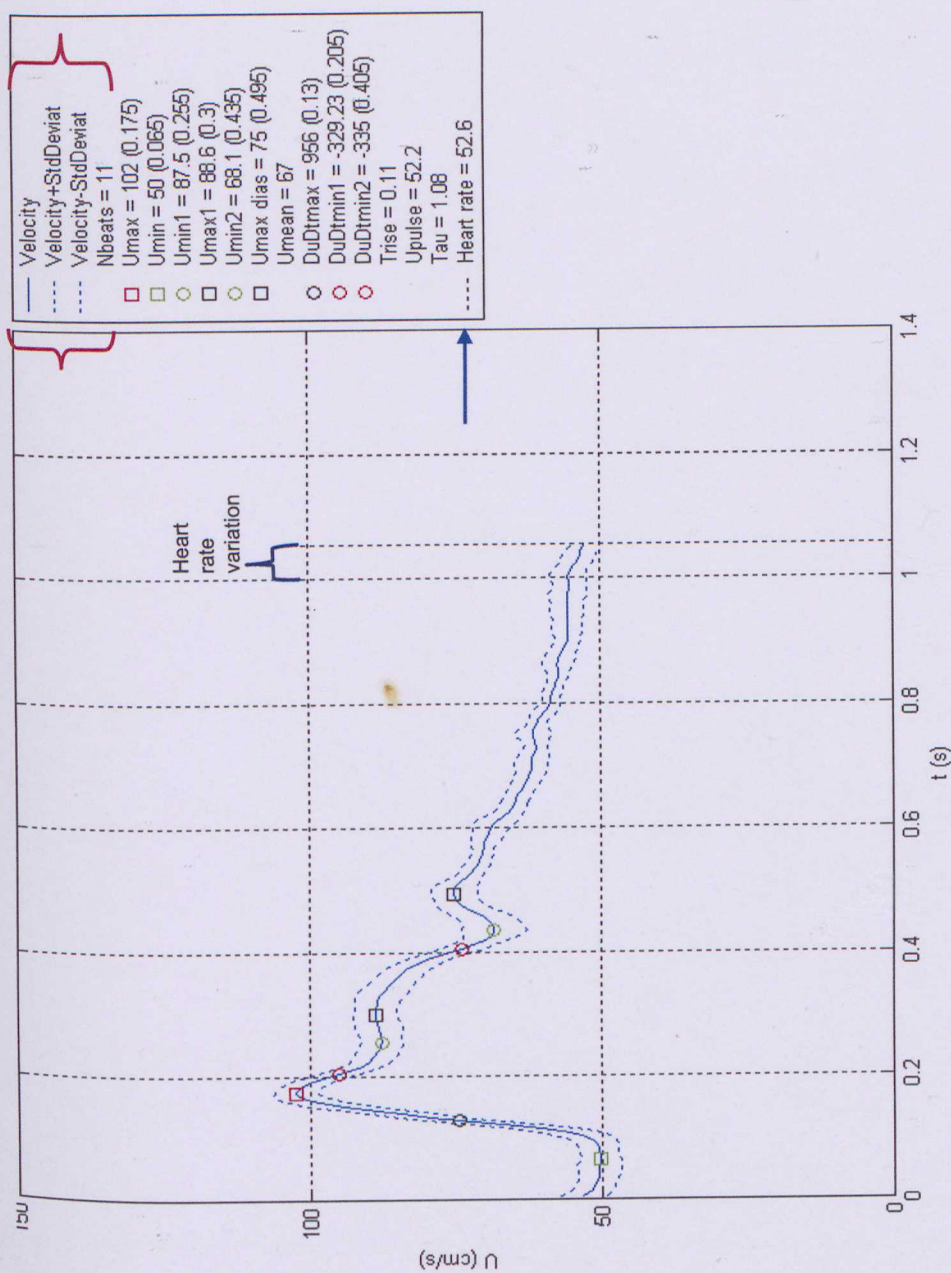


Figure 2.17 shows the peak velocity envelope (blue solid line), and the standard deviation of the envelope data (blue dotted line). In addition, the averaged heart rate is shown in the results box, and the variation is shown by the blue dotted vertical line.

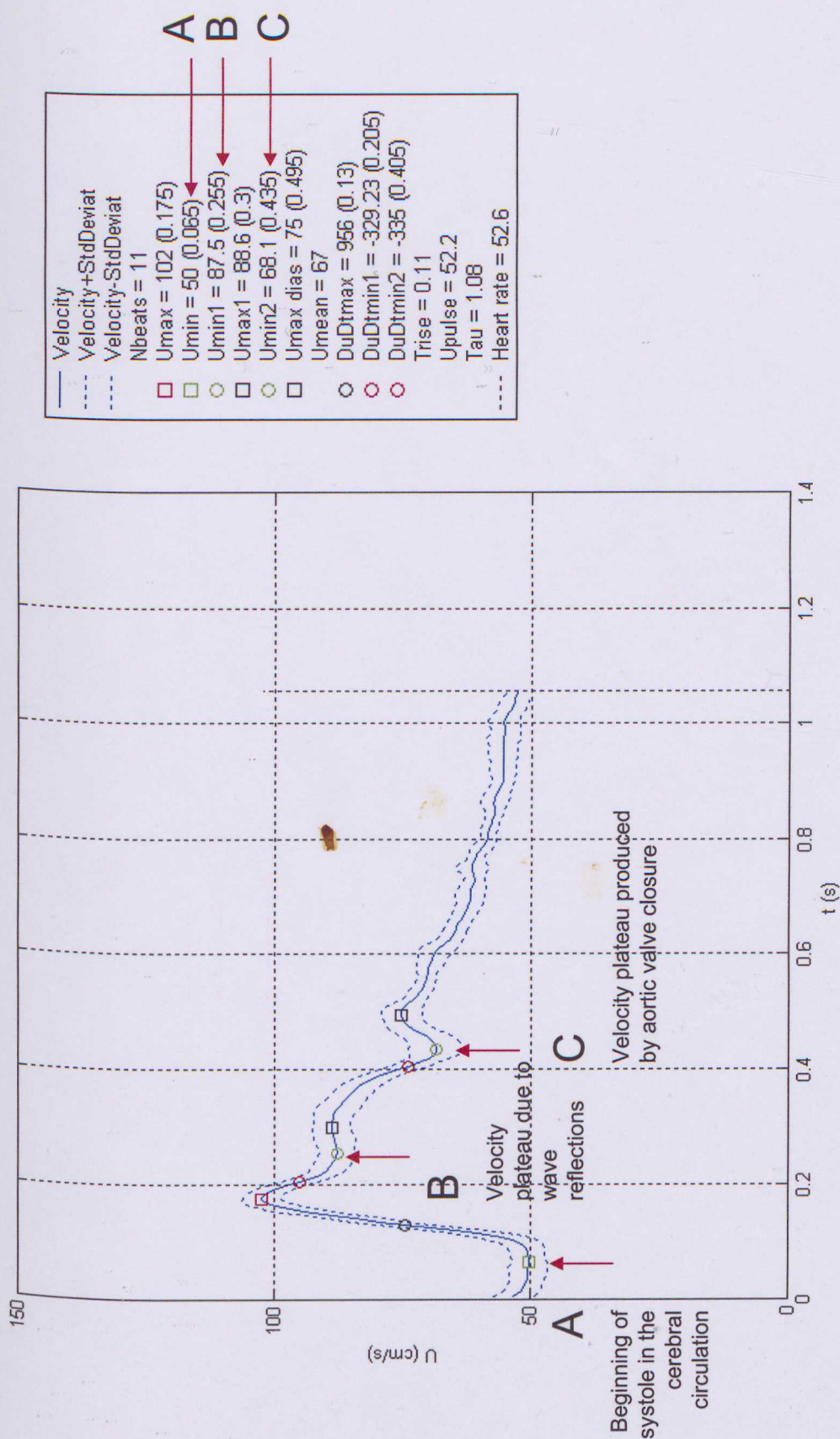


Figure 2.18 shows the three velocity minima measured in the contour analysis, and their physiological definitions. **A**) Umin (also known as EDV), **B**) Umin1, **C**) Umin2.

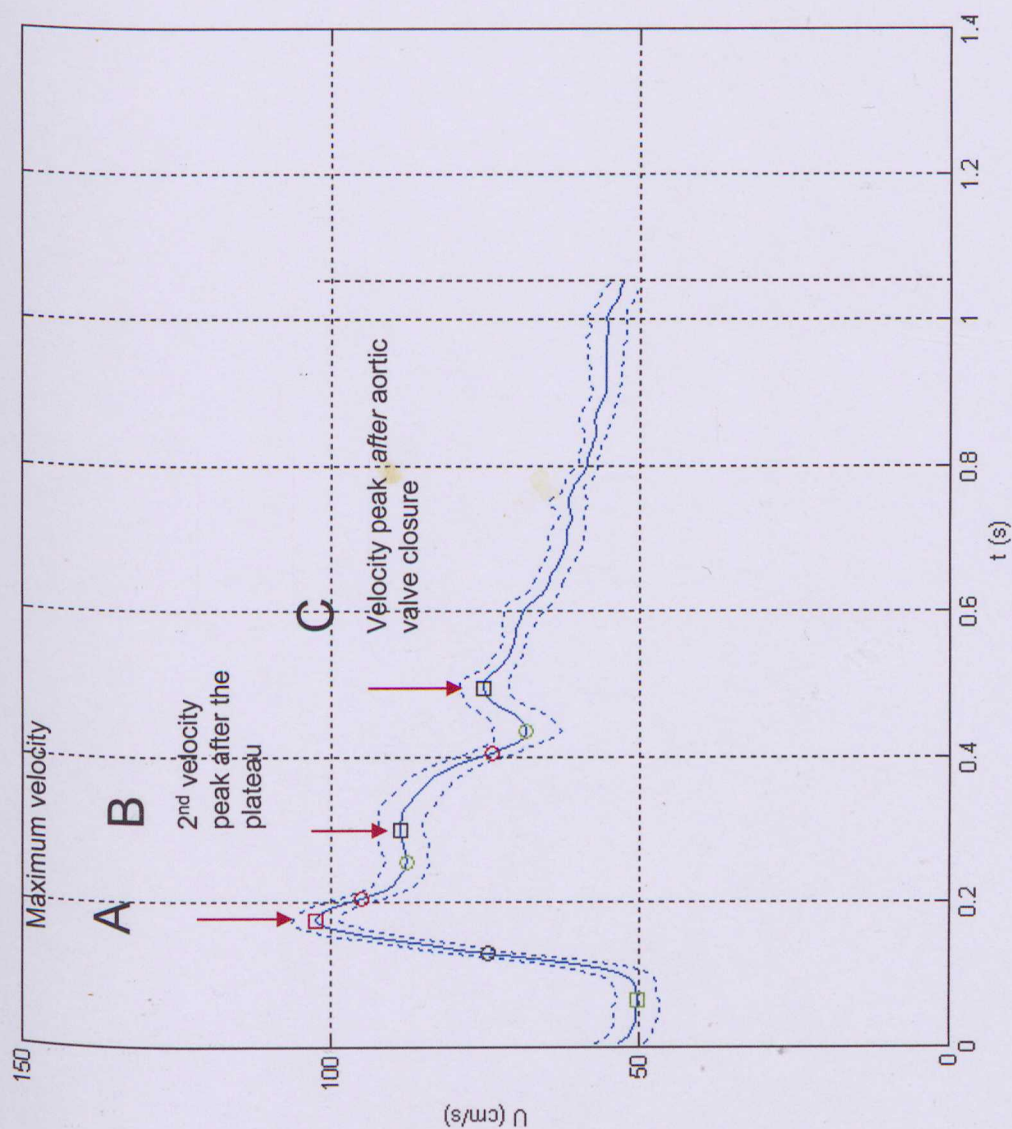


Figure 2.19 shows the three velocity maxima measured in the contour analysis, and their physiological definitions. **A)** Umax (also known as PSV), **B)** Umax1, **C)** Umaxdias.

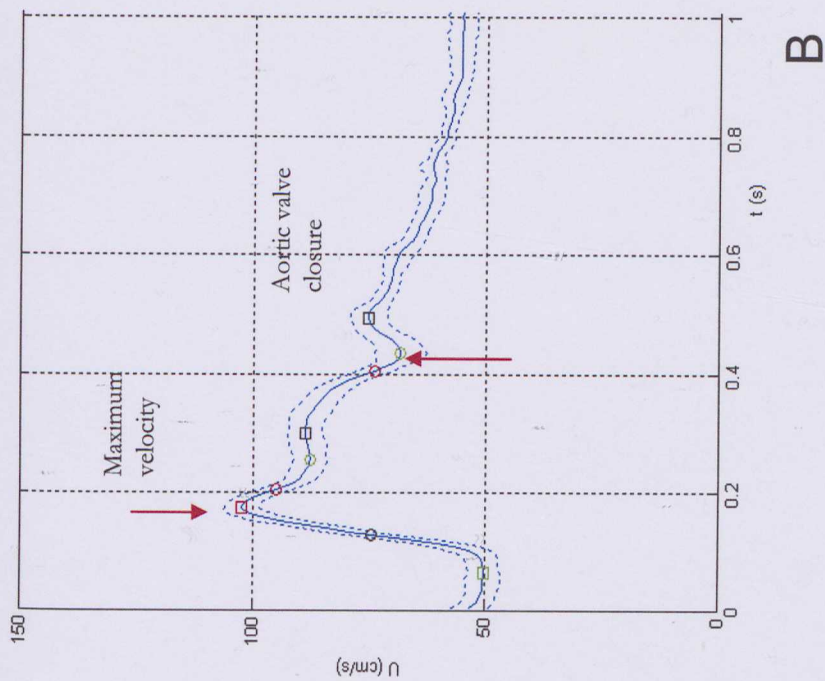
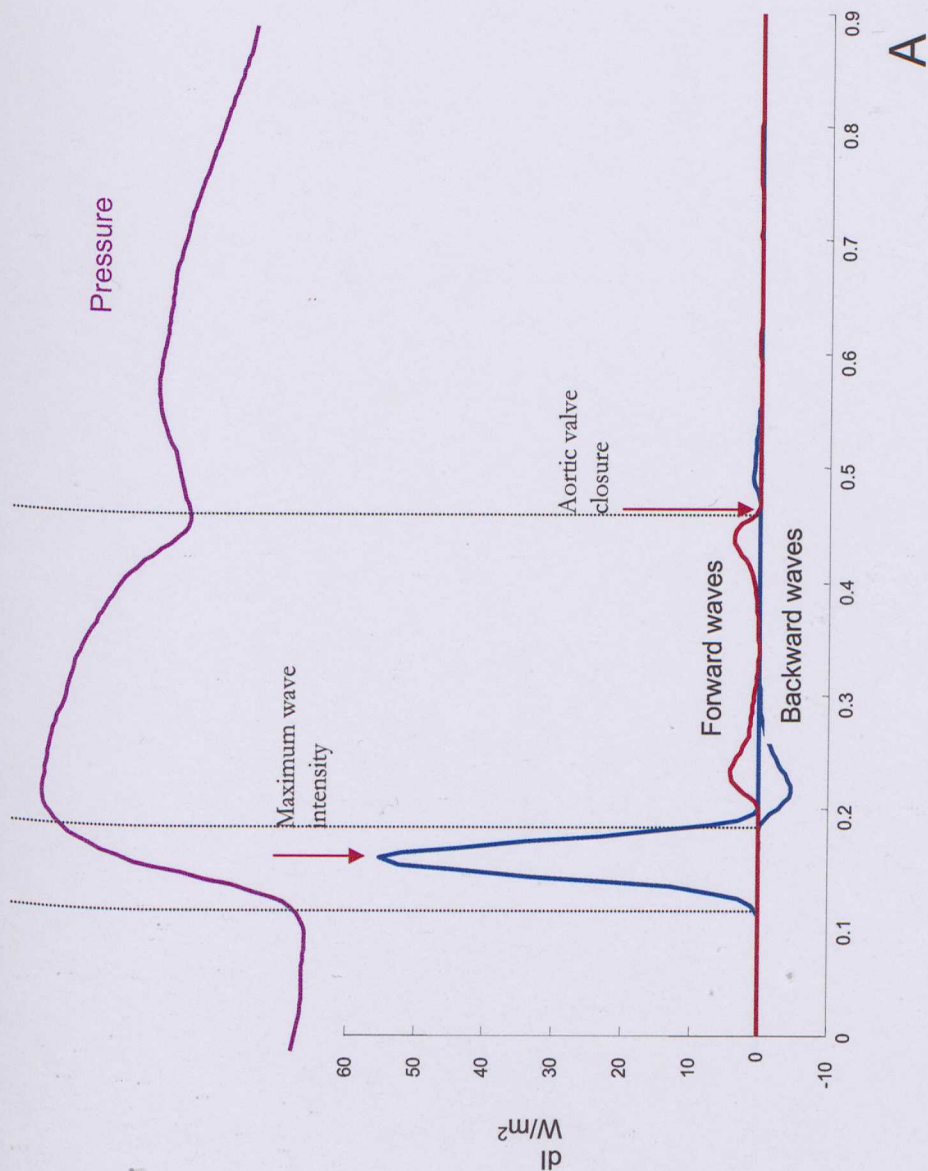


Figure 2.20 A) Schematic of forward and backward moving waves through the carotid artery during the cardiac cycle (study of wave intensity analysis in the carotid artery, courtesy of Dr. Andrew Zambanini). This depicts the complex series of waves which occurs between the point of maximum acceleration and the closure of the aortic valve. **B)** Example of a cerebral artery waveform showing the contours during this time phase.

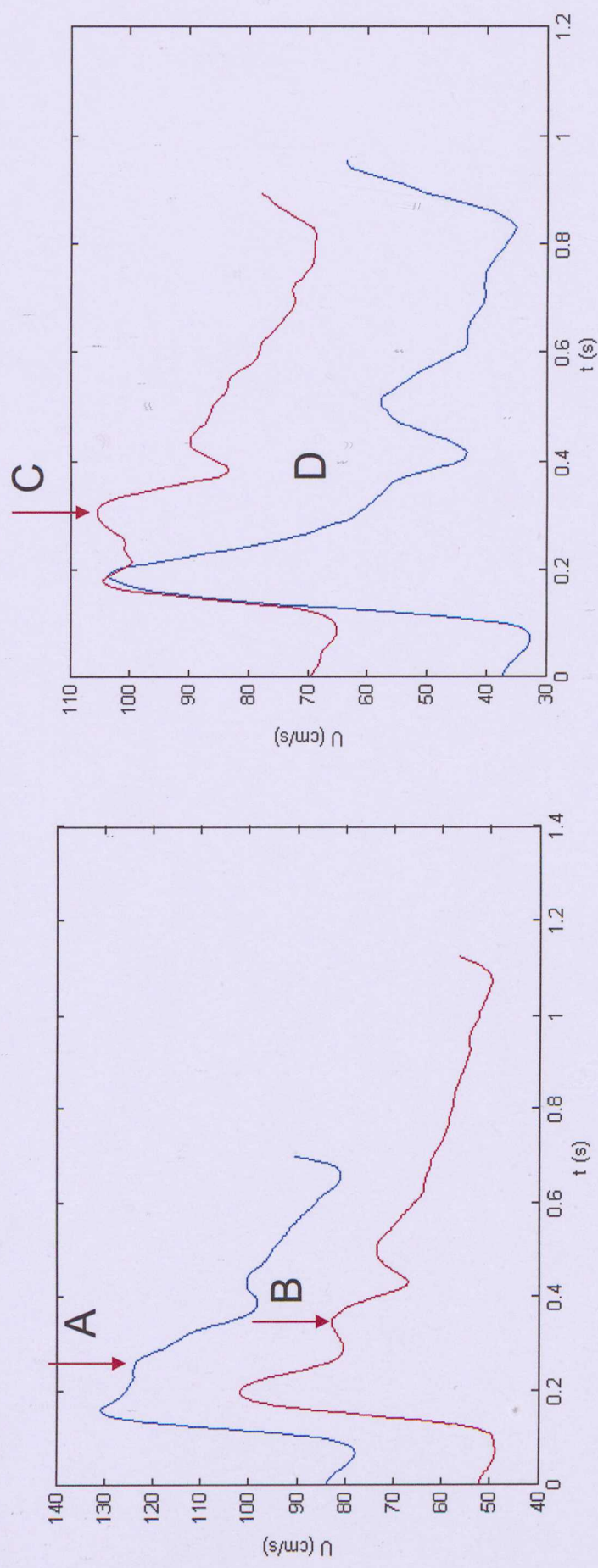


Figure 2.21 Examples of some of the possible variations of $U_{\max 1}$. **A)** This illustration shows very little velocity increase after the first velocity plateau ($U_{\min 1}$), however both **B)** and **C)** show noticeable rise in the velocity after the plateau. **D)** shows no velocity rise at all.

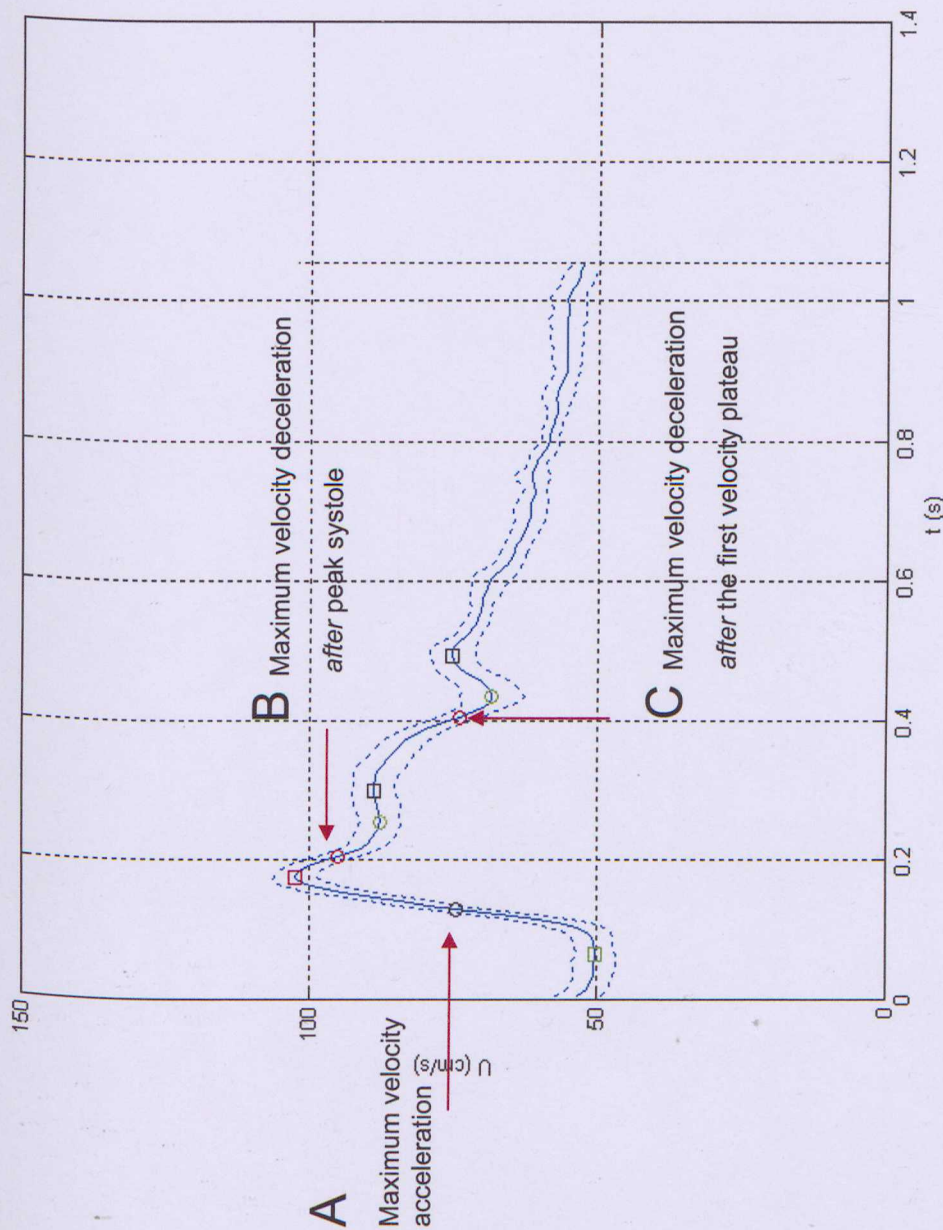


Figure 2.22 shows **A**) the maximum acceleration measured in the first portion of the Doppler waveform, and two points of velocity deceleration (**B** and **C**) which are measured from the waveform contour. The maximum slope of each of the measured points is shown by the red arrow, and corresponding circle.

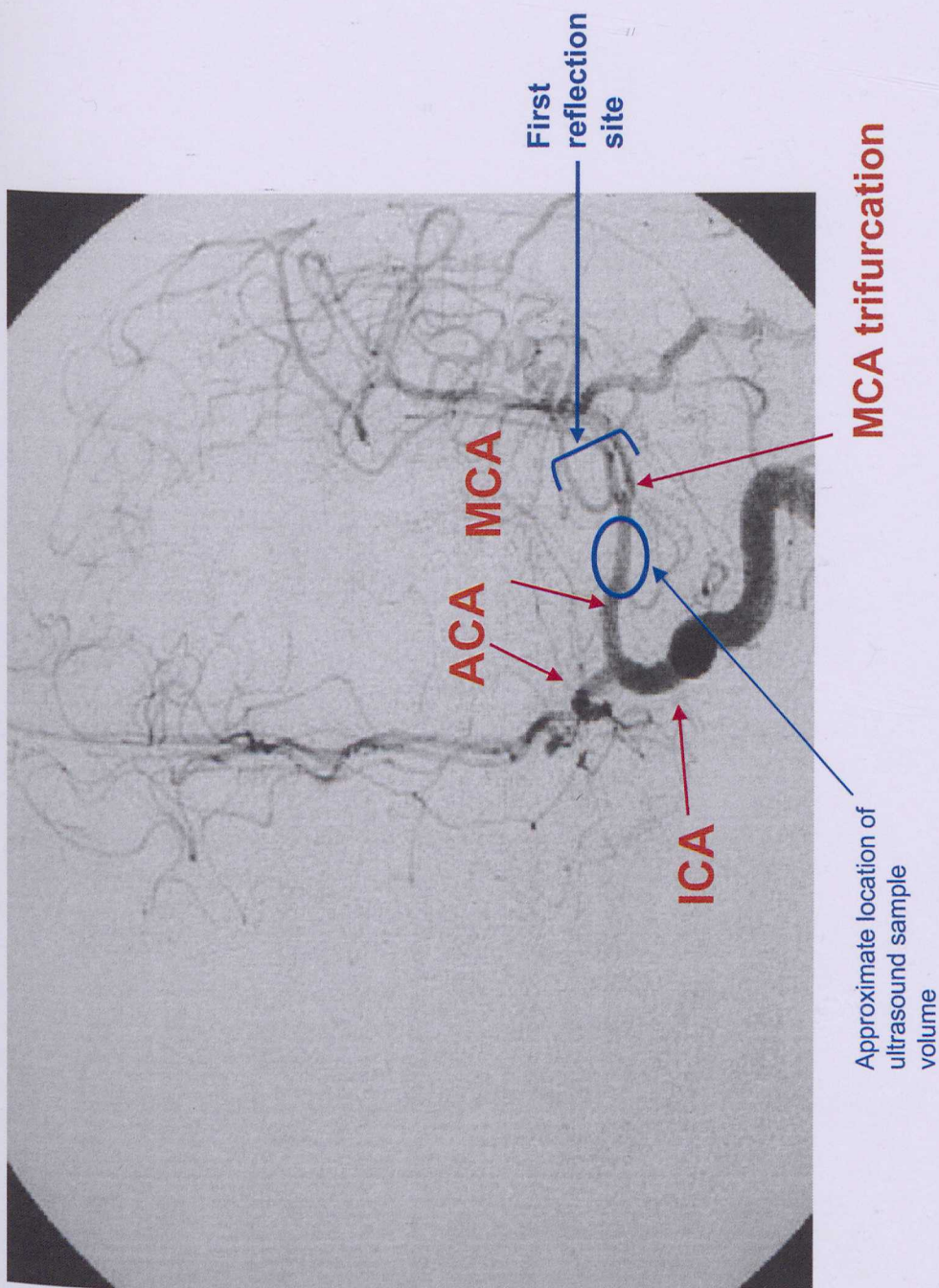


Figure 2.23 Cerebral angiogram of left MCA, ACA and ICA. Note the MCA branches into 3 vessels (known as the trifurcation). This branching may be the first site of wave reflection which is detected by the Doppler. This negative or backward wave is responsible for velocity deceleration (DuDumin1) and the first velocity plateau (Umin1). (Cerebral angiogram courtesy of Dr. Manish Shrivastav, King Edward Memorial Hospital, Mumbai, India)

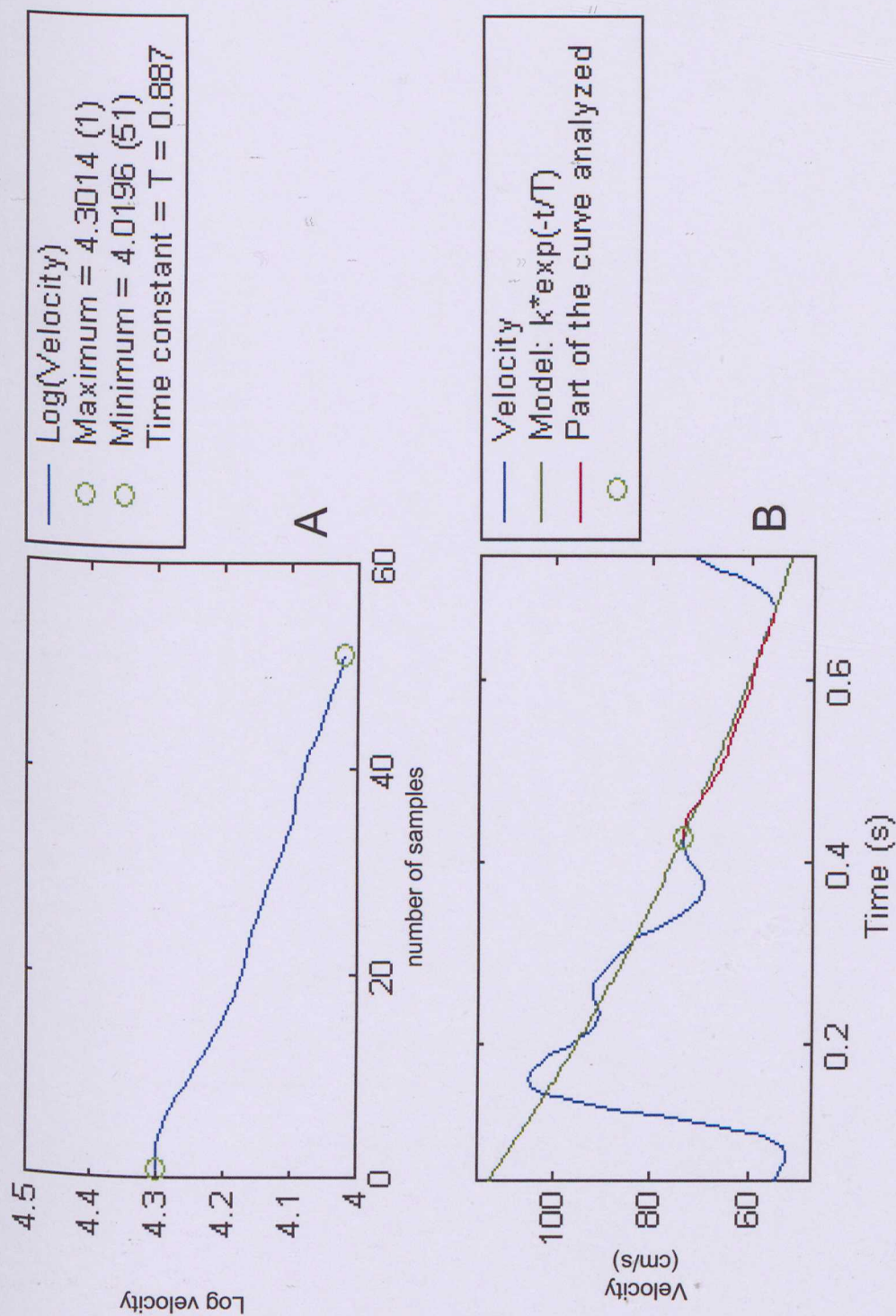


Figure 2.24 Value of the time constant that characterises the exponential decrease of the last part of the velocity curve. A) Part of the curve analysed, B) part of the curve analysed in red.

Each coloured line represents a new test on the same healthy subject, but with varying heart rates.

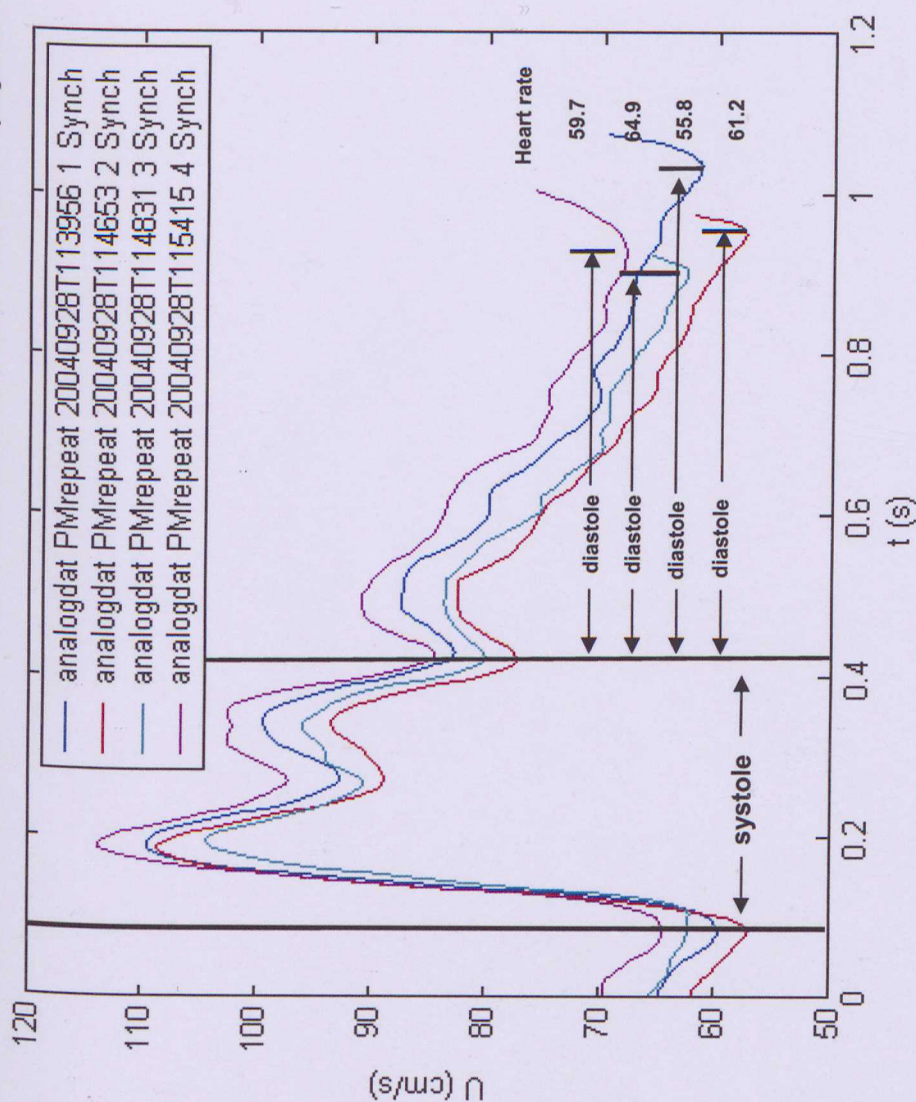


Figure 2.25 Cerebral systole begins approximately 10 ms after the peak of the ECG R wave. This is an example of the ensemble-averaged waveform from the same subject, but taken during different heart rates. Note, it is mainly diastole that changes length during changes in heart rate, whereas the length of systole appears essentially unchanged. (Bars at the end of diastole indicates the end of each cardiac cycle.)

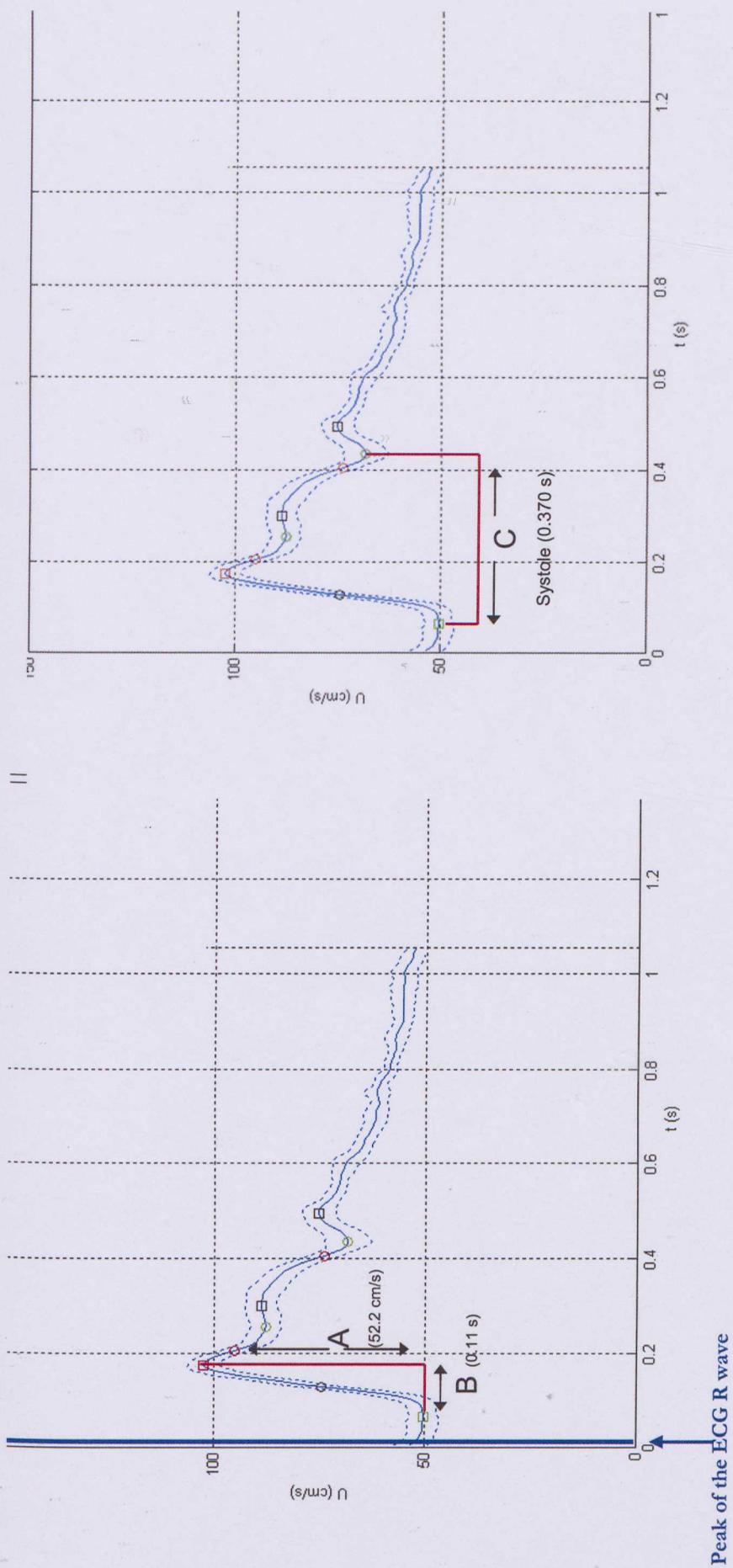


Figure 2.26 A) Upulse (cm/s), B) T-rise (s), and C) is a calculation of length of systole in the MCA derived by subtracting the time of Umin2 from the time of Umin.

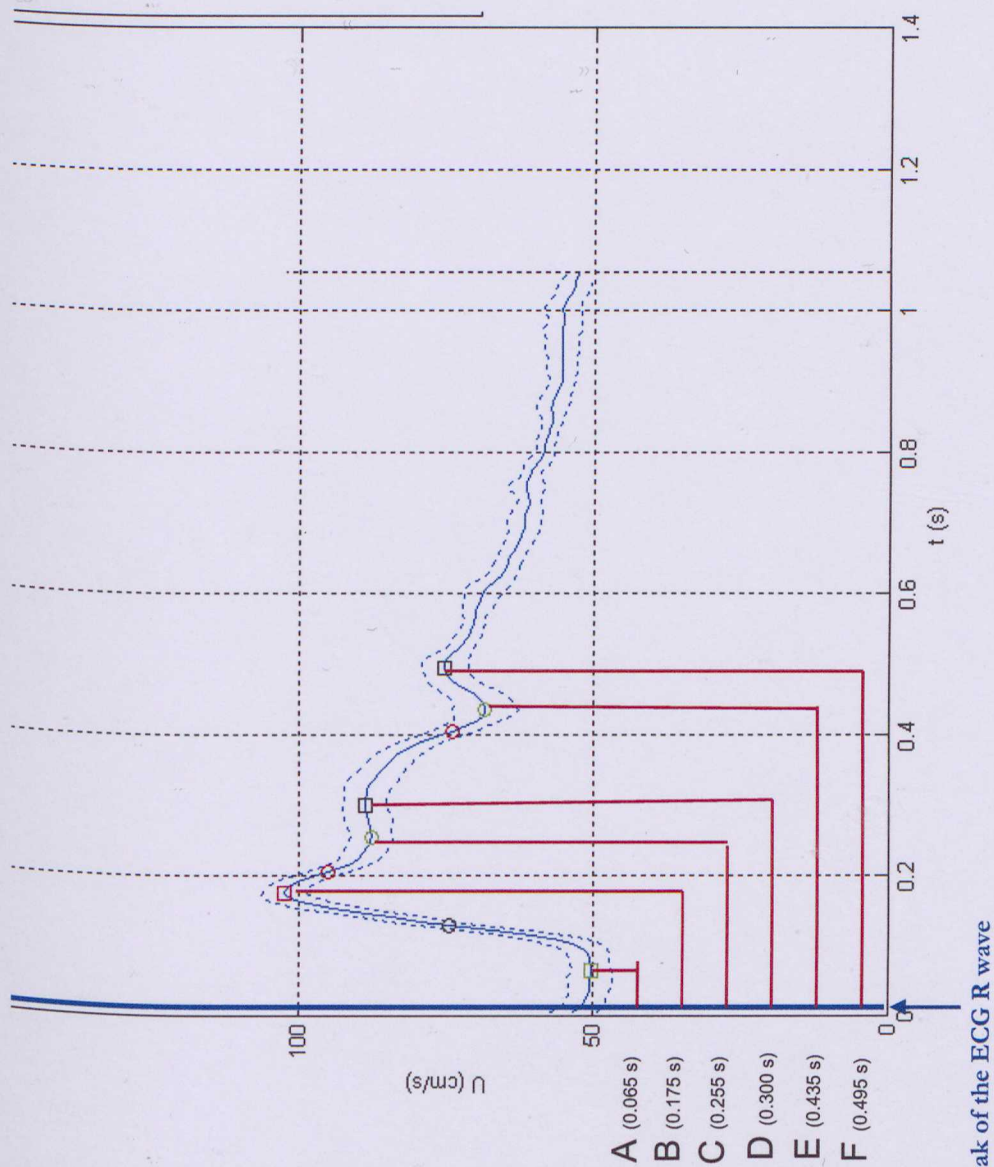


Figure 2.27 Time measurement performed by the software *from* the peak of the ECG R wave to various points on the waveform contour. **A)** Time from start of cardiac contraction to minimum velocity prior to systolic upstroke, **B)** time to maximum velocity **C)** time to first velocity rise after plateau, **D)** time to aortic valve closure, **E)** time to next velocity rise after aortic valve closure. In addition (not listed), the timings to DuD_{tmax}, Dudtmin1, and Dudtmin2 can also be extracted.

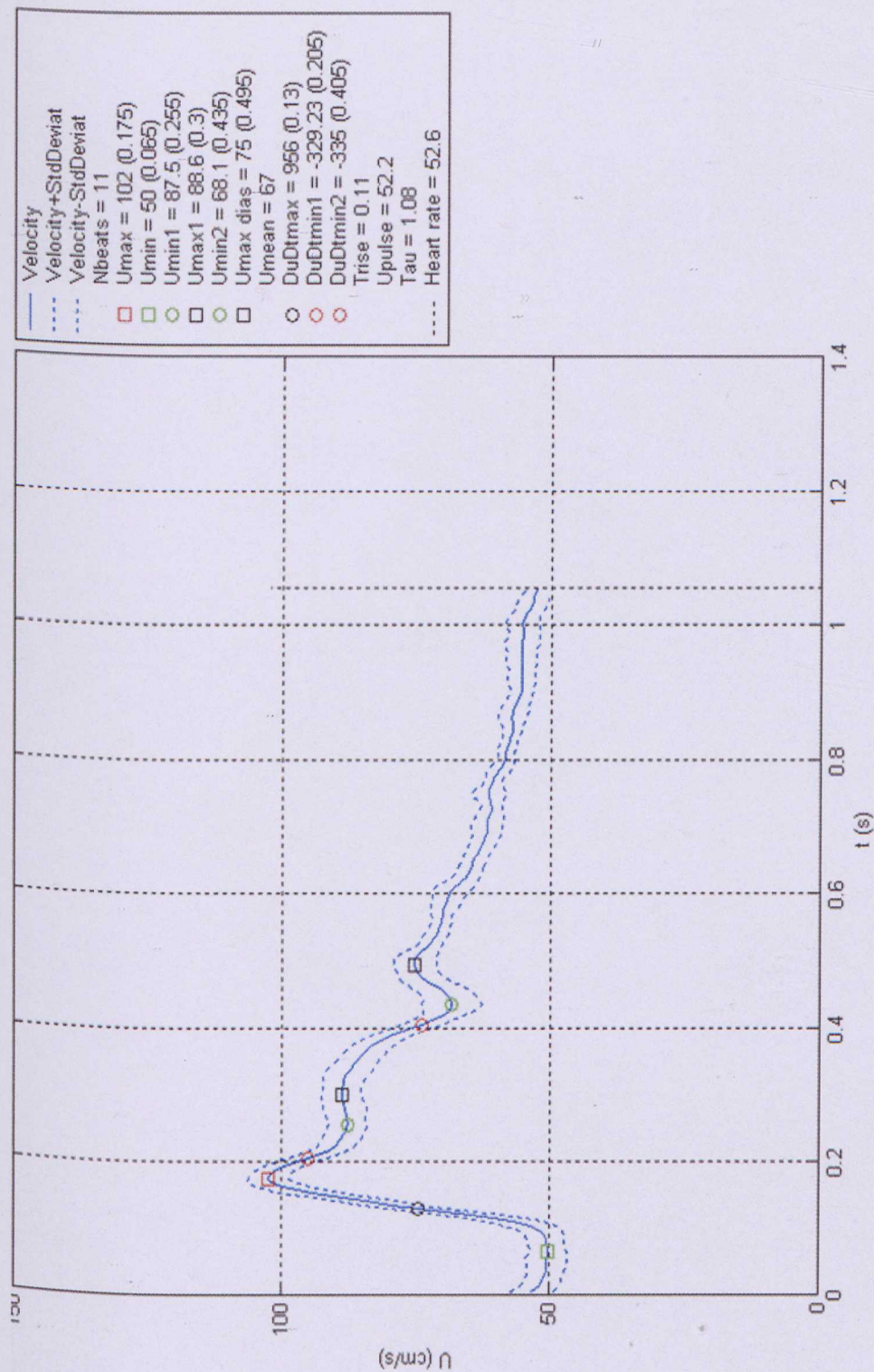


Figure 2.28 Numerical display of the data from 16 seconds of cerebral blood flow velocity information. (Values listed in brackets beside each parameter indicate the time in seconds from the peak of the ECG R wave, to the measured parameter).

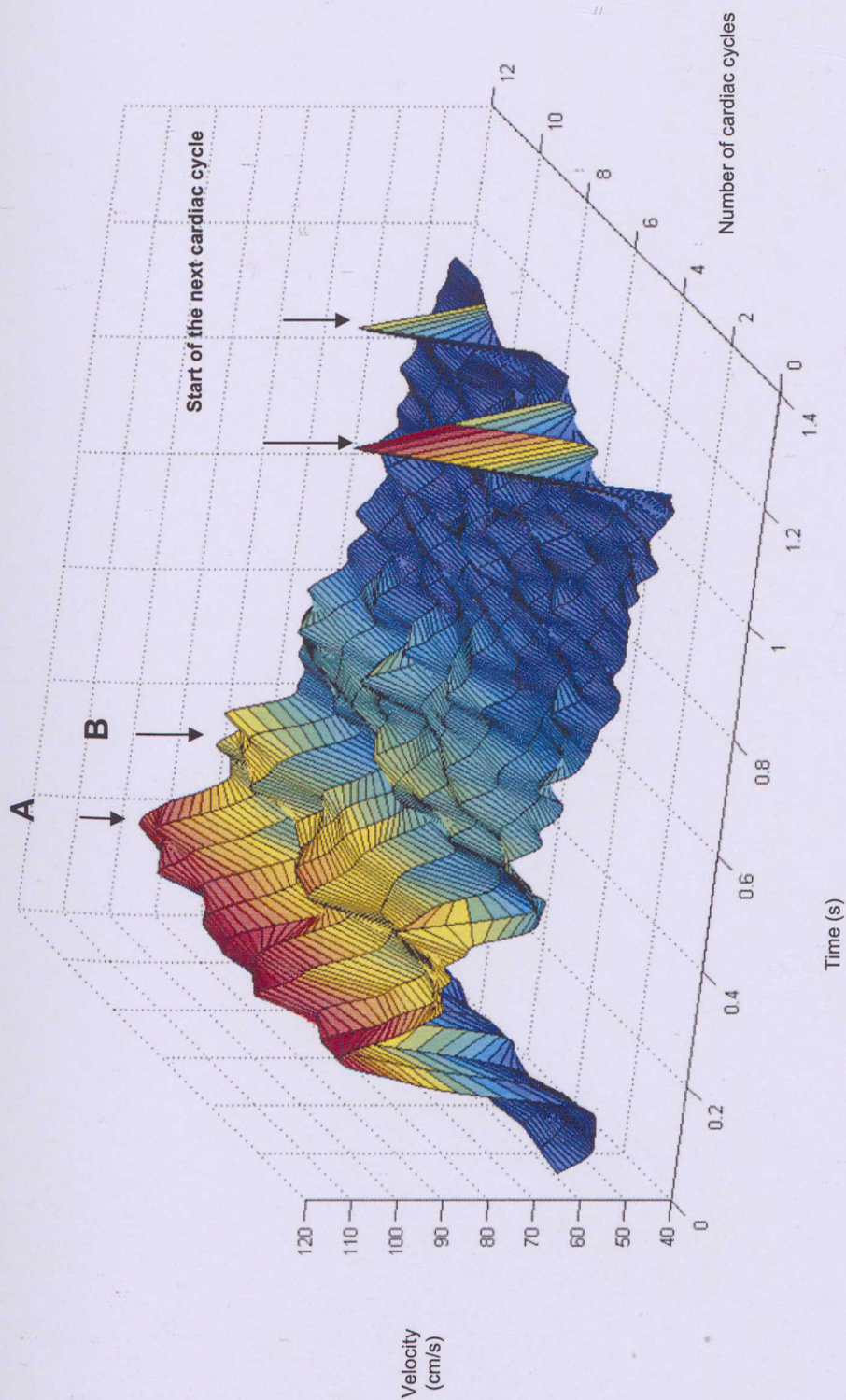


Figure 2.29 3-D representation of the beat to beat variation in 10 cardiac cycles of cerebral blood flow velocity data. **A)** Note the variations in maximum velocity peaks (U_{max}) as compared to **B)** the second velocity peak (U_{max}1).

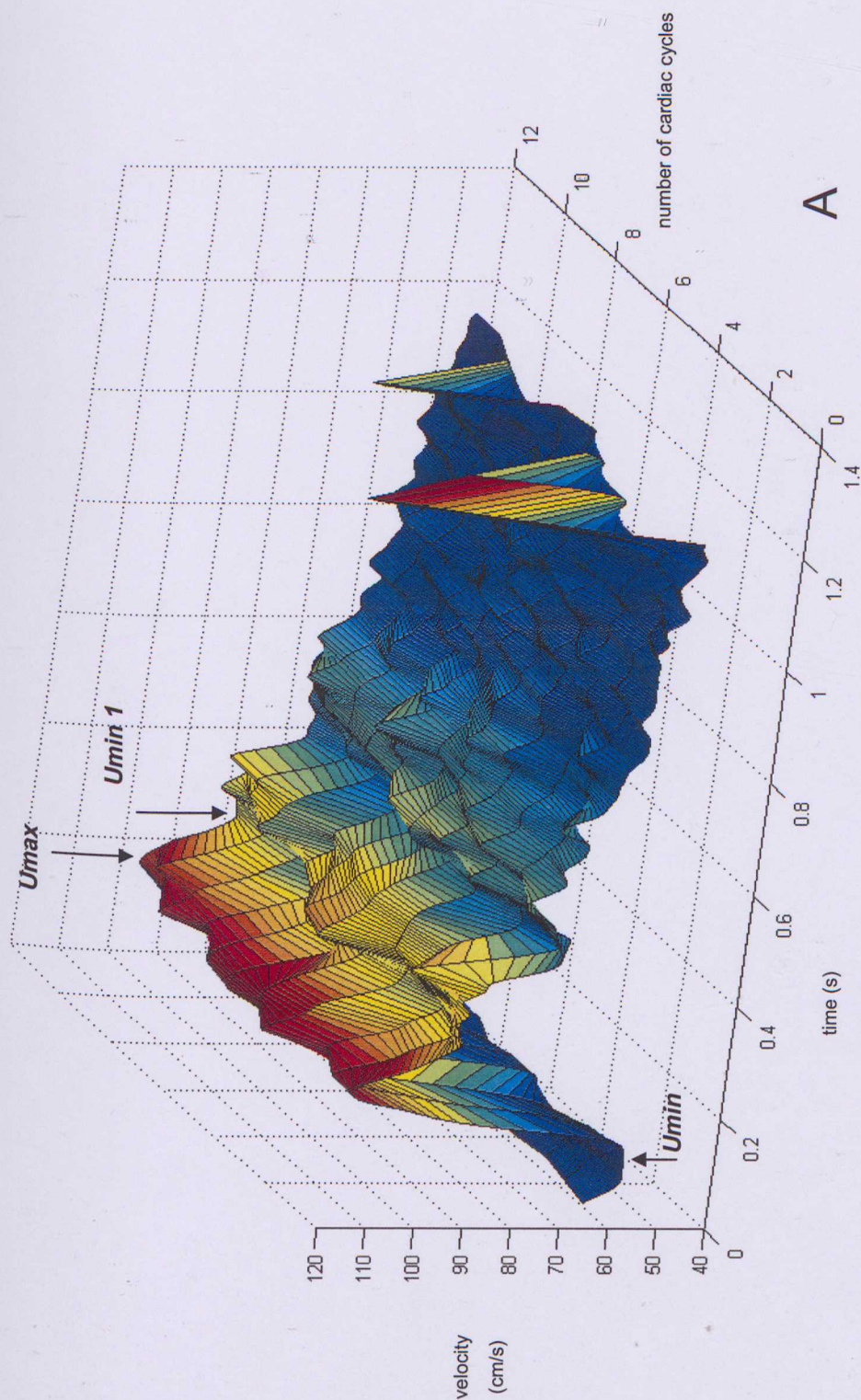


Figure 2.30 Visual representation of **A**) Shape Index 1, a ratio of the minimum velocity (U_{min}), maximum velocity (U_{max}) and ($U_{min} 1$) the *first* velocity plateau (systolic notch created by wave reflection). (Continued on next page)

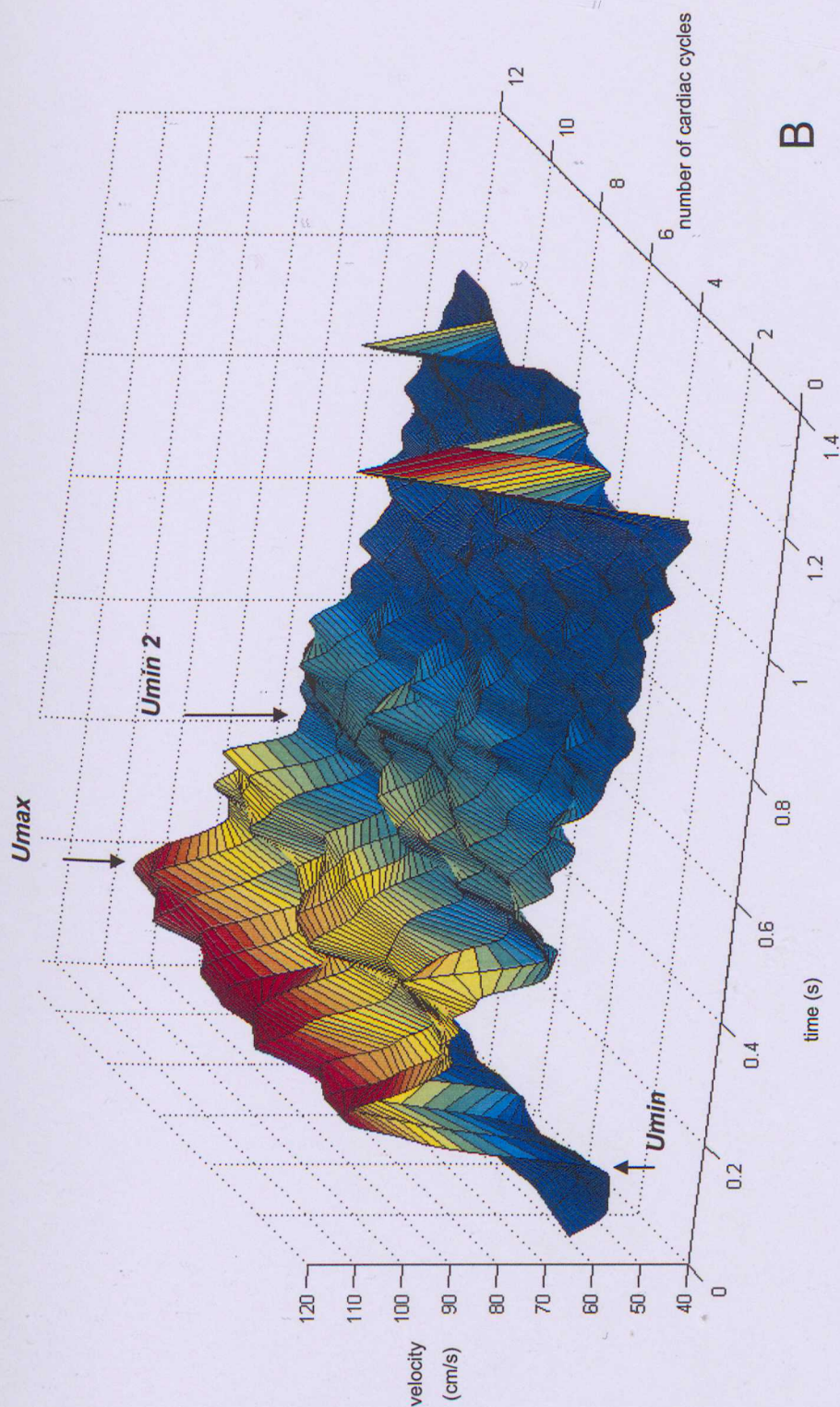


Figure 2.30 continued B) Shape Index 2, a ratio of the minimum velocity (U_{min1}), maximum velocity (U_{max}), and (U_{min2}) the second velocity plateau (dirotic notch created by aortic valve closure). (Continued on next page)

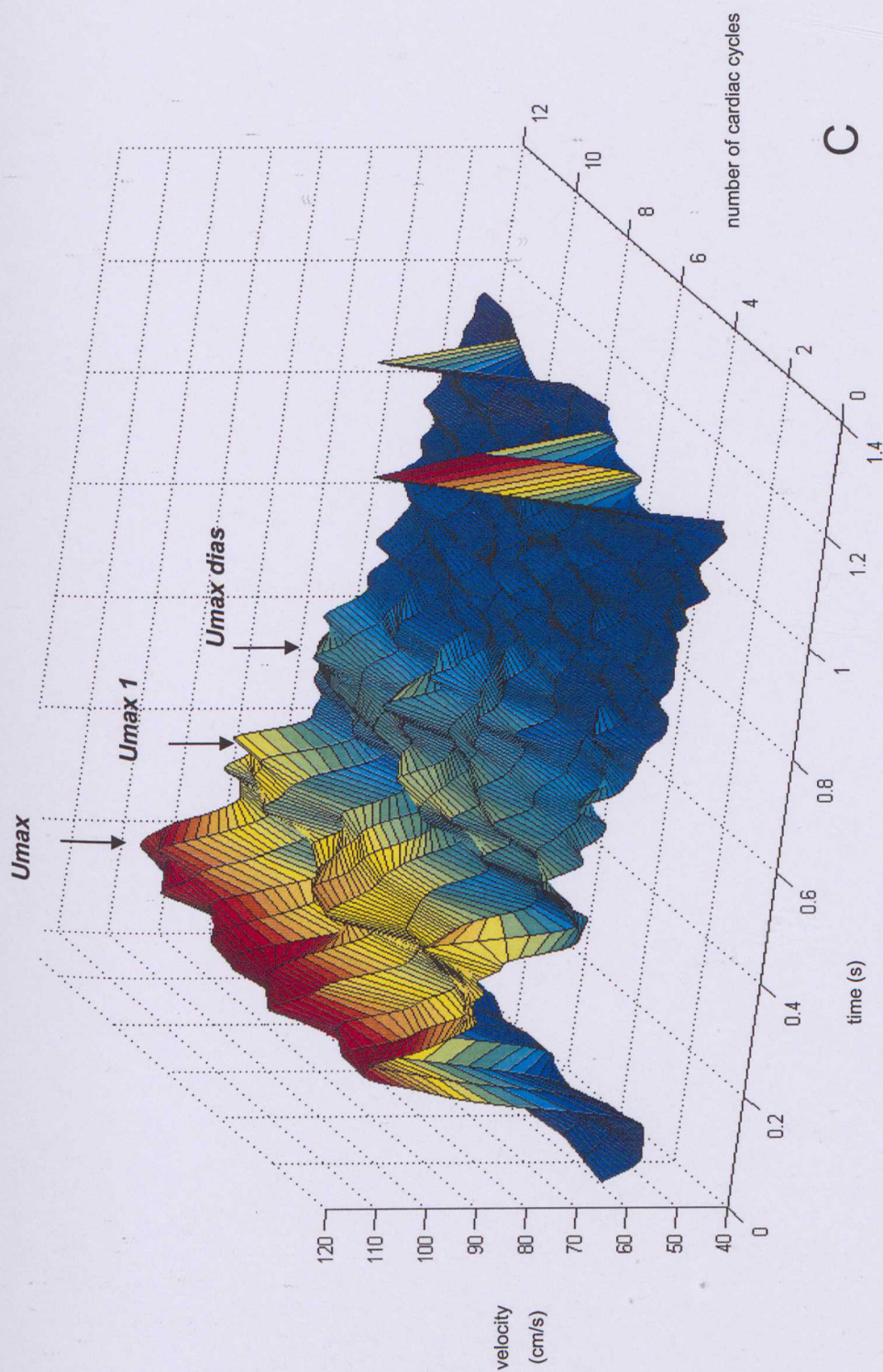


Figure 2.30 continued C) Visual representation of the Velocity Rise Index, a ratio of all of the velocity maxima (U_{max} , U_{max1} , and $U_{max\ dias}$) along the waveform.

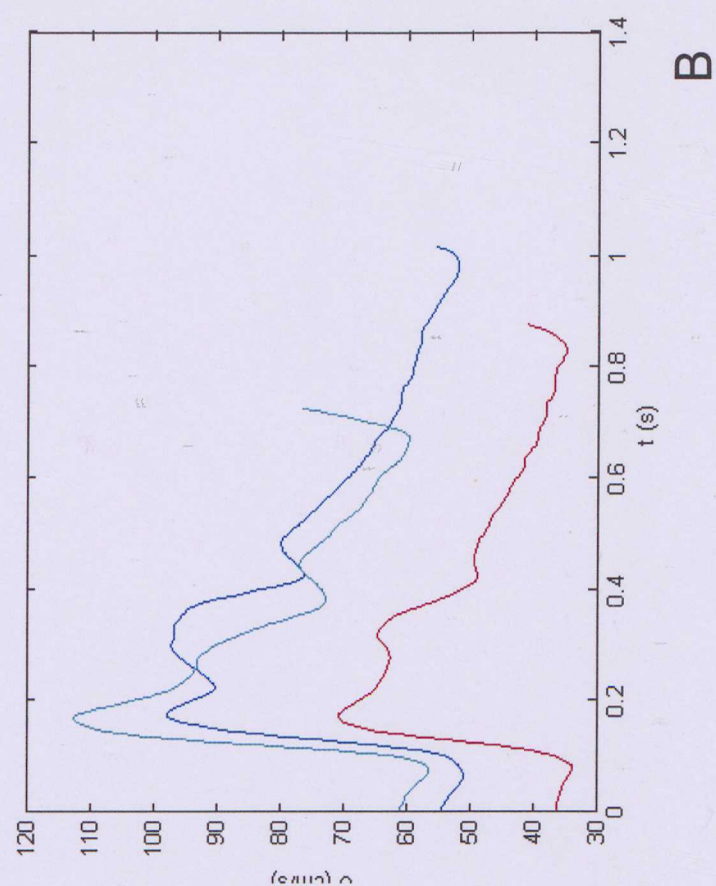
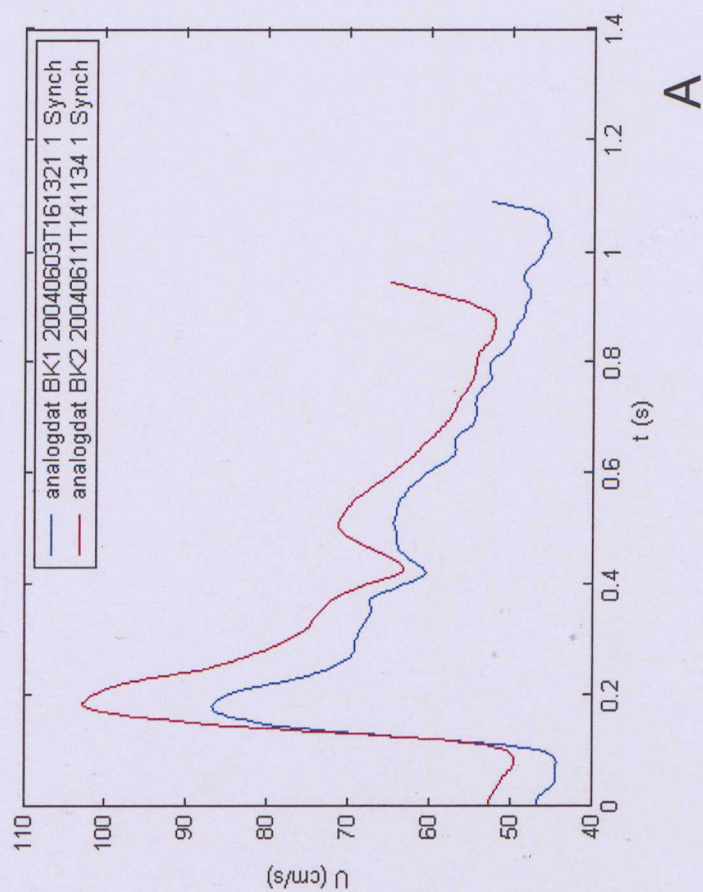


Figure 2.31 A) Depicts two tests done on a single individual (8 days apart), B) a test on 3 different female subjects (on the same day). Note the differences in wave shape. (Note: all graphs are *without* rescaling). (Continued on next page)

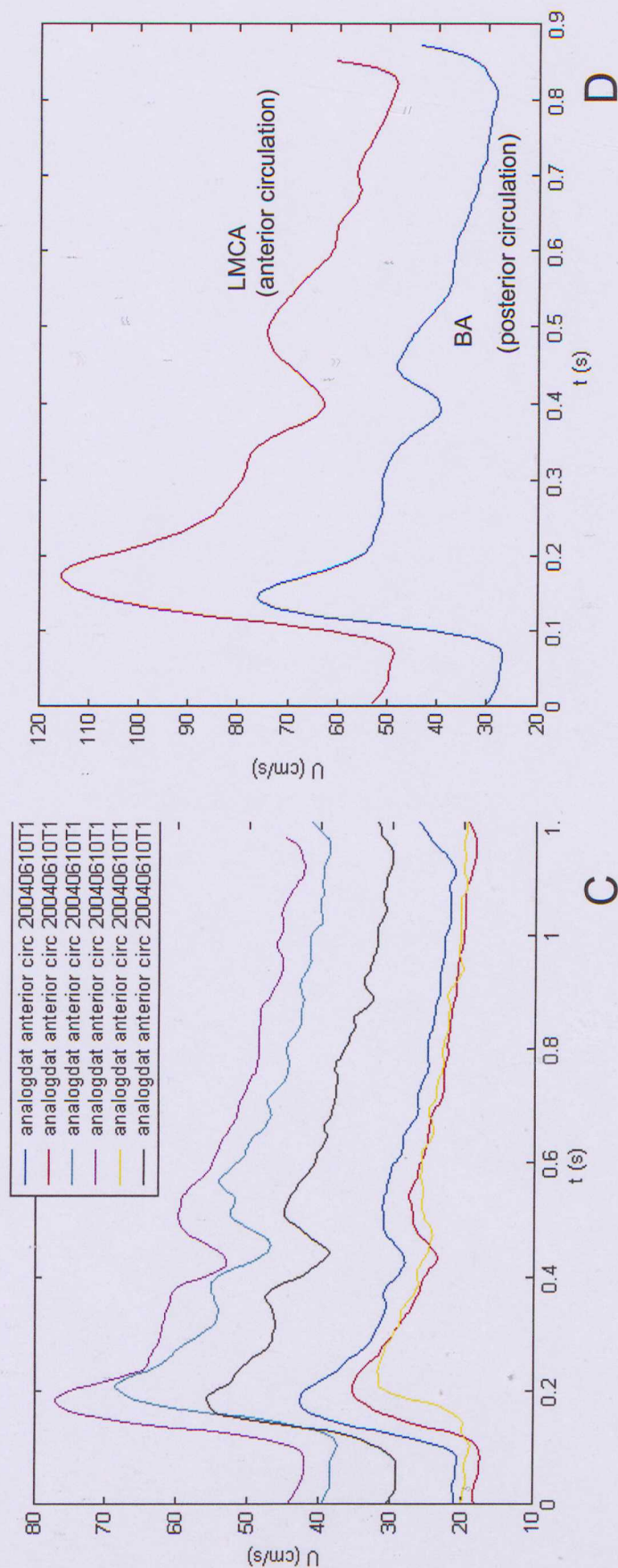


Figure 2.31 continued: **C)** different arteries in the carotid and cerebral circulation compared on a single individual. Arteries are as listed: right extracranial ICA (red), left extracranial ICA (blue), proximal L MCA (turquoise), distal L MCA (pink), distal L MCA branch (yellow), intracranial L ICA via the orbit. (black). **D)** Comparison of the MCA (flow towards the transducer), and the basilar artery (BA) with flow moving away from the ultrasound transducer on the same individual.

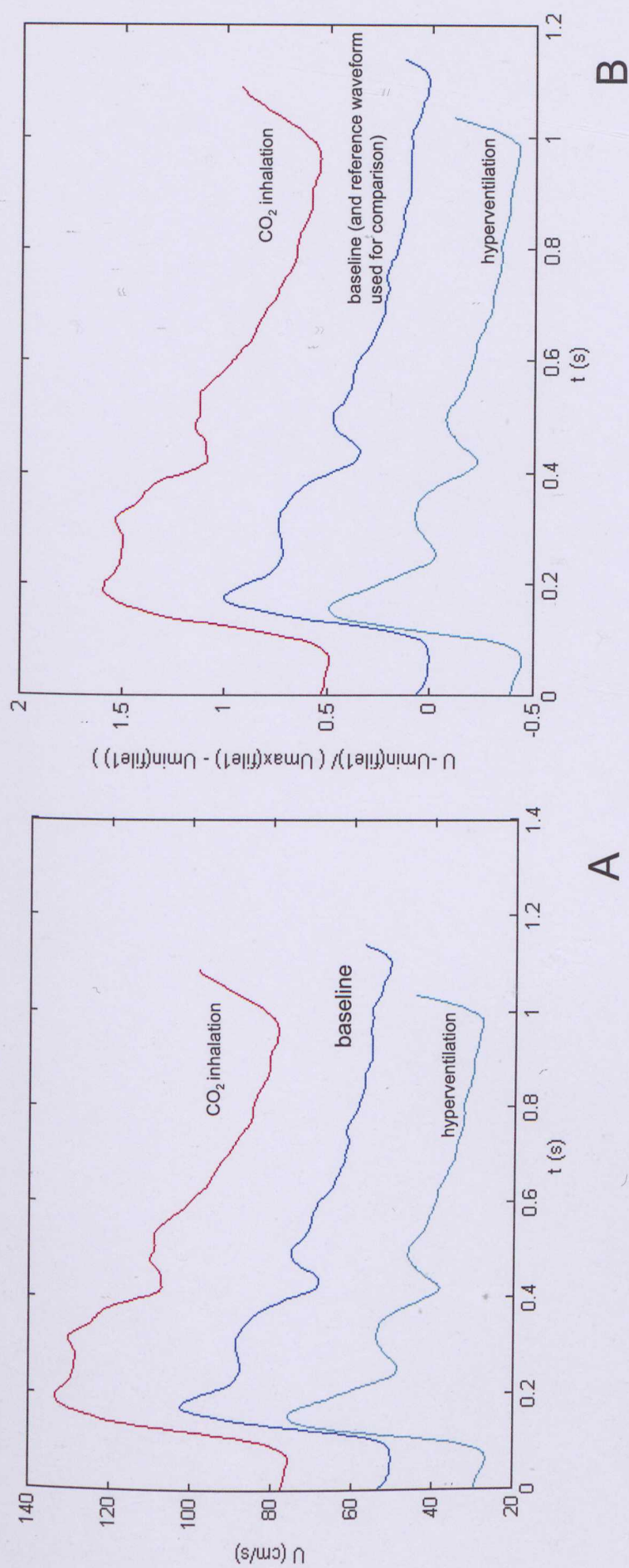


Figure 2.32 A) Ensemble-averaged waveforms from vasoreactivity testing using the standard velocity/time scale (no rescaling). **B)** *With rescaling*—an example on the same individual where the “baseline” waveform is used as a reference value, with CO₂ inhalation and hyperventilation waveforms plotted against the baseline for comparison.

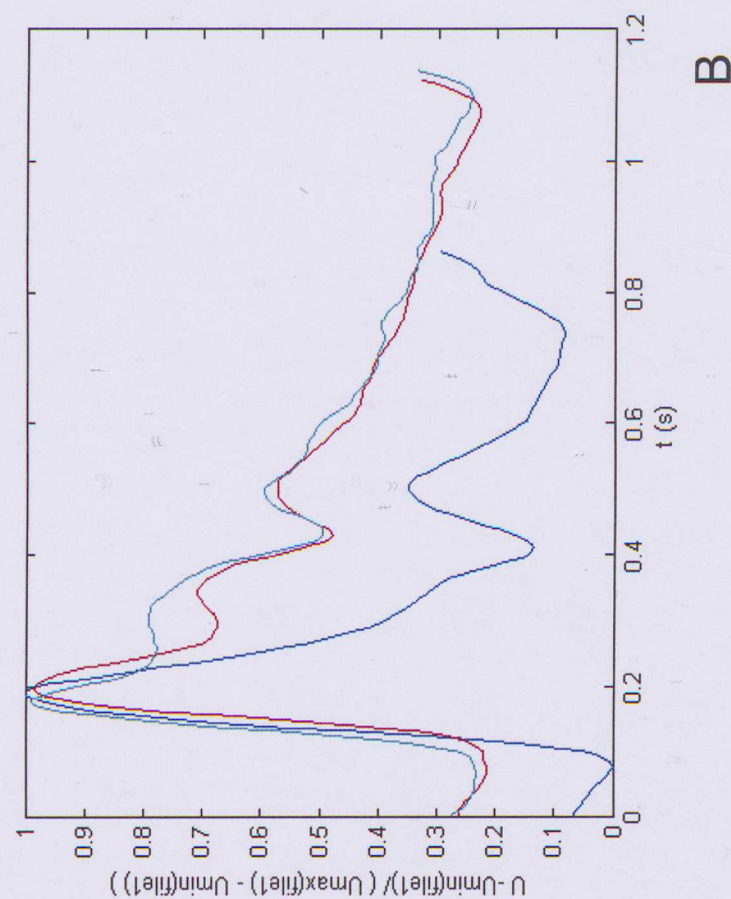
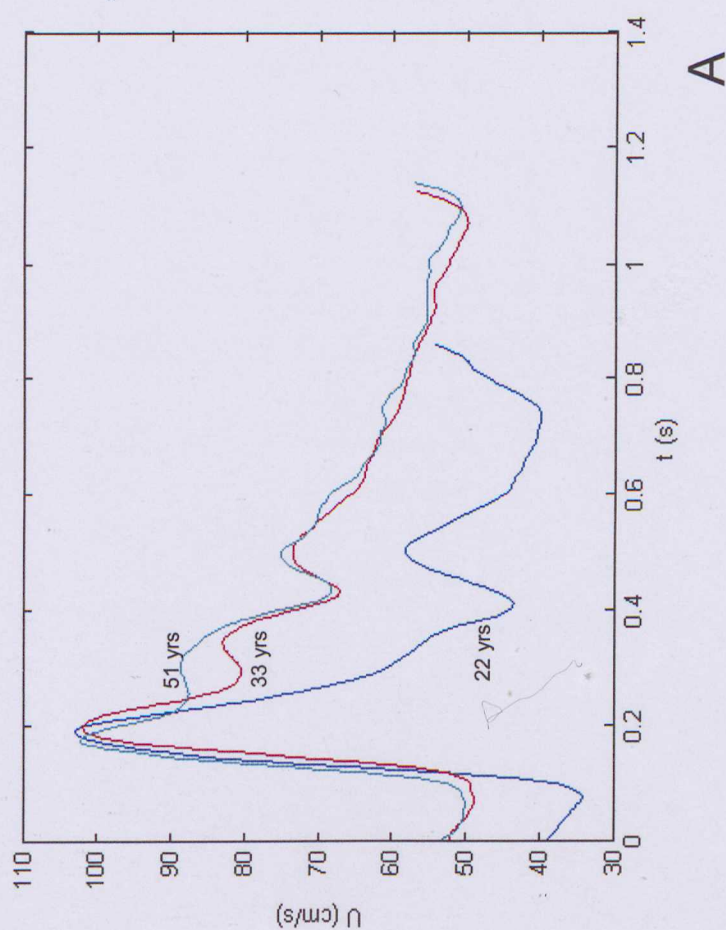
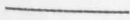


Figure 2.33 A) Comparison of baseline waveforms of three male subjects of different ages (blue- 22 yrs., red- 33 yrs., turquoise- 51 yrs.) using standard velocity/time scale, **B)** comparison of same subjects *with rescaling* based on youngest subject. Note, although the peak systolic velocity is very similar in all of the subjects, the waveform shapes are quite different.

Table 2.1 A description of each parameter in the results display and corresponding symbols. (These data are taken from Figure 2.13)

OUPTUT SYMBOL	ANALYSIS PARAMETER	PARAMETER DESCRIPTION	VALUE	TIME FROM PEAK OF ECG R WAVE
	Vel	Peak velocity envelope data	As shown	As shown
	Vel + Std Deviat	Standard deviation of peak velocity envelope	As shown	As shown
N/A	Nbeats	Cardiac cycles used in ensemble-averaging	11	N/A
	Umax	Maximum velocity (PSV)	102 (cm/s)	0.175 (s)
	Umin	Minimum velocity (EDV)	50 (cm/s)	0.065 (s)
	Umin1	First velocity plateau after max velocity	87.5 (cm/s)	0.255 (s)
	Umax1	Second velocity increase	88.6 (cm/s)	0.3 (s)
	Umin2	Second velocity plateau after max velocity	68.1 (cm/s)	0.435 (s)
	Umax dias	Peak velocity after Umin2	75 (cm/s)	0.495 (s)
N/A	Umean	Mean velocity (time-averaged peak velocity)	67 (cm/s)	N/A
	DuDtmax	Maximum acceleration	956 (cm/s ²)	0.13 (s)
	DuDtmin1	First deceleration after max velocity	-329 (cm/s ²)	0.205 (s)
	DuDtmin2	Second deceleration after max velocity	-335 (cm/s ²)	0.405 (s)
N/A	Trise	Time to maximum velocity from Umin	N/A	0.11 (s)
N/A	Upulse	Velocity increase from Umin to Umax	52.2 (cm/s)	N/A
	Tau (τ)	Best-fit exponential fall off during diastole	1.08	
	Heart rate	Heart rate	52.6 bpm	N/A

Chapter 3

Methods, repeatability and reproducibility

This Chapter details the methodology we use in developing our standardised TCD testing protocol. We examine the repeatability and reproducibility of cerebral blood flow velocities, as well as the new Doppler waveform shape parameters introduced in Chapter 2. We review three major components of potential variability in transcranial Doppler measurements: 1) the equipment set-up; 2) the operator; and 3) the inherent physiological variability of the cerebral circulation. This chapter goes on to discuss a methodology for vasomotor reactivity testing, examines the reproducibility of this technique with our system, and introduces velocity waveform shape changes that occur during testing. We conclude with a summary of the reproducibility of our new waveform shape parameters at Baseline, Hypercapnia, and Hypocapnia..

3.1 Overview

Although transcranial Doppler studies have been performed for nearly 25 years, there is no standardised testing methodology and only limited information in the literature with regard to the repeatability and reproducibility of transcranial Doppler measurements. The majority of the repeatability/reproducibility studies were performed in the early 1990s, when TCD was just emerging as a viable non-invasive technique for the assessment of cerebral blood flow. A few authors established adequate reproducibility of the technique, such as Maeda et al. [1990] who demonstrated a correlation coefficient of 0.69-0.95 and Totaro et al. [1992] who reported 0.78-0.97. Thereafter the focus of TCD development turned away from this subject toward understanding the haemodynamic effects of carotid stenosis, cerebral emboli, vasoreactivity, and cerebral autoregulation. Great advances have been made in all of these areas over recent years, and yet we often neglect to remember that technical errors, lack of standardised testing, and inherent variability of the cerebral circulation can affect TCD measurements. In the following paragraphs, we review some of the early studies of repeatability and reproducibility, with a view to establishing an appropriate protocol for the TCD studies described in this thesis.

3.1.1 History

In the summer of 1981, Aaslid used a 2 MHz pulsed Doppler manufactured by Vingmed (Trondheim, Norway) to make the first recordings from the cerebral circulation. A paper published a year later [Aaslid et al., 1982] reported the typical velocity measurements that were found in the MCA (middle cerebral artery), ACA (anterior cerebral artery) and PCA (posterior cerebral artery) in 50 healthy subjects. At the time, there was concern about the issue of vessel identification since it was a

'blinded' technique. This term simply meant that the operator was unable to visualise any of the cerebral arteries, but rather aimed the Doppler towards the anatomical region of the artery from outside the skull, and then began a search for a Doppler signal. A quotation from Katz and Whisler in *Transcranial Doppler* [1992] reflects the concerns of the time. "The TCD technique, however, is initially difficult to learn and can often be tricky, even for the experienced operator. The perception of the transducer to artery angle and spatial relationship between intracranial arteries present technical challenges that were not previously encountered in other non-invasive Doppler techniques". The issue of vessel *mis-identification*, and the consequences this may have when evaluating pathology such as vasospasm or collateral flow, prompted the development of an instrument known as the Trans-scan TCD mapping system (Eden Medical Electronics Inc., Kent, Washington). The Trans-scan produced a multi-projectional, computer-generated display of pulsed Doppler signals that the user recorded from various sites, eventually building a 'map' of the cerebral arteries and confirming the spatial difference between different signals. Although this equipment helped to address the issue of the true vessel identification, its cumbersome and time-consuming set-up procedure soon grew tiresome for the user. As the operator experience and confidence grew, other techniques for vessel identification became widely accepted and were described in detail by Fujioka and Douville in *Transcranial Doppler* [1992], in their chapter on Anatomy and Freehand Examination Techniques. They proposed six steps to determine vessel identification: 1) transducer position; 2) depth of sample volume; 3) direction of flow; 4) spatial relationship to the other arteries; 5) mean velocity measurements; and 6) response to ipsilateral and contralateral carotid compressions. This 'check system' gave the operator good accuracy in terms of vessel identification. Unfortunately, a truly standardised step-by-step testing methodology has never been instituted in TCD examinations and continues to affect the results of TCD studies. This problem accounts

for some of the variability of TCD results seen between operators, institutions, and subsequently results in the literature.

3.1.2 Accuracy

Accuracy in TCD can be thought of in two ways. First, there is the *accuracy of vessel identification*, which has been assisted by the six-step system. Second, there is the question of *accuracy in the flow velocity measurements*. For example, has the operator achieved the highest possible velocity measurement in the region? For the purposes of this thesis, we will discuss the subject only in terms of non-imaging TCD since this was used in all of our studies. The alternative technique, colour-flow transcranial duplex, uses a different testing methodology and has a unique set of potential errors.

Velocity accuracy

After positively identifying the vessel, the operator must ensure the highest velocity in the region of interest has been achieved. Therefore, the practice of fine-tuning the transducer angle, in order to optimise the angle of insonation as close to zero as possible, is a widely-used technique to achieve the highest flow velocities in any cerebral artery. However, since TCD is a blinded technique, the operator never truly knows the exact angle of insonation but assumes those angles closest to zero will yield the highest flow velocity measurements [Evans and McDicken, 2000]. When the accuracy of velocity measurements is most important, such as in vasospasm studies, searching for the highest velocities at each measurement site is a critical part of obtaining an accurate clinical diagnosis. In patients with suspected vasospasm, a velocity measurement taken at a poor Doppler angle would result in lower velocity measurement than the true velocity. Since the degree of vasospasm diagnosed by TCD is based solely on velocity measurements [Lindegard et al., 1988] [Sloan, 1989] [Newell and Winn, 1990] [Wozniak et al., 1996] [Vora et al., 1999] [Radanovic and Scaff, 2001] [Sviri et al., 2006], it could

mean that a patient was diagnosed to have a milder degree of vasospasm than was actually present. It was these types of errors that caused concern about the accuracy of TCD measurements and its use in clinical practice. This problem appears to be more of an operator error rather than the inability of TCD as a clinical tool to make an accurate diagnosis. Proper training, experience and education of all TCD operators can lessen this potential problem.

3.1.3 Repeatability

In engineering, a commonly used definition of ‘repeatability’ is the closeness of agreement among a number of consecutive measurements of *outputs* for the same *input*. Repeatability includes no ‘drift’ errors, since consecutive measurements are made over too short a time for there to be a drift error [Dataforth Solutions and Technology 2003]. The term ‘drift’ is an engineering term and relates to the gradual change of a measurement such as temperature over time. However, we would like to use this simple term to represent ‘a physiological variation within the cerebral circulation’ for the purposes of this thesis. In the cerebral circulation, we do not normally get a ‘fall-off’ of velocity over time, but rather a ‘cyclical variation’ with time.

In TCD, the concept of repeatability means repeated measurements of mean velocity, in the same individual, over a short period of time. This has been done to test the technique, without allowing time for major physiological factors to come into play. In repeatability studies, any unavoidable errors such as those already inherent in the equipment, the transducer, or indeed the operators themselves, should be kept as constant. In a sense, this serves to stabilise the *input*, so we can attempt to accurately measure the *output*. We further address the issue of repeatability of TCD measurements in Section 3.3 of this Chapter, where we test the repeatability of the system.

3.1.4 Reproducibility

To refer to engineering terminology once again, one may think of ‘reproducibility’ as similar to that of ‘repeatability’ with one important addition, it *allows for drift*.

‘Reproducibility’ is the closeness of agreement among a number of repeated measurements for the same input (thus it includes repeatability), but over *any* length of time [Dataforth Solutions and Technology, 2003]. Hence, reproducibility allows for drift in the measurement, which might occur over longer periods of time. For TCD measurements, ‘reproducibility’ would be tested by repeated measurements on the same individual, by the same operator and equipment, but over any extended time period such as days, weeks, months or even years. This allows for the influence of drift, or in our case the longer-term variability in the cerebral circulation. Reproducibility is best done by attempting to stabilise the *input* as much as possible by using a standardised examination methodology, and the same equipment and operator. In this way, best measurement of the *output* (or velocity) can be achieved. We examine this issue in terms of our system and the new parameters that we wish to measure in Section 3.4 of this Chapter.

3.2 Methods

Before we are able to start testing either the repeatability or reproducibility of TCD measurements, it is important to develop a standardised testing methodology, which will be used for all studies. In doing this we can minimise any of the avoidable errors in technique before we take our first measurement of velocity.

The technical set-up of the transcranial Doppler machine, and the attachment and positioning of the ultrasound transducer is a key to acquiring accurate velocity data from the cerebral circulation. The reliability of the information is highly dependent on the

experience of the operator: to find the best temporal window (thinnest portion of the temporal bone); adjust the angle of the transducer to maximise the cerebral Doppler signal; to set the equipment parameters (depth, sample volume size, etc.) appropriately; and to ensure accurate recordings. In the next section, we detail the standardised testing methodology, which we use for all of the TCD studies in this thesis.

3.2.1 Equipment set-up

All transcranial Doppler equipment allows for adjustment of control settings so that variations in skull thickness can be accommodated and so that the velocity measurement of the cerebral vessels, which lie at variable depths, angles, and have different flow directions and signal strengths, can be obtained. Hence, adjustments can be made in power, gain, dynamic range, depth, sample volume size, and flow direction in order to optimize the velocity waveform and give accurate velocity information. However, the *mis*-adjustment by the operator of some of these parameters may ultimately affect the velocity values, and could therefore alter important information used for clinical diagnosis or, in our case, the testing of a new system. Therefore, adherence to a well thought-out and defined set-up protocol for each test is central to achieving repeatable and reproducible results.

3.2.1.1 TCD machine and temporal window

In this thesis, all transcranial Doppler studies were performed with the same PMD100 Digital Power M-mode transcranial Doppler machine, 2 MHz probe, and by a single experienced operator. The 2 MHz transducer was fixed to the headband (Figure 3.1 A), and positioned on the thin portion of the skull just above the zygomatic arch to obtain the signal from the trunk of the middle cerebral artery (Figure 3.1 B). This is commonly known as the transtemporal window. We chose to use the middle temporal window on all of our subjects. The adjustable headband with fixed probe placement, assured that

the insonation angle would remain stable during data acquisition even if the subject moved their head during testing. Due to the (pulsed wave) Doppler equation,

$$v = -cf_s / (2f_t \cos \theta)$$

where v is the velocity, f_s is the Doppler shifted frequency, f_t is the transmit frequency, c is the speed of sound in tissue, $\cos \theta$ is the angle of insonation; changes in the insonation angle (θ) have a direct effect on the velocity measurements. Therefore, the first portion of our protocol requires that the angle of insonation must be kept constant during data acquisition and be as consistent as possible for repeated tests; and that the operator, Doppler machine and transducer remain unchanged. According to the PMD 100 TCD machine operating manual [Spencer Technologies, 2003], they tested the accuracy and ranges of the envelope related parameters (PSV and EDV) with a string phantom (Mark IV Doppler Phantom, JJ&A Instruments, Redmond WA) and found a $\pm 2\%$ error for mean velocity measurements.

3.2.1.2 Insonation side

For repeated studies, it is important to use the same side of insonation and the same vessel. Our studies are not for clinical diagnostic purposes, but rather to gather more global information about velocity waveform shapes from the cerebral circulation.

Therefore, we use only the MCA for all studies on our subjects. The MCA supplies major parts of the cerebral hemisphere (temporal and parietal regions), and therefore it recruits a large portion of the blood flow coming up the internal carotid artery.

Information from the MCA therefore is representative of a significant region of brain blood flow, and for this reason it is often used when monitoring is done of the cerebral circulation. Either the left or right MCA would have been appropriate; however, we selected the left side because the left carotid artery generally arises directly from the aortic arch. We hoped that because the blood would pass through fewer bifurcations than on the right side, it may limit the effects of blood flow disturbances caused by the

vessel branching, although this effect was likely to be minimal. It has been thought that in normal healthy subjects, the right and left MCA velocities would be very similar since no arterial pathology exists. However, most operators recognise they will not be able to duplicate the right and left MCA velocities during testing, but believe this to be due to slightly different angles of insonation or even down to the individual skill of the operator in finding the best window.

We performed a small study to look at any difference between the right and left MCA using our waveform comparison software. We selected four of our subjects to undergo velocity measurements of both the right and left MCA at identical insonation depths and equipment set-up. The 16-second data acquisition from the right and left MCA, (which generated the ensemble-averaged waveform) were taken within five minutes of each other.

Figure 3.2 shows our results of right and left MCA velocity and waveform comparisons. Interestingly, the LMCA appears to have a higher velocity than the RMCA in all of our subjects. Since this was a very limited study, it is unclear whether this finding would persist throughout all normal subjects or not. One theory may be that the blood flow volume is not different from one side to the other in a subject at rest, but that the difference in measured velocity is the result of different arterial geometry of the two arteries inherently affecting the Doppler *angle*, even though the sample volume was at the same depth on both sides. If this was true, then we would see differences between the sides, but one side would not be consistently higher. A second theory may be that there are energy losses as the propagated wave passes through more bifurcations on one side than the other, however, these losses would be small and not of the magnitude we see here [Alastruey, in press].

Figure 3.3 A shows the differences in arterial anatomy to reach the MCA on the right and left sides. Since each hemisphere can increase blood flow to meet metabolic demand, this raises another possibility for the difference. However, we had instructed our subjects to rest comfortably and not to speak. Our subjects were a mix of right and left handed, so the theory of brain dominance as a factor does not answer our question.

In a paper by Thomsen and Iversen [1993], they use TCD to assess 58 healthy volunteers (aged 18-80 years) and detected a 20% coefficient of variation between the right and left MCA, although they do not mention if a single side was consistently higher. Sorteberg et al. [1990] did a similar study looking at 35 normal subjects (aged 20-66 years) and calculated the percent difference of the LMCA from the right MCA. They found 'the average side differences in blood velocity were not significantly different from zero', which suggest the differences between the two vessels were not significant. However, they do mention that the standard deviation for the mean flow velocity was $\pm 7\%$, but they did not indicate whether there was a propensity for one side to be consistently higher than the other. Admittedly our sample is very small, so it is beyond the scope of this thesis to define the differences between the right and left MCA, but only to note our results. For consistency, we have elected always to use the left middle cerebral artery in all of our velocity measurements.

3.2.1.3 Depth

In our studies, the transducer was set at a depth between 45-50mm (head size dependent), which is indicative of the MCA territory. This depth would generally be considered to be approximately mid MCA (M1) trunk territory, and has been confirmed on our subjects through use of the power M mode facility on the machine. This function allowed for the visualisation of a red band of colour (flow towards the transducer) between depths known to be in the MCA region (approximately 35mm-

65mm in depth from the outside of the skull). This information, along with the six-step vessel identification system, allows consistent sample volume placement. Thus, if the sample volume is placed in the mid-portion of this colour band, we are likely to receive information from the middle of the MCA (M1) trunk. This particular section of the MCA is between the MCA/ACA bifurcation proximally, and the MCA trifurcation distally. In order to begin to understand the origins of wave propagation and reflections within an arterial system, it is important to have a known sample volume location within a well-defined anatomical position in the cerebral circulation.

3.2.1.4 Sample volume size

The sample volume was fixed at 6mm for all examinations. This allowed for good coverage of the MCA without too much overlap into ACA or distal MCA branch territory. According to Pai, Varma, and Kulkarni [2005], during microsurgery they observed that the length of the M1 or trunk region varied widely between 12mm-28mm with a mean of 20mm (Figure 3.3 B).

Technical errors can arise from using too small a sample volume size in TCD. A small sample volume does not lead to precise measurement of the velocity in the centre stream of blood flow, as in carotid ultrasound examinations. In fact the MCA is very small, about 2-3mm in diameter, and the transducer beam width is generally larger than the diameter of the vessel. Hence, in TCD there is the lack of a Doppler spectral window (normally found in carotid artery waveforms), since all the velocities are being sampled at once across the vessel, including the slower ones near the vessel walls. The use of a small sample volume (e.g. 2mm) can result in more difficulty locating and stabilising an adequate signal, since even a small movement of the probe can lose the signal.

In contrast, using too large a sample volume creates a signal in which several vessels may be overlapping. This can lead to several arteries being insonated simultaneously and will degrade the appearance of the velocity signal of interest, since multiple velocities arising from different vessels will be displayed at once. This can potentially lead to confusion over which velocity waveform is actually coming from the target artery. Our choice of a 6mm sample volume size achieved both good quality insonation and was free from the contamination of other major vessels in most subjects.

3.2.1.5 Doppler angle

In our studies, the probe was angled to achieve the strongest signal from the MCA, usually an anterior/superior probe angle position from the middle temporal window. The transducer Doppler angle was set at zero degrees, which is most common in TCD examinations. It is assumed that anatomically the MCA vessel lies between 0-30 degrees to the ultrasound beam, and due to the limited size of the cranial window it is nearly impossible to get steeper Doppler angles such as the 60 degrees used in carotid artery studies. This methodology is common practice in *non-imaging* transcranial Doppler examinations such as ours. However, during colour flow TCD duplex examinations the Doppler angles can be adjusted to specific arterial geometry if necessary, since the arteries can be visualised (via the colour Doppler) by the operator. Unfortunately, it is not possible to make extended recordings, or vasoreactivity testing with confidence on colour flow TCD duplex equipment since the transducer is large and cumbersome, and there is no available transducer fixation device.

The highest signal from the MCA generally indicates the closest alignment to a zero degree angle that the operator/probe/skull shape will allow. Figure 3.4 A depicts the dependence of the Doppler velocity on the Doppler insonation angle itself, whereas Figure 3.4 B shows the anatomy of the MCA. Since angles greater than approximately

30 degrees are usually not possible due to the limitations of the temporal window size, we will assume our velocity errors are rarely greater than 13% during insonation of the MCA. If we now consider the variation between the left and right MCAs we showed in Figure 3.2, the variation in peak systolic velocity is between 8-25% in our sample subjects. This again raises the issue of possible angle variations, but does not resolve the issue of the LMCA being greater than the RMCA.

3.2.1.6 Vessel identification

The vessel identification is checked by standard transcranial Doppler methods (six step system), as mentioned by Fujioka and Douville [1992]. These procedures also include utilising an anterior temporal window, anterior/superior probe angulation, flow direction towards the transducer, velocity measurements within normal MCA values, and traceability of the vessel to the bifurcation of the ACA/MCA. It is also important to recognise the spatial relationship between the anterior circulation signals, in reference to the posterior circulation signals (obtained by a posterior/inferior rotation of the transducer).

3.2.1.7 Power, gain and dynamic range

The power, gain and dynamic range settings are adjusted for each individual to obtain the optimum Doppler signal, as well as a stable, close-fitting waveform envelope trace. Figure 3.5 depicts the 'optimal' signal location and Doppler spectrogram we attempt to achieve with each of our subjects. Once this is obtained, the probe is fixed in place so that it cannot move during data acquisition, and the headband secured so that any head movement by the subject will not interfere with the recording quality or velocity measurements. We discuss the importance of the peak velocity envelope at the end of this section (3.2.1.10).

3.2.1.8 Subject positioning

The subject is placed in a supine position, with the head elevated 30 degrees. This is kept constant throughout the entire testing procedure. Since it is known that changes in vasoreactivity can occur with positional changes [Mayberg et al., 1996], each subject is standardised to a uniform position both for the baseline studies, and for the vasoreactivity studies.

3.2.1.9 Other areas of standardisation

Blood pressure device

Each subject has a blood pressure cuff placed on the left upper arm with an automated blood pressure machine (Omron) attached, and with the arm resting comfortably at the side of the body. Blood pressure readings are taken immediately after the TCD data has been acquired by the system and printed for later data entry. All blood pressures are taken in the supine position.

Subject pre-testing instructions

Each subject is asked to refrain from smoking or from taking caffeinated beverages for three hours prior to the testing, and they must be under no medication.

The study is approved by the St. Mary's Hospital ethics committee and written informed consent is taken for each subject.

3.2.1.10 Peak velocity envelope

The final adjustment made to the TCD equipment is the fine-tuning of the peak velocity envelope. From this envelope all velocity data are generated both on the machine display and also into the files of the saved digital data. Therefore, this envelope must closely follow the edge of the Doppler spectrogram for accurate velocity information to

be recorded. This may require small adjustments of gain, power and dynamic range, or even Doppler angle just before data acquisition. If the envelope traces *below* the actual peak velocity of the spectrogram, the recorded velocity will be lower than the true velocity. If the envelope is tracing *above* the top of the spectrogram, the measured velocity will be artificially high. Therefore, close attention to the transcranial Doppler machine set-up and the Doppler trace is an important step in repeatable examinations.

3.3 Repeatability study (short time frame)

3.3.1 Operator and velocity repeatability

A study by Demolis et al. [1993], examined the repeatability of mean velocity measurements and resistance index in three ways: 1) the intra-observer repeatability (i.e. the comparison of two measurements by the same observer taken five minutes apart); 2) the between-observer repeatability (i.e. the comparison of two measurements performed by a different observers taken 10 minutes apart); and 3) the long-term repeatability (i.e. two measurements taken by the same observer, but one week apart). Their methods included 30 healthy individuals in the intra-observer testing, and 14 healthy individuals for the between-observer tests, and long term repeatability tests. They used the right MCA at the bifurcation region in all subjects, and fixed the transducer to a headband for stability. Eight seconds of ‘mean velocity’ (defined as time-averaged peak velocity) information was recorded from each individual, the RI (resistance index) was calculated, and the blood pressure taken by an automatic device set to measure every 10 minutes. It is unclear from their report whether they used the highest velocity during any single cardiac cycle, or an average taken over several of the cardiac cycles. However, they used a Medasonics Transpect TCD and therefore it is likely that the “mean velocity” they recorded (read directly from the machine display) would have been an *average* calculated over the last 3-5 cardiac cycles on the screen. This technique would have been the most

feasible method given this particular make and model of TCD equipment. In their study, they attempt to stabilise the *input* by using a standardised testing methodology. Since their methodology is very similar to ours, we extract a portion of their study to compare with ours. This is detailed in the next section.

Repeatability study

Our first study looks at the repeatability of MCA velocities over a short time period, similar to Demolis et al. [1993]. However, it also incorporates the complete set-up of the machine and replacement of the headband and transducer with our standardised testing methodology. We select three healthy male subjects of similar age (mean 25 yrs ± 1.5) for the study. We perform six tests of five minutes each, which are conducted at 15 minutes intervals. This gives the subject a rest period between tests, but they are not allowed to get up from their supine position. By using a standardised testing methodology, a single experienced operator, the same equipment, along with subjects of the same sex and similar age, we seek to stabilise the *input* as much as possible. Therefore the *output* or velocity measurements would be as accurate as possible.

The velocity is recorded digitally for five minutes. The equipment records the mean velocity, peak velocity and the end-diastolic velocity every second over this period. This produces 300 data points of mean velocity, peak velocity and end-diastolic velocity measurements. At each data point (1 second), the velocity measurements recorded by the machine are composed of an *average* of the last five beats of velocity information. Our results are shown on Table 3.1. We also analyse the data from this study using only 16 seconds of the data, since this is the time frame we plan to use for our ensemble-averaging (Table 3.2). Both results are similar, however, we note that the standard deviations appear greater when the longer time frame of five minutes is used.

Since we perform more tests and have longer recording periods than those of Demolis et al. [1993] but still wish to compare our studies, we arbitrarily choose tests 3 and 4 from our battery of six tests; and then extract the first eight seconds of our velocity information to match their insonation time period. Table 3.3 compares both studies.

The repeatability coefficient of Demolis et al. [1993] is 4.83, which is better than ours of 9.78. One obvious difference between the two studies is that our study involves taking the headband and transducer off, which introduces another possible source of error. We include this step, because we are interested in looking at operator skill variability in conjunction with velocity repeatability. In the study by Demolis et al. [1993] they chose to leave the transducer and headband in place and simply re-record the velocity five minutes later.

In comparing the two studies, we must also consider the effect of even small passages of time in the cerebral circulation. There is a 15-minute time lapse in our recordings (to allow for resetting the equipment). In Figure 3.6 we show a graphical example of the 'mean velocity' recordings taken from our subjects. We have chosen to show the initial eight seconds used in our calculation of repeatability, and also the following eight seconds of the recording. It is apparent from these figures that there is a physiological variation in the cerebral circulation even over this extremely short time period.

However, since 'mean velocity' incorporates peak systolic velocity and end-diastolic velocity; we choose to examine both values to gain further insight into whether they (PSV and EDV) were changing equally or whether a difference existed between them. Figure 3.7 and 3.8 show the results. Figure 3.7 (PSV) illustrates that there is a close fit between all six of the tests performed in the three subjects, even though there is a 15-minute interval between tests. However, the graphs depicting the end-diastolic velocity (Figure 3.8) show a greater variability. One possible explanation for this is that PSV is

mainly generated from a large compression wave initiated by the heart. Thus, it may indicate that the cardiac ejection is changing very little over this 16-second period, or indeed even after a 15-minute rest period. However, any velocity parameter which comes *after* the peak is affected by wave reflections and overall vessel compliance. Since EDV is the only parameter in this simple study, which comes *after* peak velocity, we see the changes there.

The increased variability of EDV, over that of PSV (at rest), may suggest that it could represent small variations in vasomotor tone over this time period rather than any changes in cardiac ejection. Hence, it is mainly changes in EDV that are influencing the changes in mean velocity over time. A simple way to look at this is to look at the standard deviation over the time period of each of our parameters in question, PSV and EDV. Table 3.3 illustrates what we saw graphically in Figures 3.7 and 3.8, that EDV varies more than PSV.

To test this hypothesis, we look at the full five-minute recording taken from each of our subjects. We overlay the six repeated tests to see how much the velocity varies. Figure 3.9 shows this data for mean velocity. We need to determine why there is such variation over a five-minute continuous recording segment, performed on a resting subject with no change in equipment or Doppler angle. One possibility is that this is due to the natural physiological variations within the cerebral circulation. To explore this we first look at what is known regarding intracranial waves or oscillations which can affect cerebral blood flow velocities.

3.3.2 Special considerations

It is important to remember that blood pressure, heart rate, cerebral blood flow velocities and intracranial CSF volume are never entirely constant, and have been shown

to have oscillations occurring at various frequencies [Lundberg, 1960] [Mautner-Huppert et al., 1989] [Diehl et al., 1991] [Lang et al., 1999] [Friese et al., 2004]. These must be taken into consideration when performing both repeatability and reproducibility studies.

3.3.2.1 M waves (Mayer waves)

Spontaneous oscillations of arterial blood pressure, known as M waves, occur at approximately 0.1 Hz (six cycles/minute) in humans according to Julien [2006]. This is a lower frequency than that of respiration. It is believed that these oscillations in arterial blood pressure are a result of changes in sympathetic vasomotor tone and affect the total peripheral resistance. Synchronous oscillations of vascular tone have been seen in several regional circulations, including the kidney, mesentery and skeletal muscles [Janssen et al., 1995] [Julien et al., 1995]. It has even been suggested that Mayer waves trigger the liberation of endothelium-derived nitric oxide due to cyclic changes in wall shear stress [Nafz et al., 1997], and perhaps this is beneficial to end organ function. Since M waves are tightly coupled with sympathetic activity, it has been proposed as a surrogate measure. Studies using simultaneous recording of sympathetic nerve activity and arterial blood pressure, have shown that M waves in the arterial blood pressure correlate with discharges of sympathetic neurons which in turn account for the 0.05-0.15 Hz (3-9 cycles/minute) variations in the cerebral blood flow velocity [De Molina, Perl, 1965] [Diehl et al., 1998]. However, the identification of the precise underlying mechanisms of Mayer waves is still elusive.

3.3.2.2 B waves

Intracranial B waves were first described by Lundberg in 1960 as rhythmic spontaneous oscillations of 0.008-0.03 Hz (0.5-2 cycles/minute) of intracranial pressure in patients with acute brain lesions [Lundberg, 1960]. Studies done on healthy subjects found that

their rhythmic spontaneous oscillations were in a similar frequency range [Diehl et al., 1997]. Mautner-Huppert et al. [1989] studied five subjects and measured both ventricular pressure and middle cerebral artery flow velocities with TCD. They found that oscillations in the range of 0.008-0.03 Hz (0.5-2 cycles/minute) occurred simultaneously in both ventricular pressure and TCD flow velocity. They speculated that these B wave oscillations are a result of rhythmic changes in the diameter of the cerebral vessels, with a concomitant change in cerebral blood volume thus producing the changes we see in both intracranial pressure (ICP) and cerebral blood flow velocity. They went on to explore healthy subjects with TCD only (no ventricular pressure monitors) and found similar oscillations in middle cerebral velocity, producing a variation of around 10%. Newell et al. [1992] initially looked at 20 head-injured patients and recorded simultaneous MCA velocity, ICP, arterial blood pressure and expired CO₂. They noted synchronous fluctuations of the MCA velocity and the B waves of the ICP. However, they had no fluctuations in systemic arterial blood pressure and a constant CO₂ concentration (i.e. ventilated patients). They concluded that B waves in the ICP are a secondary effect of vasomotor waves, which produce the blood flow volume fluctuations. In times of reduced intracranial compliance, such as in head injury, these waves can become amplified in the ICP tracing. Interestingly, they went on to look at a group of 10 normal subjects and monitored the MCA velocity for one hour. They found velocity waves with similar characteristics and frequency to the head-injured group, but noted a shorter duration of the waves. Indeed some studies have even reported rises in blood pressure shortly *after* rises in intracranial B waves (4.2 ± 2.4 second delay) [Newell et al., 1992]. The generators and pathways of B waves are not fully understood, but it has been postulated that they are a result of an autonomic brain stem rhythm [Einhäupl et al., 1986]. The effect of B waves on TCD flow velocities should be considered when assessing variations of velocity measurements.

3.3.2.3 Respiratory waves

During inhalation, the internal jugular venous pressure rises, and the blood flow from the brain is slowed. This increases the intracranial blood flow volume, and thereby increases the arterial blood flow velocities. During expiration, the internal jugular venous pressure decreases, and the venous outflow increases [Daley et al., 1993]. This decreases the intracranial blood volume, and therefore can decrease the arterial blood flow velocities. Cerebral blood flow oscillations caused by the respiratory cycle are in the range of 0.15-0.6 Hz (9-36 cycles/minute [Thomsen and Iversen, 1993]).

3.3.2.4 A waves (Intracranial pressure plateau waves)

Although Lundberg A waves, or intracranial pressure (ICP) plateau waves, are unlikely to affect the velocity recordings in the normal subjects used in this thesis, we have included this topic for completeness. Lundberg A waves are sudden rises in intracranial pressure to high levels (50-100 mmHg) for time periods of about 5-20 minutes [Lundberg, 1960] [Czosnyka et al., 1999] [Rosner, 1986]. The hypothesis is that active vasodilatation and vasoconstriction underlie the occurrence of intracranial pressure plateau waves, which have been identified in head-injury patients. It is the sudden change in blood volume produced by cerebral vasodilatation that leads to the rise in ICP. The onset of the wave has been described by the vasodilatory cascade [Rosner, 1986]. The sudden increase in blood volume leads to increases in the ICP, and therefore to decreased cerebral perfusion pressure (CPP). The plateau lasts as long as the CPP remains stable and above ischemic levels. If the CPP drops further, there may be an increase in the systemic blood pressure to bring the CPP back toward normal. The resolution of the wave is characterised by a rapid decline in the ICP to baseline level and a stabilisation of both the systemic blood pressure and CPP. This is best explained by cerebral vasoconstriction.

3.3.2.5 Summary

Thomsen and Iversen [1993] concluded that it is difficult to sort out how much of the variation seen in cerebral blood flow velocity recordings are biological and how much are methodological, since all the waves are superimposed on one another. In addition, the waves themselves are not consistent and may be intermittent. In their reproducibility study, they show that the inter-observer variation is lower than the day-to-day variation, and both of these were lower than the inter-subject variation. The minute-to-minute variation was 5-7%. At the end of their study, their belief was that the *biological* variation in the cerebral circulation exceeds any *methodological* variation in the technique.

We would like to illustrate this important point by showing the variation in mean velocity during time periods of 16 seconds to 15 minutes, in a single individual during a continuous recording. (Figure 3.10 A-D) The variability, or *drift*, occurring in the cerebral circulation simply means that it will be difficult to exactly reproduce velocity recordings with TCD. However, minimising the *input* variations through a standardised testing methodology will assist in achieving accurate *output* data. Table 3.4 summarises the waves described in this Section.

To search for the presence of waves in our data, we randomly select a five-minute velocity recording from an individual (subject 1, test 1) in our repeatability study. We use a fast Fourier transform on the velocity data and examine the result (Figure 3.11). This simple example shows four distinct peaks. The first we believe to be drift, after analysing the velocity variation around the mean. The second peak represents slow oscillations at approximately 1.4 cycles/minute, which fits into our category for B-waves. The next large peak shows oscillations of approximately 4 cycles/minute and may be related to an M wave. The final large peak shows oscillations of 6 cycles/minute

and perhaps is linked with respiration (although this would be considered as slow breathing) (Table 3.4). We believe that the small peaks near the baseline, we believe represent noise in the data.

3.3.3 Waveform shape repeatability

After assessing the repeatability of common Doppler velocity measurements (mean velocity, PSV and EDV), we evaluate the repeatability of the velocity waveform shape itself over short time periods. To do this, we randomly chose two healthy male subjects (aged 33 and 45 years) from our main study group, to have repeated measurements over a 30-minute period using our standardised testing protocol. The subjects remain in the supine position, and the TCD headband and probe are reset each time. Sixteen seconds of continuous recorded data are acquired by the system. Off-line analysis is performed using our waveform comparison software. Figures 3.12 and 3.13 show graphical representations of our results on both subjects. Note that the waveform shape itself appears very similar over the 30-minute time period. Subject A appears to have more variation than Subject B, although these appear to consist more of shifts upwards or downwards on the velocity scale rather than changes in the waveform shape over time.

3.4 Reproducibility study (long time frame)

As defined at the start of this chapter, reproducibility is similar to repeatability but allows for a longer time period between measurements. This allows for more *drift* in the measurement to appear, if it is present.

In Table 3.5 we summarise two studies of MCA mean velocity reproducibility [Maeda et al., 1990] [Totaro et al., 1992], and add extracted data from our own reproducibility study done with ensemble-averaged mean velocity measurements (detailed below in

Section 3.4.1). We include our results on ETCO_2 and blood pressure in a similar fashion to those reported by Maeda et al. [1990]. When these three studies are compared, we can see that the correlation coefficient (r) is lower in our study than in either of the other studies, suggesting poor reproducibility. We assume that this may be related to the amount of *drift* in the cerebral circulation over longer time periods, as opposed to shorter. Our mean time period of 63.5 days between tests is greater than the 22-day interval reported by Maeda et al. [1990], or the one day interval reported by Totaro et al. [1992]. Understanding that there is some inherent *drift* in simple mean velocity measurements, we performed a study to look at the reproducibility of all our new waveform shape parameters and indices.

3.4.1 Baseline

3.4.1.1 Ensemble-averaged waveform parameter results

We chose five subjects (three male/two female) ages 22-51 (mean age 34 years $\pm$ 10.6) from the main study group described further in Chapter 4. These subjects are tested twice over an extended time period of 8-85 days (mean 63.6 days), with complete analysis of all waveform shape measurements as well as ETCO_2 and blood pressure measurements.

Our results are represented according to Bland and Altman [1999] and we quote the mean difference between test 1 and 2, and the coefficient of repeatability. The results are grouped into the following categories: Traditional TCD Parameters; Velocity Minima; Velocity Maxima; Acceleration/Deceleration; Miscellaneous; Measurements of time; and waveform Indices in Figure 3.14 A-X. These are labelled as **BASELINE**, since HYPERCAPNIA and HYPOCAPNIA are to follow in Section 3.6. The

discussion of these results will be presented at the end of this Chapter (Section 3.7.2) when a comparison is made with both HYPERCAPNIA and HYPOCAPNIA.

3.4.1.2 Waveform shape variation results

We present the graphical waveform representation of the ensemble-averaged waveforms from both tests 1 and 2 for each subject for visual assessment of waveform shapes (Figure 3.15, subjects A-E).

If we examine the overall shape of the Doppler waveform in each subject, we notice that every individual has a unique shape with differences primarily in the offset of the velocity. Perhaps this could be somewhat likened to the human fingerprint; except this ‘cerebral print’ corresponds to the brain rather than to the hand, and may change over a lifetime. As we know each person’s fingerprint is unique, although there are commonalities between all fingerprints. So when we look at tests 1 and 2, we see that all our subjects (except for Subject C) reproduce a visually distinctive waveform shape, whether it is 8 or 85 days later. Hence, the ‘cerebral print’ or Doppler velocity waveform shape remains the same but it is shifted up or down in velocity as we have seen before. This does not seem to be the effect of simple blood pressure differences at the time of measurement, nor does the higher blood pressure measurement always correlate with the higher velocity waveform. What does appear to be reproducible for each individual is the sequence of velocity minima, and maxima which make up the overall waveform shape.

In regard to Subject C, whose waveform shape has been slightly altered in shape between test 1 and 2 we note that it is primarily U_{min1} and U_{max1} that appear different. From the studies of wave propagation and reflection mentioned in Chapter 2 (Section 2.2.3.3), we know that these two parameters are largely influenced by wave reflections coming from the peripheral cerebral circulation and therefore changes in

vascular tone of the small vessels will change the strength of these reflections. Brackley et al. [1999] found, in a group of 19 women studied over 27 ovulatory menstrual cycles, PI, RI and systolic/diastolic ratios in the RMCA were all significantly higher in the luteal as compared to the follicular phase since oestrogen is a cerebral vasodilator. Although very speculative, this variation may be producing the variation in the waveform shape since it was 70 days between tests, and therefore the subject would have been in a different part of the menstrual cycle in tests 1 and 2. Whereas, if we look at our other female in the group, Subject B, test 1 and 2 were 85 days apart and hence the subject may have been in a nearly identical part of the cycle at each test. Subject B shows a very close duplication of the 'cerebral print' between tests 1 and 2.

Whether this 'cerebral print' would change during the lifespan of an individual is yet to be investigated. Indeed factors such as changes in cardiac function, or development of large and/or small vessel disease would all have an impact on the waveform shape according to our assumptions and therefore the 'cerebral print' may alter over the long-term. However, for women, if we hypothesise that the changing levels of oestrogen throughout the month may have an effect on the cerebral waveform shape, then it is possible that there could be both short and long-term changes in cerebral waveform shape possible.

3.4.2 Summary

We have seen that we can minimise the potential technical errors in transcranial Doppler recordings and stabilise the *input* to repeatability and reproducibility studies by using a standardised set-up protocol, and a probe fixation device. However, there will always be normal cyclical variations in cerebral blood flow which are governed by complex mechanisms still not completely understood. With these variations in mind,

we have selected a recording time period (16 seconds) which incorporates enough information to comprise a reliable sample of the blood flow (usually 10-12 cardiac cycles) and which is appropriate for ensemble-averaging, but is not long enough to incorporate the cyclical variations of M waves, B waves and respiratory waves. In addition, we evaluate the variability of waveform shape over time in this sample group. The subject of waveform shape variability is worthy of significantly more research in the future.

3.5 Cerebral vasomotor reactivity testing

3.5.1 Overview

Perfusion pressure in the brain cannot be directly measured. However, parameters which indirectly reflect cerebral perfusion pressure can be measured. These tests include: a) regional cerebral blood flow volume ratio (rCBF) evaluated by PET (positive emission tomography), or SPECT (single photon emission computed tomography); and b) the reactivity of the cerebral vasculature to various vasodilating stimuli (CO_2 , acetazolamide) evaluated by either rCBF techniques or a transcranial Doppler. Techniques such as PET, SPECT and rCBF demonstrate true flow volume and have relatively good spatial resolution, but have poor temporal resolution. In contrast, TCD gives flow velocity data representative of the vascular territory under study, and has excellent time resolution in the millisecond range.

The relationship between basal cerebral arteries and CBF is a linear one (Figure 3.16 A), with changing end-tidal CO_2 concentrations. This is possible *only* if the cerebral conducting vessel (MCA being monitored by TCD) do not change in size. Studies have shown this to be true, and therefore the effect of CO_2 seems to be restricted to the peripheral vascular bed, leaving the proximal arterial diameters constant [Bradack et al.,

1976] [Gillar, 1991]. In this way, TCD is a reliable technique to evaluate CO₂ induced cerebral arterial vasomotor reserve.

The CO₂ mediated alteration of brain extracellular pH is the initial step leading to changes in cerebral vascular tone. The effect of pH is mediated by nitric oxide (NO), prostanoids, cyclic nucleotides, potassium channels and intracellular calcium; although there is no comprehensive understanding of how these mediators interact [Brian, 1998]. Reducing the PaCO₂ to 20-25 mmHg decreases the cerebral blood flow by 40-50%, by producing vasoconstriction. In contrast, increasing the PaCO₂ to 80 mmHg or more produces a maximal increase in blood flow of 100-200% in animals, due to vasodilatation [Iadecola, 1994]. In our study, the range of ET-CO₂ will be between 25 mmHg and 60 mmHg.

Ringlestein and Otis [1992] measured the mean blood flow velocity during inhalation of normal room air at 100%, and then compared the percentage change during CO₂ inhalation (2-6% CO₂) and hyperventilation. They used 40 healthy adults (28 men, 12 women) aged 20-75 years with a mean age of 51 years. On average, the mean blood flow velocity in the MCA increased by 52.5% during CO₂ inhalation, and decreased by 35.3% with hyperventilation. The mean vasomotor reserve (VMR) from the cohort was $86 \pm 15\%$. This represented the % change in velocity between hypercapnia and hypocapnia. Today, this is considered the 'normal' value for cerebral vasomotor reserve in most vasoreactivity studies performed on patients with pathology, such as carotid stenosis. Yonas et al. [1987] reviewed the rCBF literature and reported a 3-5% change in CBF per unit change in arterial CO₂. When Ringlestein and Otis [1992] looked again at their data they found it would correspond to a 5% blood flow velocity change per mmHg of CO₂.

We have selected vasomotor reactivity testing to evaluate the Doppler waveform shapes because of its effect on arteriolar resistance in the brain. By altering the distal resistance, we hope to alter wave reflections coming from the small arteries. In turn, this should indicate which waveform parameters are representative of vasomotor tone.

In this section we describe CO₂ stimulation (hypercapnia) known to produce cerebral vasodilation and hyperventilation (hypocapnia) which produces cerebral vasoconstriction. We detail our standardised testing protocol and the techniques used with our system.

3.5.2 Methods and technique

3.5.2.1 Hypercapnia (CO₂ inhalation)

Hypercapnia involves the inhalation normally of between 6-8% CO₂ in a mixture of room air. We have selected 6% CO₂ since it is easily tolerated. The preparation involves the subject resting comfortably while the TCD transducer is optimised on the velocity signal of the LMCA. Once this has been accomplished and the blood pressure and heart rate have stabilised, the subject breathes through a one-way 'Rudolph' valve (Hans Rudolph Inc, Missouri USA) (Figure 3.16 B-C), with a sampling tube leading from the mouthpiece to the end-tidal CO₂ monitor. The subject wears nose clips, so that all breathing is done through the mouthpiece. A small sampling tube comes from the valve section containing only exhaled air, and goes directly into the end-tidal CO₂ monitor for measurement. A wide flexible tube delivers the CO₂ gas mixture from the reservoir bag to the one-way Rudolph valve used by the subject. Another valve is attached to the reservoir bag and is used to direct the CO₂ mixture, or the room air, into the subject's breathing tube; depending on what stage of the reactivity test is taking place.

During administration of CO_2 , blood flow volume in the cerebral conducting vessel will increase, secondary to the vasodilatation of the resistance vessels (small arterioles). In turn, TCD blood flow velocities will also increase. There is a linear relationship between the TCD blood flow velocity in the conducting vessel (MCA) and rCBF, as long as CO_2 does not affect the diameter of the conducting vessel. It has been shown that influence of CO_2 is restricted mainly to the peripheral vascular bed of the brain [Bradack et al., 1976] [Gillar, 1991] and not to larger vessels like the MCA. This theory is supported by the fact that if the MCA was dilating during CO_2 inhalation, the velocity would indeed go down and not up, as the vessel diameter increased. The reverse would occur with hyperventilation. However, this does not appear to be the case. Therefore we use changes in TCD flow velocities, to reflect changes in flow in the cerebral circulation during vasoreactivity testing.

The effect of CO_2 inhalation is quick and the velocities rise and then stabilise within 3-5 minutes. At this point, we acquire 16 seconds of data for off-line analysis.

3.5.2.2 Hypocapnia (Hyperventilation)

For the hyperventilation portion of the test, the valve is directed to provide room air, and the subject quickens his breathing to a pace set by the investigator. This allows the investigator to create either a maximum or a controlled hyperventilation protocol for the subject, as the investigator gauges and directs the subject to appropriate levels, while assessing the values on the end-tidal CO_2 monitor. During the study by Ringlestein and Otis [1992], they tried several different intensities of hyperventilation but came to the conclusion that an important part of hyperventilation was for the examiner to dictate the rhythm of hyperventilation, or use a metronome. This is indeed a good method in the attempt to standardise the *input* of this part of the test. We choose to have the

examiner set the rhythm for hyperventilation, but decided to include a small study to determine whether to use maximal or a controlled hyperventilation, as we wish to understand the overall cardiovascular effects of both techniques.

3.5.2.3 Maximal versus controlled hyperventilation study

Maximal hyperventilation is a technique whereby the observer initially leads the subject into a pace of rapid breathing. The subject is then left to breathe deep and fast to whatever level they are able to sustain for a two-minute period, without becoming markedly light-headed or fainting. Since this technique is completely subject dependent, there is considerable variability in performance and results between subjects and tests. Furthermore, during maximal effort, other physiological variables may change, such as heart rate and blood pressure, which may be linked to the overall fitness of each subject. Although many studies of vasoreactivity have been performed, there is little in the literature regarding the techniques utilised during the hyperventilation phase. Therefore, we perform this study to test the differences before deciding on the final protocol for the studies in this thesis.

In the first part of the study, we select eight of our subjects (four male/four female) with a mean age of 35 ± 8.4 (28-51 years) from the main study group in Chapter 4. We require them to perform two minutes of maximal hyperventilation and measure their blood pressure in the last few seconds. The graph in Figure 3.17 shows the % change from their baseline blood pressure at the end of hyperventilation. It can be seen that blood pressure changes vary widely between individuals and may possibly be due to the overall fitness of the subject.

We then use six of these subjects (mean age 35 ± 9.4) and perform a baseline measurement of ETCO_2 , blood pressure and heart rate. First they perform a controlled

hyperventilation, where they are directed by the examiner. The examiner monitors their ETCO_2 and directs them into a rhythm of hyperventilation which lowers their ETCO_2 approximately 10 mmHg below their baseline value. They were then asked to continue to follow this rhythm for two minutes. At the end of this time, the ETCO_2 , blood pressure, and heart rate were measured simultaneously. This is the test that the subjects tolerated best.

Figure 3.18 A-B show the results of this study as % change from each individual baseline value in ETCO_2 , blood pressure and heart rate. The graphs show that controlled hyperventilation does not produce large fluctuations in cardiovascular parameters. The benefits of the controlled hyperventilation technique are that it is well tolerated by the subjects, easy to perform and does not rely on the fitness of the subject to sustain it. However, we can also see that this technique does not drop the ETCO_2 to the same level as maximal hyperventilation, and therefore will also not decrease the velocity measurements to the same extent during vasoreactivity.

This technique may not provide maximum stress to the individual, although it is unclear whether this is necessary during vasomotor reactivity testing. For standardisation purposes, we choose to have all subjects perform 'controlled hyperventilation' for our testing in this thesis. When reviewing our final results, we will consider that the level of hyperventilation may be milder than is performed in other studies in the literature, so our results will not be directly comparable. However, our aim is to conduct reproducible tests in order to adequately measure and interpret our waveform parameter measurements; hence we elect to control this portion of the *input* to vasoreactivity testing through this method.

3.5.2.4 Standardised testing protocol

The protocol detailed below has been used in all of the vasoreactivity studies in this thesis.

General preparation

The subject rests for five minutes with the mouthpiece and nose-clips in place and breathes room air only. This allows the subject to become accustomed to the breathing apparatus. It also allows the velocity signal, heart rate and blood pressure to stabilise.

The subject is supine with a 30 degree head elevation, as this is a comfortable position for most individuals and assists standardisation.

1) The test begins with the subject breathing three minutes of room air. At the end of this time period, 16 seconds of data (velocity, ECG, end-tidal CO_2) are recorded from all equipment. Once completed, the blood pressure is measured with an automated blood pressure machine (Omron) and noted on the worksheet. This is noted as *Baseline* 1.

2) The valve is now turned to allow delivery of the 6% CO_2 gas mixture. After 3-5 minutes, the data are recorded once again and the blood pressure measured. (Note: each subject needs to reach a plateau in velocity before the gas is stopped. This normally occurs after three minutes, but can take up to five minutes.) The valve is returned to room air position. A blood pressure reading is taken and recorded. This is noted as *CO₂ inhalation*.

3) The subject is allowed to rest again for three minutes breathing room air. The velocities drop rapidly and are generally near to baseline at the end of the three-minute

rest period. The data are then recorded once more, and the blood pressure taken. This is noted as *Baseline 2*.

4) The subject is now ready to perform controlled hyperventilation of room air. The investigator leads the subject into rhythmic breathing until the subject's ETCO_2 reaches a level 10 mmHg below his baseline ETCO_2 . The subject is then asked to continue this rhythm for three minutes. The data are then recorded again, and the blood pressure taken. The subject is now instructed to relax. This is noted as *Hyperventilation*. It should be noted, however, that the velocities do not return immediately to baseline values. The time to 'normalise' appears to be greater with hypocapnia, than hypercapnia.

5) After 3-5 minutes of rest, the data are recorded for a final time before the mouthpiece is removed. This is recorded as *Baseline 3*, and the test is stopped.

The frequent recording of the various stages of the test allow more information to be gathered regarding the recovery of the cerebral circulation from stress testing. All waveform shape changes and values in this thesis will be compared to *Baseline 1*.

3.6 Vasoreactivity reproducibility study results

3.6.1 Hypercapnia

3.6.1.1 Ensemble-averaged waveform parameter results

For this test, we use the same five subjects who were described in Section 3.4.1

BASELINE, since we carry on with the vasoreactivity testing immediately after taking their baseline measurements. We also use the standardised testing protocol described in Section 3.5.2.4.

Again, the results are represented according to Bland and Altman [1999], and we quote the mean difference between test 1 and 2, and the coefficient of repeatability. The results are grouped into the same categories for comparison (Figure 3.19 A-X). These results are labelled **HYPERCAPNIA**. Discussion of these results will follow at the end of this Chapter (Section 3.7.2) when a comparison is made with both BASELINE and HYPOCAPNIA.

3.6.1.2 Waveform shape reproducibility results

Figure 3.20 (subjects A-E) shows the waveform shape changes produced by the inhalation of CO₂ and compares the reproducibility of waveform shape when this is performed a mean of 63.6 days apart. Although the waveform shape has changed from BASELINE, the ‘cerebral print’ between the two tests is very similar in most of our subjects, except for Subject B. In this subject, U_{max1} exceeds U_{max} in test 1 whereas it does not in test 2. We analysed the ET_{CO₂} but there was only a small difference, 59 mmHg on test 1 and 57 mmHg on test 2. We did note, however, that this particular subject was very anxious (as seen by the marked heart rate difference) during Hypercapnia on test 1, since she felt as if she needed to cough.

It appears that the *drift* we are getting in these results has more to do with shifts up or down on the velocity scale, rather than a change in the ‘cerebral print’. This may have to do with oscillations from the waves we described in Section 3.3.2.

When we compare these results (Figure 3.20 A-E) to our BASELINE waveform shapes (Figure 3.15 A-E), the velocity maxima and minima are seen to have increased, as expected. However, if we only look at waveform shape (not the velocity measurement), we see that the segment of the waveform between U_{max} (peak velocity) and U_{min2} (closure of the aortic valve) has altered in shape from the baseline results. Dudtmin1

(first deceleration after peak velocity) displays a reduction in the deceleration during HYPERCAPNIA, compared with that seen in the BASELINE waveforms. This is detectable even with the naked eye. We hypothesise that this is due to a change in the wave reflection coming from the peripheral vascular bed in the brain. As the small vessels dilate due to the effect of CO₂, the strength of the reflections is decreased. A physiological change in the cerebral circulation, in this case vasodilatation, influences the ‘cerebral print’. The individual waveform shape changes are dependent on the individual’s ability to vasodilate under a known stimulus.

3.6.2 Hypocapnia

3.6.2.1 Ensemble-averaged waveform parameter results

As in Sections 3.4.1 BASELINE, and 3.6.1 HYPOCAPNIA, our results are listed in identical formats, and will be discussed at the end of this Chapter in Section 3.7.2.

These are labelled **HYPOCAPNIA** and detailed in Figure 3.21 A-X.

3.6.2.2 Waveform shape reproducibility results

Our results are shown in Figure 3.22, subjects A-E.

In terms of waveform shape, the main feature of hyperventilation is the sharp reduction in velocity immediately after the peak. This is present in all of our subjects. If our hypothesis is correct, this indicates that a very strong reflected wave is coming back from the periphery due to the vasoconstriction of the small vessel. The result of this wave is to force a reduction in the velocity. If we compare this section of the waveform to HYPERCAPNIA, we can visually see the difference in DuDtmin1. Another effect of hyperventilation is that overall velocity falls. This is to be expected due to the small vessels being vasoconstricted; less volume of blood to the brain is required. However the ‘cerebral print’ is preserved in each individual. Slight differences are seen in Umax1

(Subject E); a parameter which has been seen to vary in both BASELINE and HYPERCAPNIA. We will summarise all waveform shape changes during vasoreactivity testing in Section 3.7.

3.7 Summary

Assessment of vasomotor reactivity reproducibility can be complex when there are many new parameters, and also visual waveform shape changes to address. Therefore we summarise and simplify our findings in the sections below.

3.7.1 Ranking

We have chosen to use a ranking score table for easy comparison of our many parameters during testing. Our reproducibility ranked score for each parameter is calculated as follows:

$$\text{Ranked score} = \frac{\text{Mean value (tests 1 and 2)}}{\text{Coefficient of repeatability}}$$

The resultant value or score for the parameter is entered into the chart by category and presented in Table 3.6. We have included all three segments of vasoreactivity testing including **BASELINE**, **HYPERCAPNIA**, and **HYPOCAPNIA** in our results. Higher scores indicate better reproducibility for the parameter. In addition we provide Figure 3.23 A, which depicts *graphically* the individual ranked score for the parameter *by test* (BASELINE, HYPERCAPNIA, and HYPOCAPNIA). We use Figure 3.23 B to show the distribution of reproducibility ranked scores *by bracket*.

Figure 3.23 A, indicates that during BASELINE parameters such as Tmin2, RI have good reproducibility, along with ETCO₂. In contrast, Velocity Rise Index, DuD_{tmin1}

and DuD_{tmin}2 have poor reproducibility. The other parameters are fairly evenly distributed.

During HYPERCAPNIA T_{min}2, Rise time, and ETCO₂ appear to have good reproducibility. (We expect the ETCO₂ reproducibility to be excellent since we are delivering a fixed amount of gas and air.) The poorest scores appear to be from the Velocity Rise Index and DuD_{tmin}1. Most of the other parameters are again fairly evenly distributed.

T_{min}2, and Rise time are the most reproducible parameters during HYPOCAPNIA, but the majority of the parameters lie at the poorer end of the reproducibility ranked scores.

Mean scores for ranked reproducibility are:

BASELINE- 4.60

HYPERCAPNIA- 4.34

HYPOCAPNIA- 4.00

Our study has shown that reproducing a BASELINE measurement during testing has the best reproducibility overall. However, during vasomotor reactivity testing, reproducibility is more difficult. HYPERCAPNIA is a more reproducible technique because a known stimulus or *input* (in this case the CO₂ gas mixture) is being given to all subjects. However, the reactivity of the cerebral vessels may vary from individual to individual and suffer the effect of time, or *drift*, in the measurements. In summary, the cerebral circulation may vary in its ability to react from day-to-day, or from month-to-month.

Reproducibility during HYPOCAPNIA does not score so well. This could arise from difficulty in stabilising the *input*, or the hyperventilation technique. It is left to the individual to attempt to stabilise this (even though guidance is provided), and the result is increased variability in the test results as we can see by the rather low reproducibility score for ETCO_2 during HYPOCAPNIA.

The most reproducible parameters by category during vasoreactivity testing are:

Traditional TCD parameters - RI

Velocity Minima - $U_{\min}$

Velocity Maxima - $U_{\max\text{dias}}$

Acceleration/Deceleration - $DuDt_{\max}$

Miscellaneous - ETCO_2

Time Measurements - $T_{\min 2}$

Indices - Mean Resistance Index

It is important to note that although a parameter may have poor reproducibility; this may be reflecting the difficulty of the measurement technique itself, and not the potential diagnostic value the parameter may have for the cerebral circulation.

3.7.2 Waveform shape variations during vasomotor reserve testing

This study demonstrates that it is likely that each individual has a distinctive 'cerebral print', or Doppler waveform shape for the cerebral circulation (MCA). This 'print' appears to alter with changes in vasomotor tone produced by vasoreactivity testing in similar patterns during both HYPERCAPNIA and HYPOCAPNIA. These velocity waveform shapes appear to remain fairly consistent within each individual even over an

extended period of time between tests. In Chapter 4, we continue to look at waveform shapes in our main study group, and explore whether patterns exist in subjects of similar age or gender.

3.7.3 Synopsis

- The Doppler waveform shape is remarkably reproducible within both short and long time frames.
- Doppler velocities have more inherent *drift* because of ‘cyclical oscillations’ present in the cerebral circulation.
- The coefficient of repeatability can be compared to changes seen during interventions to give a measure of the confidence in the results.
- Inter-subject differences are greater than differences in the same subject.

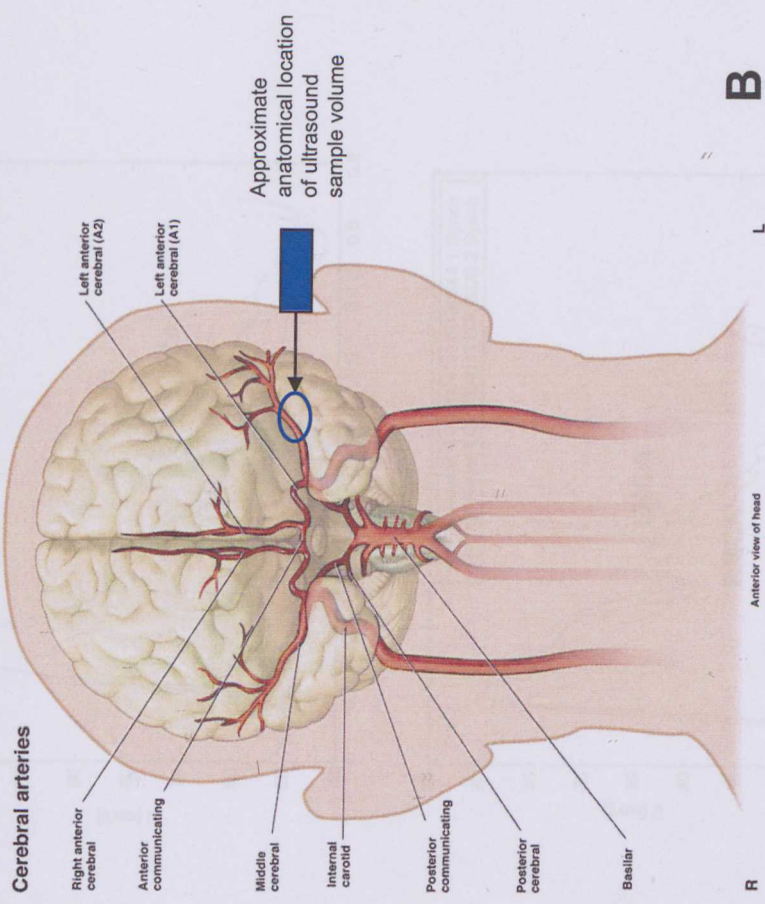


Figure 3.1 **A)** Example of a subject with the Doppler transducer on the left middle temporal window, held in place by the MARC 600 headband. **B)** The arrow points to the approximate anatomical location in the left MCA where we gather the velocity data. (Diagram with permission. Copyright © 2006 Nucleus Medical Art, Inc. All rights reserved.)

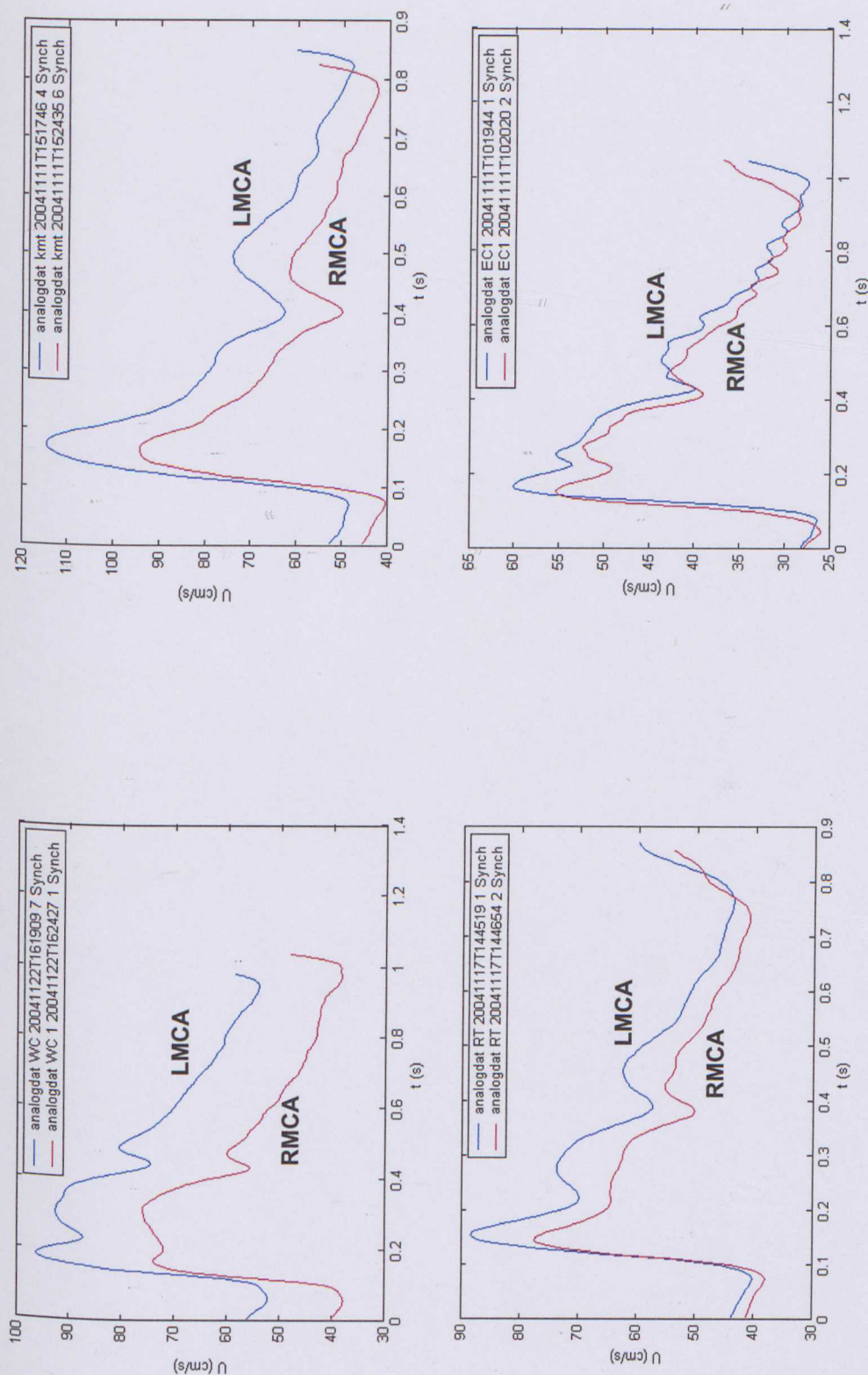


Figure 3.2 The comparison of the left and right MCA on four healthy subjects. Note that the LMCA appears to have higher velocities than the right in these subjects, although the waveform shape appears similar.

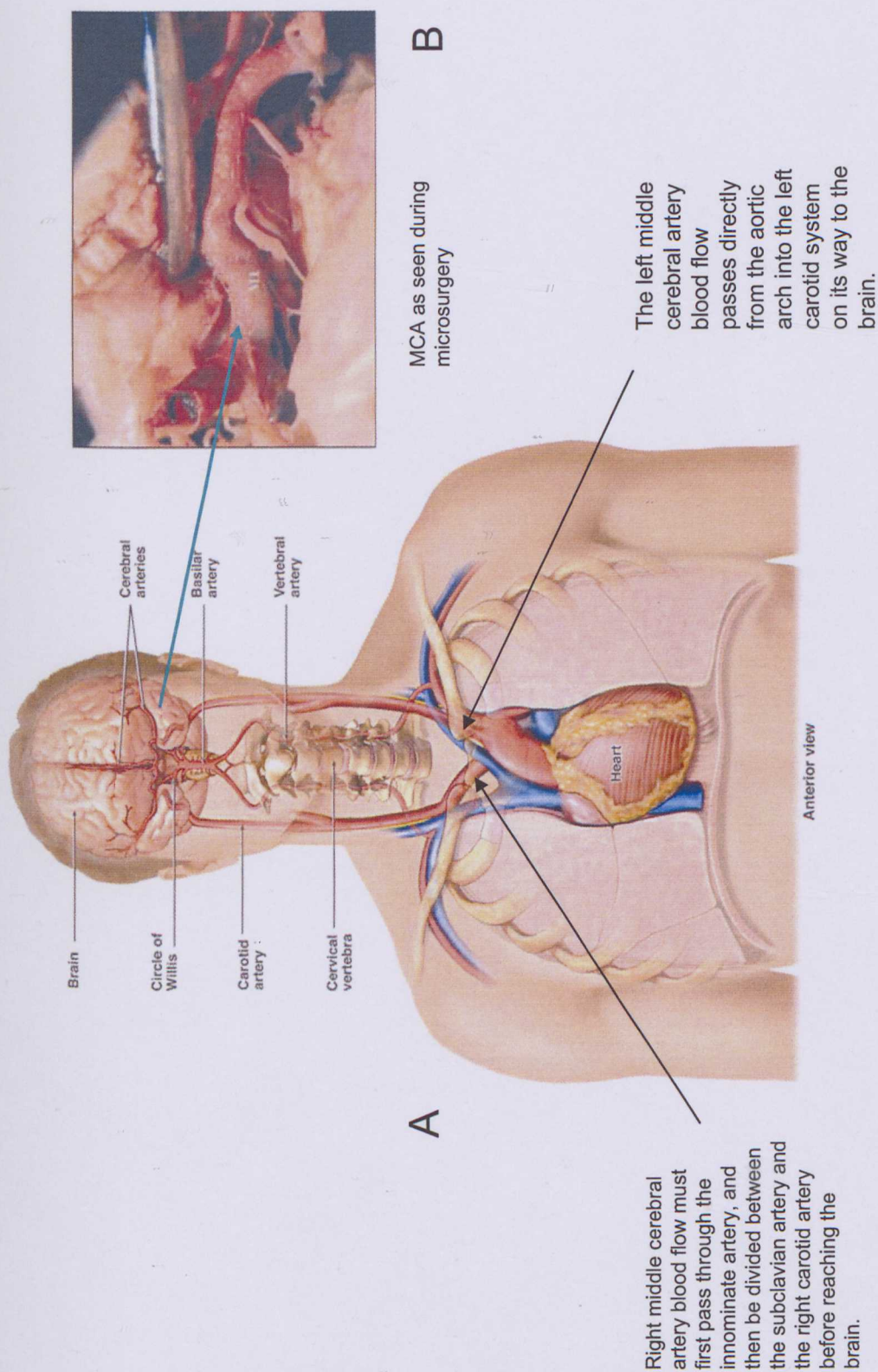


Figure 3.3 A) Depiction of the arterial anatomy between the heart and the brain. (Diagram with permission. Copyright © 2006 Nucleus Medical Art, Inc. All rights reserved); B) Photograph of the MCA (M1) taken during microsurgery from Pai et al., [2005] with permission.

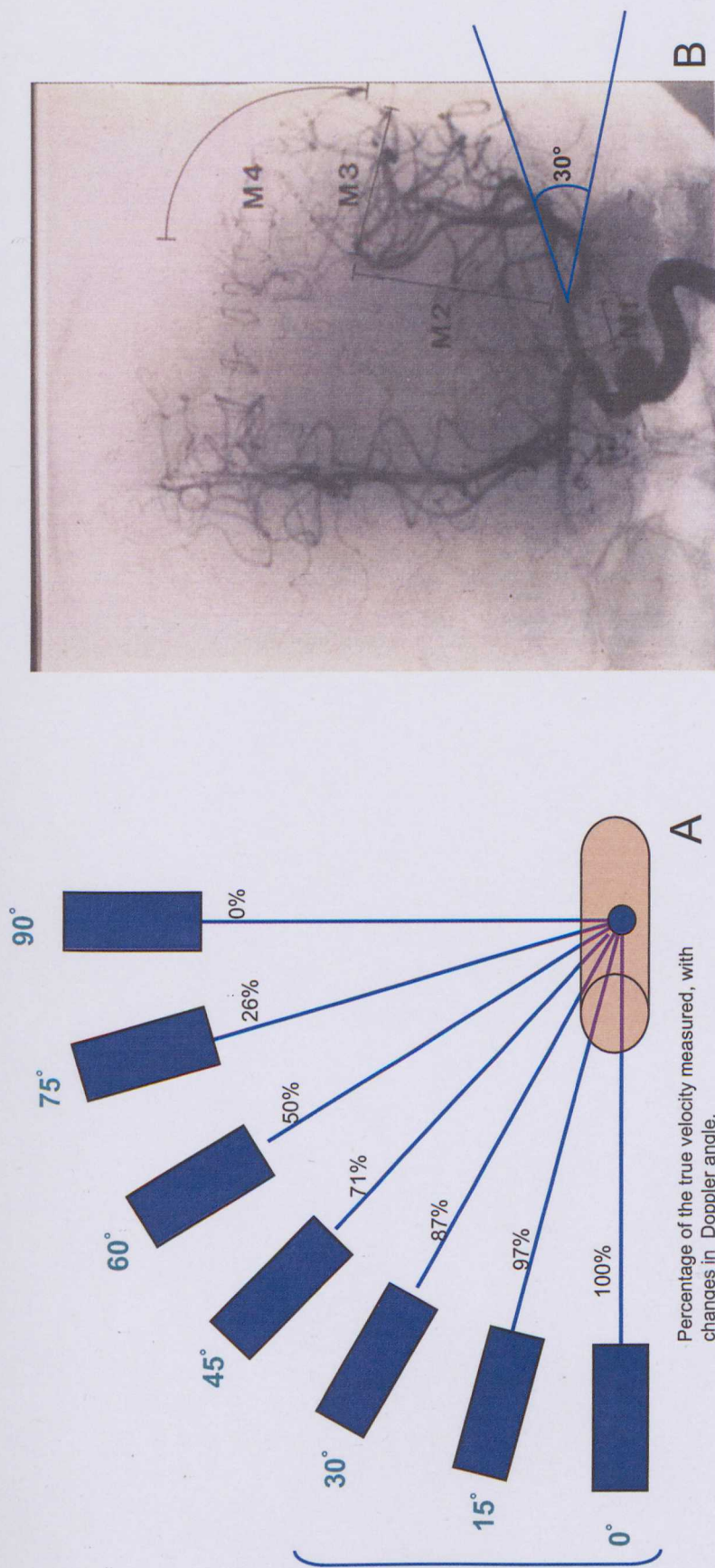


Figure 3.4 A) Depicts the dependence of the measured Doppler velocity on the cosine of the Doppler angle with respect to the direction of flow. We believe the velocities in the MCA to be acquired at between 0° and 30°. This would mean that there is up to a 13% error in the true velocity (that at 0°) when measured.

B) Cerebral angiogram of the anterior circulation depicting the MCA territory (courtesy of the Univ. of Washington). The anatomical course of the MCA together with the limitations of the skull window above the zygomatic arch, are major factors in determining what Doppler angles are available for insonation of the MCA. In general, steep angles are simply not possible therefore limiting larger errors.

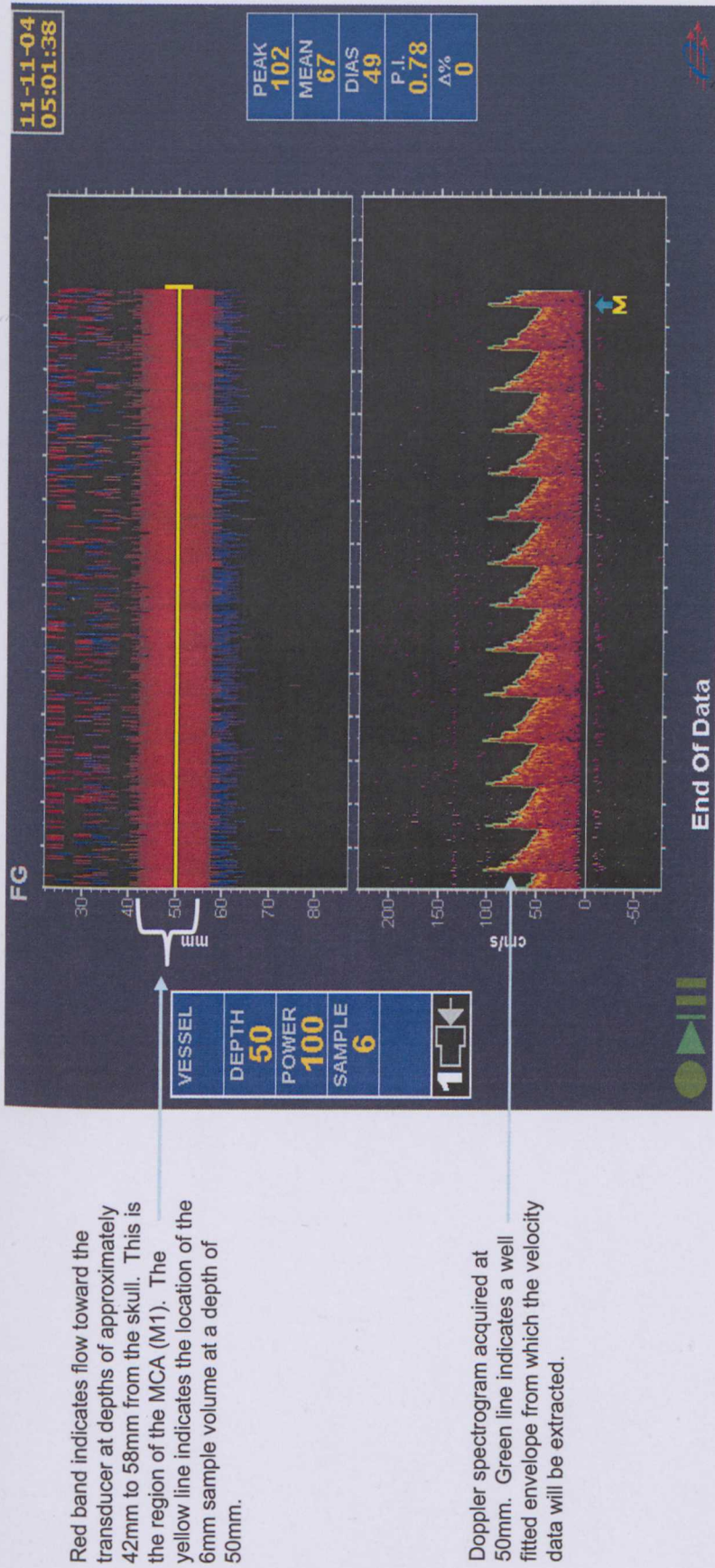


Figure 3.5 Shows an optimal signal location and Doppler spectrogram we tried to achieve in this study.

Mean velocity variations

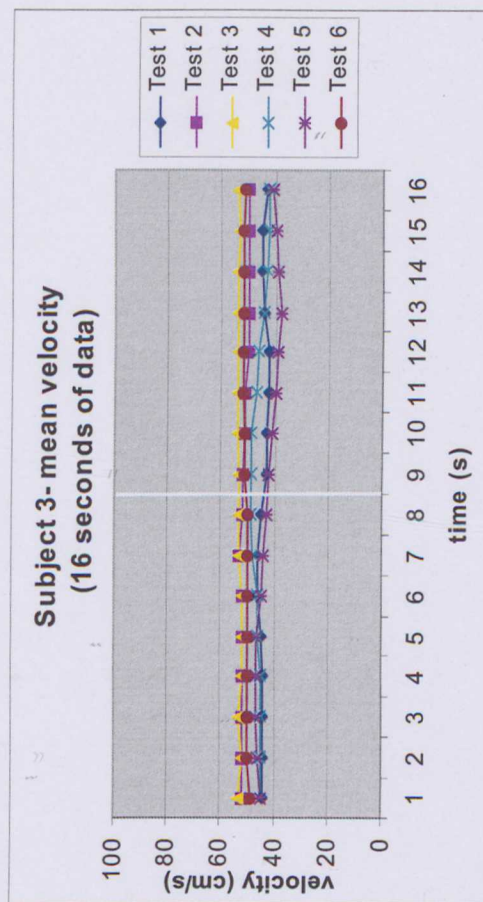
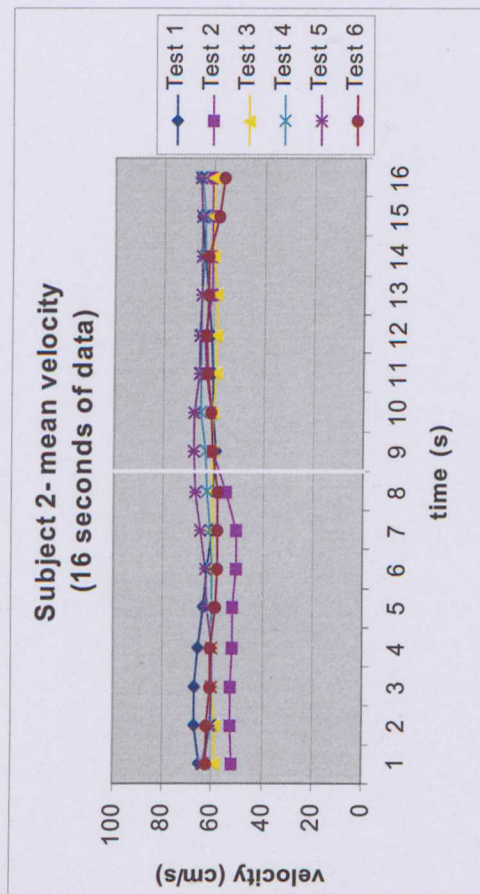
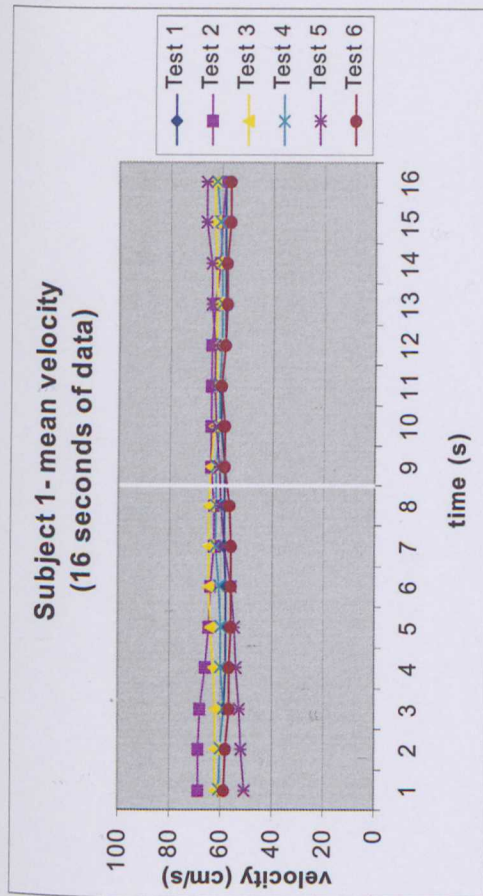


Figure 3.6 The variation in *mean velocity* over 16 seconds in our three subjects. The area to the left of the white line in the centre, denotes the velocity data used for our repeatability comparison. The area to the right shows the variability in the data in the following 8 seconds.

Peak velocity variations

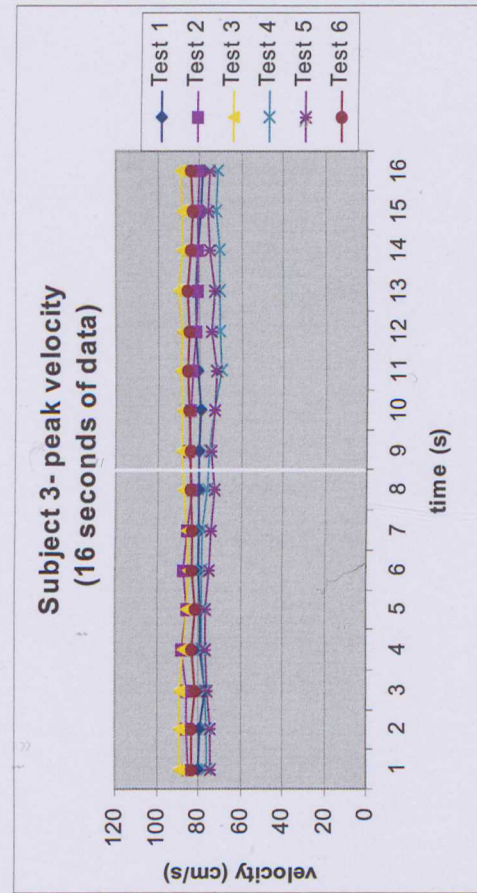
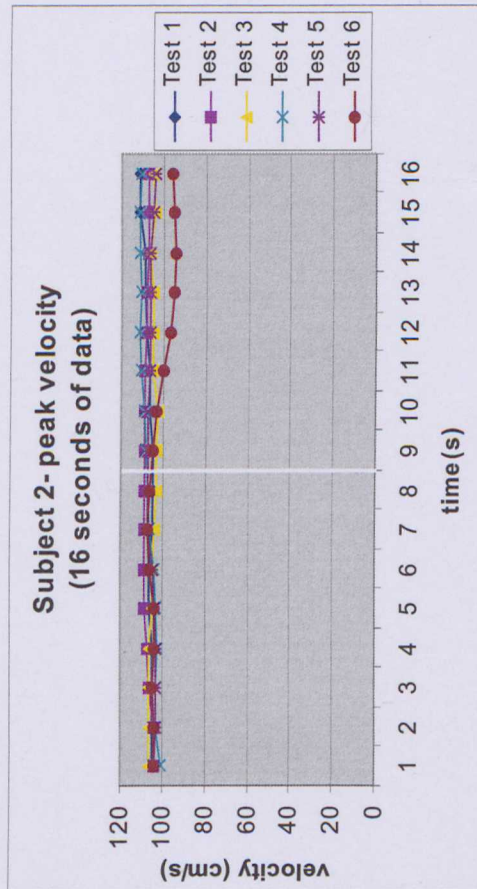
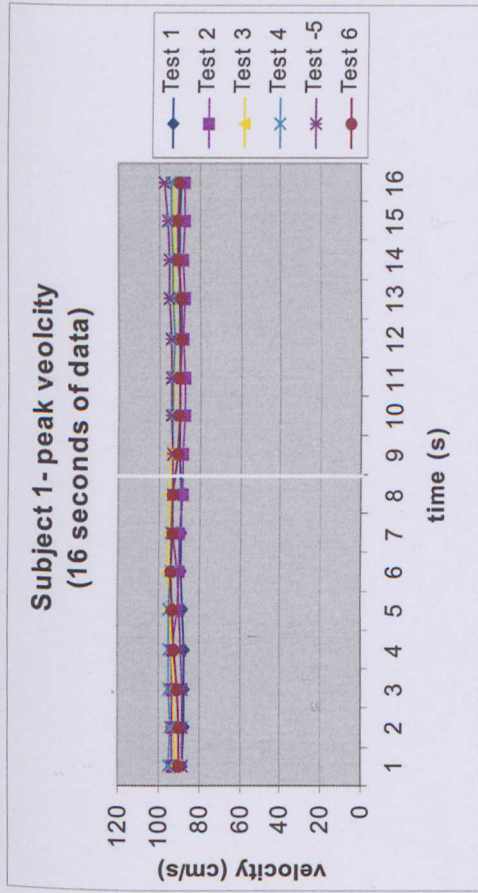


Figure 3.7 The variation in *peak systolic velocity* over 16 seconds in our three subjects. The area to the left of the white line in the centre, denotes the velocity data used for our repeatability comparison. The area to the right shows the variability in the data in the following 8 seconds.

End-diastolic velocity variations

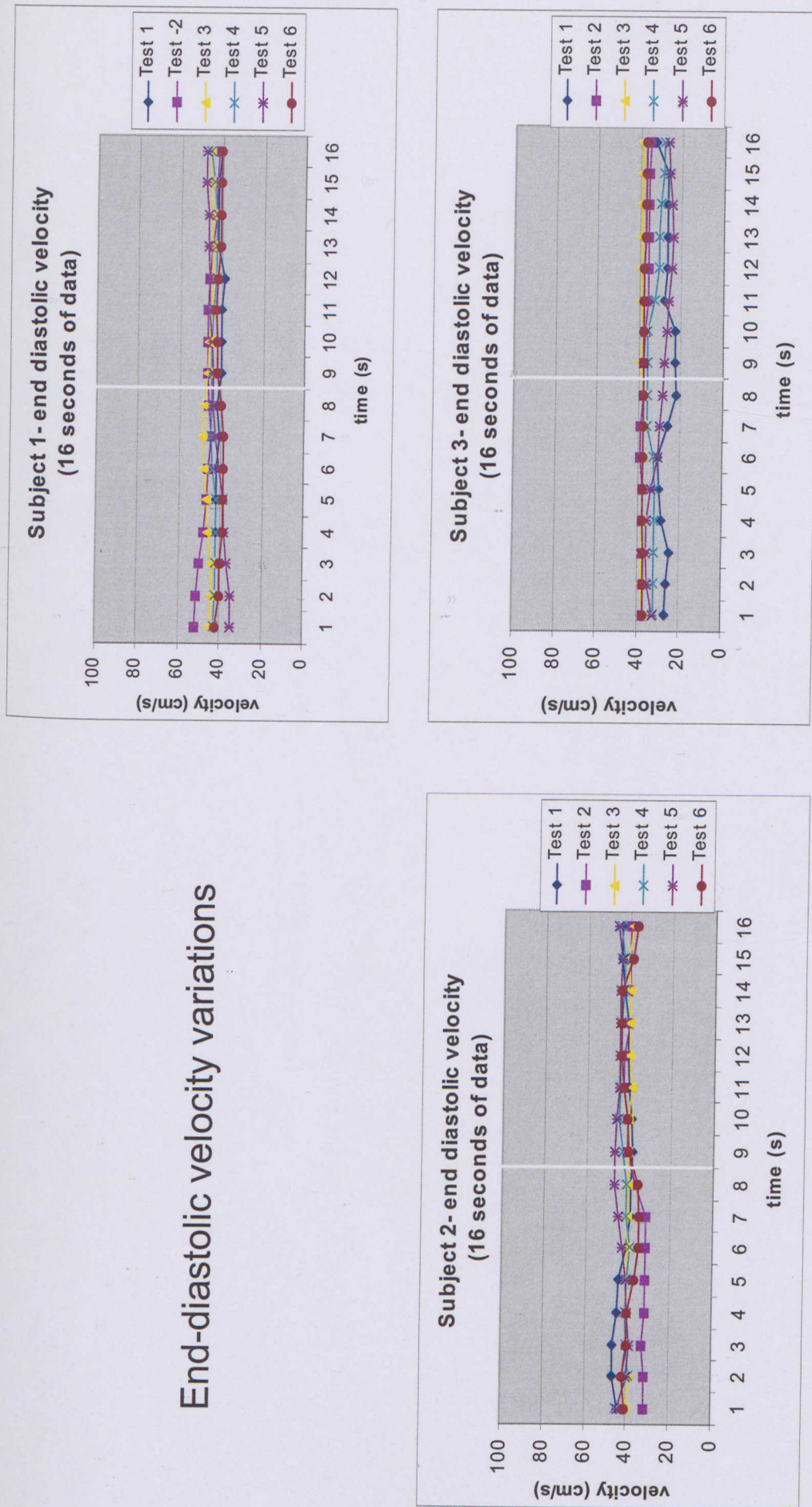


Figure 3.8 The variation in *end-diastolic velocity* over 16 seconds in our three subjects. The area to the left of the white line in the centre, denotes the velocity data used for our repeatability comparison. The area to the right shows the variability in the data in the following 8 seconds.

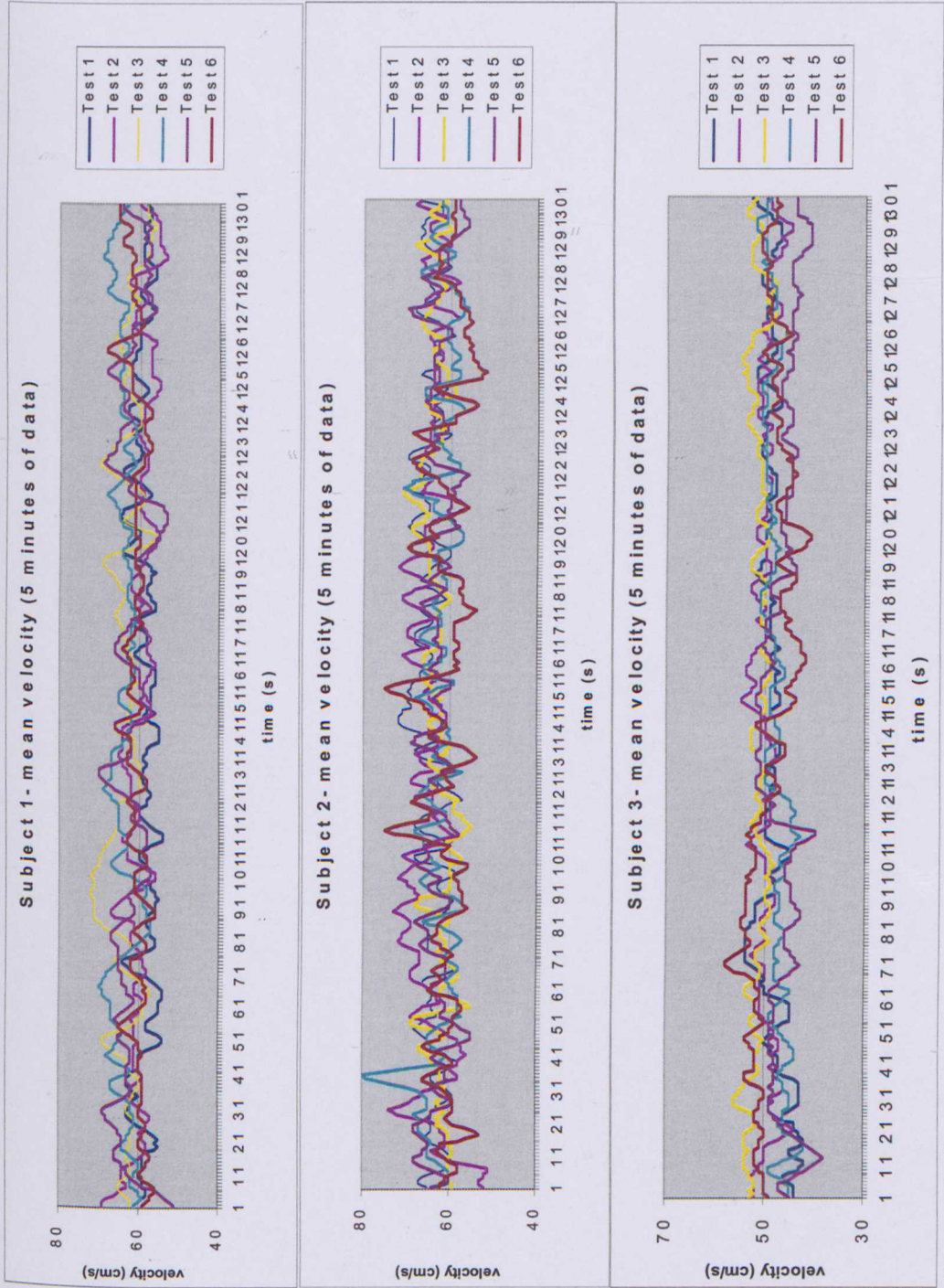
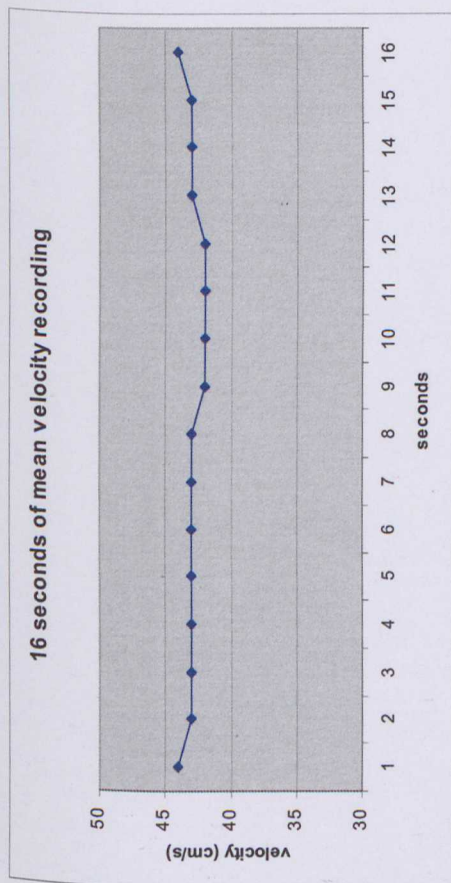
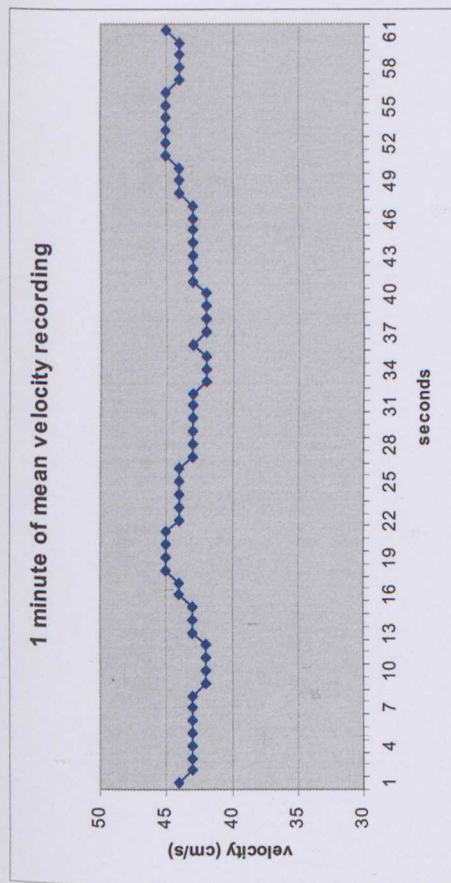


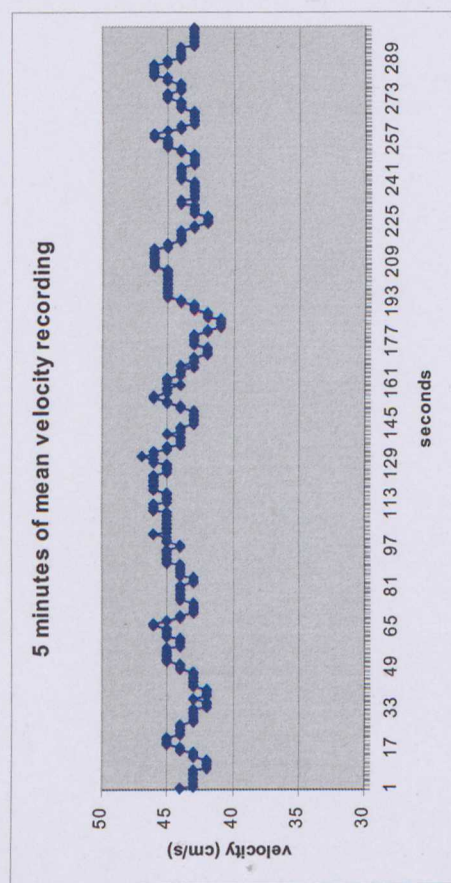
Figure 3.9 Five minutes of continuous mean velocity recording in each of our 3 subjects (6 tests shown). There is greater velocity variability over longer time frames.



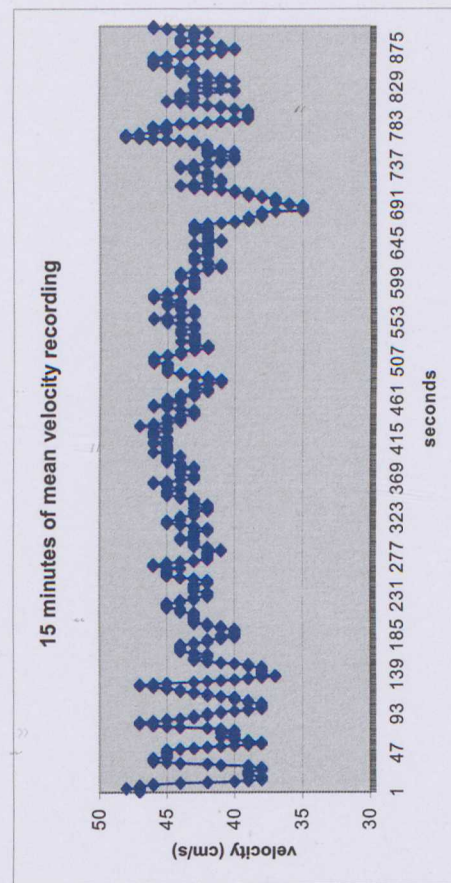
A



B



C



D

Figure 3.10 Velocity variations in a single individual over time **A)** 16 seconds, **B)** 1 minute, **C)** 5 minutes, **D)** 15 minutes

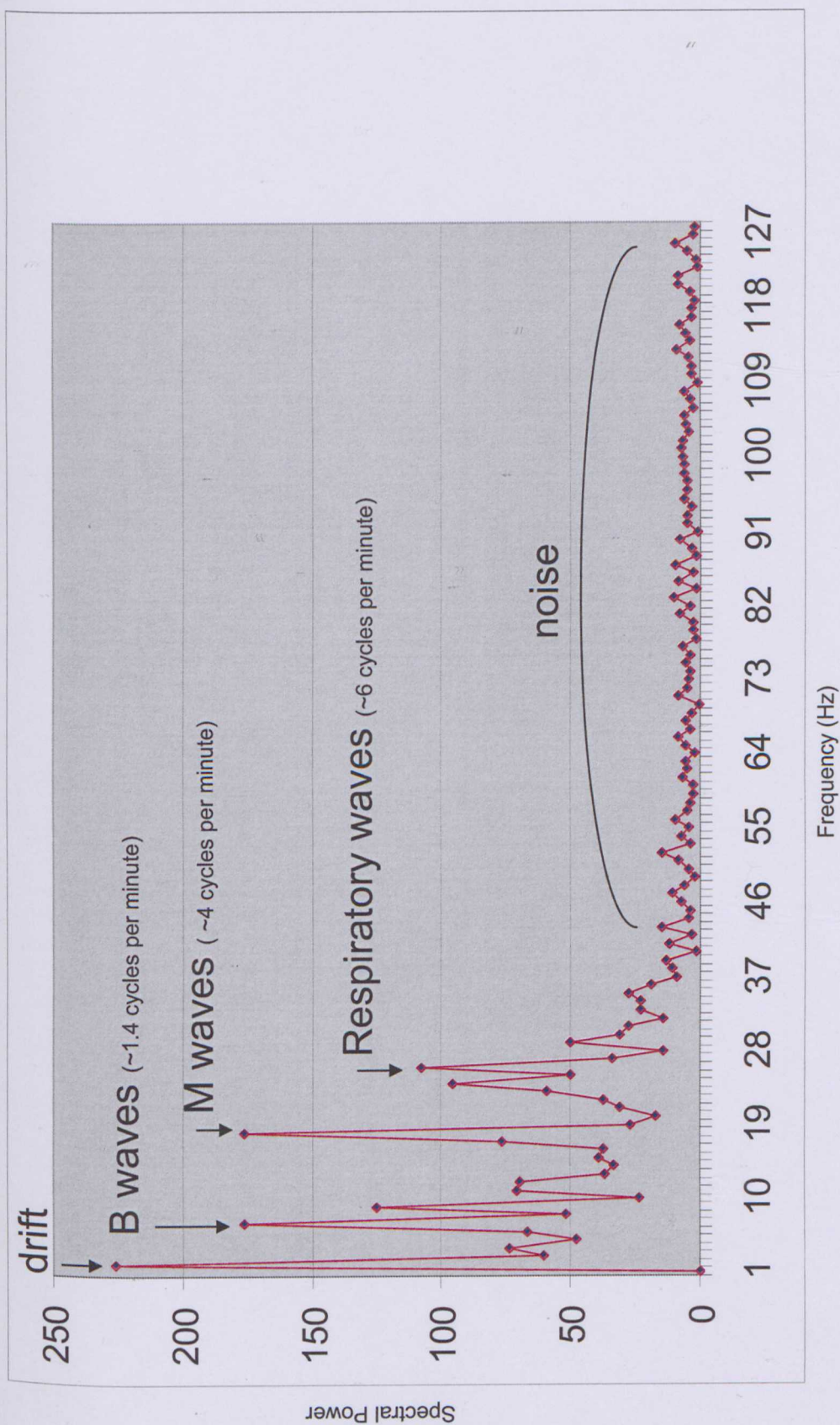


Figure 3.11 Fast Fourier transform of 5 minutes of mean velocity data from a subject showing the presence of B waves, M waves, and respiratory waves.

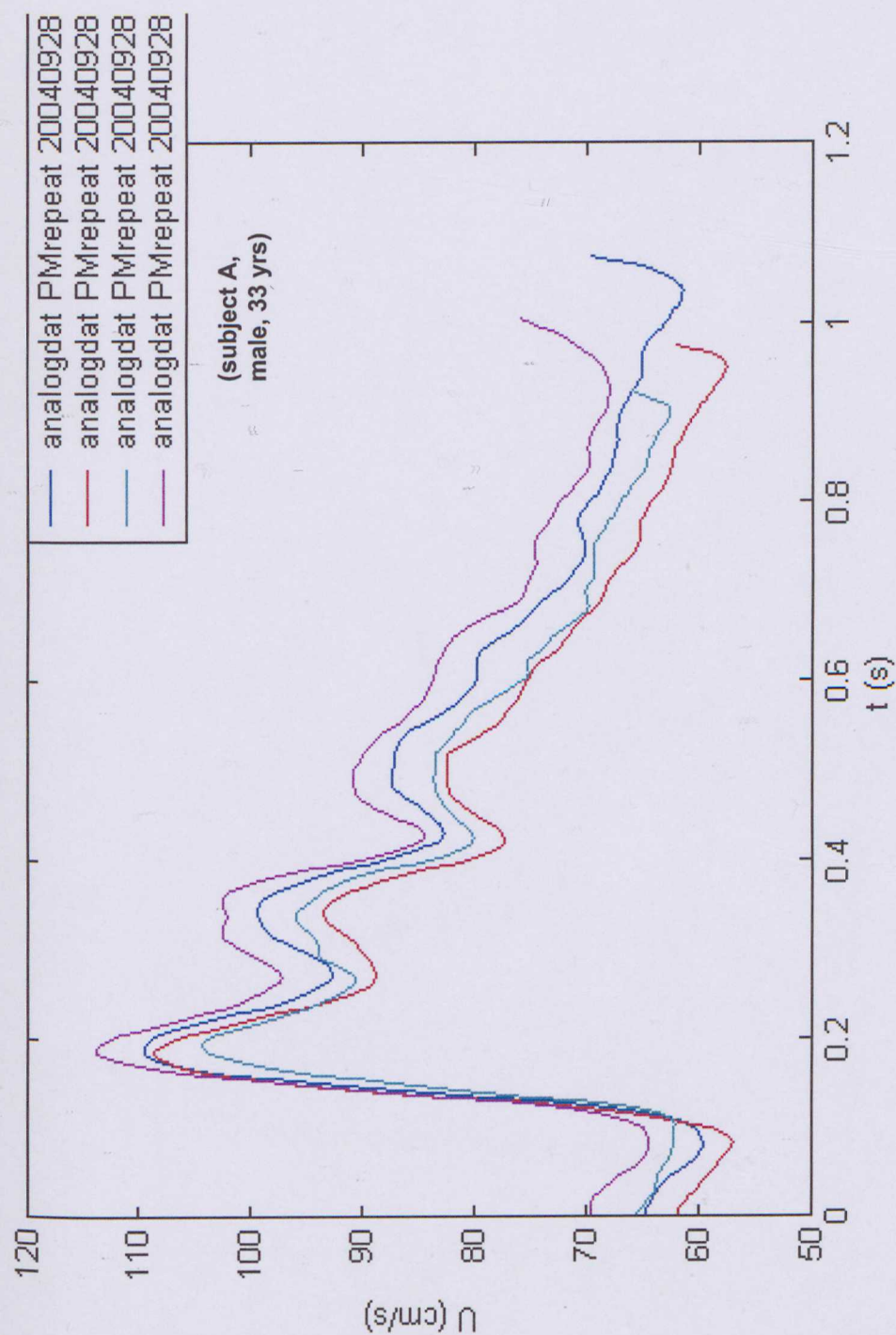


Figure 3.12 Doppler wave shape repeatability in subject A done 4 times over 30 minute time period with complete set-up and restart of equipment

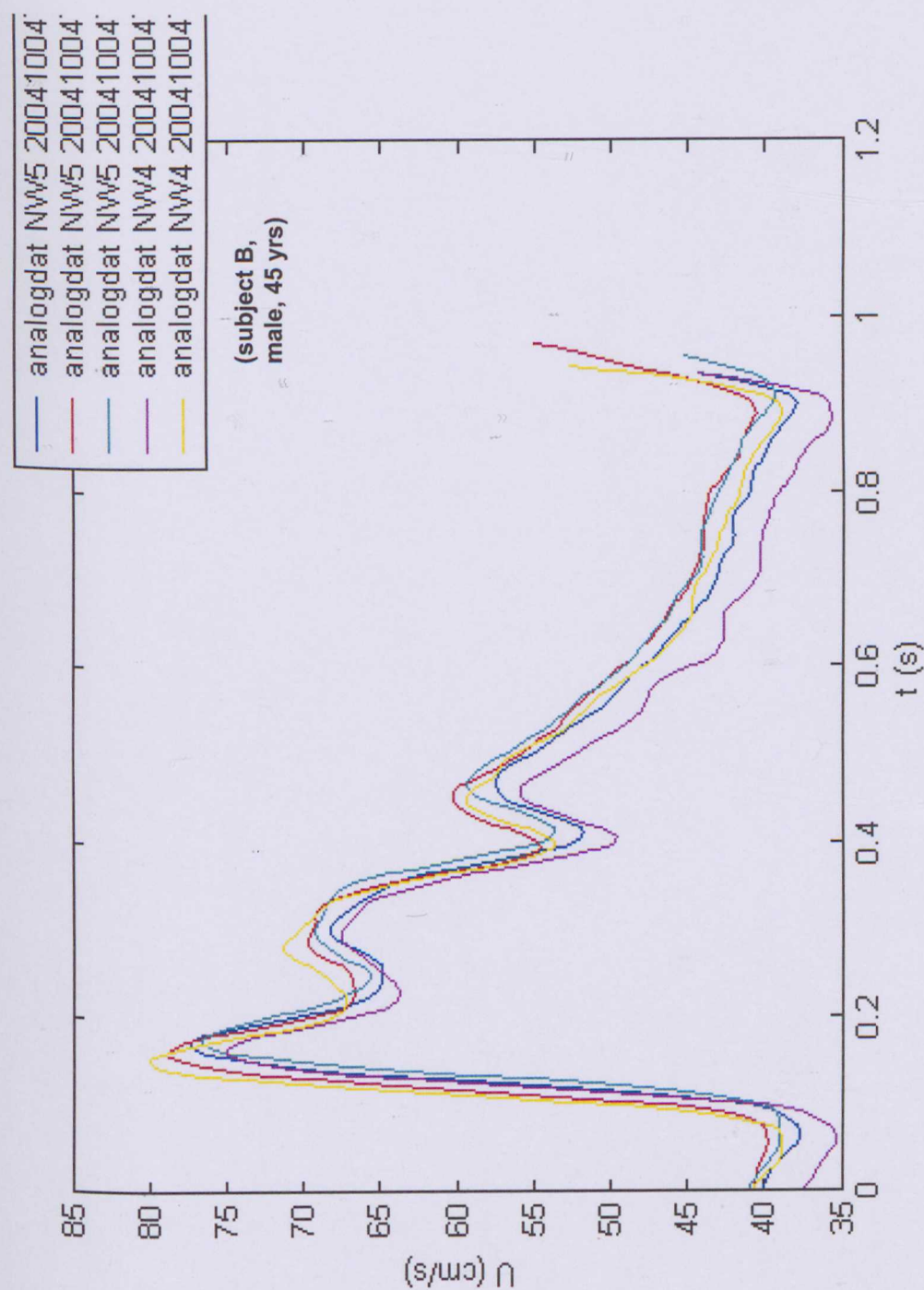
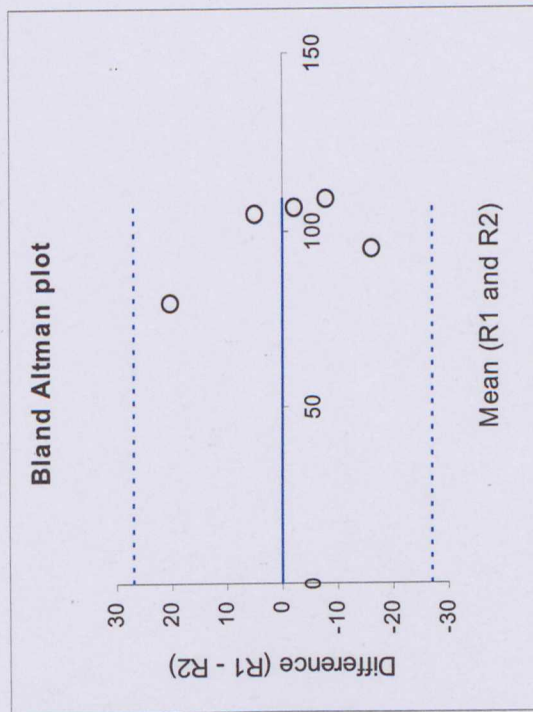


Figure 3.13 Doppler wave shape repeatability in subject **B** done 6 times over 30 minute time period with complete set-up and restart of equipment.

Waveform parameter reproducibility - TRADITIONAL TCD PARAMETERS

BASELINE



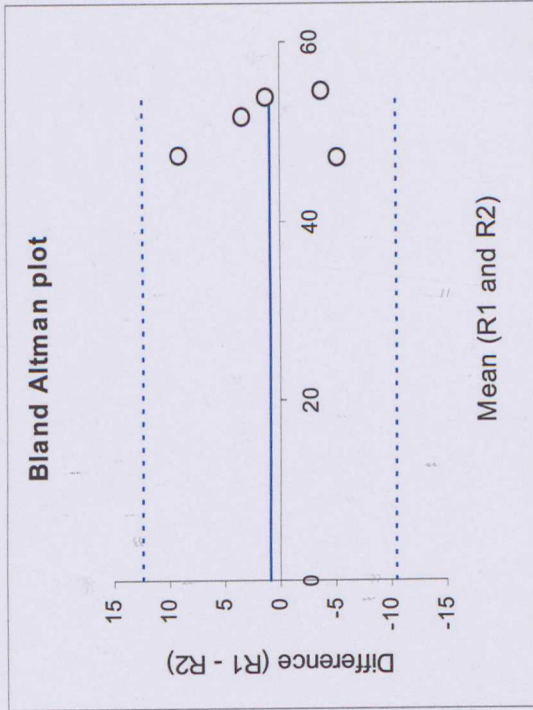
PSV (Umax)

Mean difference:

- 0.10 cm/s

Coefficient of repeatability:

27.03 cm/s



EDV (Umin)

Mean difference:

0.94 cm/s

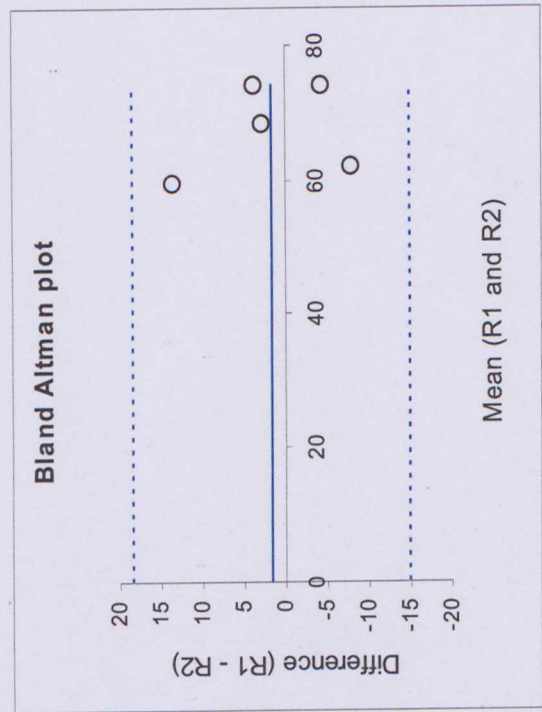
Coefficient of repeatability:

11.42 cm/s

Figure 3.14 A-X Waveform parameter reproducibility plots, mean difference and coefficient of repeatability results. Continued on the next 13 pages.

Waveform parameter reproducibility - TRADITIONAL TCD PARAMETERS

BASELINE

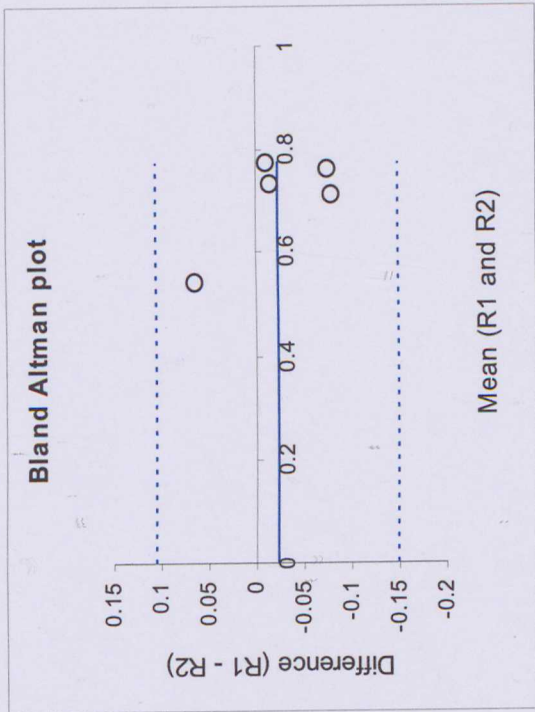


C

Mean velocity (Umean)

Mean difference: 1.64 cm/s

Coefficient of repeatability: 16.62 cm/s



D

PI

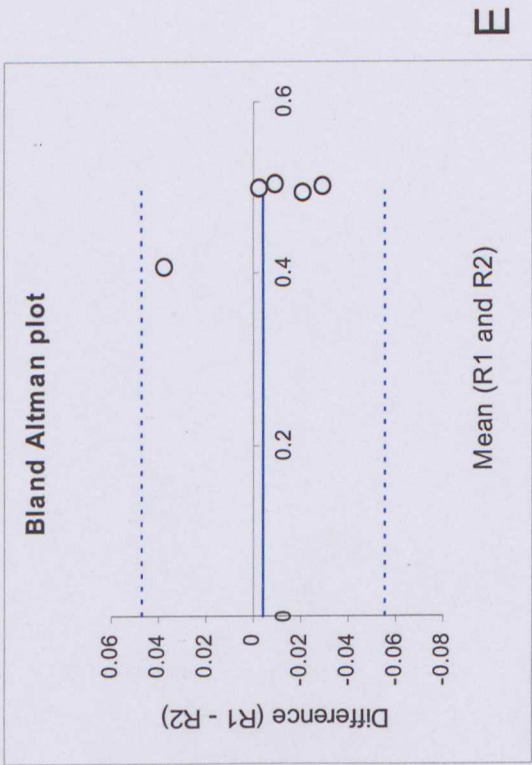
Mean difference: -0.02

Coefficient of repeatability: 0.13

Figure 3.14 (continued).

Waveform parameter reproducibility - TRADITIONAL TCD PARAMETERS

BASELINE



RI

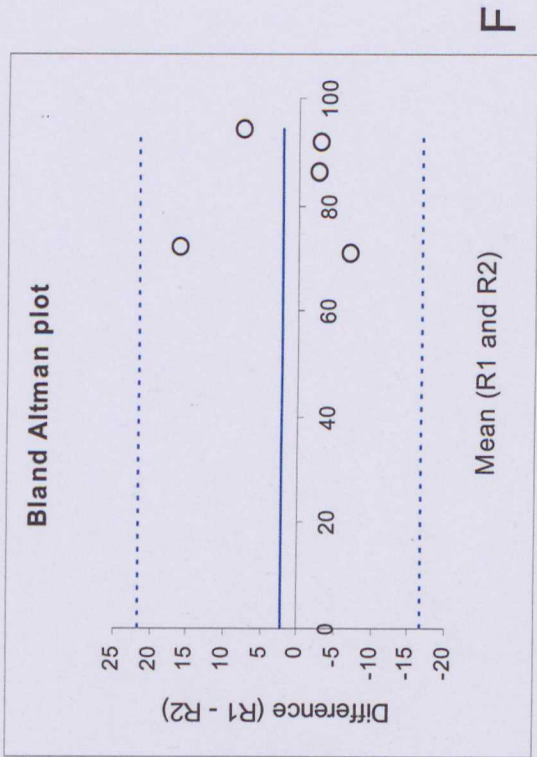
Mean difference: 0.00

Coefficient of repeatability: 0.05

Figure 3.14 (continued).

Waveform parameter reproducibility - VELOCITY MINIMA

BASELINE



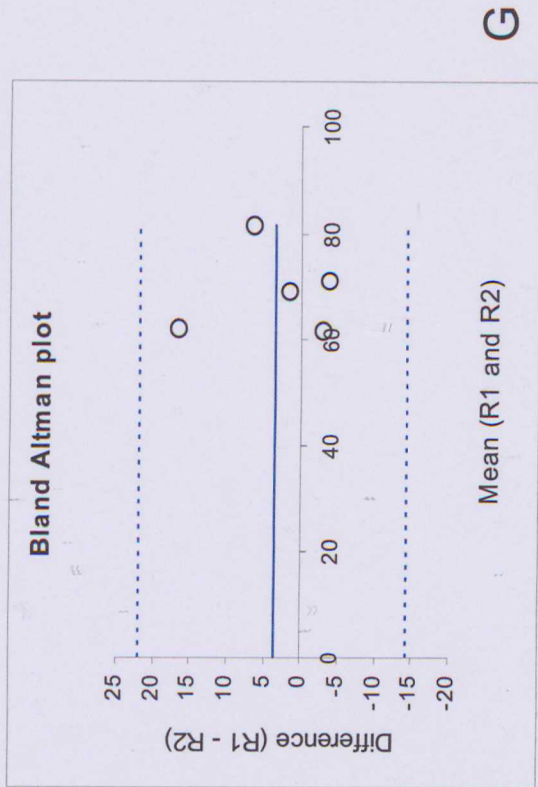
Umin1

Mean difference:

2.27 cm/s

Coefficient of repeatability:

19.15 cm/s



Umin2

Mean difference:

3.70 cm/s

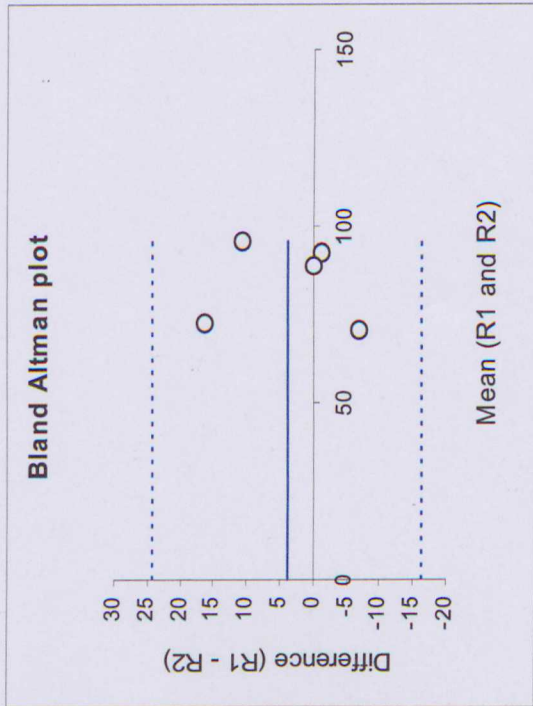
Coefficient of repeatability:

18.17 cm/s

Figure 3.14 (continued). (Note: Umin has been shown under EDV- Traditional TCD parameters).

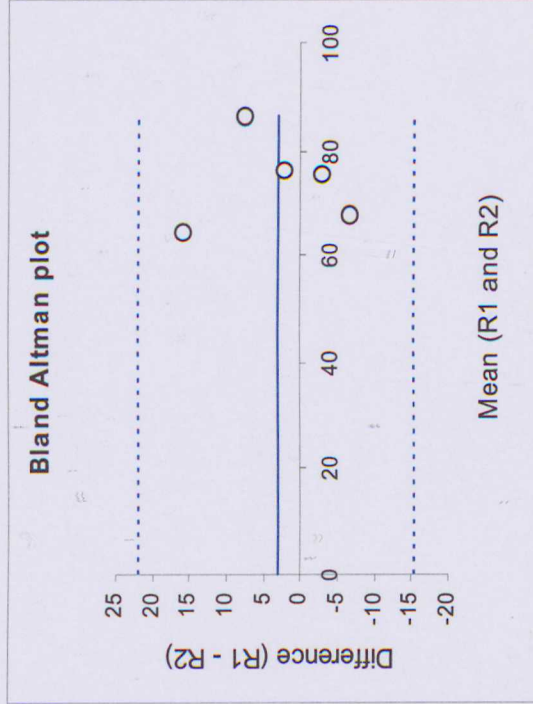
Waveform parameter reproducibility - VELOCITY MAXIMA

BASELINE



Umax1

Mean difference: 3.75 cm/s
Coefficient of repeatability: 20.23 cm/s



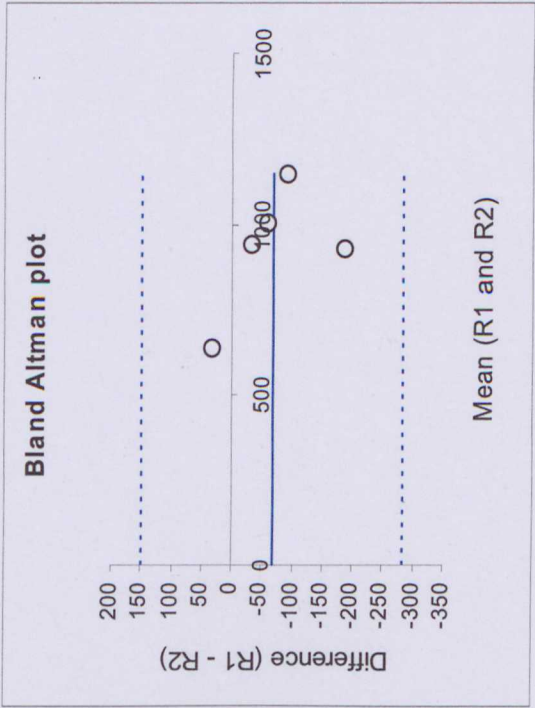
Umaxdias

Mean difference: 3.16 cm/s
Coefficient of repeatability: 18.69 cm/s

Figure 3.14 (continued). (Note: Umax has been shown under PSV- Traditional TCD parameters).

Waveform parameter reproducibility - ACCELERATION/DECELERATION

BASELINE

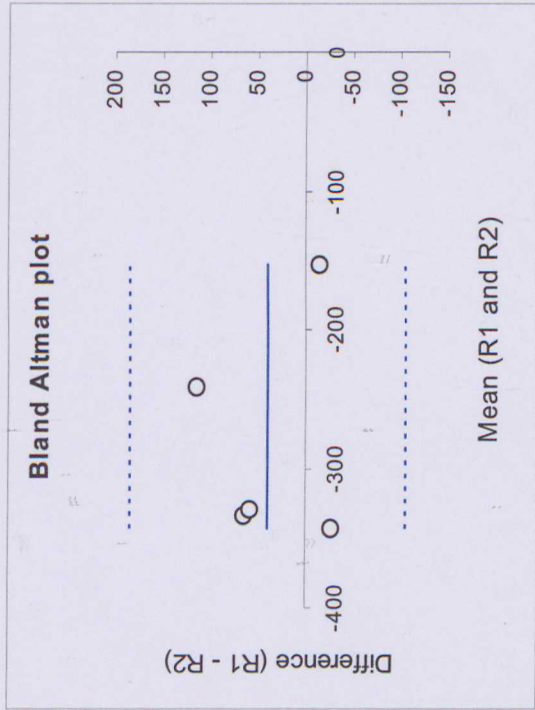


J

DuDtmax

Mean difference: - 67.34 cm/s²

Coefficient of repeatability: 216.05 cm/s²



K

DuDtmin1

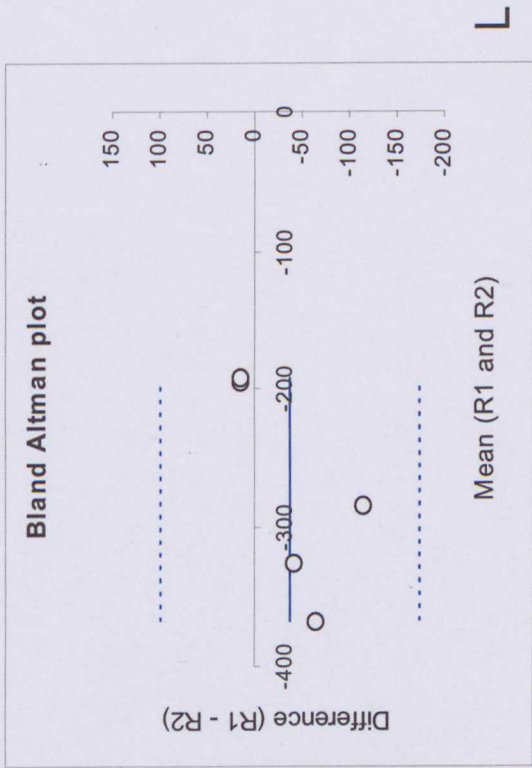
Mean difference: 39.10 cm/s²

Coefficient of repeatability: 144.84 cm/s²

Figure 3.14 (continued)

Waveform parameter reproducibility - ACCELERATION/DECELERATION

BASELINE



DuDtmin2

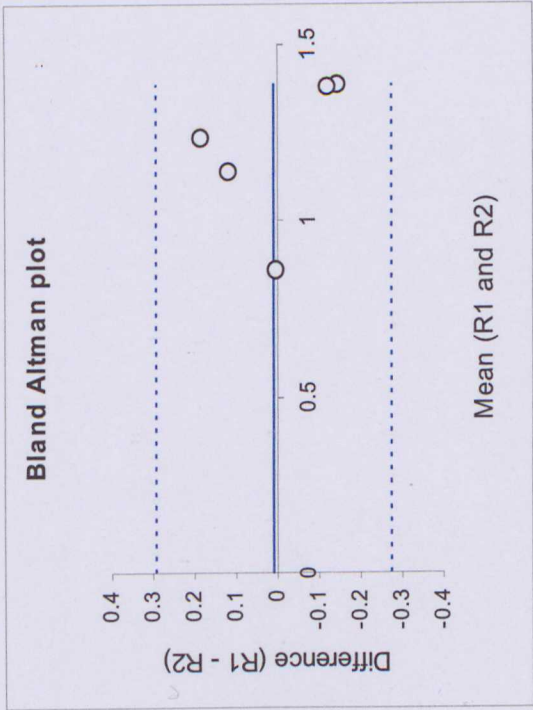
Mean difference: - 38.26 cm/s²

Coefficient of repeatability: 136.89 cm/s²

Figure 3.14 (continued). (Note: 2 of the points in graph L overlay each other).

Waveform parameter reproducibility - MISCELLANEOUS

BASELINE

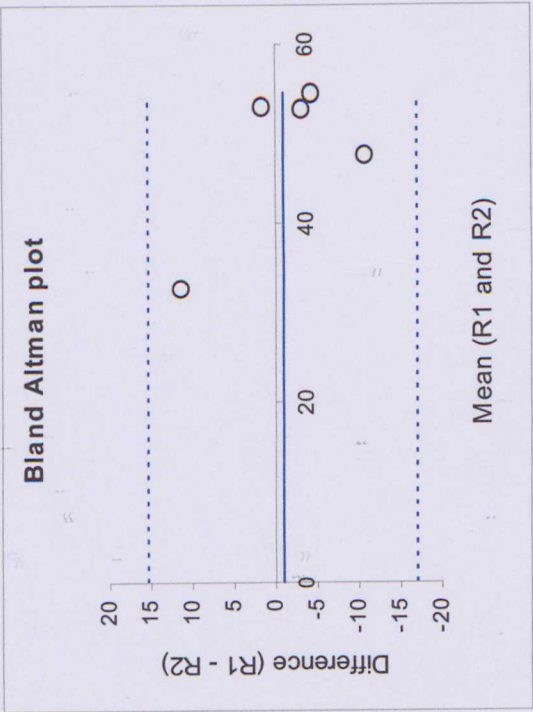


M

Tau

Mean difference: 0.01

Coefficient of repeatability: 0.28



N

Upulse

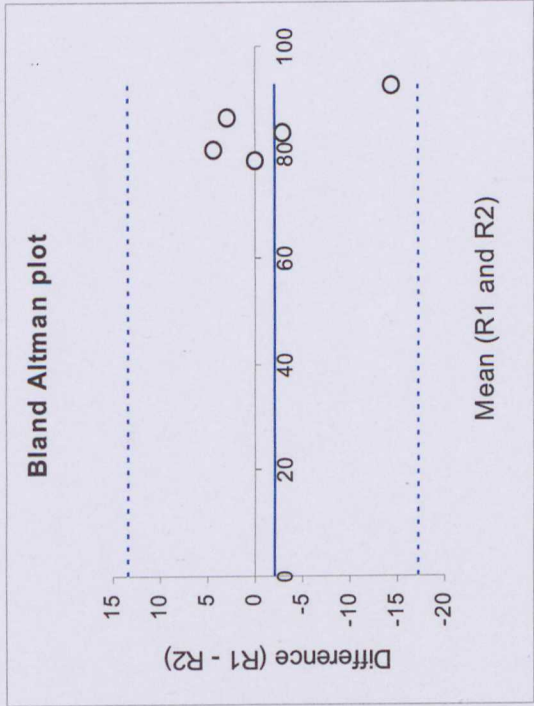
Mean difference: -1.04 cm/s

Coefficient of repeatability: 16.21 cm/s

Figure 3.14 (continued)

Waveform parameter reproducibility - MISCELLANEOUS

BASELINE



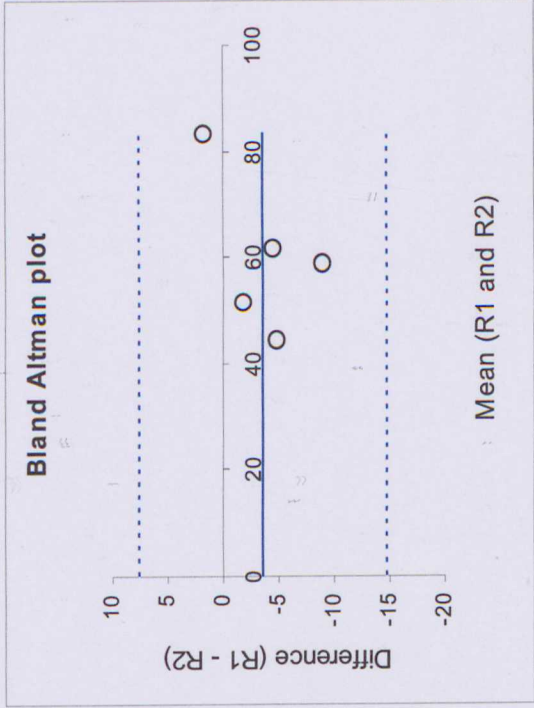
Blood pressure (mean)

Mean difference:

- 2.00 mmHg

Coefficient of repeatability:

15.25 mmHg



Heart rate

Mean difference:

- 3.63 bpm

(bpm = beats per minute)

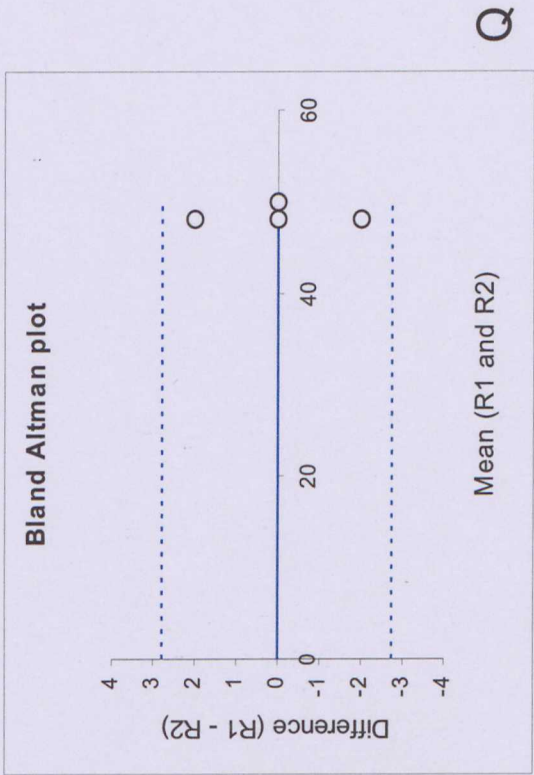
Coefficient of repeatability:

11.11 bpm

Figure 3.14 (continued)

Waveform parameter reproducibility - MISCELLANEOUS

BASELINE



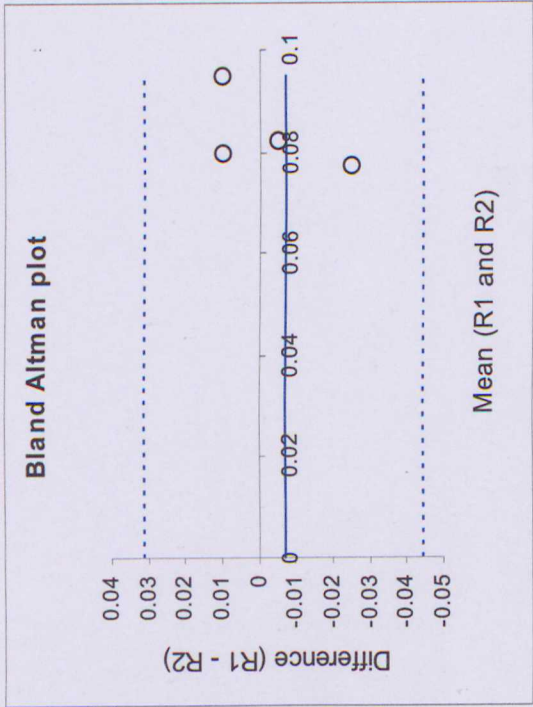
ETCO₂

Mean difference: 0.00 mmHg
Coefficient of repeatability: 2.77 mmHg

Figure 3.14 (continued). (Note: 2 of the points in graph Q overlay each other).

Waveform parameter reproducibility - TIME MEASUREMENTS

BASELINE

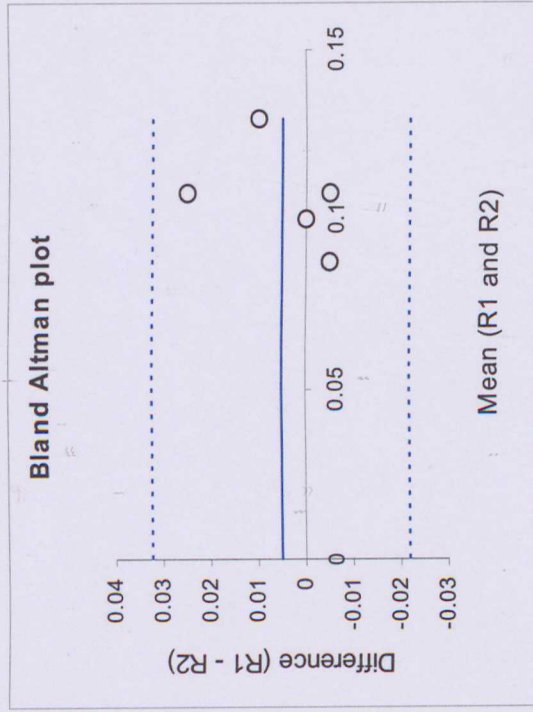


R

Tmin

Mean difference: - 0.01 s

Coefficient of repeatability: 0.04 s



S

Rise time

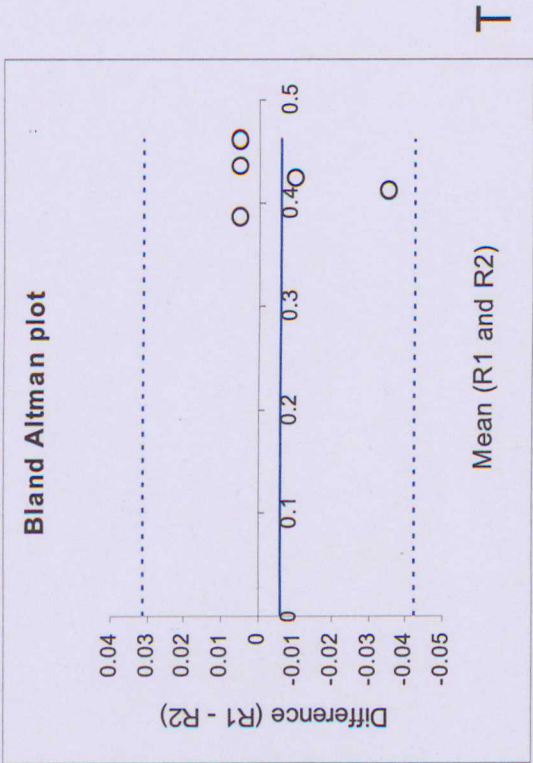
Mean difference: 0.01 s

Coefficient of repeatability: 0.03 s

Figure 3.14 (continued). (Note: 2 of the points in graph R overlay each other).

Waveform parameter reproducibility - TIME MEASUREMENTS

BASELINE



Tmin2

Mean difference:

- 0.01 s

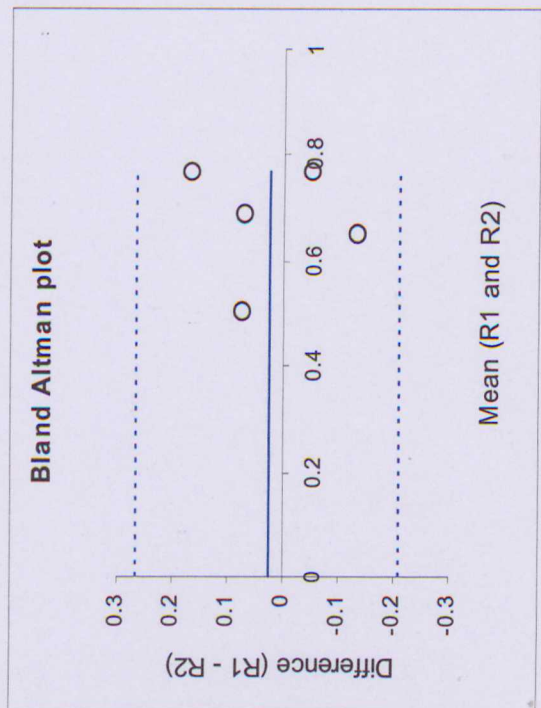
Coefficient of repeatability:

0.04 s

Figure 3.14 (continued)

Waveform parameter reproducibility - INDICES

BASELINE

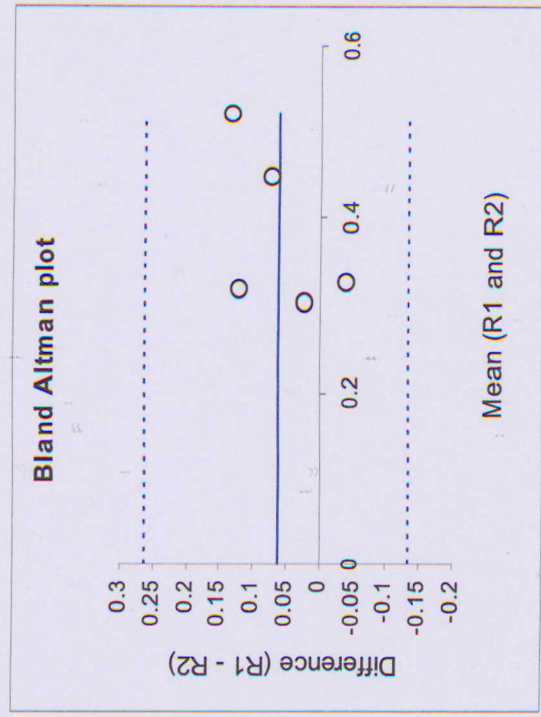


U

Shape Index 1

Mean difference: 0.03

Coefficient of repeatability: 0.24



V

Shape Index 2

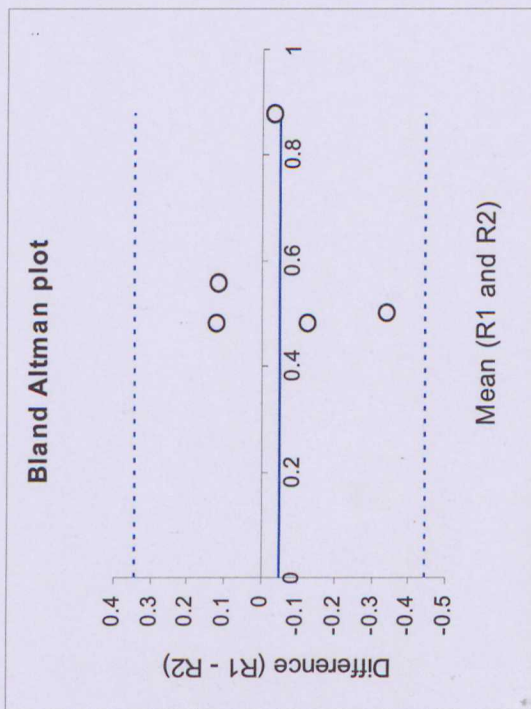
Mean difference: 0.06

Coefficient of repeatability: 0.20

Figure 3.14 (continued)

Waveform parameter reproducibility - INDICES

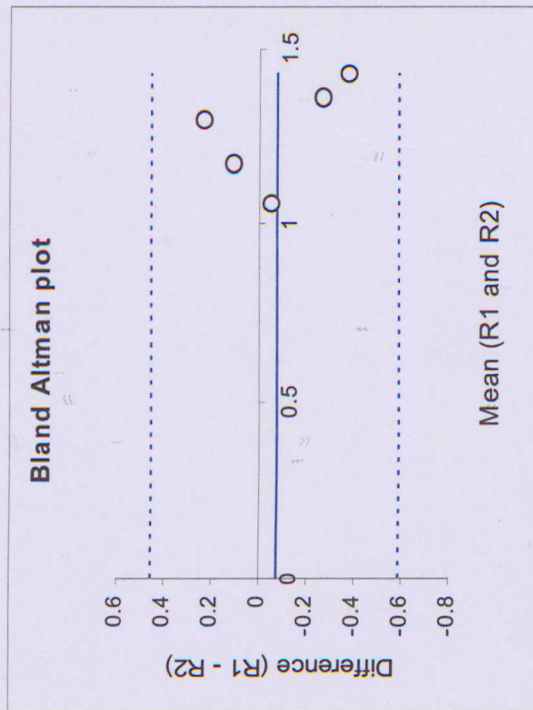
BASELINE



Velocity Rise Index

Mean difference: - 0.05

Coefficient of repeatability: 0.39



Mean resistance index

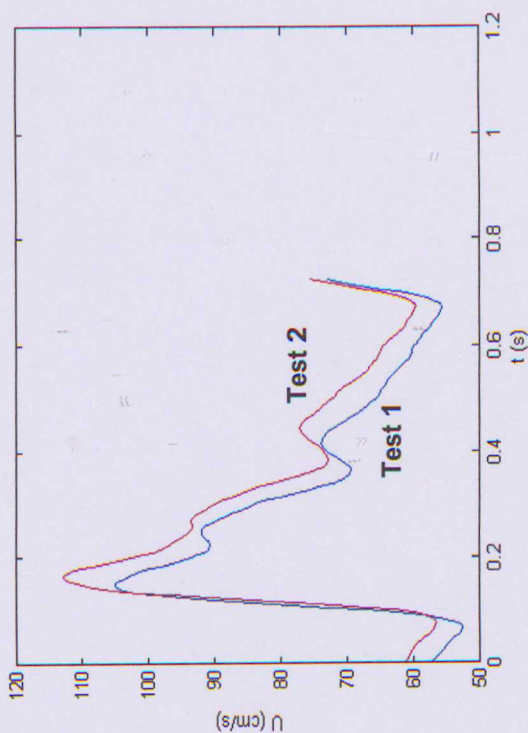
Mean difference: - 0.07 mmHg per s/cm

Coefficient of repeatability: 0.52 mmHg per s/cm

Figure 3.14 (continued)

Waveform shape reproducibility results

BASELINE



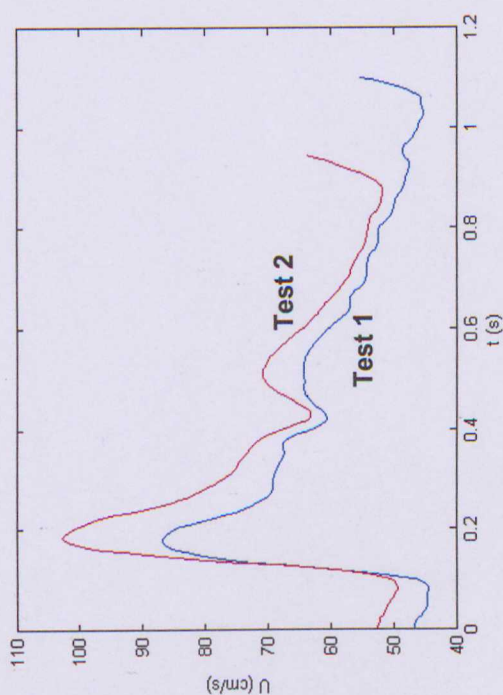
Subject B

Female, 34 yrs, time between tests = 85 days

Mean blood pressure (mmHg):

Test 1= 88

Test 2= 85



Subject A

Male, 22 yrs, time between tests = 8 days

Mean blood pressure (mmHg):

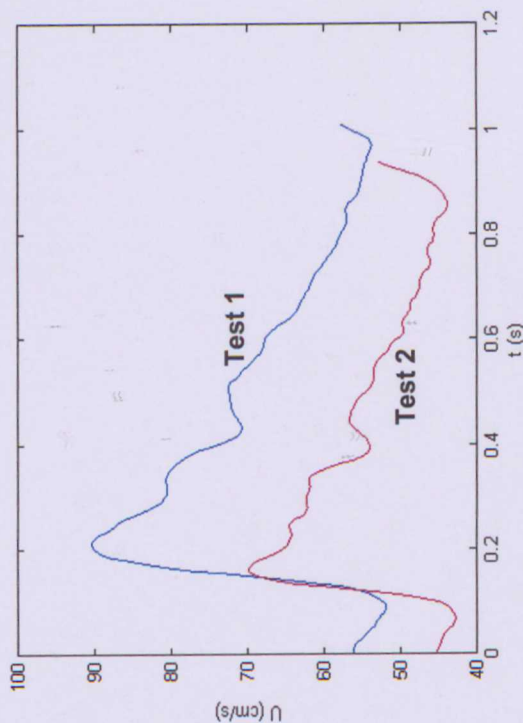
Test 1= 82

Test 2= 78

Figure 3.15 Waveform shape variations between test 1 and 2 for 5 subjects (A-E) Continued on next 2 pages.

Waveform shape reproducibility results

BASELINE



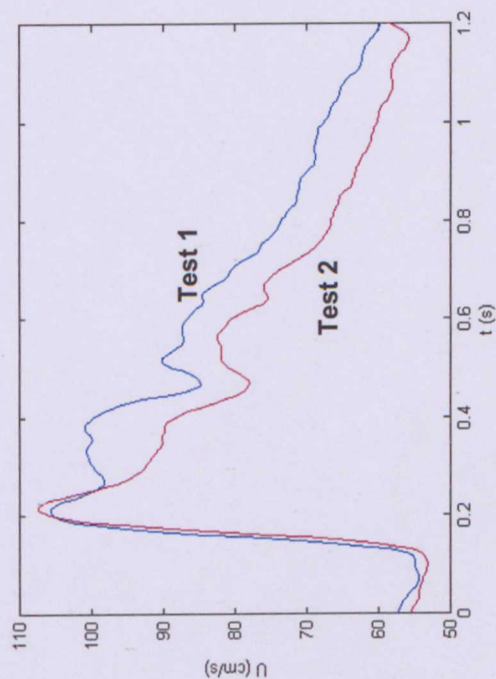
Subject D

Male, 33 yrs, time between tests = 71 days

Mean blood pressure (mmHg):

Test 1= 82

Test 2= 85



Subject C

Female, 30 yrs, time between tests = 70 days

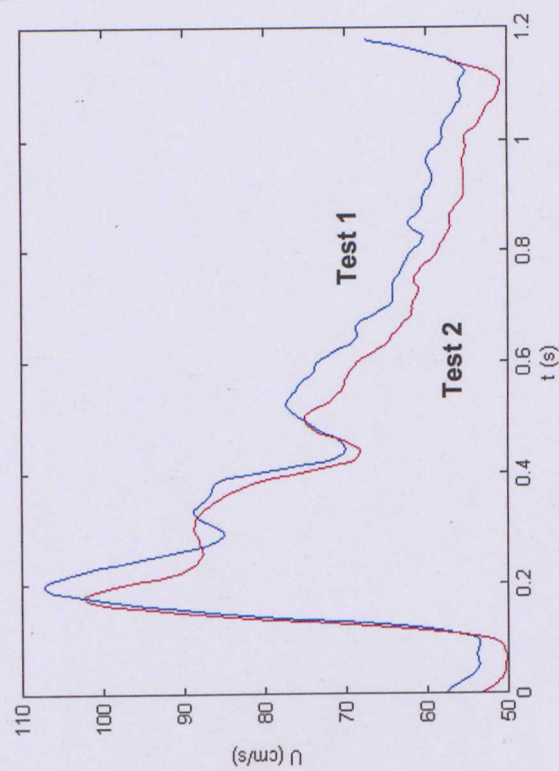
Mean blood pressure (mmHg):

Test 1= 78

Test 2= 78

Figure 3.15 (continued).

Waveform shape reproducibility results



BASELINE

Subject E

Male, 51 yrs, time between tests = 84 days

Mean blood pressure (mmHg):

Test 1= 85

Test 2= 100

Figure 3.15 (continued).

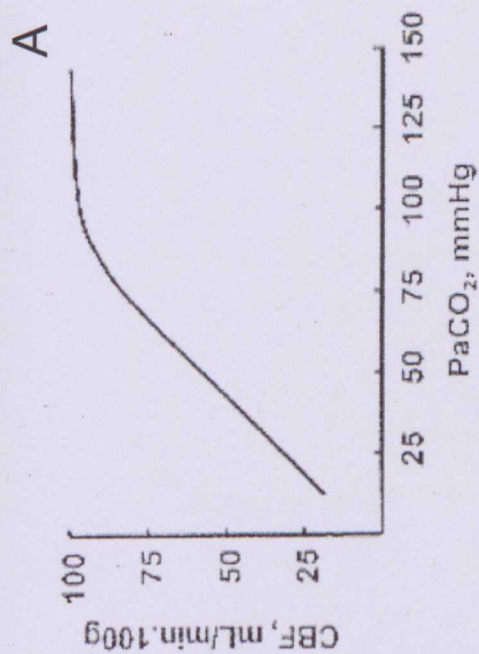


Figure 3.16 **A)** Changes in CBF in relationship with PaCO₂ [Berré, 2000]. **B)** One of the subjects during Hypercapnia; **C)** “Rudolph” one-way valve for gas delivery and sampling of ET CO₂.

Blood pressure during maximum hyperventilation

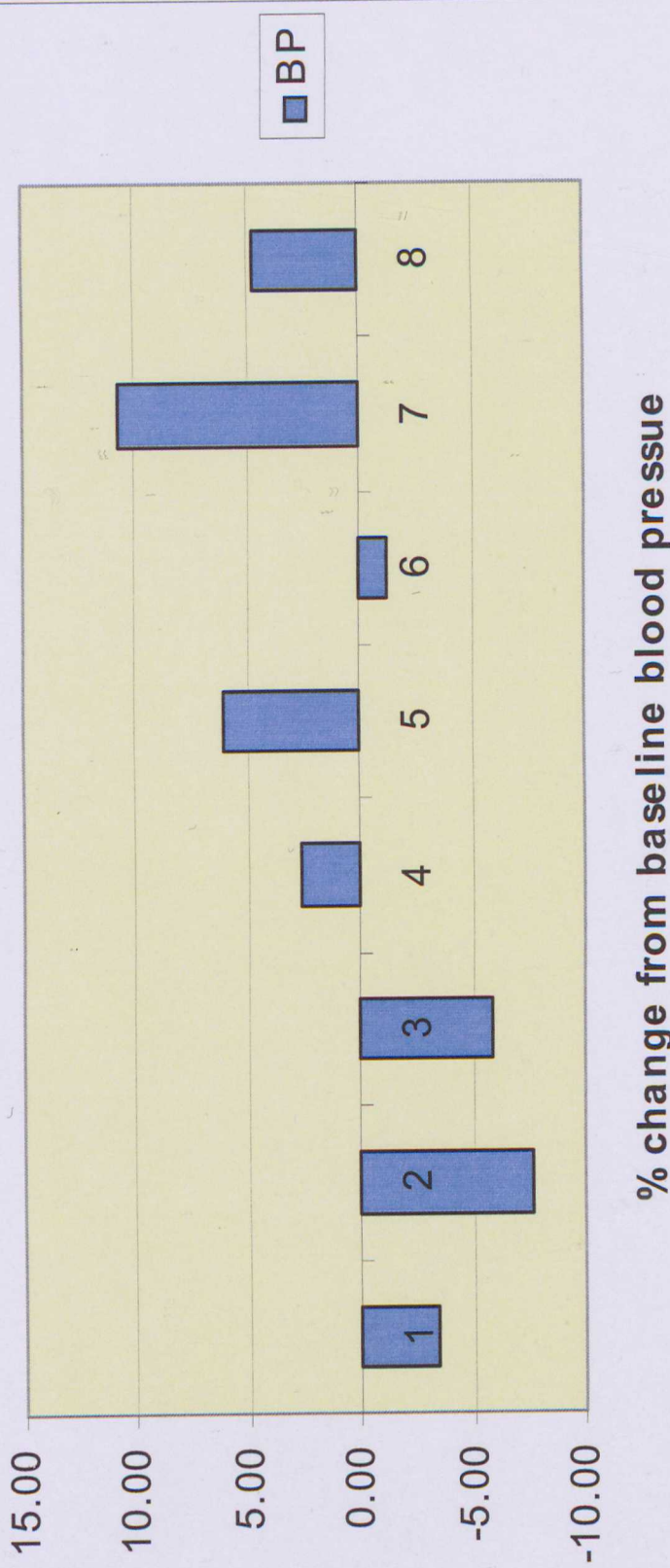
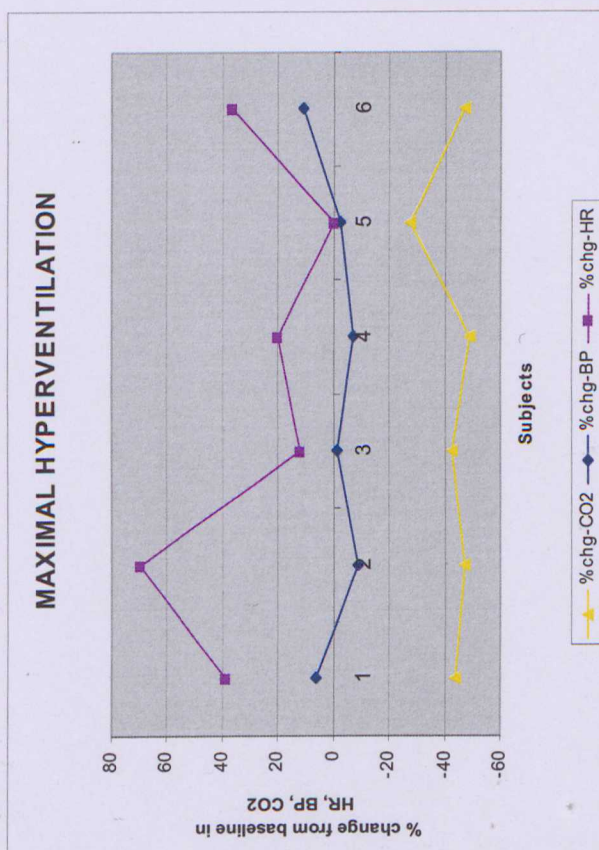
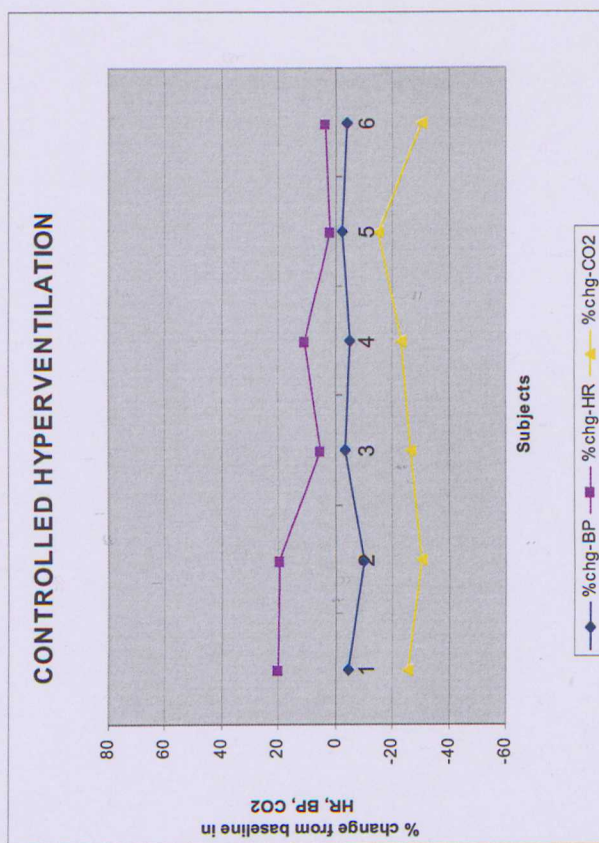


Figure 3.17. Blood pressure changes alone during maximal hyperventilation in 8 subjects. This graph demonstrates that at maximal exertion some subjects have a rise in blood pressure, while others have a drop in blood pressure.



A

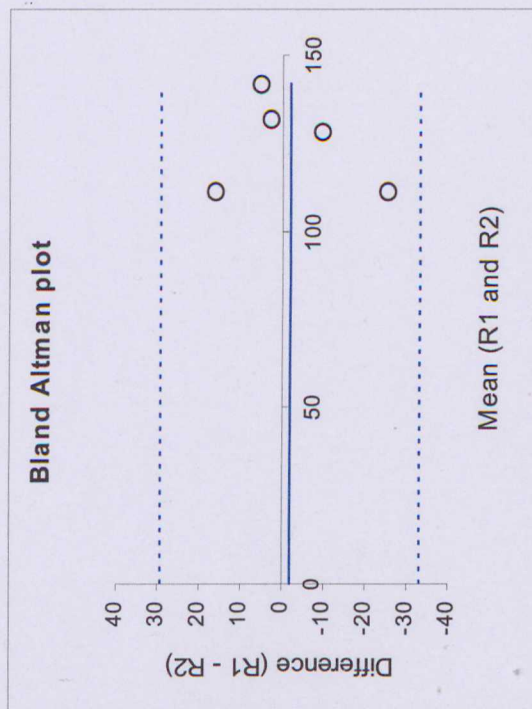


B

Figure 3.18 A) Maximal versus **B)** controlled hyperventilation effects on ETCO_2 (CO_2), heart rate (HR) and blood pressure (BP) on 6 subjects. Results are shown as a % change from the baseline value on each subject. The yellow line shows that ETCO_2 is lower during maximal hyperventilation, however the HR and BP become more erratic. (Note: connecting lines have been used only for visual clarity of parameter variability).

Waveform parameter reproducibility - TRADITIONAL TCD PARAMETERS

HYPERCAPNIA



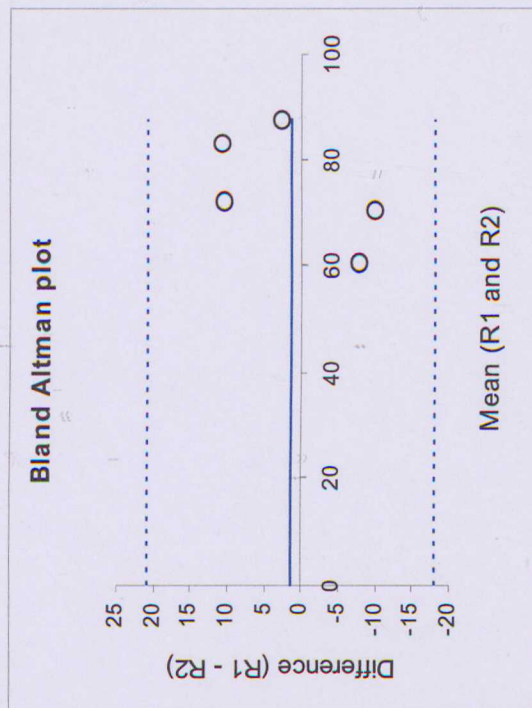
PSV (Umax)

Mean difference:

- 2.09 cm/s

Coefficient of repeatability:

31.32 cm/s



EDV (Umin)

Mean difference:

1.34 cm/s

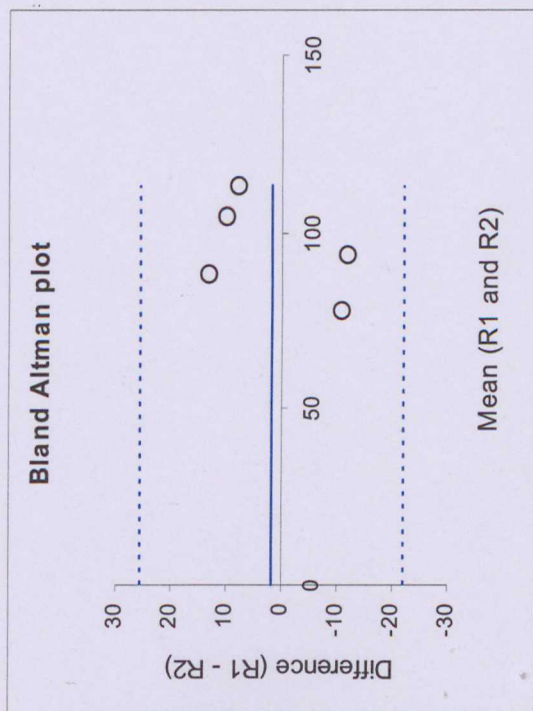
Coefficient of repeatability:

19.34 cm/s

Figure 3.19 A-X Waveform parameter reproducibility plots, mean difference and coefficient of repeatability results. Continued on next 13 pages.

Waveform parameter reproducibility -TRADITIONAL TCD PARAMETERS

HYPERCAPNIA



C

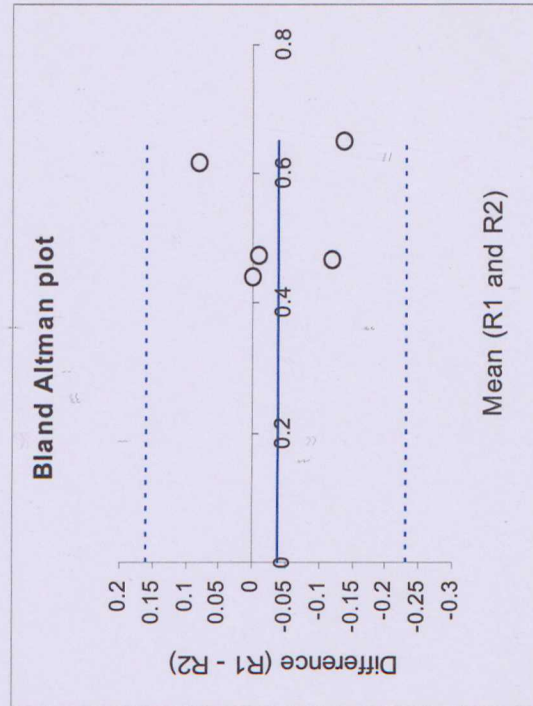
Mean velocity (Umean)

Mean difference:

1.63 cm/s

Coefficient of repeatability:

23.76 cm/s



D

PI

Mean difference:

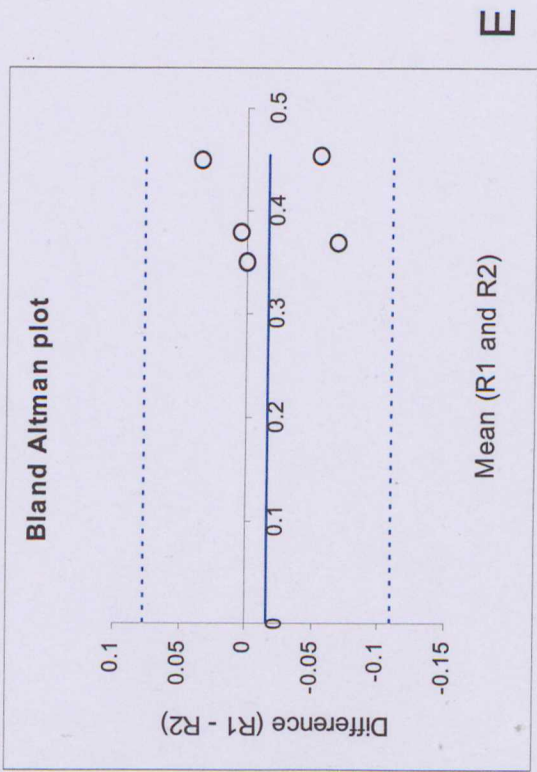
- 0.04

Coefficient of repeatability:

0.19

Figure 3.19 (continued).

Waveform parameter reproducibility - TRADITIONAL TCD PARAMETERS



RI

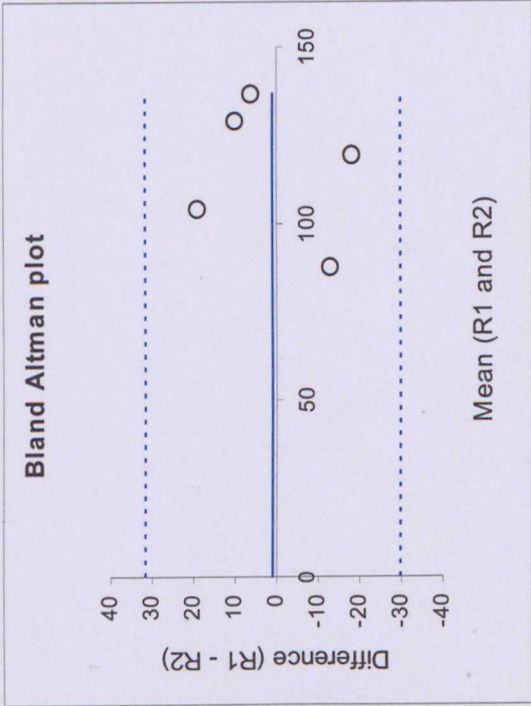
Mean difference: -0.02

Coefficient of repeatability: 0.09

Figure 3.19 (continued).

Waveform parameter reproducibility - VELOCITY MINIMA

HYPERCAPNIA

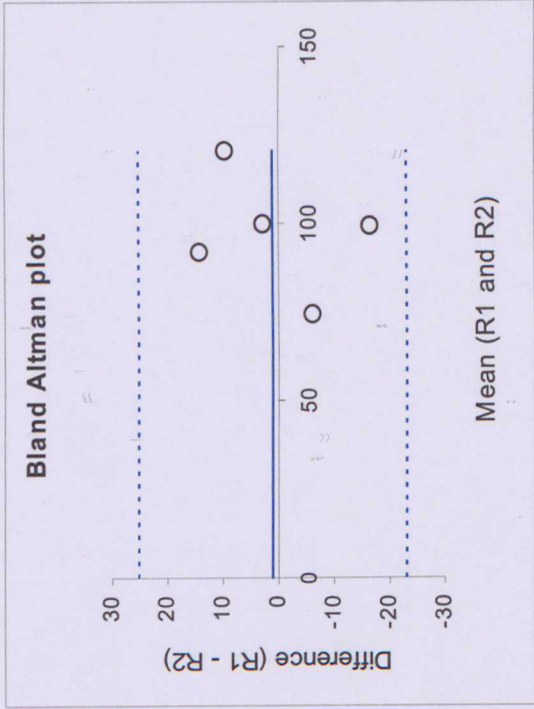


F

Umin1

Mean difference: 0.81 cm/s

Coefficient of repeatability: 30.80 cm/s



G

Umin2

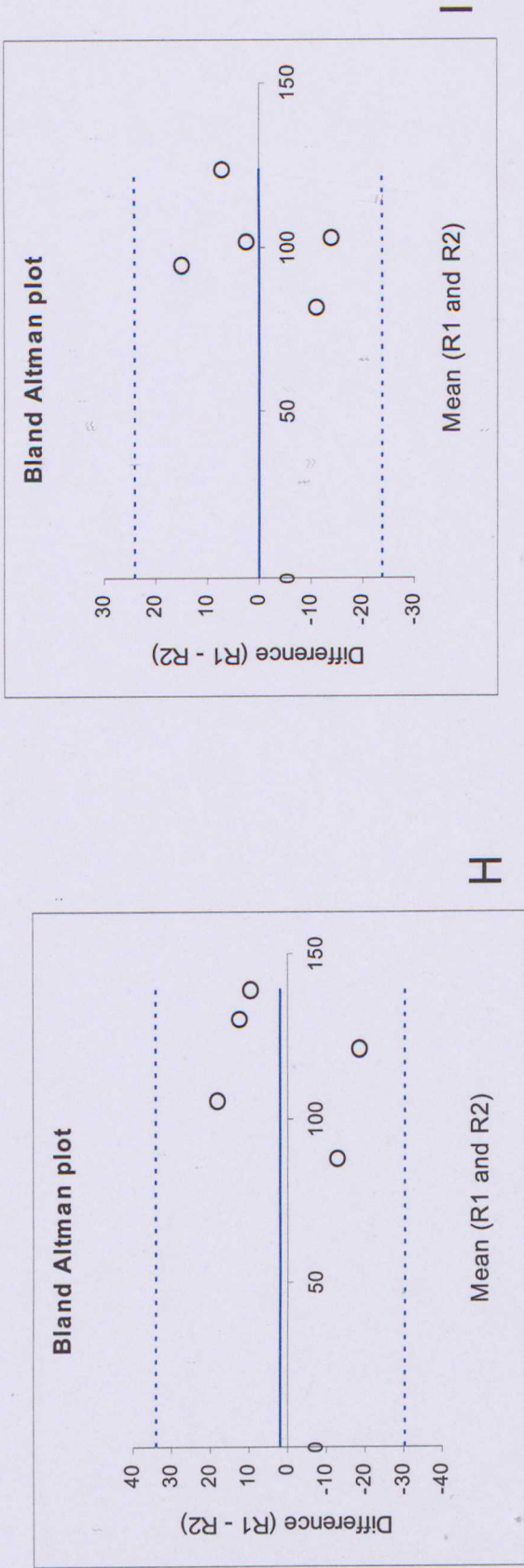
Mean difference: 0.94 cm/s

Coefficient of repeatability: 24.24 cm/s

Figure 3.19 (continued). (Note: Umin has been shown under EDV - Traditional TCD parameters).

Waveform parameter reproducibility - VELOCITY MAXIMA

HYPERCAPNIA



Umax1

Mean difference: 1.75 cm/s
Coefficient of repeatability: 32.20 cm/s

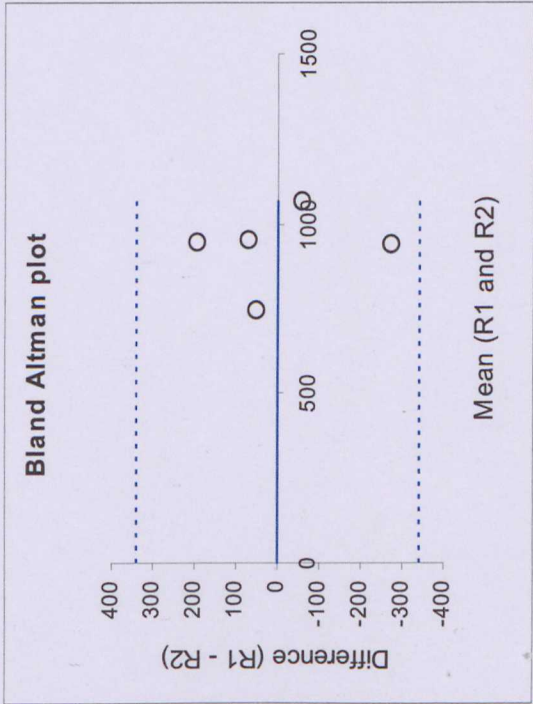
Umaxdias

Mean difference: 0.01 cm/s
Coefficient of repeatability: 24.01 cm/s

Figure 3.19 (continued). (Note: Umax has been shown under PSV - Traditional TCD parameters).

Waveform parameter reproducibility - ACCELERATION/DECELERATION

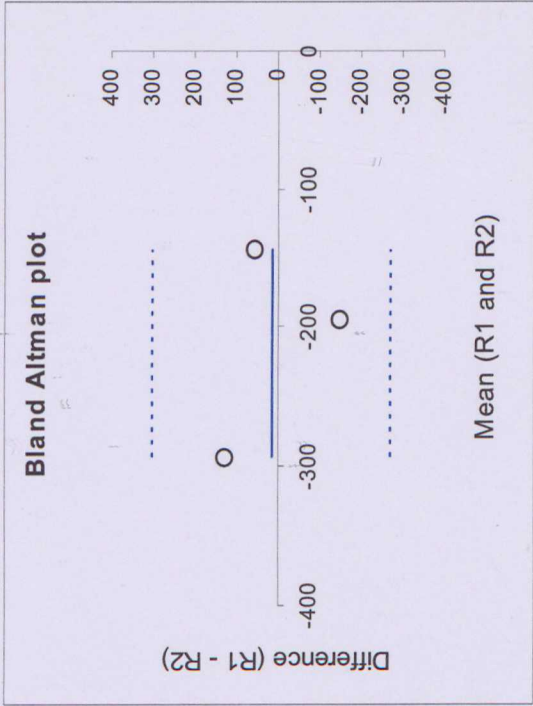
HYPERCAPNIA



DuDtmax

Mean difference: - 1.55 cm/s²

Coefficient of repeatability: 340.90 cm/s²



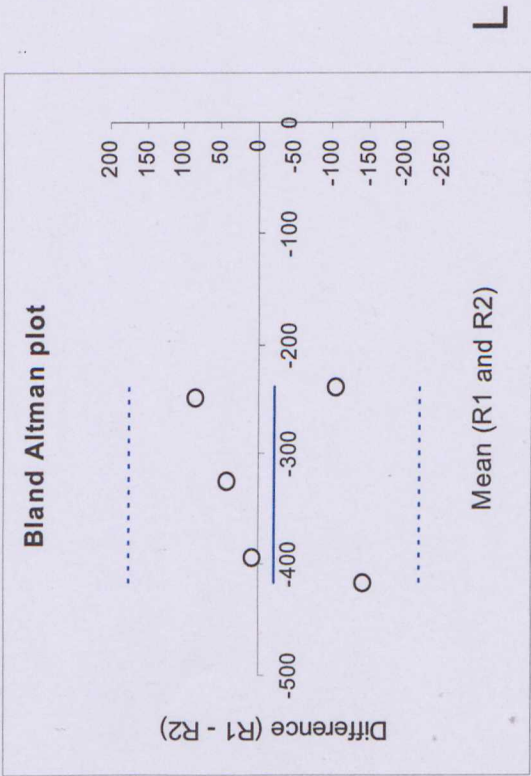
DuDtmin1

Mean difference: 12.41 cm/s²

Coefficient of repeatability: 286.15 cm/s²

Figure 3.19 (continued). (Note: Graph K has 3 subjects only).

Waveform parameter reproducibility - ACCELERATION/DECELERATION



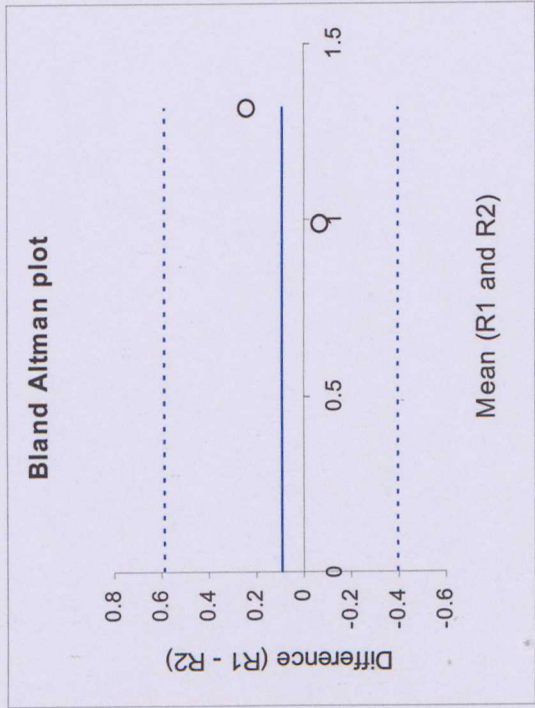
Mean difference: - 22.57 cm/s²

Coefficient of repeatability: 197.05 cm/s²

Figure 3.19 (continued).

Waveform parameter reproducibility - MISCELLANEOUS

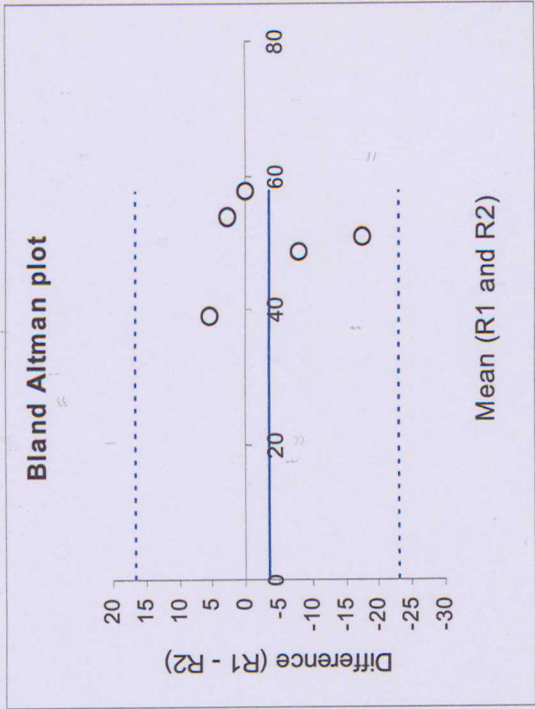
HYPERCAPNIA



Tau

Mean difference: 0.09

Coefficient of repeatability: 0.49



Upulse

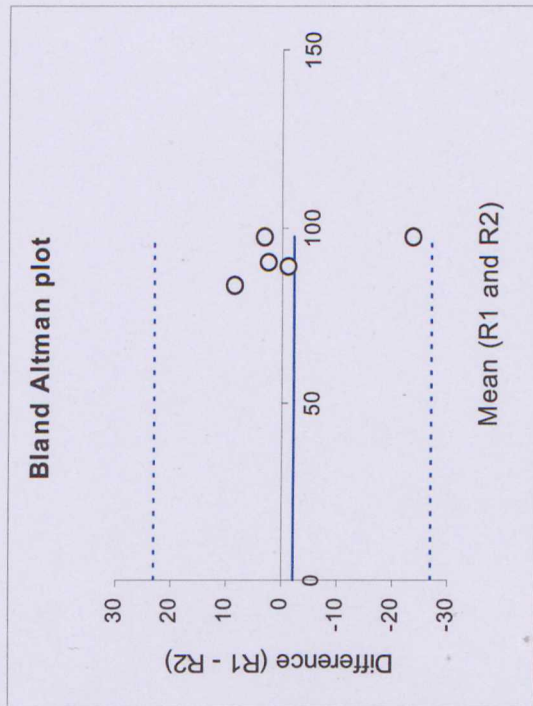
Mean difference: - 3.43 cm/s

Coefficient of repeatability: 10.10 cm/s

Figure 3.19 (continued). (Note: Graph M has 2 subjects only).

Waveform parameter reproducibility - MISCELLANEOUS

HYPERCAPNIA



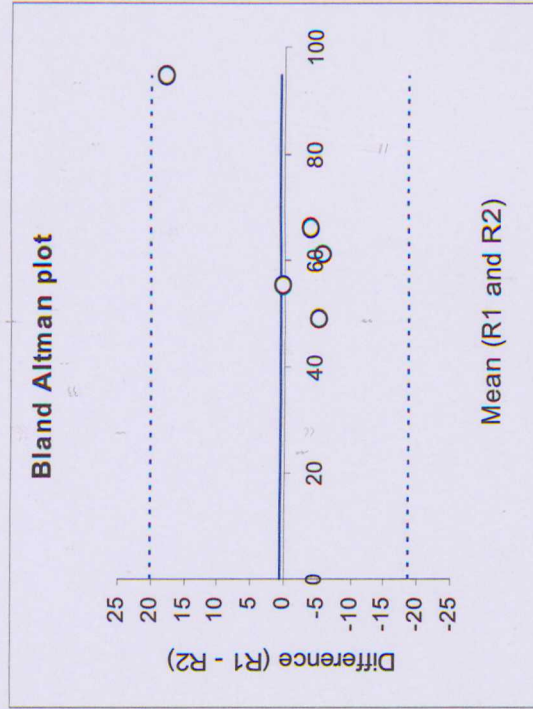
Blood pressure (mean)

Mean difference:

- 2.07 mmHg

Coefficient of repeatability:

25.04 mmHg



Heart rate

Mean difference:

0.68 bpm

Coefficient of repeatability:

19.34 bpm

Figure 3.19 (continued).

Waveform parameter reproducibility - MISCELLANEOUS



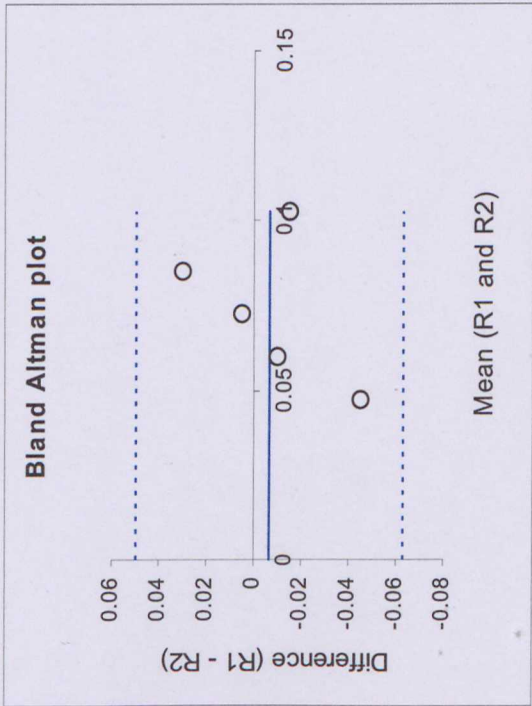
0.60 mmHg

2.59 mmHg

209

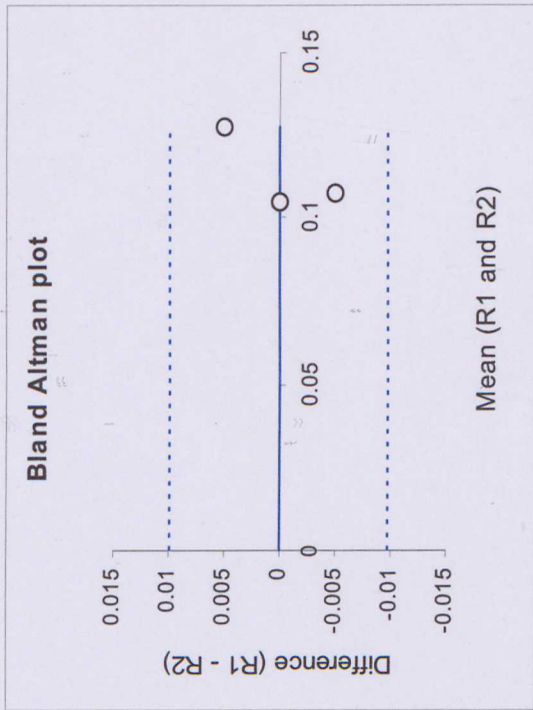
Waveform parameter reproducibility - TIME MEASUREMENTS

HYPERCAPNIA



Tmin

Mean difference: -0.01 s
Coefficient of repeatability: 0.06 s



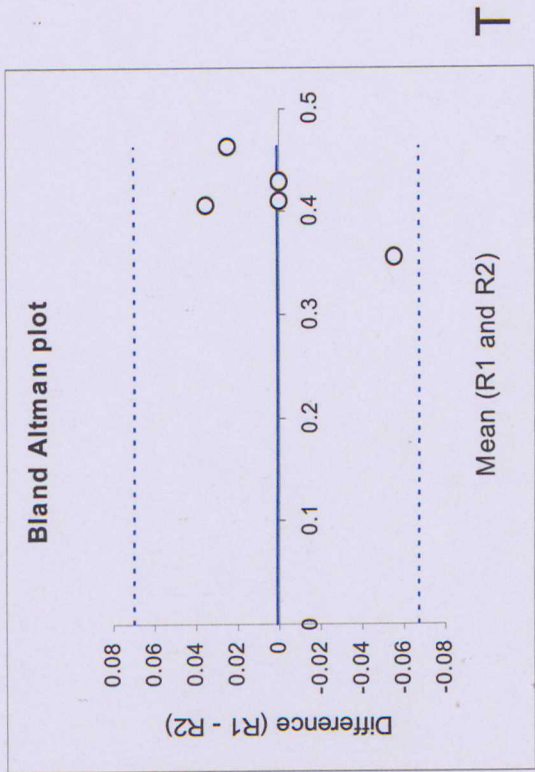
Rise time

Mean difference: 0.00 s
Coefficient of repeatability: 0.01 s

Figure 3.19 (continued). (Note: Graph S has three subjects only).

Waveform parameter reproducibility - TIME MEASUREMENTS

HYPERCAPNIA



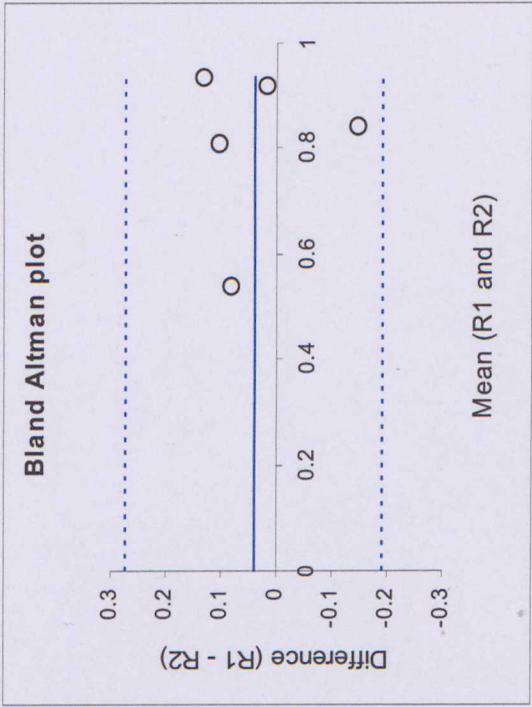
Mean difference: 0.00 s

Coefficient of repeatability: 0.07 s

Figure 3.19 (continued).

Waveform parameter reproducibility - INDICES

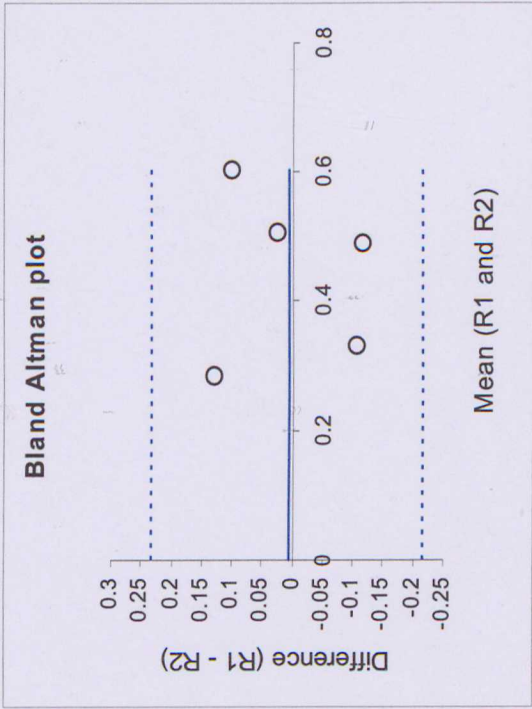
HYPERCAPNIA



Shape Index 1

Mean difference: 0.04

Coefficient of repeatability: 0.23



Shape Index 2

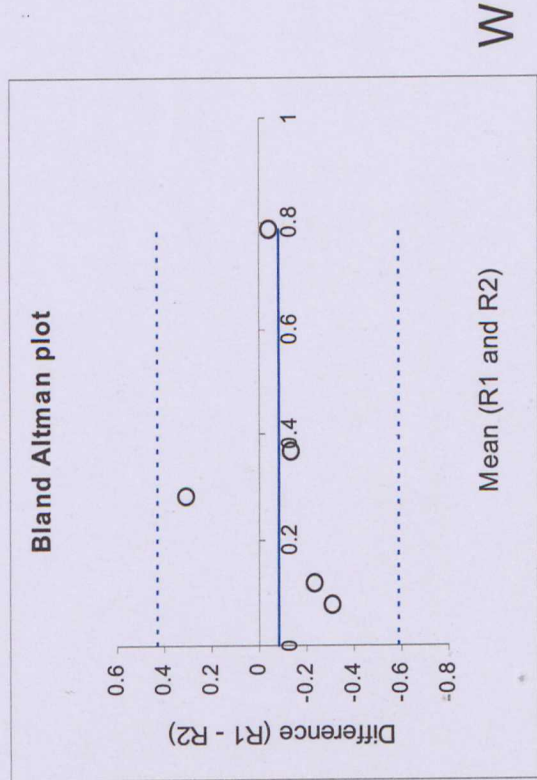
Mean difference: 0.01

Coefficient of repeatability: 0.22

Figure 3.19 (continued).

Waveform parameter reproducibility - INDICES

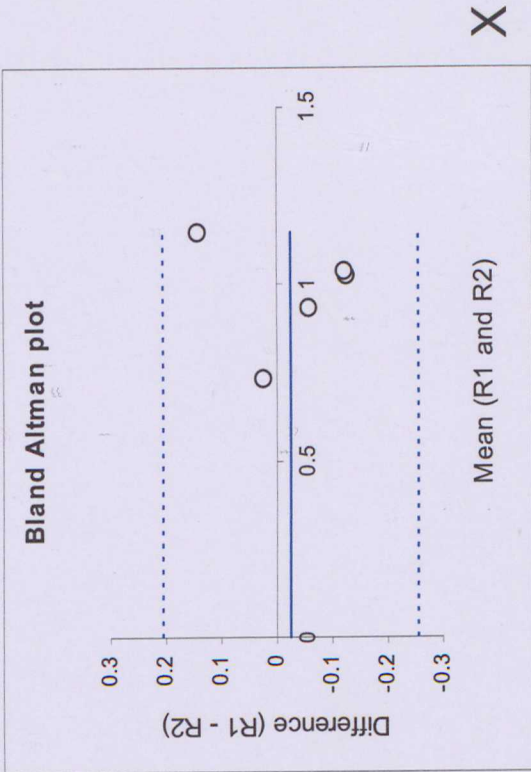
HYPERCAPNIA



Velocity Rise Index

Mean difference: -0.08

Coefficient of repeatability: 0.51



Mean resistance index

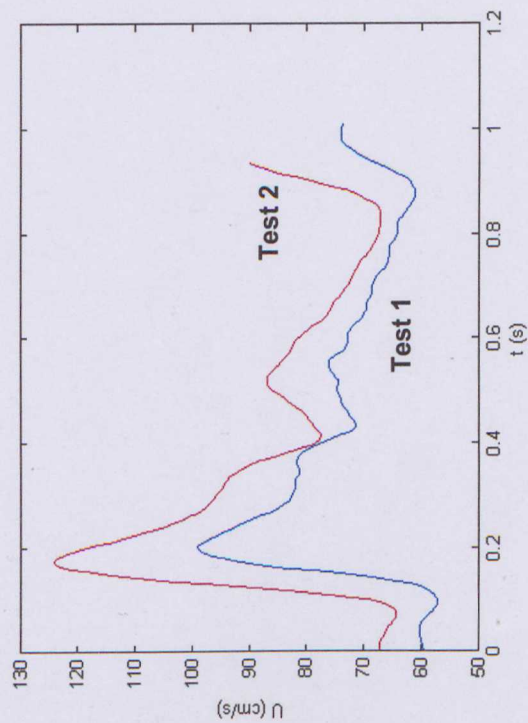
Mean difference: -0.03 mmHg per s/cm

Coefficient of repeatability: 0.23 mmHg per s/cm

Figure 3.19 (continued). (Note: 2 of the points in X overlay each other).

Waveform shape reproducibility results

HYPERCAPNIA



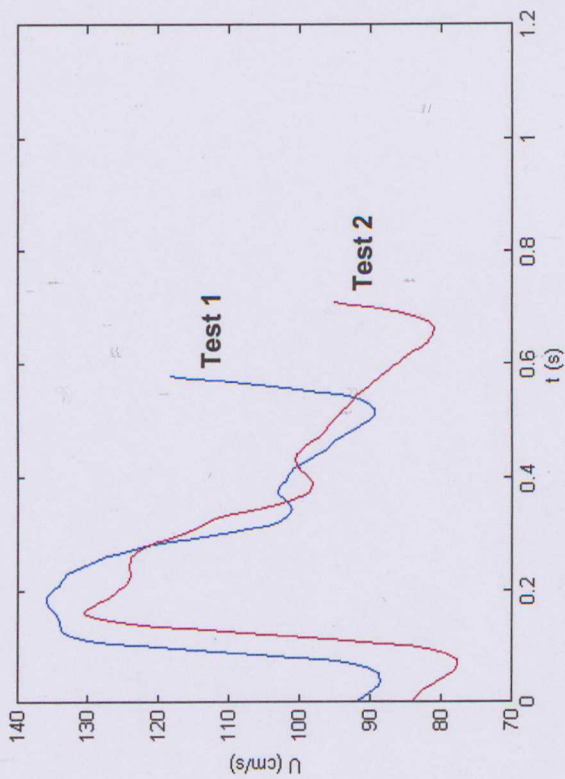
Subject A

Male, 22 yrs, time between tests = 8 days

Mean blood pressure (mmHg):

Test 1= 88

Test 2= 89



Subject B

Female, 34 yrs, time between tests = 85 days

Mean blood pressure (mmHg):

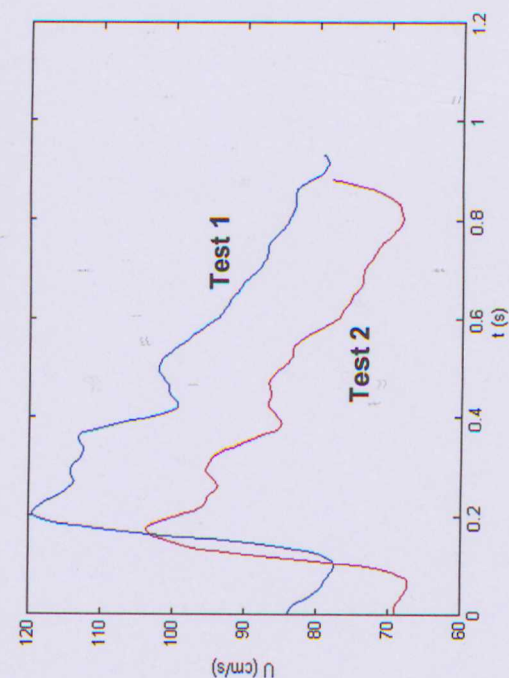
Test 1= 99

Test 2= 96

Figure 3.20 Waveform shape variations between test 1 and 2 for 5 subjects (A-E) Continued next 2 pages.

Waveform shape reproducibility results

HYPERCAPNIA



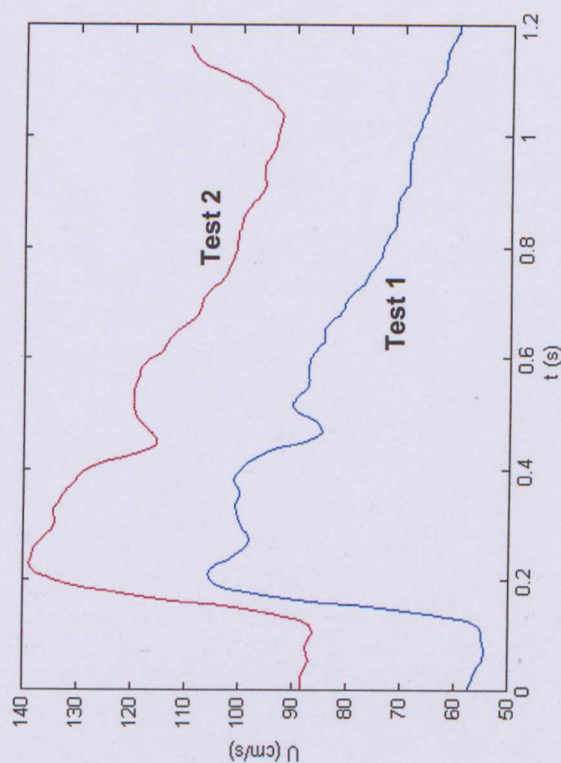
Subject D

Male, 33 yrs, time between tests = 71 days

Mean blood pressure (mmHg):

Test 1= 91

Test 2= 89



Subject C

Female, 30 yrs, time between tests = 70 days

Mean blood pressure (mmHg):

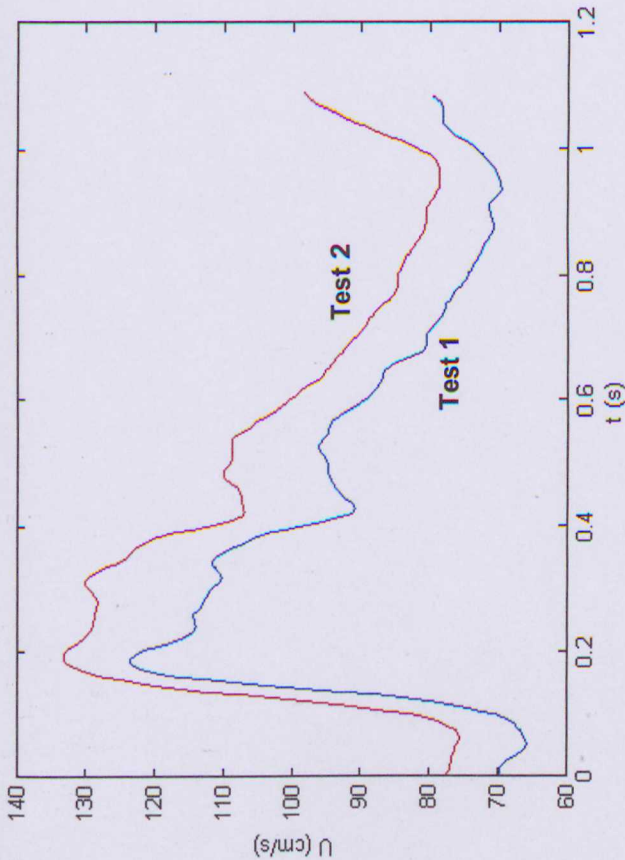
Test 1= 88

Test 2= 79

Figure 3.20 (Continued).

Waveform shape reproducibility results

HYPERCAPNIA



Subject E

Male, 51 yrs, time between tests = 84 days

Mean blood pressure (mmHg):

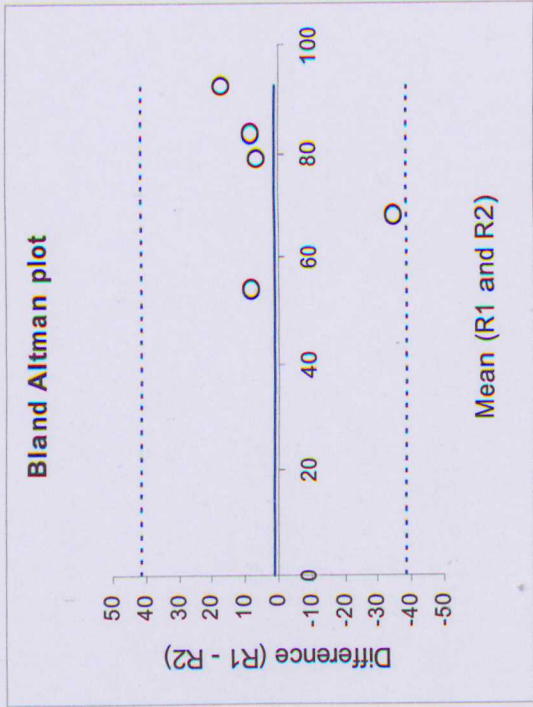
Test 1= 86

Test 2= 109

Figure 3.20 (Continued).

Waveform parameter reproducibility -TRADITIONAL TCD PARAMETERS

HYPOCAPNIA

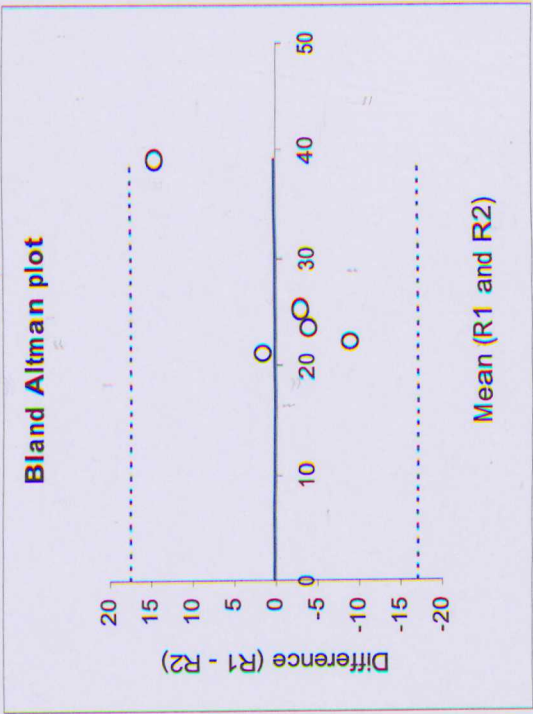


A

PSV (Umax)

Mean difference: 1.10 cm/s

Coefficient of repeatability: 39.98 cm/s



B

EDV (Umin)

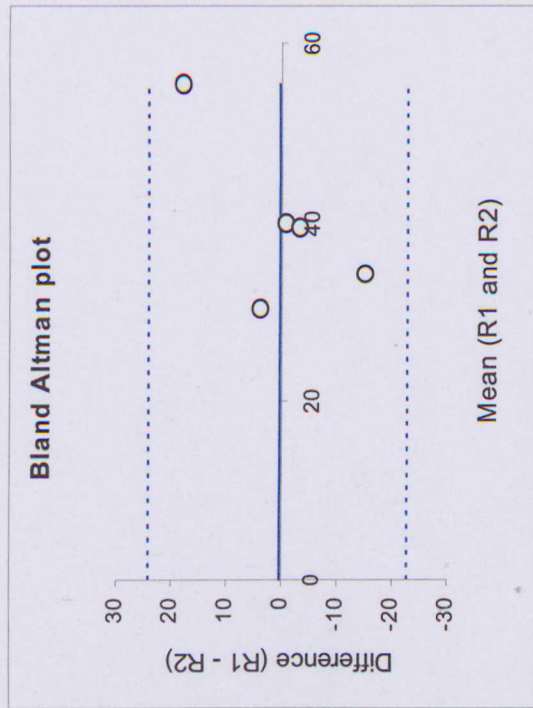
Mean difference: 0.14

Coefficient of repeatability: 17.29

Figure 3.21 A-X Waveform parameter reproducibility plots, mean difference and coefficient of repeatability results. Continued next 13 pages.

Waveform parameter reproducibility - TRADITIONAL TCD PARAMETERS

HYPOCAPNIA



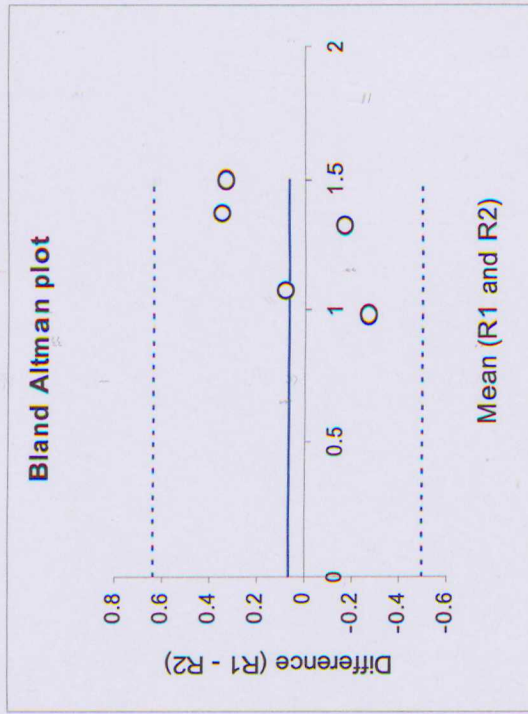
Mean velocity (Umean)

Mean difference:

0.50 cm/s

Coefficient of repeatability:

23.49 cm/s



PI

Mean difference:

0.06

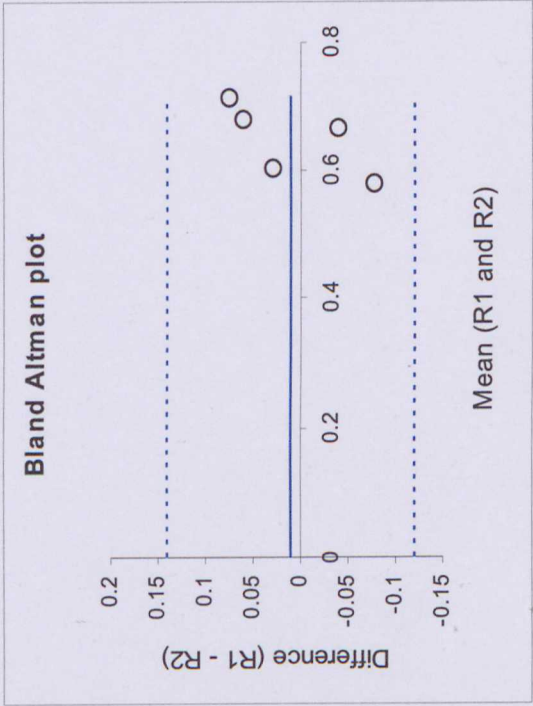
Coefficient of repeatability:

0.57

Figure 3.21 (Continued).

Waveform parameter reproducibility - TRADITIONAL TCD PARAMETERS

HYPOCAPNIA



E

RI

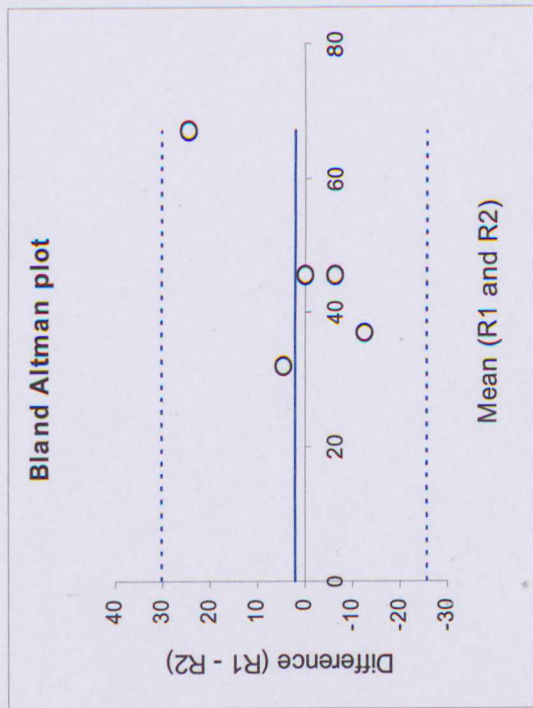
Mean difference: 0.01

Coefficient of repeatability: 0.13

Figure 3.21 (Continued).

Waveform parameter reproducibility - VELOCITY MINIMA

HYPOCAPNIA

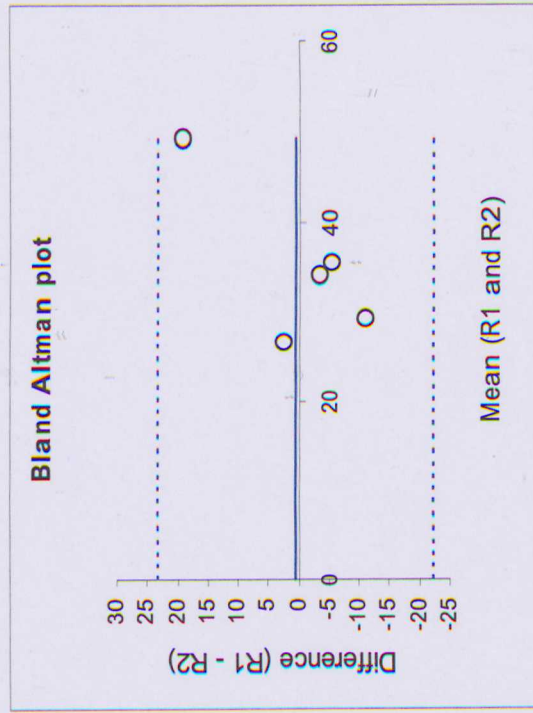


F

Umin1

Mean difference: 2.05 cm/s

Coefficient of repeatability: 28.07 cm/s



G

Umin2

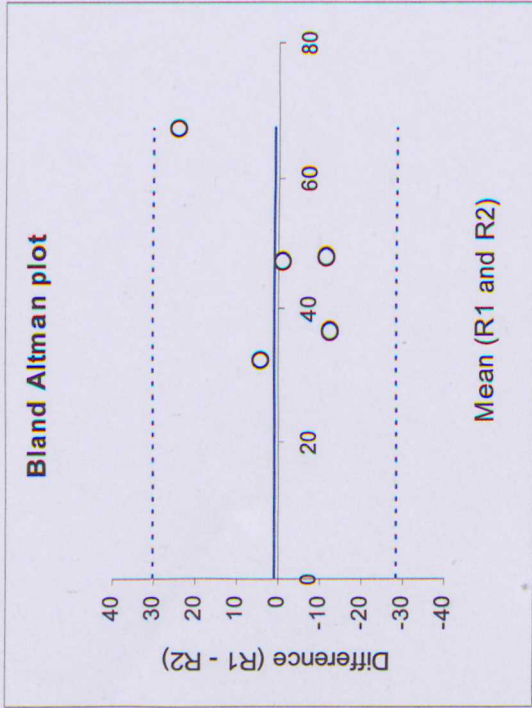
Mean difference: 0.46 cm/s

Coefficient of repeatability: 22.70 cm/s

Figure 3.21 (Continued). (Note: Umin has been shown under EDV - Traditional TCD parameters).

Waveform parameter reproducibility - VELOCITY MAXIMA

HYPOCAPNIA



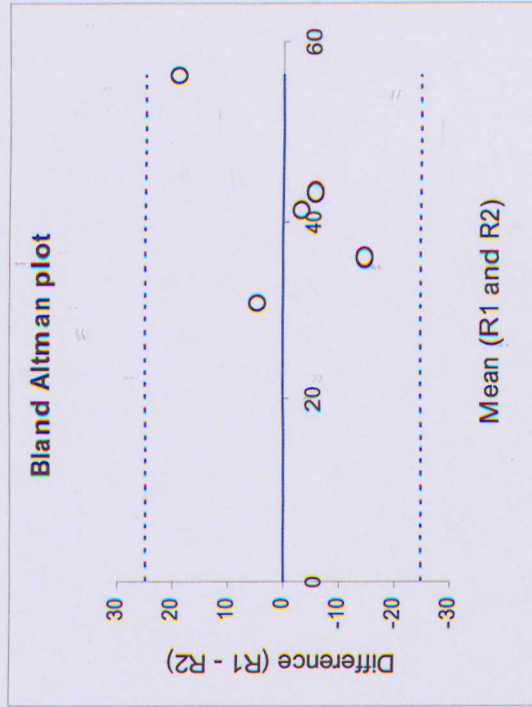
Umax1

Mean difference:

0.74 cm/s

Coefficient of repeatability:

29.29 cm/s



Umaxdias

Mean difference:

- 0.07 cm/s

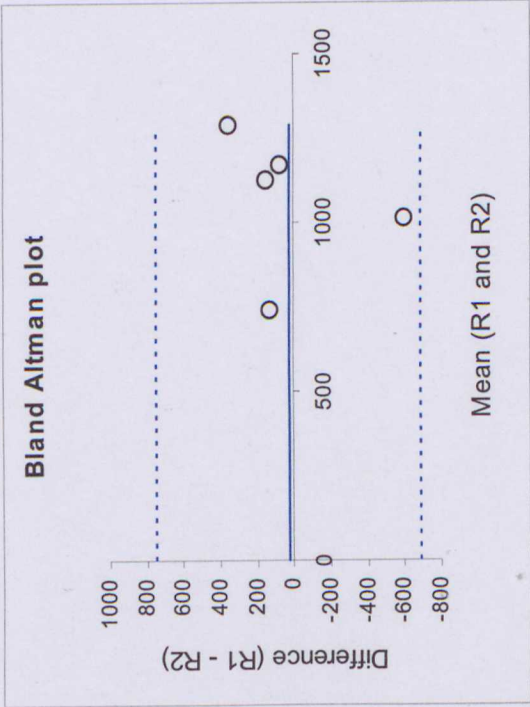
Coefficient of repeatability:

24.81 cm/s

Figure 3.21 (Continued). (Note: Umax has been shown under PSV - Traditional TCD parameters).

Waveform parameter reproducibility - ACCELERATION/DECELERATION

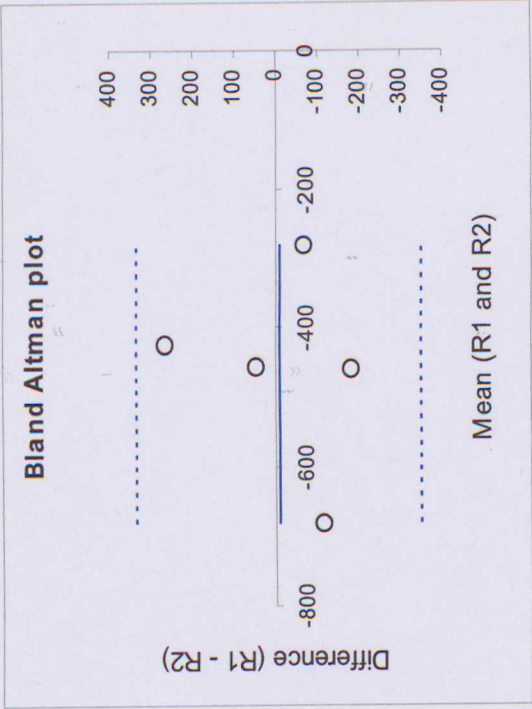
HYPOCAPNIA



J

DuDtmax

Mean difference: 24.19 cm/s²
 Coefficient of repeatability: 715.19 cm/s²



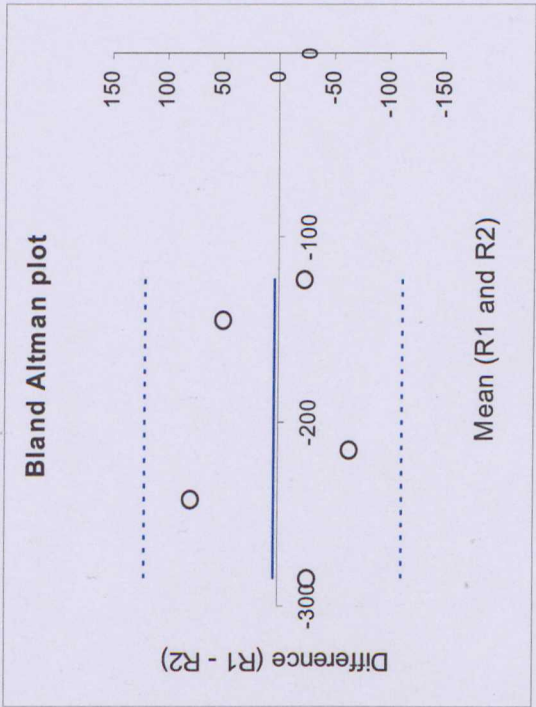
K

DuDtmin1

Mean difference: -9.67 cm/s²
 Coefficient of repeatability: 343.75 cm/s²

Figure 3.21 (Continued).

Waveform parameter reproducibility - ACCELERATION/DECELERATION



HYPOCAPNIA

DuDtmin2

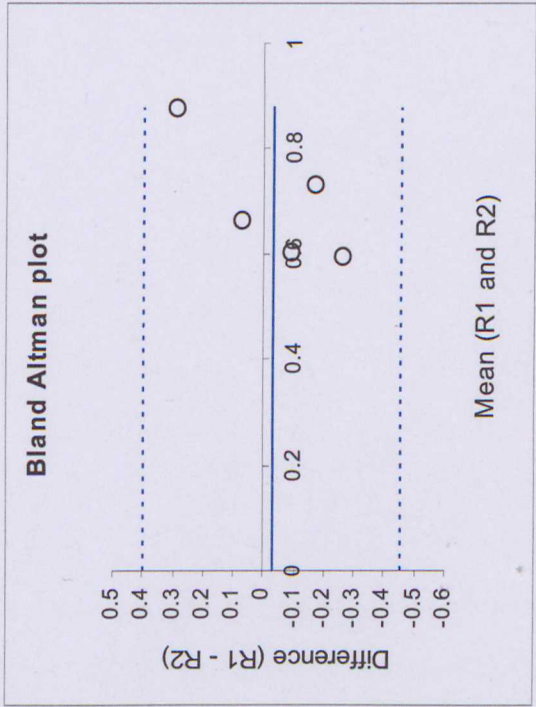
Mean difference: 3.09 cm/s²

Coefficient of repeatability: 116.12 cm/s²

Figure 3.21 (Continued).

Waveform parameter reproducibility - MISCELLANEOUS

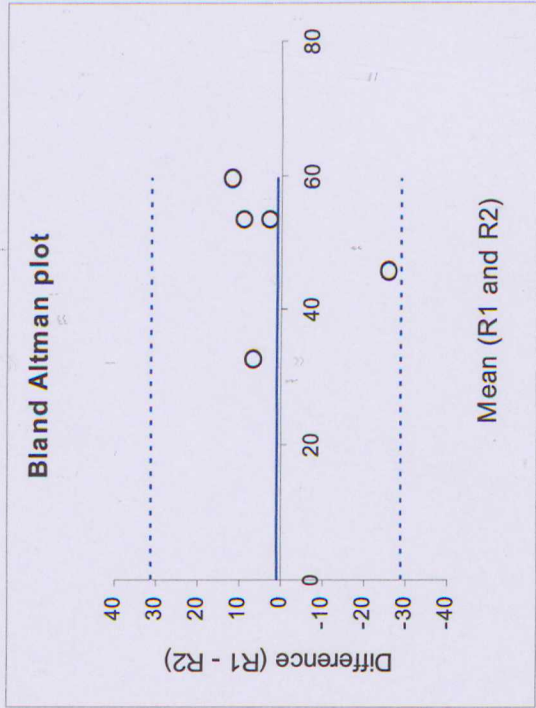
HYPOCAPNIA



Tau

Mean difference: - 0.03

Coefficient of repeatability: 0.43



Upulse

Mean difference: 0.97 cm/s

Coefficient of repeatability: 30.04 cm/s

Figure 3.21 (Continued).

Waveform parameter reproducibility - MISCELLANEOUS

HYPOCAPNIA



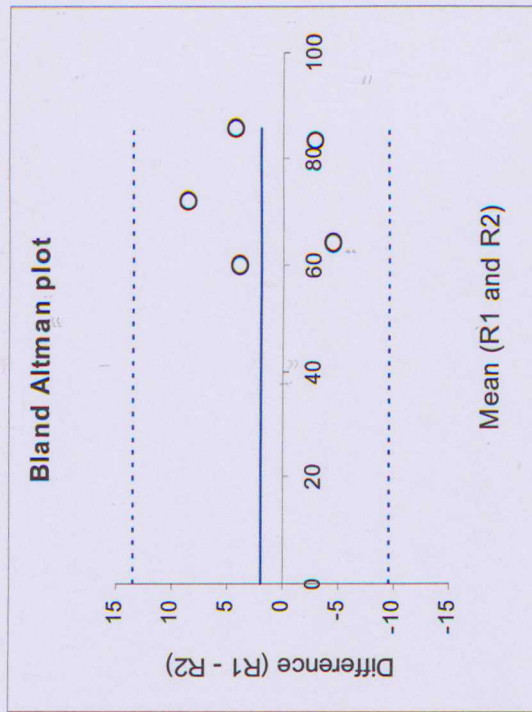
Blood pressure

Mean difference:

- 2.27 mmHg

Coefficient of repeatability:

17.39 mmHg



Heart rate

Mean difference:

1.90 bpm

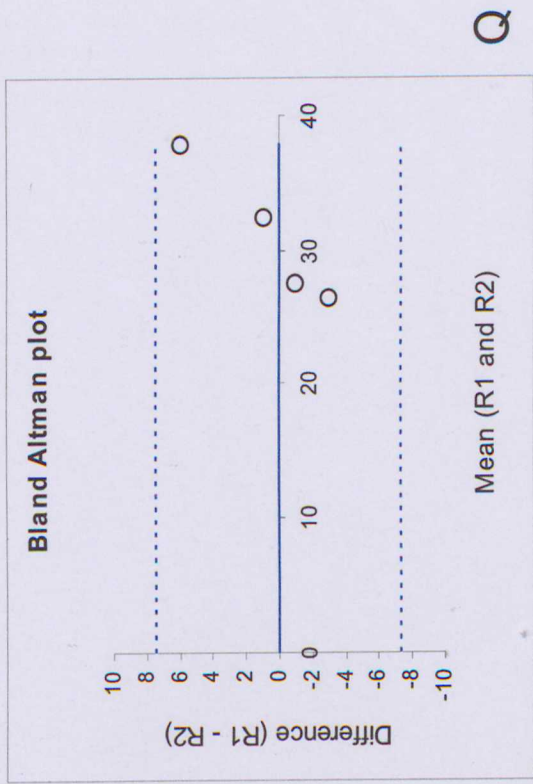
Coefficient of repeatability:

11.45 bpm

Figure 3.21 (Continued).

Waveform parameter reproducibility - MISCELLANEOUS

HYPOCAPNIA



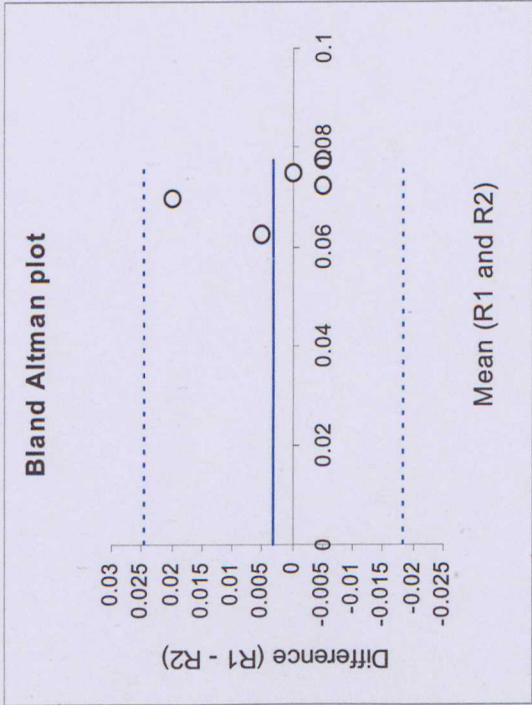
ETCO₂

Mean difference: 0.00 mmHg
Coefficient of repeatability: 7.33 mmHg

Figure 3.21 (Continued). (Note: 2 of the points in graph Q overlay each other).

Waveform parameter reproducibility - TIME MEASUREMENTS

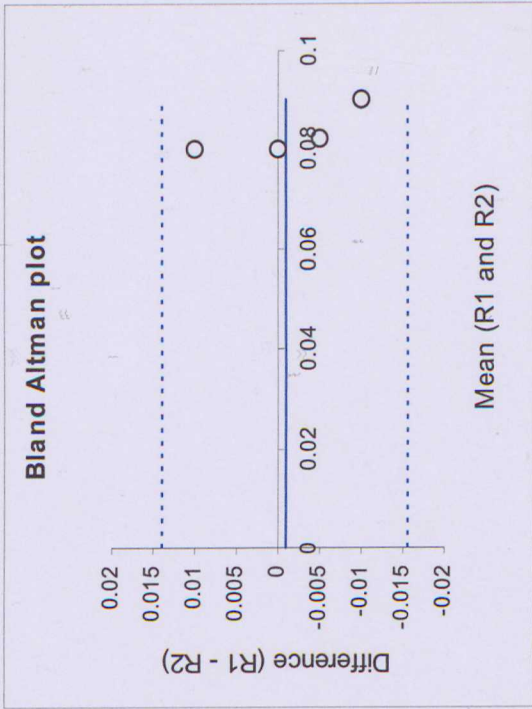
HYPOCAPNIA



R

Tmin

Mean difference: 0.00 s
Coefficient of repeatability: 0.02 s



S

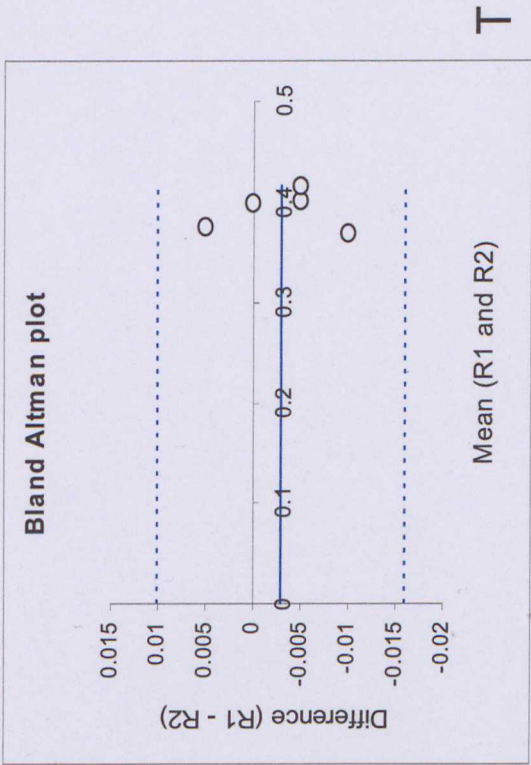
Rise time

Mean difference: 0.00 s
Coefficient of repeatability: 0.01 s

Figure 3.21 (Continued). (Note: 2 of the points if graph S overlay each other).

Waveform parameter reproducibility - TIME MEASUREMENTS

HYPOCAPNIA



Tmin2

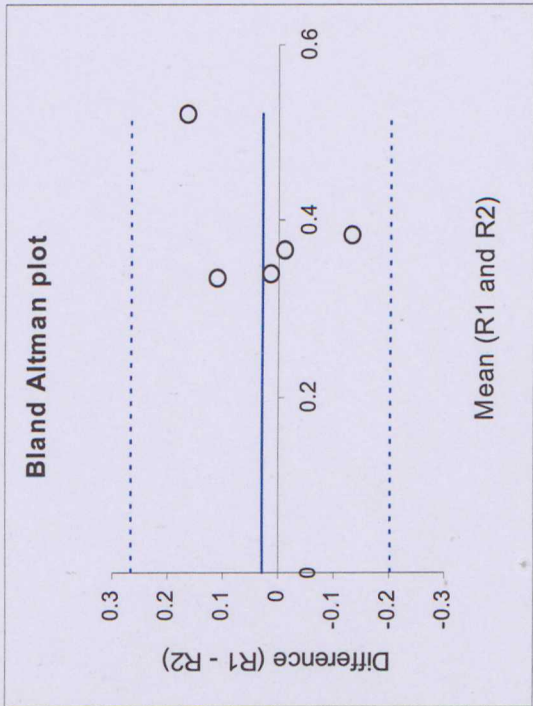
Mean difference: 0.00 s

Coefficient of repeatability: 0.01 s

Figure 3.21 (Continued).

Waveform parameter reproducibility - INDICES

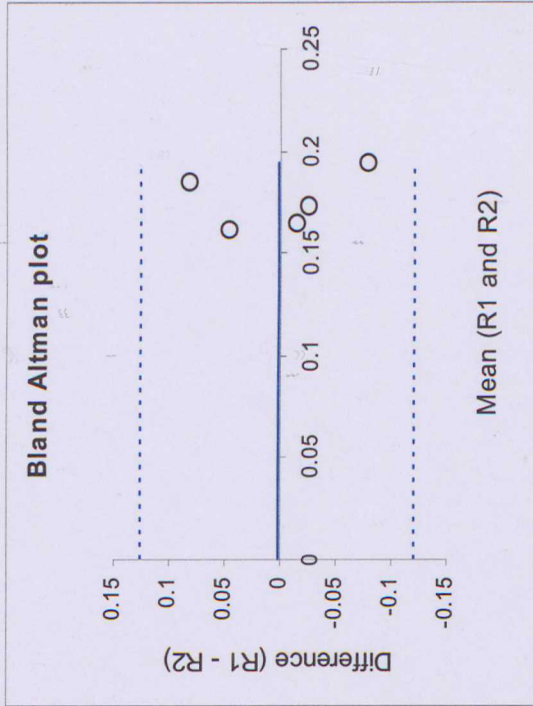
HYPOCAPNIA



Shape Index 1

Mean difference: 0.03

Coefficient of repeatability: 0.23



Shape Index 2

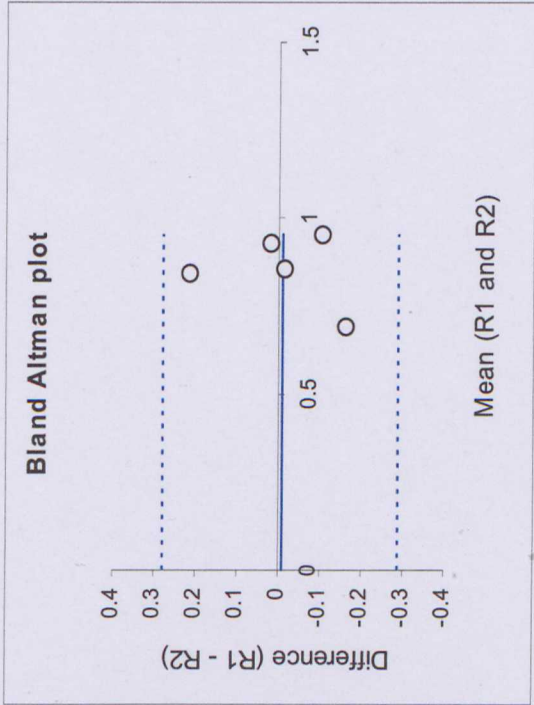
Mean difference: 0.00

Coefficient of repeatability: 0.12

Figure 3.21 (Continued).

Waveform parameter reproducibility - INDICES

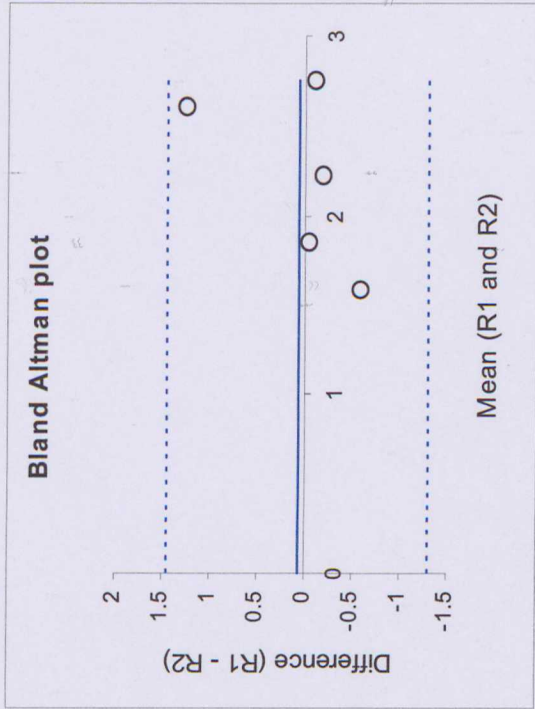
HYPOCAPNIA



W

Velocity Rise Index

Mean difference: - 0.01
Coefficient of repeatability: 0.28



X

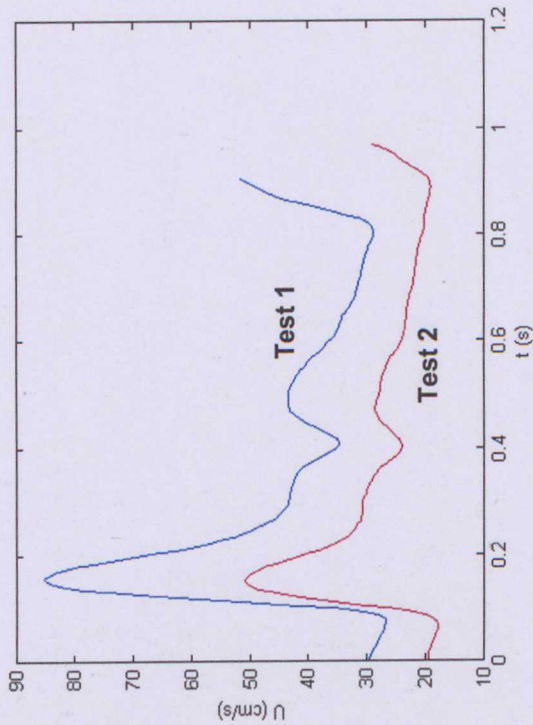
Mean resistance index

Mean difference: 0.06 mmHg per s/cm
Coefficient of repeatability: 1.37 mmHg per s/cm

Figure 3.21 (Continued).

Waveform shape reproducibility results

HYPOCAPNIA



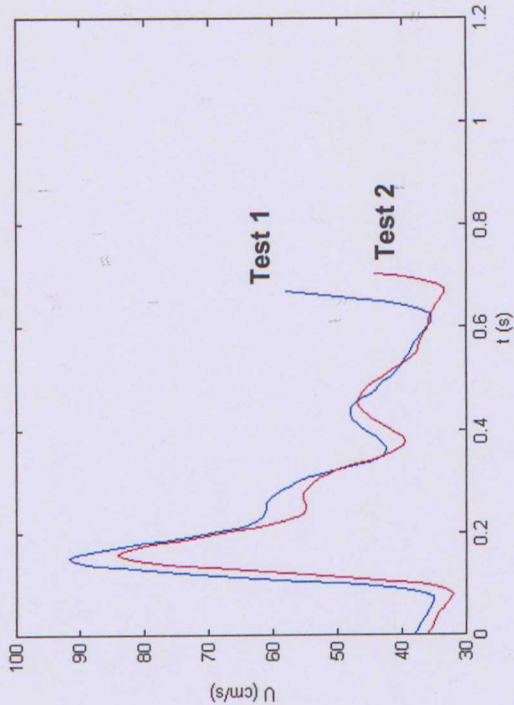
Subject A

Male, 22 yrs, time between tests = 8 days

Mean blood pressure (mmHg):

Test 1= 86

Test 2= 83



Subject B

Female, 34 yrs, time between tests = 85 days

Mean blood pressure (mmHg):

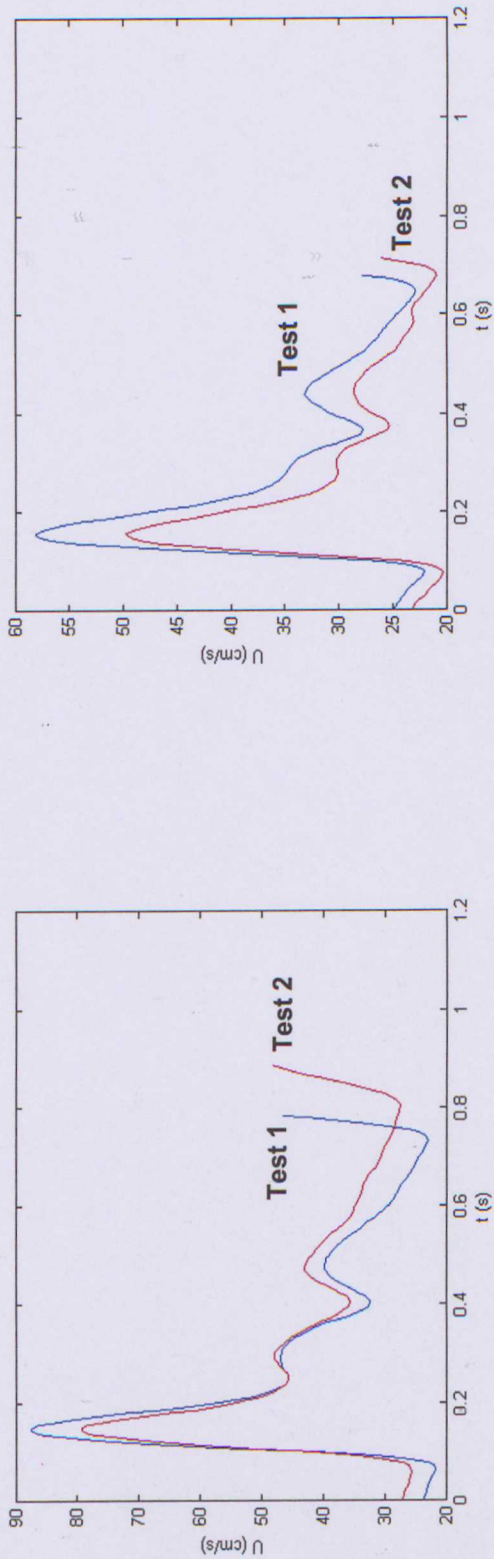
Test 1= 83

Test 2= 87

Figure 3.22 Waveform shape variations between test 1 and 2 for 5 subjects (A-E). Continued next 2 pages.

Waveform shape reproducibility results

HYPOCAPNIA



Subject C

Female, 30 yrs, time between tests = 70 days

Mean blood pressure (mmHg):

Test 1= 72

Test 2= 76

Subject D

Male, 33 yrs, time between tests = 71 days

Mean blood pressure (mmHg):

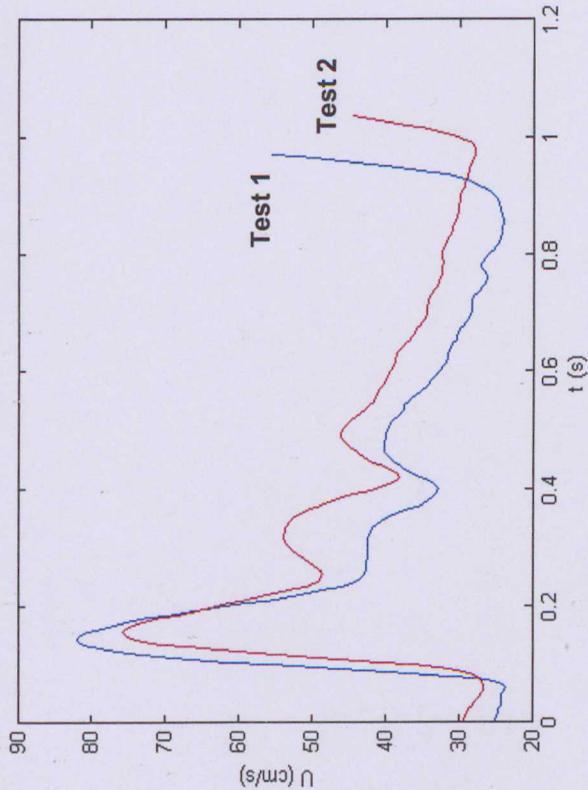
Test 1= 87

Test 2= 79

Figure 3.22 (Continued) .

Waveform shape reproducibility results

HYPOCAPNIA



Subject E

Male, 51 yrs, time between tests = 84 days

Mean blood pressure (mmHg):

Test 1= 80

Test 2= 95

Figure 3.22 (Continued).

Reproducibility (ranked) Scores by Parameter

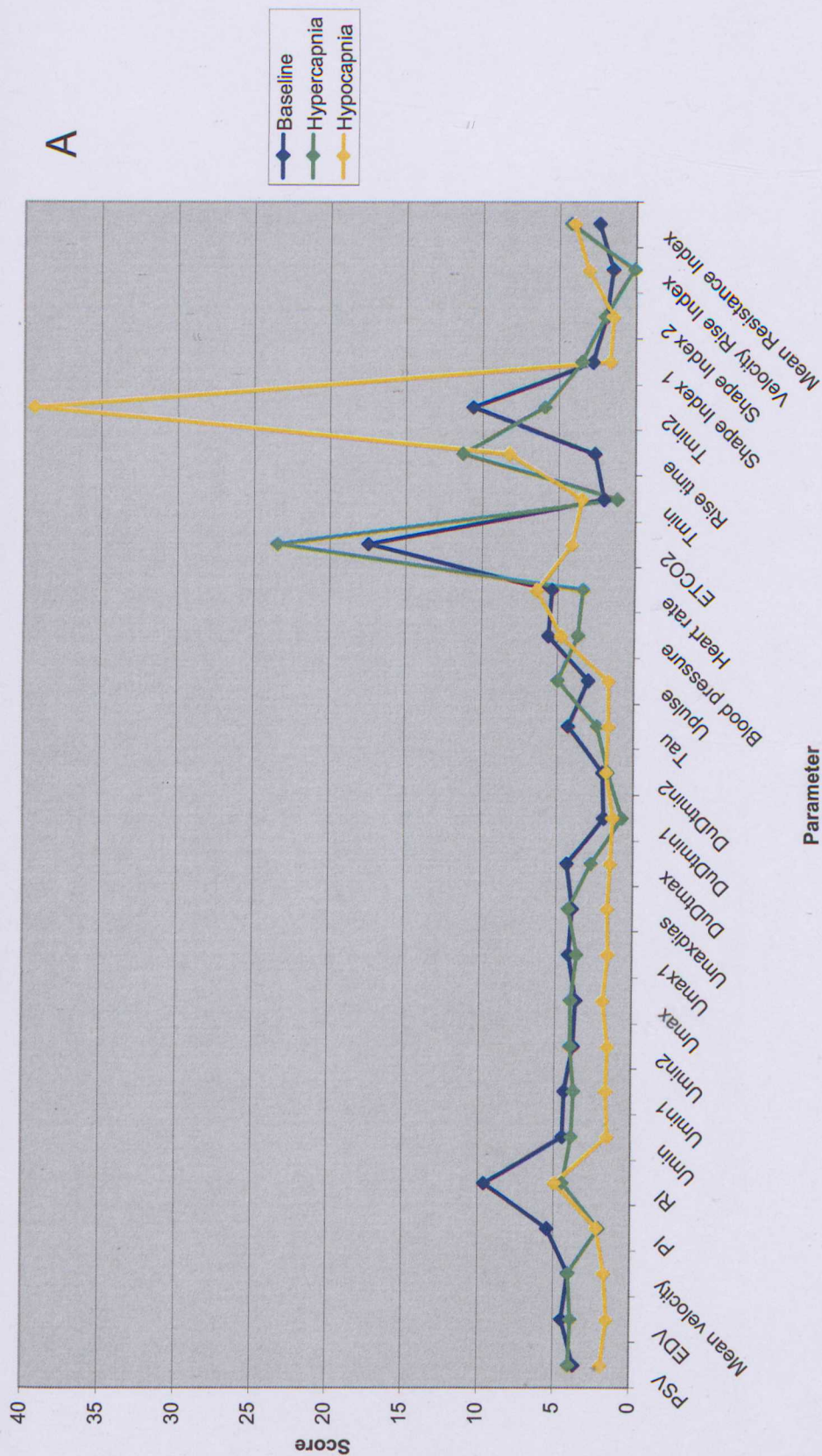


Figure 3.23 A) Graphical comparison of reproducibility (ranked) scores at BASELINE, HYPERCAPNIA and HYPOCAPNIA, by parameter, (as defined in Table 3.6).

Distribution of Reproducibility (ranked) Scores

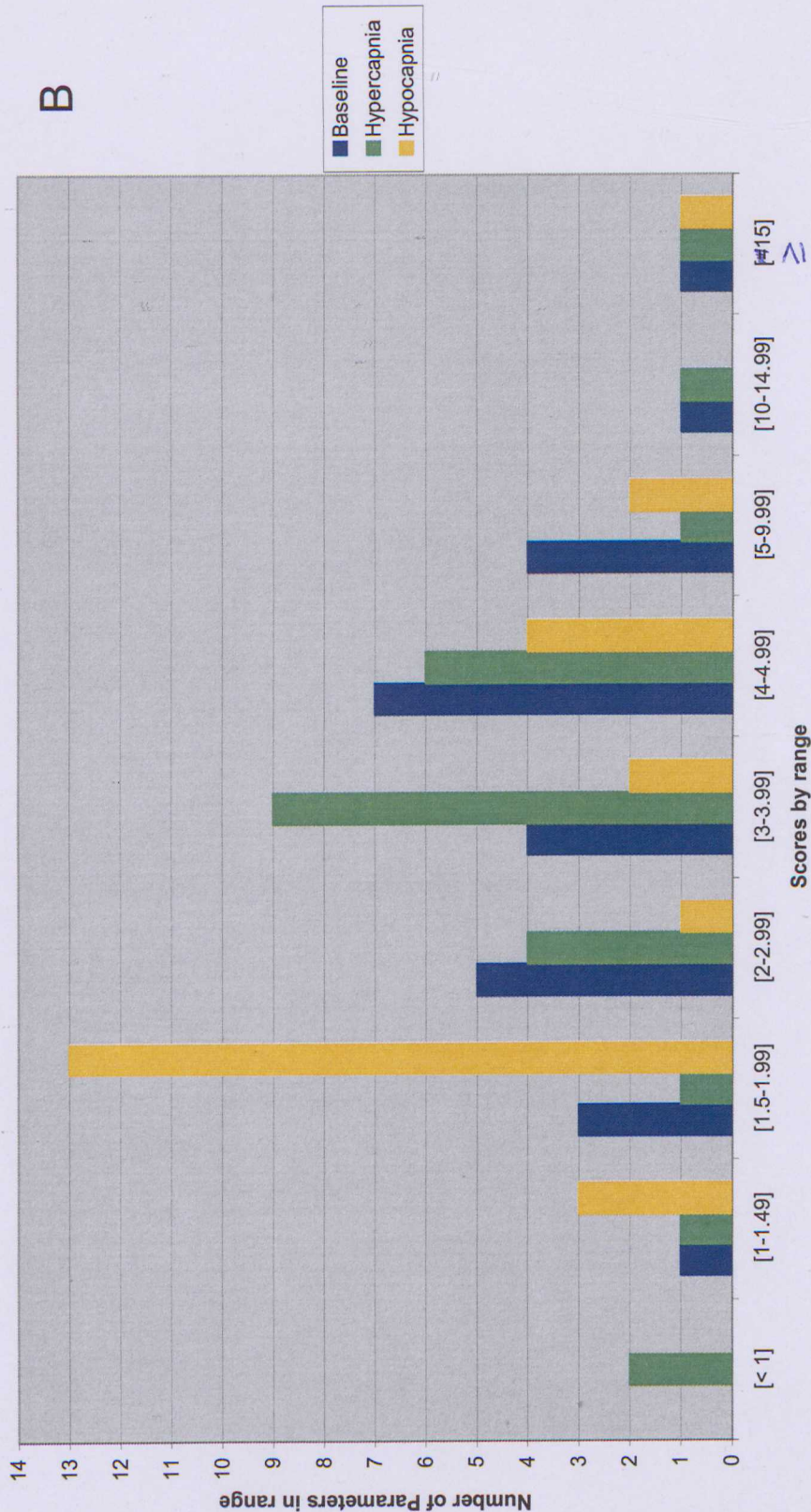


Figure 3.23 B) This graph depicts a comparison of the number of parameters that fall into each reproducibility (ranked) scoring range, grouped by BASELINE, HYPERCAPNIA and HYPOCAPNIA. This includes both traditional and new waveform shape parameters, as set out in Table 3.6.

5 minutes of velocity data									
	SUBJECT 1			SUBJECT 2			SUBJECT 3		
	PSV (cm/s)	EDV (cm/s)	Mean Velocity (cm/s)	PSV (cm/s)	EDV (cm/s)	Mean Velocity (cm/s)	PSV (cm/s)	EDV (cm/s)	Mean Velocity (cm/s)
Test 1	87.75 ± 2.05	42.40 ± 2.51	58.68 ± 2.41	107.16 ± 2.84	43.61 ± 2.97	64.27 ± 2.98	81.87 ± 2.70	34.19 ± 2.79	48.60 ± 2.52
Test 2	88.84 ± 2.44	42.95 ± 2.52	59.77 ± 2.82	108.12 ± 3.34	43.77 ± 3.99	64.56 ± 4.09	81.60 ± 2.31	35.35 ± 1.95	49.89 ± 1.95
Test 3	94.34 ± 3.42	45.47 ± 3.35	63.12 ± 3.61	108.23 ± 3.32	42.13 ± 2.82	62.72 ± 2.89	85.43 ± 2.11	37.00 ± 1.68	51.53 ± 1.68
Test 4	98.13 ± 2.49	46.22 ± 2.58	63.82 ± 2.68	105.46 ± 2.87	42.28 ± 3.69	62.43 ± 3.60	79.99 ± 4.48	34.49 ± 1.81	47.92 ± 2.07
Test 5	93.49 ± 2.79	44.64 ± 3.34	61.70 ± 3.74	105.32 ± 2.48	42.66 ± 2.99	62.75 ± 2.95	77.90 ± 4.43	33.07 ± 2.77	46.46 ± 2.89
Test 6	92.69 ± 2.63	43.71 ± 1.90	60.63 ± 2.16	103.63 ± 4.20	40.77 ± 4.03	60.93 ± 4.21	83.39 ± 3.56	34.62 ± 3.33	49.16 ± 3.41

Table 3.1 This table shows the average of 5 minutes of peak velocity envelope data and the standard deviation results, over 6 tests on each of our subjects.

16 seconds of velocity data									
	SUBJECT 1			SUBJECT 2			SUBJECT 3		
	PSV (cm/s)	EDV (cm/s)	Mean Velocity (cm/s)	PSV (cm/s)	EDV (cm/s)	Mean Velocity (cm/s)	PSV (cm/s)	EDV (cm/s)	Mean Velocity (cm/s)
Test 1	88.94 ± 1.18	41.38 ± 1.09	59.13 ± 0.81	106.69 ± 2.18	42.25 ± 2.89	63.00 ± 2.80	79.75 ± 1.34	26.94 ± 2.93	44.06 ± 1.24
Test 2	89.38 ± 2.47	46.56 ± 2.78	64.13 ± 2.87	107.56 ± 1.71	36.88 ± 4.51	59.94 ± 4.88	84.00 ± 2.48	37.13 ± 1.20	51.31 ± 1.01
Test 3	92.94 ± 1.44	46.00 ± 1.46	63.06 ± 1.18	104.75 ± 1.24	39.88 ± 0.50	56.69 ± 0.48	87.88 ± 1.36	38.38 ± 0.62	53.13 ± 0.81
Test 4	93.75 ± 0.93	43.63 ± 1.31	60.75 ± 0.93	106.81 ± 3.64	42.38 ± 2.22	62.63 ± 2.16	74.19 ± 3.39	32.50 ± 2.39	45.69 ± 2.30
Test 5	92.38 ± 2.99	42.69 ± 4.57	59.31 ± 5.11	105.19 ± 1.52	43.88 ± 2.55	64.44 ± 2.58	74.50 ± 1.46	29.50 ± 4.16	42.75 ± 3.15
Test 6	91.06 ± 1.53	40.69 ± 1.30	57.69 ± 1.25	101.56 ± 4.59	39.88 ± 3.14	60.19 ± 2.07	83.75 ± 1.24	37.56 ± 0.51	50.75 ± 1.0

Table 3.2 This table shows the average of 16 seconds of peak velocity envelope data and the standard deviation results, over 6 tests on each of our subjects.

TCD repeatability	Subjects	Number of tests per subject	Equipment set-up	Length of recording	Number of averaged data points	Time Interval between tests	Coefficient of repeatability
Demolis et al., [1993]	n = 30 M/F (21/9) Age: 29.8 yrs ± 9.9	2	RMCA bifurcation Transducer fixed to headset (left in place between tests)	8 seconds of mean velocity	3-5 (mean velocity)	5 minutes	4.83
Our Study, [2006]	n = 3 M/F (3/0) Age: 25 yrs ± 1.5	2 (tests number 3 & 4 of 6 used for this study comparison)	LMCA Mid-trunk at 50mm Transducer fixed to headset (on and off between tests)	8 seconds of mean velocity	8 (mean velocity)	15 minutes	9.78 (mean difference = 2.75)

Table 3.3 Details the similarities and differences between a TCD repeatability study performed by Demolis et al., [1993] and the one done for this thesis. Note: although our study included a series of six repeated tests, we arbitrarily selected tests 3 and 4 from 6 for this comparison.

Waves affecting cerebral blood flow velocities	Frequency (Hz)	Cycles per minute	Description
M Waves	0.05-0.15	3-9 [Lang et al., 1999]	Blood pressure oscillations due to changes in peripheral resistance (coupled with sympathetic activity)
B Waves	0.008-0.05	0.48-3 [Lang et al., 1999] 0.50-2 [Lundberg, 1960]	Vasomotor tone changes in the cerebral circulation
Respiratory waves	0.15-0.6	9-36 [Thomsen, Iversen, 1993]	Due to changes in intracranial blood volume with respiration
A waves (ICP plateau waves)	(periods lasting 5-20 minutes)	[Rosner, 1984]	Sudden rises of ICP (linked to cerebral vasodilatation and vasoconstriction)

Table: 3.4 Waves or oscillations can produce changes in cerebral blood flow velocity measurements. This table summarises the waves described in Section 3.3.2.

TCD Reproducibility	Subjects	Number of tests per subject	Equipment set-up	Length of recording	Additional measures	Time Interval between tests	Correlation coefficient (r)
Maeda et al., [1990]	n = 15 (7M) (healthy) Age: 21-38 yrs (mean 26.5 ± 5.6)	2	RMCA (45-60mm) hand held transducer Single observer	One 4 second sweep (mean velocity)	ETCO ₂ Test 1= 41.0 ± 3.0 Test 2= 41.3 ± 3.6 Blood pressure Test 1= 91.8 ± 12.0 Test 2= 89.9 ± 11.4	Mean interval 22 days	r = 0.84 (however same day repeatability was r = 0.95)
Totaro et al., [1992]	n = 36 (23M) (18 asymptomatic) Age: 21-75 (mean 47.8 yrs ± 15.5)	2	MCA (side undefined) (45-60mm) hand held transducer Single observer	unclear (mean velocity)	None	Approx. 1 day later	r = 0.94 male r = 0.93 female
Our study, [2006]	n = 5 (3M) Age: 22-51 (mean 34 ± 10.6)	2	LMCA (50mm) Fixed transducer Single observer	16 seconds Ensemble- averaged data (mean velocity)	ETCO ₂ Test 1= 48.4 ± 1.1 Test 2= 48.4 ± 1.1 Blood pressure Test 1= 83.53 ± 3.7 Test 2= 85.53 ± 8.8	Mean interval 63.6 days	r = .58

Table 3.5 Our reproducibility study results of mean velocity on the MCA, along with those done by Maeda et al., [1990], and Totaro et al., [1992]. Note that Maeda et al., [1990] had a mean of 22 days between tests, whereas Totaro et al., [1992] had only one day. Our study had the longest interval between tests.

	PARAMETER	BASELINE	HYPERCAPNIA (CO2 inhalation)	HYPOCAPNIA (Hyperventilation)
Traditional TCD Parameters	PSV	3.66	3.99	1.89
	EDV	4.45	3.87	1.52
	Mean velocity	4.08	4.02	1.70
	PI	5.43	2.06	2.19
	RI	9.62	4.44	4.96
Velocity Minima	Umin	4.45	3.87	1.52
	Umin1	4.34	3.74	1.62
	Umin2	3.80	4.00	1.54
Velocity Maxima	Umax	3.66	3.99	1.89
	Umax1	4.15	3.62	1.58
	Umaxdias	3.96	4.20	1.67
Acceleration / Deceleration	DuDtmax	4.32	2.73	1.49
	DuDtmin1	1.93	0.74	1.33
	DuDtmin2	1.99	1.65	1.74
Miscellaneous	Tau	4.27	2.35	1.62
	Upulse	2.96	4.96	1.63
	Blood pressure	5.60	3.65	4.77
	Heart rate	5.41	3.37	6.39
	ETCO ₂	17.47	23.44	4.12
Time Measurements	Tmin	2.06	1.17	3.50
	Rise time	2.66	11.30	8.26
	Tmin2	10.63	5.90	39.35
Indices	Shape Index 1	2.81	3.51	1.67
	Shape Index 2	1.92	2.01	1.47
	Velocity Rise Index	1.48	0.06	3.06
	Mean Resistance Index	2.41	4.23	4.00
MEAN SCORE		4.60	4.34	4.00

Table 3.6 Summary table of the reproducibility (ranked) scores by category, for BASELINE, HYPERCAPNIA and HYPOCAPNIA. (Higher scores represent better reproducibility).

Chapter 4

Results

This Chapter presents the results of the Doppler waveform shape parameters during vasoreactivity testing on the main study group. We assess the similarities and differences of parameter measurements on male and female subjects, and examine the relationship with age. The graphical waveform shape variations at Baseline and during Hypercapnia and Hypocapnia are presented on each of our subjects. In addition, we examine the use of the Mean Resistance Index as an indicator of changes in cerebral vascular resistance. We use non-dimensional data to investigate the relationship between Hypercapnia and Hypocapnia, to the Baseline values.

4.1 Introduction

From the results of our repeatability and reproducibility study, we believe that every individual shows a distinctive waveform shape, which we term their ‘cerebral print’. This ‘print’ remains fairly consistent over both the short and long periods that we tested. Although we demonstrate that the ‘print’ could be altered by interventions which affect cerebral vascular tone, such as Hypercapnia (vasodilatation) or Hypocapnia (vasoconstriction); the shape of the Doppler waveform was largely reproducible for each individual. However, we note that although the waveform shape is similar, there could be an offset in the velocity either upwards or downwards. Hence, this can affect the reproducibility of velocity measurements alone. The influences behind this offset (increase or decrease) may be related to changes in the amplitude of the cerebral blood flow oscillations which we described in Section 3.3.2, although this is still speculative.

4.1.1 Subjects

We recruited 35 healthy volunteers to undergo TCD examinations of the LMCA at Baseline, and during Hypercapnia and Hypocapnia, using the system and protocol described in Chapter 3. Our goal is to determine the normal values of the new waveform shape parameters and indices, in males and females of different ages. We also wanted to know if there were any trends with age and gender for our new parameters.

It has already been reported in the literature, by Gur et al. [1987], that women have higher CBF than men, measured by Xenon inhalation techniques, and this is reflected in the 3-5% velocity difference between men and women [Vriens et al., 1989] [Grolimund, and Seiler, 1988]. It was thought that the difference was due to lower hematocrit in

premenopausal women, however, Adams et al. [1998] and Brouwers et al., [1990] presented conflicting evidence. They reported that young women still had higher velocities than men even when no hematocrit difference was present. It was left as a subject for further investigation.

However, authors such as Hennerici et al. [1987] and Arnolds, and von Reutern [1986] have explored the relationship of mean velocity and age, and consistently found that mean velocity decreases with age in both males and females. The effect of age is likely multifactorial, with the decrease in TCD velocity primarily reflecting age-related changes in CBF such as small vessel disease.

The demographics for the main study group in this thesis are:

(Data is expressed as mean $\pm$ SD where applicable)

- Number of subjects = 35
- Mean age = 35.8 ± 11.3 yrs (range 22-63 yrs)
- Male n = 17, Mean age = 33.1 ± 11.3 yrs (range 22-63 yrs)
- Female n = 18, Mean age = 38.4 ± 11.1 yrs (range 23-59 yrs)

4.1.2 **Methods**

We use the standardised testing protocol described in Chapter 3 for all of our testing. The Baseline values are recorded on each subject, after which the vasomotor reactivity test is performed. In this section, we present the results of the Baseline, Hypercapnia and Hypocapnia. The results are from 16 seconds of ensemble-averaged waveform data, analysed off-line using our custom-designed waveform analysis software. We present the results for the group in the same categories as in Chapter 3: Traditional TCD Parameters, Velocity Minima, Velocity Maxima, Acceleration/Deceleration, Miscellaneous, Time Measurements, and Indices.

Statistical analysis

All data were analysed using SPSS version 12.0 for Windows in this thesis. Descriptive statistics are conducted on Baseline, Hypercapnia, and Hypocapnia for the group overall and also by gender. In addition, Pearson correlations are performed between age and all other variables for Baseline, Hypercapnia, and Hypocapnia.

4.2 Results - parameter measurements

The results of our study are presented in two ways. First, overall group measurements are shown, followed by a sub-division of results by gender. Means and standard deviations are shown by each test (Baseline, Hypercapnia, Hypocapnia) for:

Traditional TCD Parameters Table 4.1A (group overall)

(PSV, EDV, Mean Velocity, PI, RI) Table 4.1B (by gender)

Velocity Minima Table 4.2A (group overall)

(Umin, Umin1, Umin2) Table 4.2B (by gender)

Velocity Maxima- Table 4.3A (group overall)

(Umax, Umax1, Umaxdias) Table 4.3B (by gender)

Acceleration/Deceleration Table 4.4A (group overall)

(DuDtmax, DuDtmin1, DuDtmin2) Table 4.4B (by gender)

Miscellaneous Table 4.5A (group overall)

(Tau,Upulse, Blood pressure, Heart Rate, ETCO₂) Table 4.5B (by gender)

Time Measurements	Table 4.6A (group overall)
<i>(T_{min}, Rise Time, T_{min2})</i>	Table 4.6B (by gender)
Indices-	Table 4.7A (group overall)
<i>(Shape Index 1, Shape Index 2, Velocity Rise Index, Mean Resistance Index)</i>	Table 4.7B (by gender)

We discuss these results in Chapter 5 (Discussion and conclusions).

4.2.1 Relationship with age

On the **Baseline** values, 26 Pearson correlations were conducted to examine if a relationship exists between Age and Traditional TCD Parameters, Velocity Minima, Velocity Maxima, Acceleration/Deceleration, Miscellaneous, Time Measurements, and Indices.

The results revealed significant positive correlation coefficients (Table 4.8) between Age and DuDtmin1, Shape Index 1 and Shape Index 2. The results revealed a significant negative correlation coefficient (Table 4.8) between Age and Velocity Rise Index. No other significant relationships were shown with all other parameters.

Similar analysis was performed on the data at **Hypercapnia**. The results revealed significant positive correlation coefficients (Table 4.8) between Age and DuDtmin1, Blood Pressure, Shape Index 1, Shape Index 2 and Mean Resistance Index.

The results also showed a significant negative correlation coefficient (Table 4.8) between Age and Velocity Rise Index. No other significant relationships were revealed with all other parameters.

We performed the same analysis on **Hypocapnia**. The results revealed significant positive correlation coefficients (Table 4.8) between Age and DuDtmin1, Shape Index 1 and Shape Index 2. No other significant relationships were revealed with all other parameters.

We will further discuss these results in Chapter 5 (Discussion and conclusions).

4.3 Doppler waveform shape results

The tables above have detailed the numerical values of all of the new waveform parameters during testing, however it is important to also show the *visual representation* of changes in the waveform shape in the individuals during vasomotor reactivity testing. Using our waveform comparison software, we have provided the ensemble-averaged waveform shapes from each of our 35 subjects taken at Baseline, and during Hypercapnia and Hypocapnia. The subjects are grouped by gender, and presented in ascending age. Figure 4.1 depicts all male subjects, and Figure 4.2 shows the female subjects. These are discussed in Chapter 5 (Discussion and conclusions).

4.4 Derived results

4.4.1 % change from Baseline per mmCO₂

In this section, we use the data from our 35 subjects to derive further information about the cerebral circulation. Vasomotor reserve (VMR) is normally calculated as the % change in mean velocity from Baseline, during Hypercapnia and Hypocapnia.

$$\text{VMR} = |\% \Delta \text{Hypercapnia}| + |\% \Delta \text{Hypocapnia}|$$

According to Ringlestein and Otis [1992], normal VMR = $86\% \pm 16$. However, since Hypocapnia is dependent on the effort of the individual to perform adequate hyperventilation this can result in a lower overall VMR if a poor effort occurs. An alternative parameter can be calculated; it is the % change from Baseline *per mm of CO₂*.

$$\text{VMR}^* = \text{VMR} / (\text{ETCO}_2 \text{ Hypercapnia} - \text{ETCO}_2 \text{ Hypocapnia})$$

This calculation may be more useful, especially in elderly subjects where hyperventilation to an appropriate standard is difficult to elicit. Ringlestein and Otis [1992] determined that a 5% change in MCA flow velocity from Baseline *per mmCO₂* was normal for their subject group referred to above. This was supported by the literature review by Yonis [1987] who found a 3-5% change in regional cerebral blood flow (rCBF) per unit change in arterial CO₂. Others have reported cerebral blood flow volume (CBV) changes of 1-2 ml/100 g of brain/min for each 1 mmHg change in CO₂ [Sato et al., 1984]. They have noted however that the overall effect on CBF, on changing the arterial CO₂, is affected by the starting point of the Baseline CBF itself, as well as the CPP (cerebral perfusion pressure). Hence, changes in CO₂ have less of an affect on CBF if it is already at the extreme end of the spectrum, such as during hypotension [Phelps et al., 1973].

In summary, for every 1 mmHg change in CO₂ there is a:

- 5% change from Baseline in TCD mean velocity
- 3-5% change from Baseline in cerebral blood flow (CBF)
- 1-2 ml/100g of brain/minute change in cerebral blood flow volume (CBV).

In this thesis, we present the results of our new waveform shape parameters in terms of % change per mmCO₂ from Baseline for both Hypercapnia and Hypocapnia. We believe this allows for easier comparison to what is already known in the literature, as discussed above, with regards to CBF, CBV, and TCD velocities during variations in CO₂.

Statistical analysis

Descriptive statistics are conducted on the % change per mmCO₂ from Baseline, for Hypercapnia and Hypocapnia for the group overall, and by gender. Means and standard deviations are listed for Traditional TCD Parameters, Velocity Minima, Velocity Maxima, Acceleration/Deceleration, Miscellaneous, Time Measurements, and Indices.

Traditional TCD Parameters

Table 4.9 (group overall & by gender)

(PSV, EDV, Mean Velocity, PI, RI)

Velocity Minima

Table 4.10 (group overall & by gender)

(Umin, Umin1, Umin2)

Velocity Maxima

Table 4.11 (group overall & by gender)

(Umax, Umax1, Umaxdias)

Acceleration/Deceleration

Table 4.12 (group overall & by gender)

(DuDtmax, DuDtmin1, DuDtmin2)

Miscellaneous

Table 4.13 (group overall & by gender)

(Tau,Upulse, Blood pressure, Heart Rate, ETCO₂)

(*T_{min}*, *Rise Time*, *T_{min2}*)

(*Shape Index 1*, *Shape Index 2*, *Velocity Rise Index*, *Mean Resistance Index*)

These findings will be discussed in Chapter 5 (Discussion and conclusions).

4.4.2 Velocity and resistance

In transcranial Doppler, vasomotor reactivity testing is reported in terms of mean *velocity* changes, and yet the pertinent clinical question is about *resistance* changes. How effectively do the cerebral resistance vessels dilate and constrict, or what is their vasomotor capacity? Baumgartner and Regard [1994] found that reduced CO₂ reactivity was associated with cerebral low flow infarctions. In addition, Fu et al. [2004] suggested that vasoconstrictor capability of the cerebral circulation may be one mechanism underlying individual variability in orthostatic intolerance.

The vasomotor reactivity test is designed to induce a change in vascular resistance in the small vessels of the brain by promoting either vasodilatation via CO₂ inhalation, or vasoconstriction through hyperventilation. We equate increased blood flow velocities to increased volume flow, a result of vasodilatation. We use this change in velocity to indicate a change in the resistance. The reverse is true of hyperventilation, where a decrease in volume flow occurs secondary to vasoconstriction of the peripheral vascular bed, thus producing a decrease in the blood flow velocities recorded by TCD. Hence, a decrease in velocities indicates a change in cerebrovascular resistance. We are keenly interested in these changes in resistance, since this is a mechanism used by the cerebral circulation to maintain constant blood flow to the brain during alterations of systemic

blood pressure. If cerebral vasomotor reserve becomes exhausted (the resistance arteries are maximally dilated), the vessels are refractory to any further vasodilator stimulus. Hence, inhalation of CO₂ will not increase the MCA velocities any further [Ringlestein et al. 1988]. This can be a critical situation because after this point cerebral blood flow will passively follow arterial blood pressure. A sudden drop in systemic blood pressure could create ischemia. Yonas et al. [1993] looked at vasomotor reserve using acetazolamide (a cerebral vasodilator) and consecutive xenon/computerized tomography (Xe/CT). They found that in subjects with a symptomatic carotid stenosis or occlusion, those with the lowest reserve had a 36% incidence of a stroke on the ipsilateral side after 1 year. In TCD, VMR (vasomotor reserve) is sometimes referred to as an *indirect* method of looking at the cerebral autoregulation. However, this link made between blood flow velocities and vascular resistance, although convenient, is not without fault.

In fact, the optimal method would be to visualise and measure the diameter changes in the small regulating vessels in response to stimuli; unfortunately this cannot be done non-invasively. Therefore, TCD flow velocity increases or decreases are used as a surrogate indicator of changes of cerebral resistance or tone. But is this the best we can do with TCD?

The mechanics of flow in the cerebral vascular bed can be described by three simplified concepts: 1) perfusion pressure (mean arterial blood pressure minus the intracranial pressure), 2) resistance to flow, and 3) the resultant volume flow rate [Aaslid, 1992]. The volume flow rate (volume/time) is the primary measure of perfusion, and is equal to the velocity multiplied by the area of the vessel. The concept of cerebrovascular resistance (CVR) is based on the haemodynamics Ohm's Law:

$$F = \Delta P/R$$

(F is flow, P is pressure difference, R is resistance)

According to this formula, cerebral blood flow (CBF) should be:

$$CBF = (ABP - ICP)/CVR = CPP/CVR$$

(ABP is arterial blood pressure, ICP is intracranial pressure)

If we assume for a moment that the calibre of the resistance vessels is constant, then flow (CBF) and pressure (CPP) would be perfectly proportional. Therefore a 20% drop in pressure, would mean a 20% drop in flow (Figure 4.3 A.) However, this is not the case. If we look at the familiar autoregulation curve [Lassen, 1959], we can see that changes in resistance allow for flow to be maintained even if there is a drop in pressure (Figure 4.3 B and C). However, there have been doubts about the validity of using a simple proportional CVR model, since one complicating factor is the compliance of the vascular bed.

Although we cannot track the true pressure-flow relationships of the cerebral circulation non-invasively we are able to follow the pressure-velocity relationships with TCD and arterial blood pressure measurements. By using pressure-velocity information from our data, we hope to gain further quantitative information about the cerebral circulation; since this is closely related to changes in vasomotor tone [Dewey et al. 1974]. For purposes of this study, we will rearrange the equation:

$$CVR = CPP/CBF$$

and for CPP, the pressure component of the equation, we will use mean arterial blood pressure measurements; and for CBF we will use the mean flow velocity by TCD. (We will assume that intracranial pressure is nominal, as normal values are normally <10 mmHg).

In this section we present the results our pressure-velocity data, as represented by our 'mean resistance index' (*mean arterial blood pressure/ mean flow velocity*) as a surrogate for tracking changes in CVR. We analyse this data as a % change from the Baseline during Hypocapnia and Hypercapnia and show the standard deviations. This is a similar reporting method to that of Ringlestein and Otis [1992], however they reported only in terms of overall % change in velocity and did not link this with simultaneous changes in blood pressure. Table 4.16 Hypercapnia compares the results of both methods. Results are presented as a % *change in mean velocity* in the first column, and % *change in mean resistance index* in the second column for direct comparison. We believe that the mean resistance index has a closer link with changes in vascular tone, than mean velocity alone. We have also subdivided our data by gender and age.

From our results (Table 4.16) we can see that Hypercapnia produces 33-46% increase in mean MCA velocities from Baseline in our group of subjects, which might be expected due to vasodilatation of the peripheral vascular bed. However, let us look at the mean resistance index, which shows only an 18-26% change (decrease) in resistance for a much larger change (increase) in velocity. If we examine the results for Hypercapnia (vasodilatation) (Table 4.16) we see that:

- for the group overall, a 39.3 ± 19.9 (cm/s) increase in velocity corresponds to a 21.9 ± 9.9 (mmHg s/cm) decrease in mean resistance index;

- women have a greater change in mean velocity, and mean resistance index than men during CO₂ inhalation;
- women show a decreasing effect with age. Whereas, men show no clear pattern with age.

In contrast, the reverse is true during Hypocapnia. The data in Table 4.17 shows that for a 24-36% change (decrease) in flow velocity, there appears to be an increase in mean resistance index of 33-60%.

If we examine the results for Hypocapnia (vasoconstriction) (Table 4.17) it shows:

- for the group overall, a 32.4 ± 9.3 (cm/s) increase in velocity is equal to a 48.9 ± 22.3 (mmHg s/cm) decrease in mean resistance index;
- men have a greater change in mean velocity and mean resistance index than women during hyperventilation;
- women again show a decreasing effect with age in mean velocity. Although no clear pattern is seen in mean resistance index, younger women appear to have a greater effect from hyperventilation than the other two age groups;
- men show a decreasing effect with age in mean resistance index. However, no clear pattern is seen in mean velocity changes.

If we review the results of Table 4.18, depicting Vasomotor Reserve (VMR) in terms of both velocity and mean resistance index, we see that:

- overall VMR by velocity and VMR by mean resistance index are similar in value;
- both men and women have similar overall VMR by velocity;

- however, VMR by mean resistance index shows that men have greater changes than women during vasomotor testing;
- women show a decrease in VMR by velocity, with increasing age. However, no clear pattern is seen in mean resistance index, other than the youngest group of women have the greatest % change in VMR over the other two groups;
- whereas, men show no clear pattern in VMR in velocity with age; but do show a decrease in mean resistance VMR with age.

Overall summary

- The cerebral circulation appears to be able to constrict more than to dilate.
- Mean resistance index is not proportional to the % change in mean velocity.
- Large velocity increases during Hypercapnia, do not represent large resistance changes, but in fact small resistance changes.
- Smaller velocity decreases found during Hypocapnia, actually represent much larger changes in resistance.

4.4.2.1 Graphical representations

To demonstrate the relationship of velocity and mean resistance index; we plot the actual mean velocity measurements against the mean resistance index for each of our subjects during all three phases: Baseline, Hypercapnia, and Hypocapnia. Therefore each individual is represented three times on the graph (once for each test) (Figure 4.4). In one sense, this graph represents the physiological testing range we induced in our group through the vasoreactivity testing protocol. This graph allows us to see the relationship of mean velocity, to changes to mean resistance index. We can see from this graph that for a subject with high mean velocities, for example, 80 cm/s, an increase or decrease in velocity would result in a relatively small change in mean resistance index. Whereas, for a subject who has much lower velocities, for example, 40 cm/s, a similar

increase or decrease in velocity results in a larger change in mean resistance index.

Hence, this graph shows why *velocity and resistance are not proportional to each other*.

In Figure 4.5 we further investigate the three aspects of vasomotor reactivity testing: Baseline, Hypercapnia, and Hypocapnia. We have plotted the result for each subject (once), on each of these three graphs. These graphs show how all subjects appear to shift to the left during the vasodilatation phase (Hypercapnia), with higher velocities and decreased resistance (mean resistance index). In contrast, there is a shift to the right during the vasoconstriction phase (Hypocapnia), demonstrating a decrease in velocities and an increase in resistance (mean resistance index). These graphs depict the physiological testing range during each phase of the vasomotor testing, as well as demonstrating how changes in velocity relate to changes in mean resistance index.

We knew from our results in Section 4.2 (Tables 4.16-4.18) that there are gender differences; therefore we also subdivided these graphs into Men and Women. Figure 4.6 A and B shows that the physiological testing ranges are slightly different for men and women, and Figure 4.7 elaborates on the gender differences by testing segment (Baseline, Hypercapnia, and Hypocapnia).

4.4.2.2 Resistance and mean resistance index

Mean resistance index appears to be showing some interesting results but we wanted to investigate the relationship between mean resistance index and changes in cerebrovascular downstream resistance. This is difficult to do non-invasively; and the only method available was to compare our results with those of a computer model.

A one-dimensional model of a vascular network in space-time variables, created by Sherwin et al. [2003], was adapted to simulate flow in compliant vessels in the circle of

Willis by Dr. J. Alastruey [Alastruey et al., in press]. His model is based on average physiological values for length, radius, elastic modulus, and peripheral resistance and compliance for the cerebral circulation from the literature. We wanted to understand how resistance changes and mean resistance index, compare during Hypercapnia and Hypocapnia utilizing his model and our in-vivo measurements.

We tried two different techniques.

A) From results in a sample subject during vasomotor reactivity testing, we knew the % change from Baseline in mean arterial blood pressure, the mean blood flow velocity, and mean resistance index during Hypercapnia. We began by supplying the model with only 2 of the 3 parts of the information, and asked for missing result. We input the observed 9% increase in mean blood pressure, and the observed 15% decrease in mean resistance index. We calculated the % change in the MCA mean velocity (from Baseline), under these circumstances. Dr. Alastruey was blinded to our results. For Hypercapnia, the model predicted a 14% change (increase) in MCA velocity would occur, as a result of the specified pressure and resistance (mean resistance index) changes. Our in-vivo results showed a 35% change (increase) in MCA velocity.

We repeated the same steps for Hypocapnia. Our data showed a 79% increase in mean resistance index, and a 4% increase in mean blood pressure, from Baseline. The result of the simulation showed that the MCA would decrease in mean velocity by 40% in this situation. Our in-vivo results showed the MCA had decreased by 45%, which is much closer to the computer simulation. However, we still wanted to investigate why our results for Hypercapnia were so different from the model, while our results for Hypocapnia seemed reasonably close.

B) In the second technique, we allowed for adjustment of the original computer model, so it could be set as closely as possible to the Baseline values for another of our test

subjects (#98). No adjustments were made to the basic model in the first study. Dr. Alastruey began by changing the peripheral resistances of all the terminal branches of the cerebral circulation until it matched the mean resistance index of our test subject. He then adjusted the calibre of the MCA, and the cardiac output at the ascending aorta to the measured mean blood pressure we had supplied at Baseline.

For Hypercapnia and Hypocapnia, he re-adjusted the terminal resistances of the six cerebral arteries in the model by the % change in mean resistance index we had measured in our in-vivo experiment. He modified the cardiac output on the model to obtain the new measured mean blood pressure. The results for Subject #98 are shown in Table 4.19.

You can see (Table 4.19) that mean resistance index is related to cerebral peripheral resistance predicted by the computer model. For this particular subject, the correlation is better during Hypercapnia than Hypocapnia.

We repeated the process for another Subject #73. This time the subject's Baseline values were already close to those of the original computer model. The results for this subject are shown in Table 4.20.

In this example, there is very close relationship between our *in-vivo* data from Subject #73, and the computer predictions. These data demonstrate that changes in mean resistance index and cerebral peripheral resistance changes in the model are closely linked.

Of course a computer model does not represent the true changes in the cerebral circulation, but in the absence of other methods it was a worthwhile comparison. The main limitation of this experiment is the lack of detailed information on the geometry and elasticity of the arterial network and the boundary conditions on each of our test subjects (cardiac output and peripheral impedances). The results strongly depend on

the physiological data used, and the model is based on published measurement in healthy young adults. The numerical model considers an Ohm's Law relationship between pressure and flow. This appears to reproduce our in-vivo measurements quite well and hence Hypercapnia and Hypocapnia are shown to have an affect on the cerebral terminal resistances.

The results from our simple experiment support our hypothesis that the mean resistance index is linked with peripheral resistance changes in the cerebral circulation and would perhaps be a useful TCD measurement to incorporate in future studies.

4.4.3 Non-dimensional parameter results

The results of our study group can be looked at in many different ways. However, one difficulty arises from the fact that some of the parameters of the waveform shape are in units of velocity (cm/s), whereas others are in terms of acceleration (cm/s²), or units of time (s). It was important for comparison purposes that we address this problem, so correlations between the parameters and tests (Hypercapnia and Hypocapnia) could be conducted. We decided to non-dimensionalise the data first, before running the statistical comparisons between the parameters. This, in effect, is a scaling process for the data.

We non-dimensionalised by the following method:

- All *velocity* data (U) were divided by the mean velocity (U*).

Therefore: $U/U^* = \text{non-dimensional } U (U')$

(e.g. $U_{min}' = U_{min}/U^*$)

The velocity parameters are: PSV, EDV, U_{min} , U_{min1} , U_{min2} , U_{max} ,

$U_{maxdias}$, U_{pulse} .

- All *time* related data (t) were divided by the time of systole, $t^* = T_{min2} - T_{min}$, the time of the beginning of systolic upstroke to time of aortic valve closure in the cerebral circulation waveform.

(e.g. $T'_{min} = T_{min}/t^*$)

The time parameters are: T_{min} , Rise time, and T_{min2} ; chosen because they represented important time points on the waveform. T_{min} represents the time from the peak of the ECG R wave to the beginning of the systolic upstroke in the cerebral circulation. Rise time represents the time from T_{min} to peak velocity; and T_{min2} is indicative of the time from T_{min} to aortic valve closure, or the dicrotic notch of the cerebral circulation waveform.

- All *acceleration/deceleration* data (a) were divided by U^*/t^* (mean velocity/time of systole)

(e.g. $DuDt_{max}' = DuDt_{max} / (U^*/t^*)$)

The acceleration parameters are: $DuDt_{max}$, $DuDt_{min1}$, $DuDt_{min2}$.

- All parameters involving pressure are divided by the mean blood pressure (p^*).

(e.g. $P'_{systolic} = P_{systolic}/p^*$)

The pressure parameters are: systolic blood pressure and diastolic blood pressure.

Statistical analysis

Non-dimensional data were analysed using SPSS version 12.0 for Windows.

Preliminary analysis: a one sample K-S test revealed all non-dimensional parameters were normally distributed.

A Pearson correlation was conducted to examine if a relationship exists between Baseline and Hypercapnia, and between Baseline and Hypocapnia for each *non-dimensional parameter*.

In addition, a repeated measure ANOVA was then conducted to examine if a mean difference exists for each *non-dimensional parameter* between the Baseline, and the two interventions.

Table 4.21 shows the means, standard deviations, and the mean differences from the ANOVA analysis. For simplicity, we have created Table 4.22 (extracted mean differences from Table 4.21) which show the mean differences ranked by absolute value and grouped by Hypercapnia and Hypocapnia. We have colour-coded these tables for easier visual interpretation. We can see that some parameters show very little difference from the Baseline during Hypercapnia and Hypocapnia. For example, Umin2' and Umin1' show no absolute mean difference from Baseline during Hypercapnia. While DuDtmin1' and DuDtmax' show the most change from the Baseline during Hypercapnia. Note that Hypercapnia and Hypocapnia colour-coded parameter groupings are similar, but not identical. For instance, Rise Time has a small mean difference from the Baseline during Hypercapnia, but a large difference during Hypocapnia.

For clearer understanding of our statistical data from our non-dimensional parameters, we chose to plot 4 representative examples of the data from each of the colour-coded areas in Table 4.22. These examples (Figures 4.8 A – D) simplify the results of the Pearson correlations and the ANOVA analyses found in Tables 4.23 (Hypercapnia) and 4.24 (Hypocapnia).

In Figure 4.8 A, we see the non-dimensional values from the group for Umin2', both Hypercapnia and Hypocapnia, plotted against the Baseline values. In the box below the plotted area, we show the mean difference values found in Table 4.22, and also the Pearson correlation for the parameter found in Tables 4.23 (Hypercapnia) and 4.24 (Hypocapnia). Both Hypercapnia and Hypocapnia showed a nominal mean difference from the Baseline. If we look at the trend line fitted to our data, we can see the lines are very close to each other. The Pearson correlations demonstrate a similar relationship to the Baseline, for both Hypercapnia and Hypocapnia ($r = 0.73$ and 0.79 respectively). If we look again at the trend lines we can see that these lines appear nearly parallel to each other.

In Figure 4.8 B there is a slightly different scenario. Here we see that both trend lines for the data (Umax') have a greater distance between them than in Figure 4.8 A. Again look at the mean difference (box below the plotted area); it shows that the mean difference between these two interventions and the Baseline, is larger than in Figure 4.8 A. However, the trend lines still remain relatively parallel to each other in this example (note the r values).

However, Figure 4.8 C is unlike both of the other plots. Although the absolute mean difference from the Baseline for systolic blood pressure is again nominal in value for both interventions; the trend lines no longer appear to be parallel. Note that the

Pearson correlations are different for the two interventions ($r = .38$ for Hypercapnia, and $r = 0.60$ for Hypocapnia).

Our final example, Figure 4.8 D, shows there is disparity for $\text{DuDtmin1}'$ in both absolute mean differences from the Baseline (Hypercapnia 0.73 ± 0.46 , and Hypocapnia 1.50 ± 0.83), and also in the Pearson correlations ($r = 0.76$ for Hypercapnia, and $r = 0.41$ for Hypocapnia). The plot of the data is distinctly different from our other examples.

We discuss these results further in Chapter 5 (Discussion and conclusions).

Males

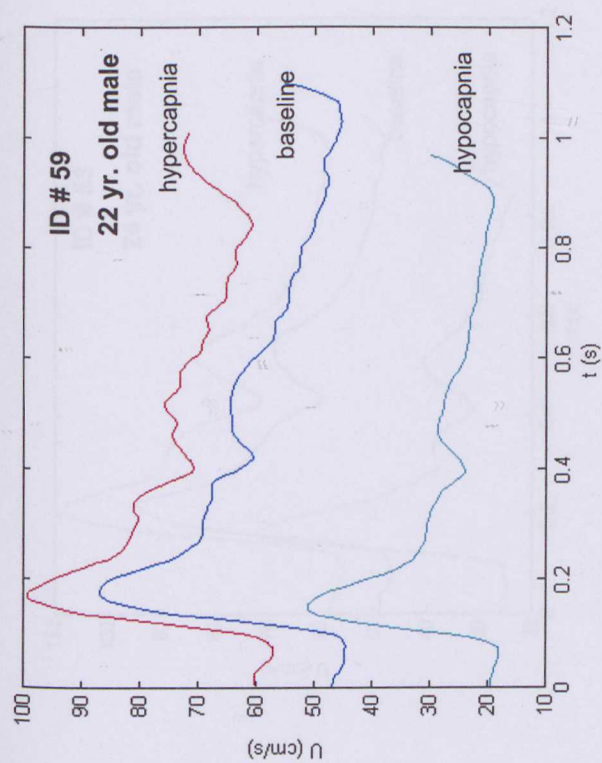
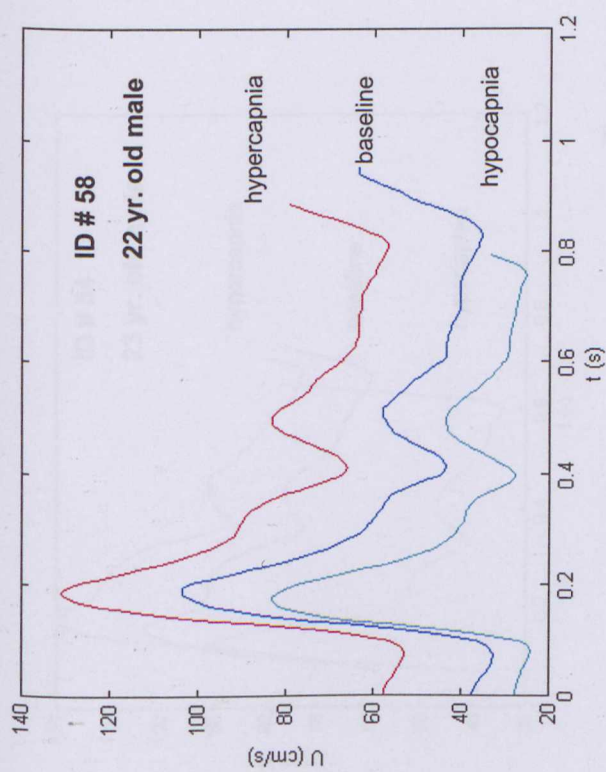


Figure 4.1 Doppler waveform shape changes during vasomotor testing. Male subjects in ascending age (next 5 pages).

Males

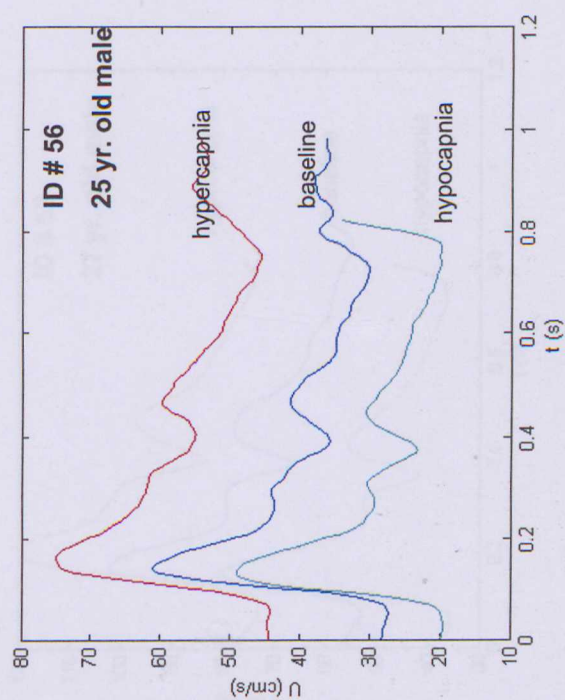
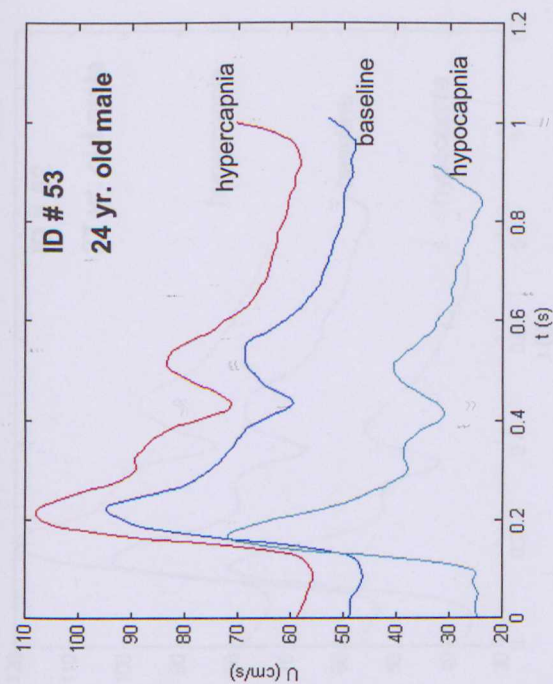
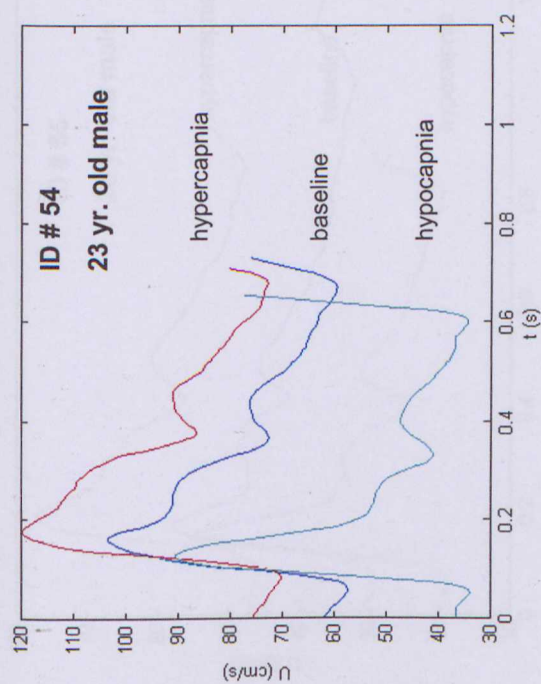


Figure 4.1 Continued.

Males

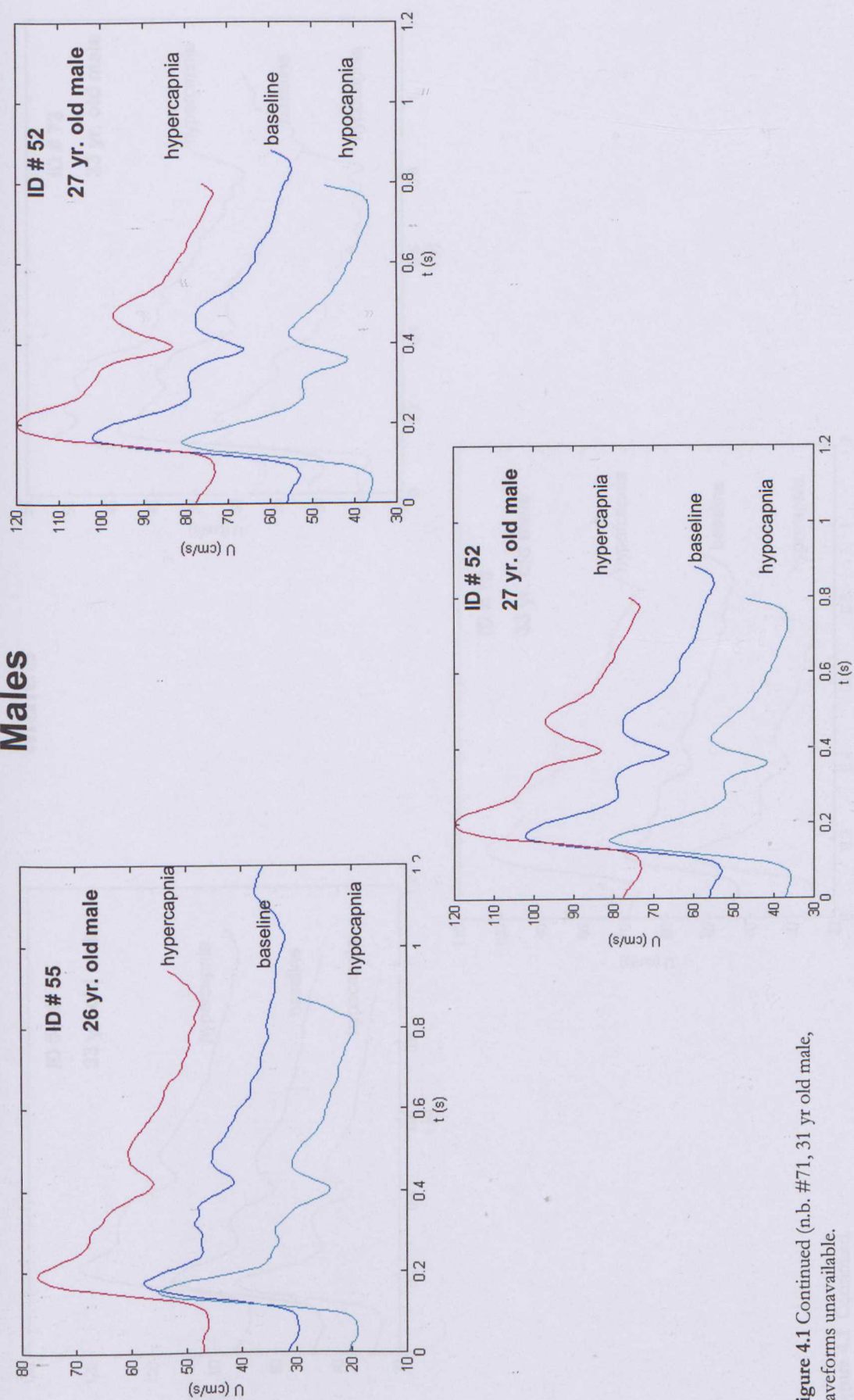


Figure 4.1 Continued (n.b. #71, 31 yr old male, waveforms unavailable).

Males

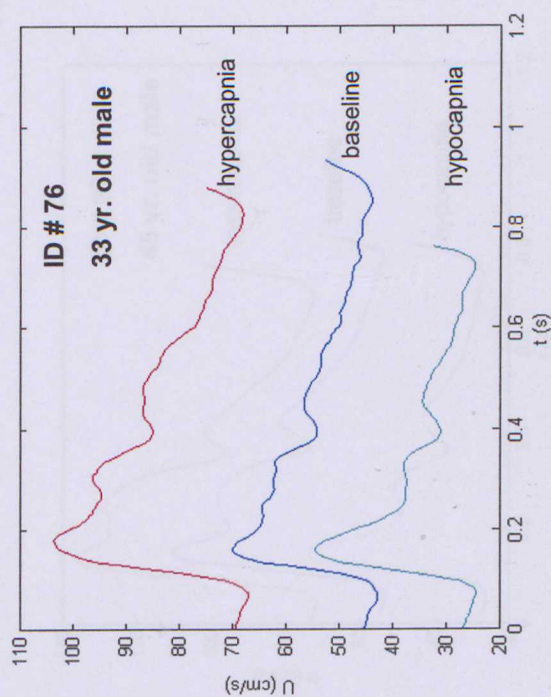
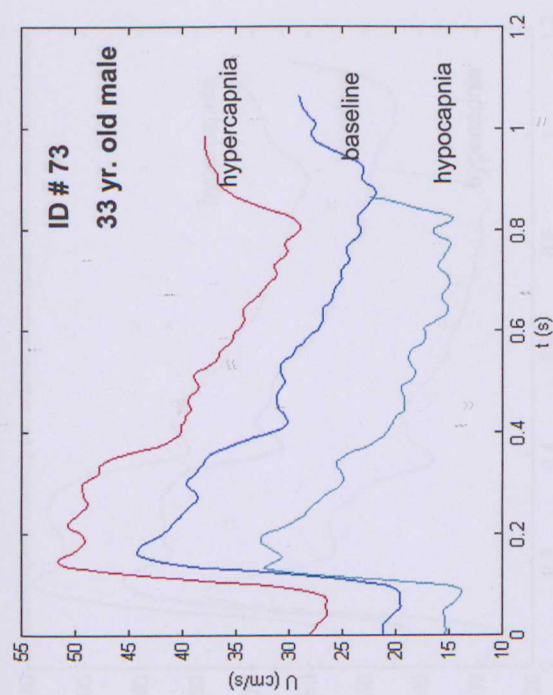
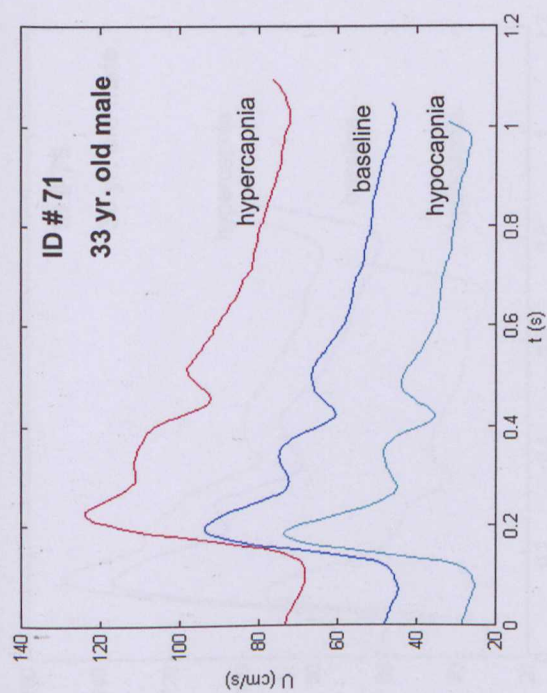


Figure 4.1 Continued.

Males

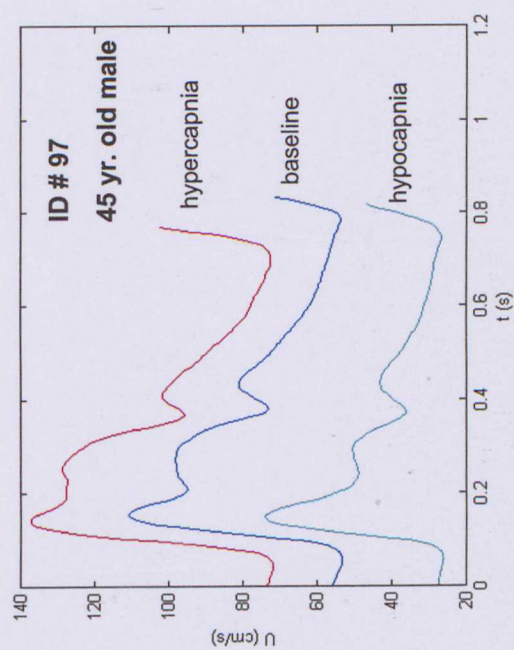
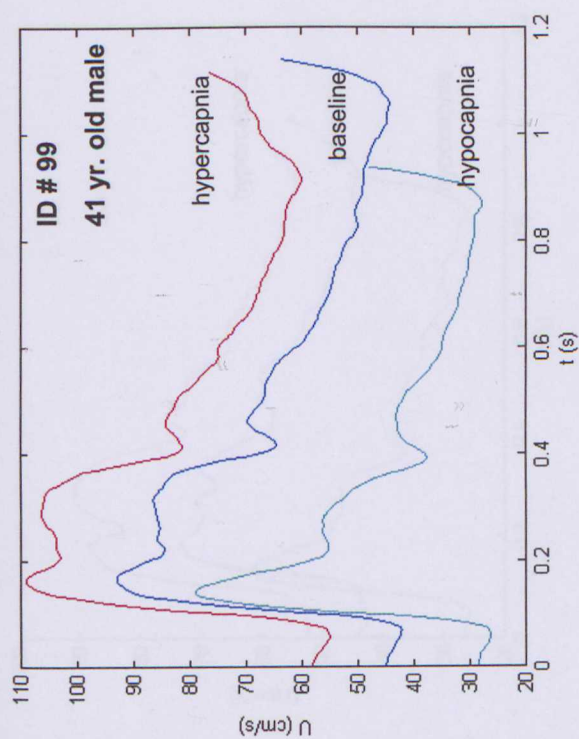
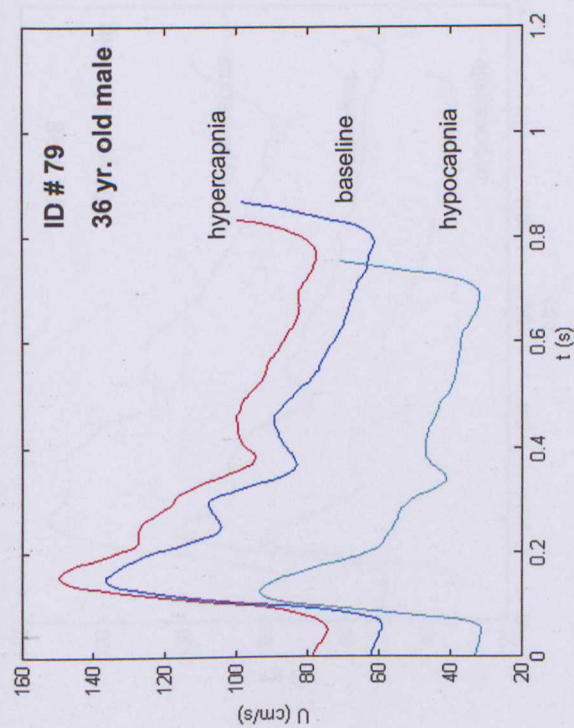


Figure 4.1 Continued.

Males

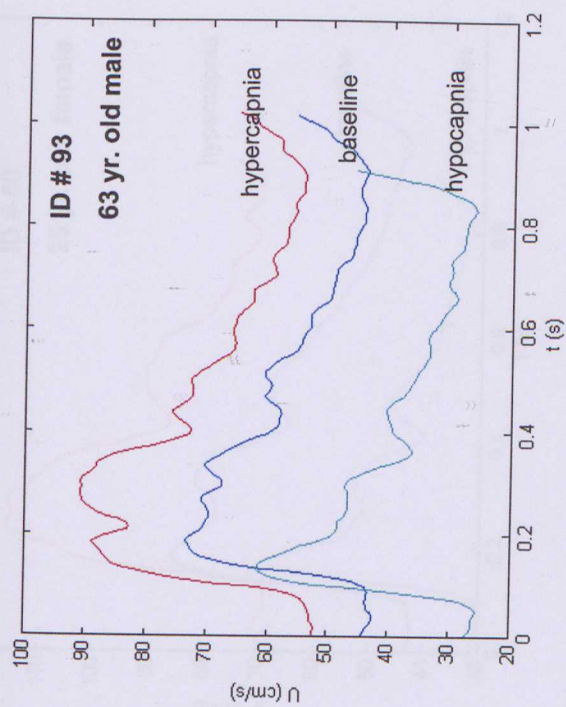
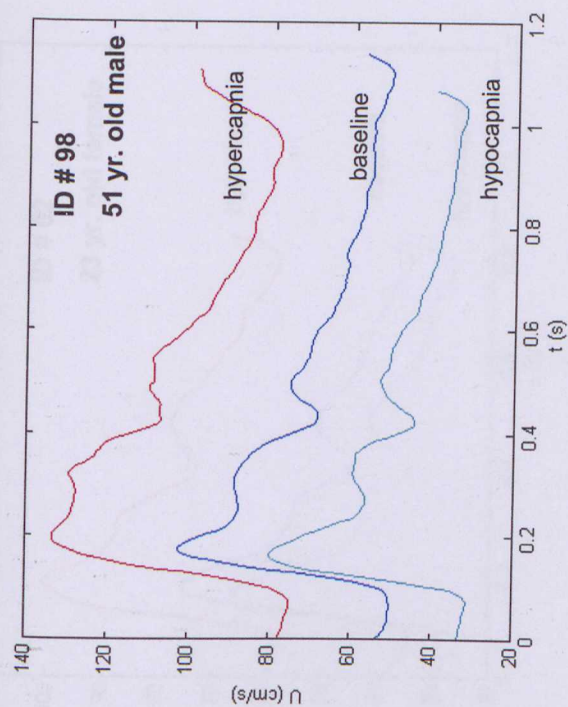


Figure 4.1 Continued.

Females

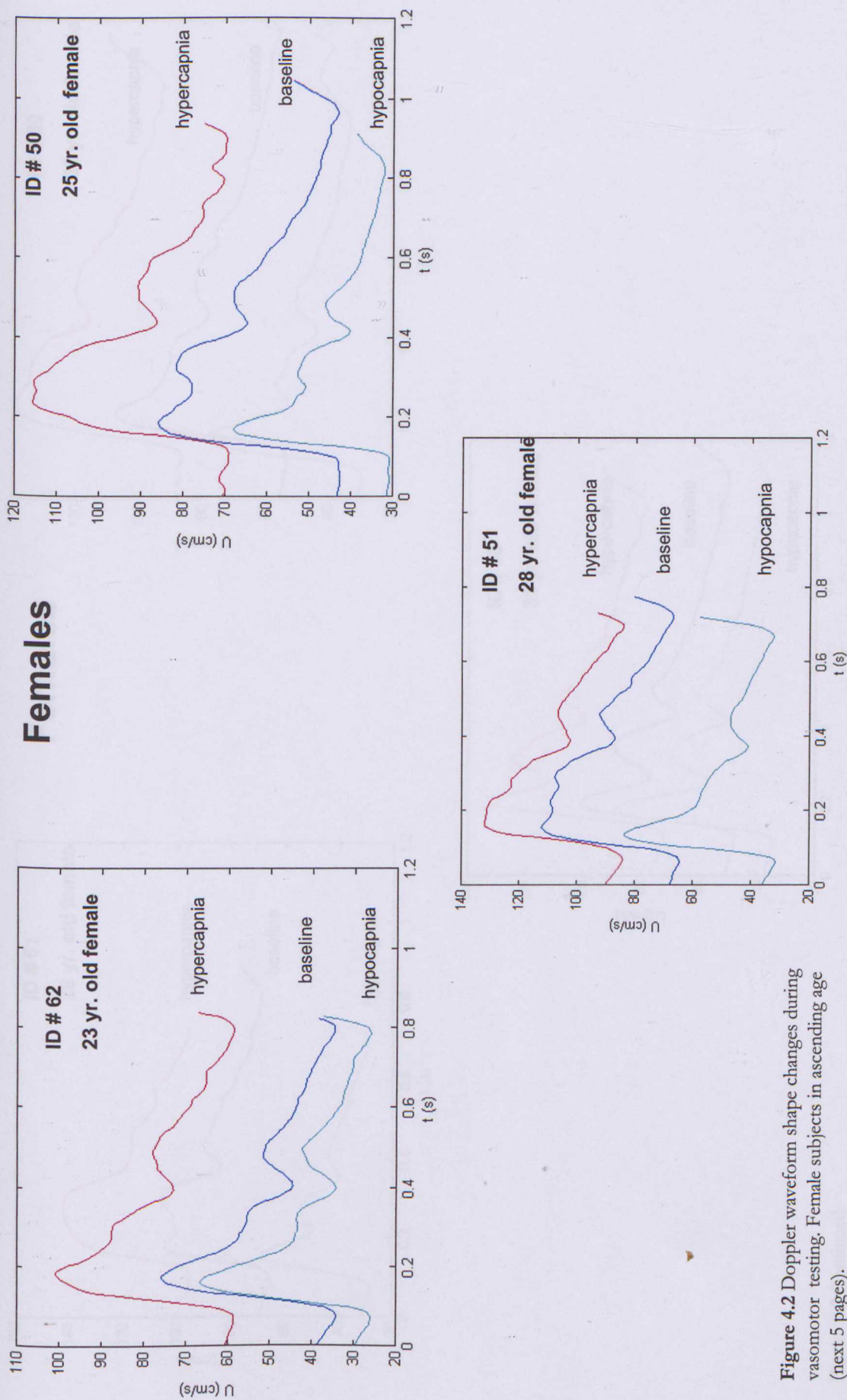


Figure 4.2 Doppler waveform shape changes during vasomotor testing. Female subjects in ascending age (next 5 pages).

Females

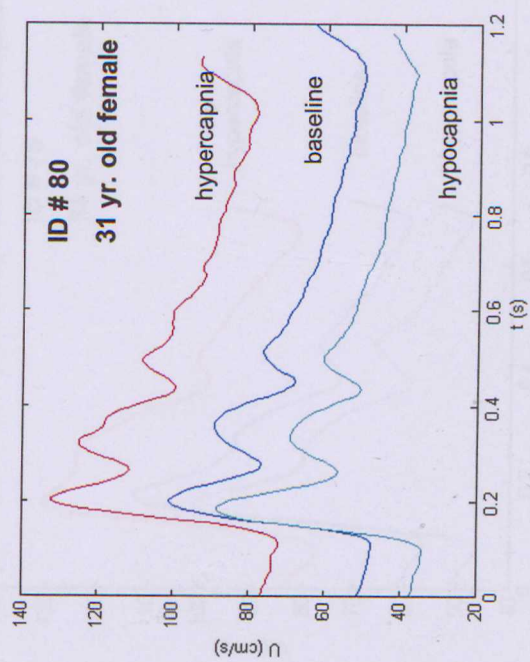
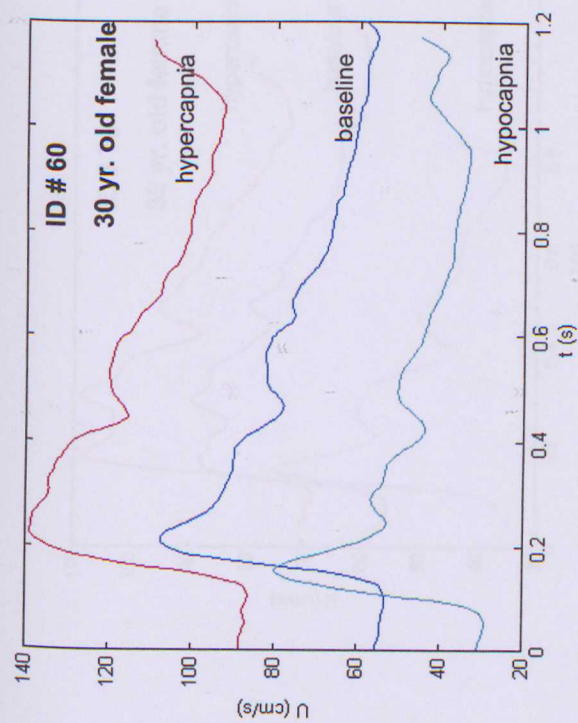
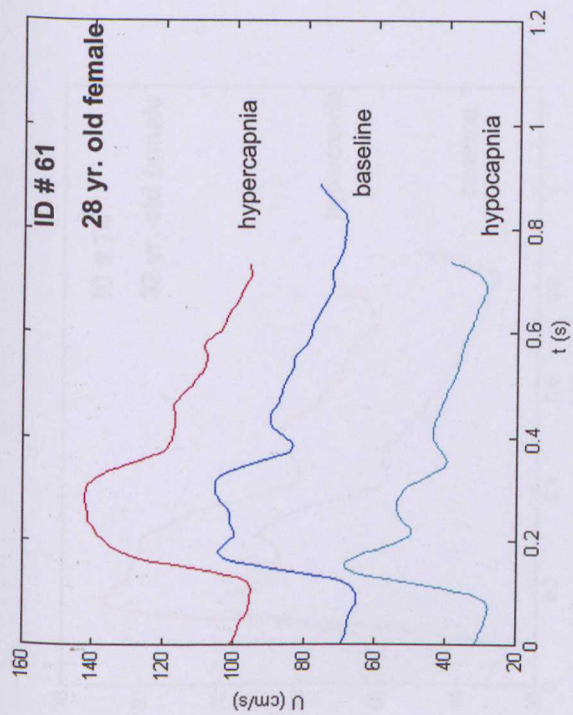


Figure 4.2 Continued.

Females

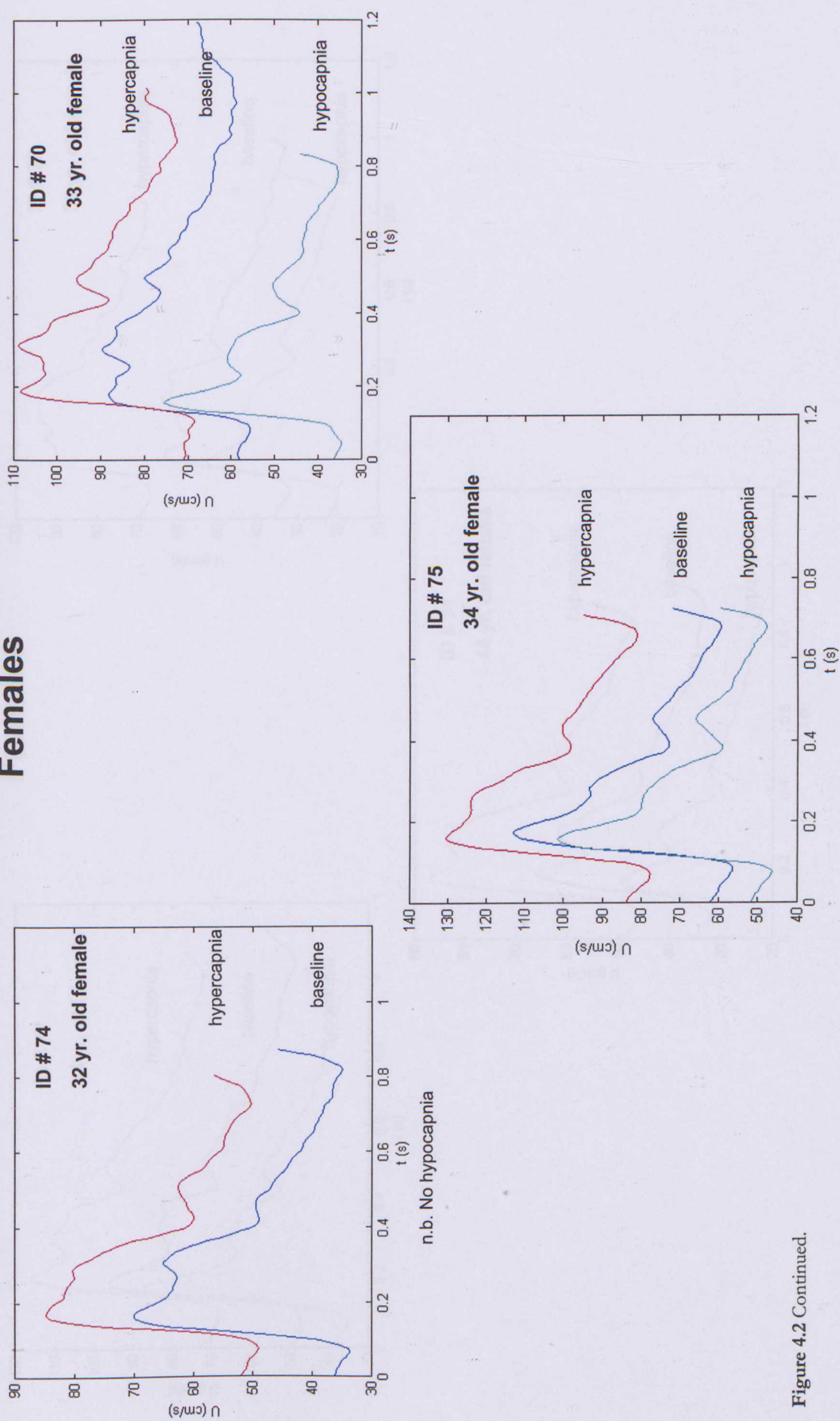


Figure 4.2 Continued.

Females

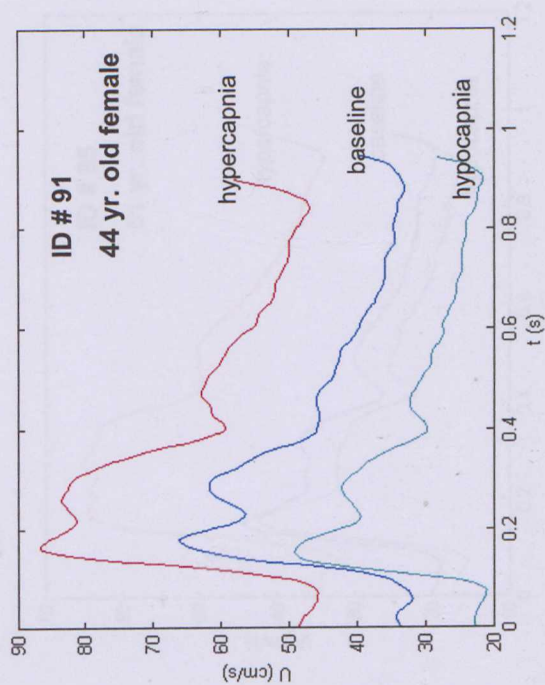
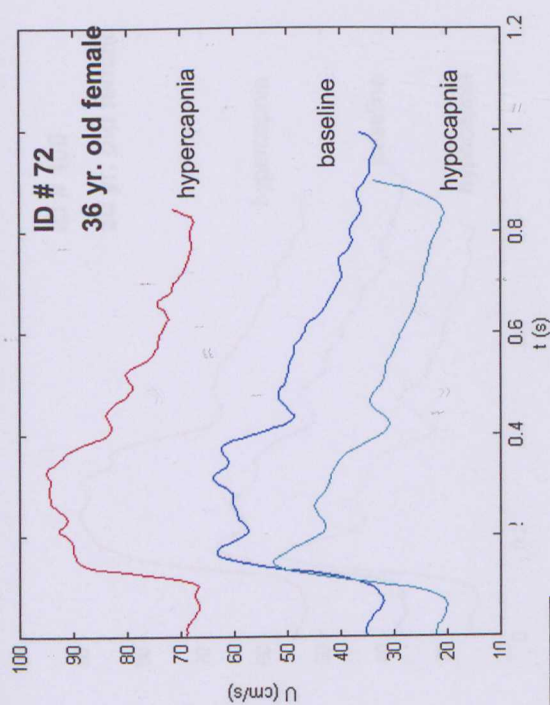
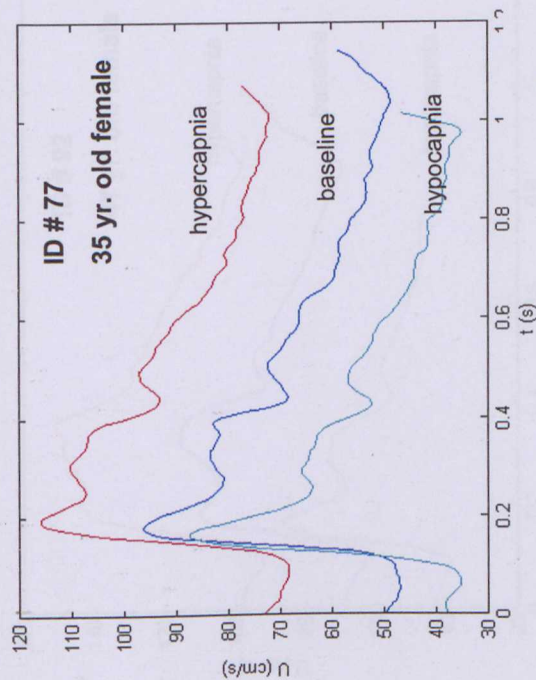


Figure 4.2 Continued.

Females

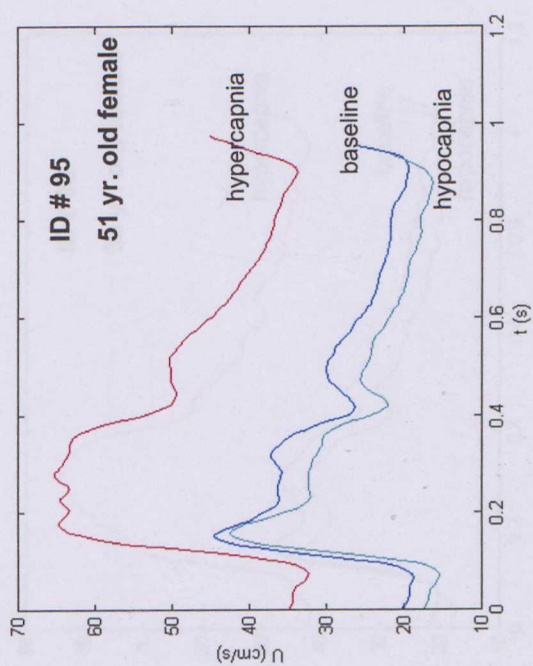
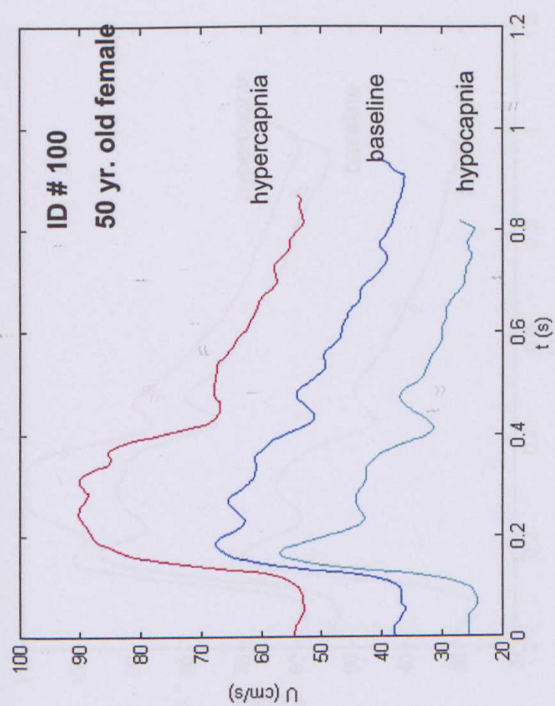
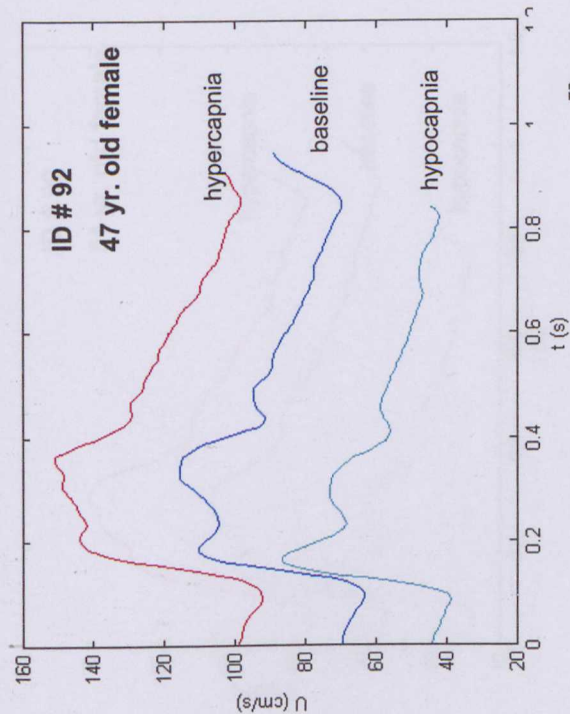


Figure 4.2 Continued.

Females

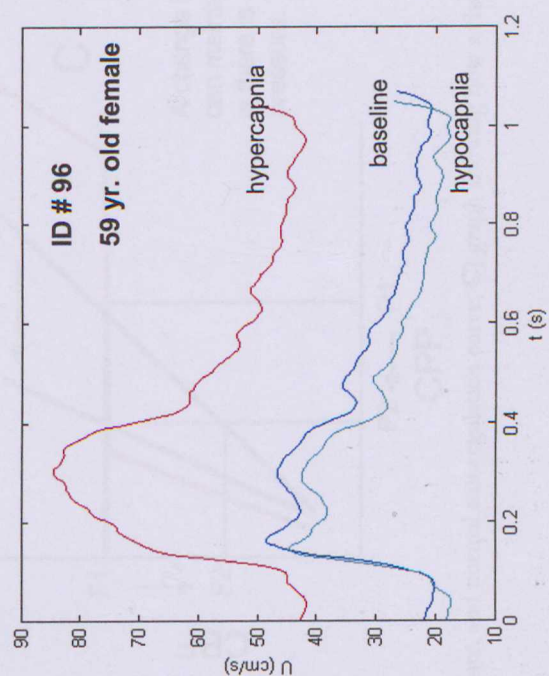
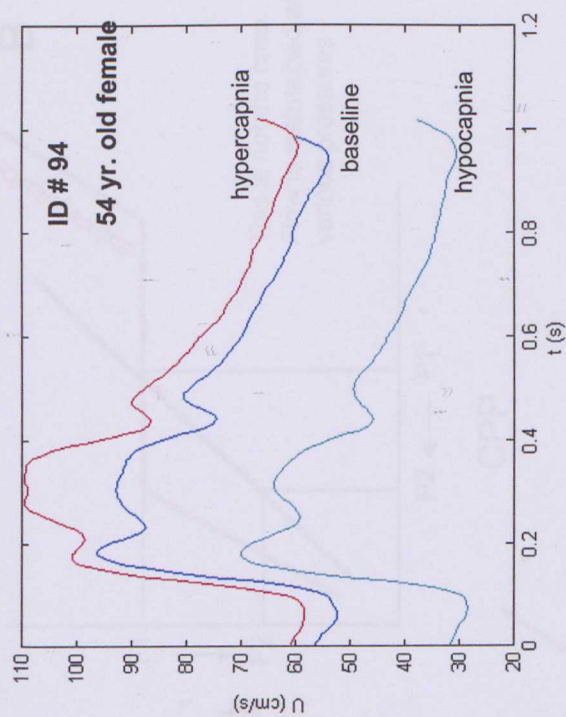
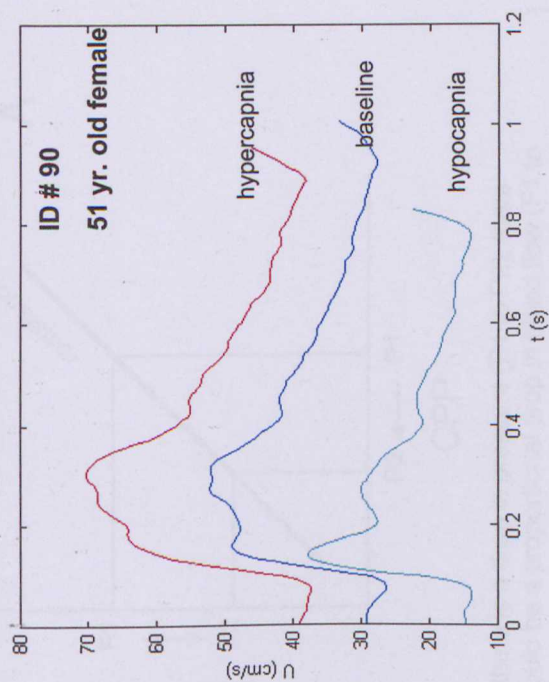
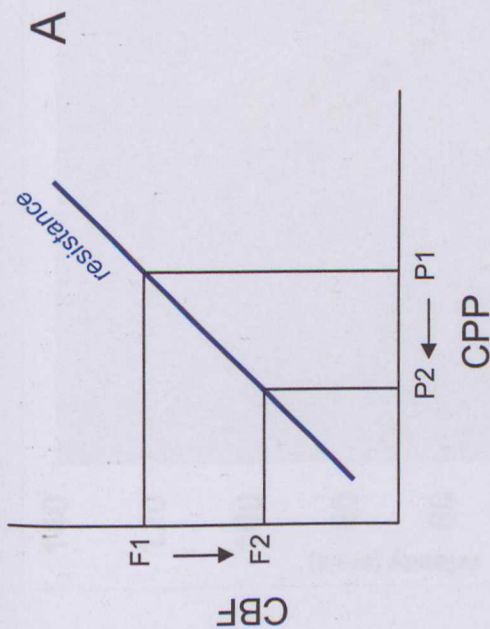
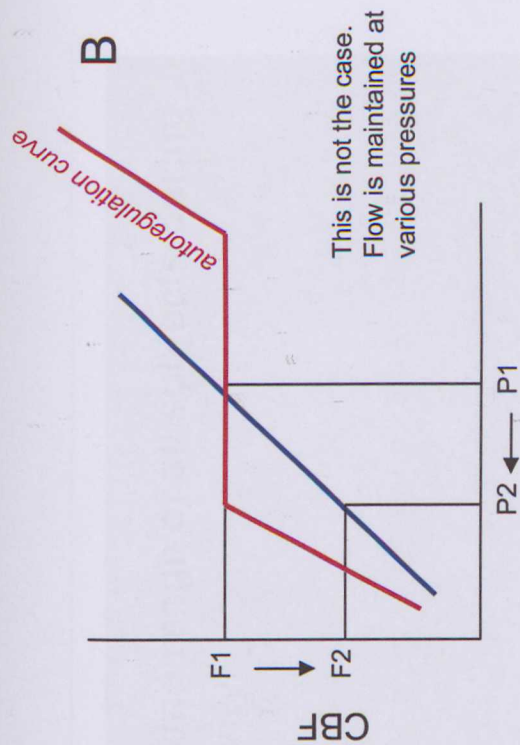


Figure 4.2 Continued.



If there is a drop in pressure (P_1 to P_2), there would be a proportional drop in blood flow (F_1 to F_2), if resistance remained constant.



CPP

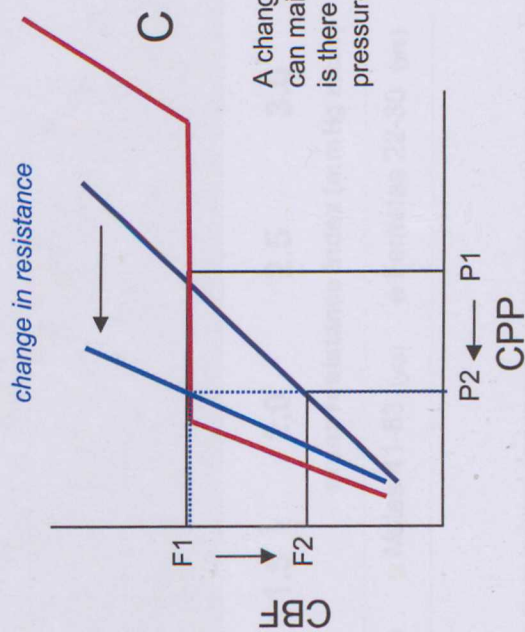


Figure 4.3 A) Flow and pressure graph, B) flow, pressure, and normal autoregulation curve, C) graph showing how a change in resistance can be used to maintain flow during drops in pressure. (Redrawn from Aaslid [1992])

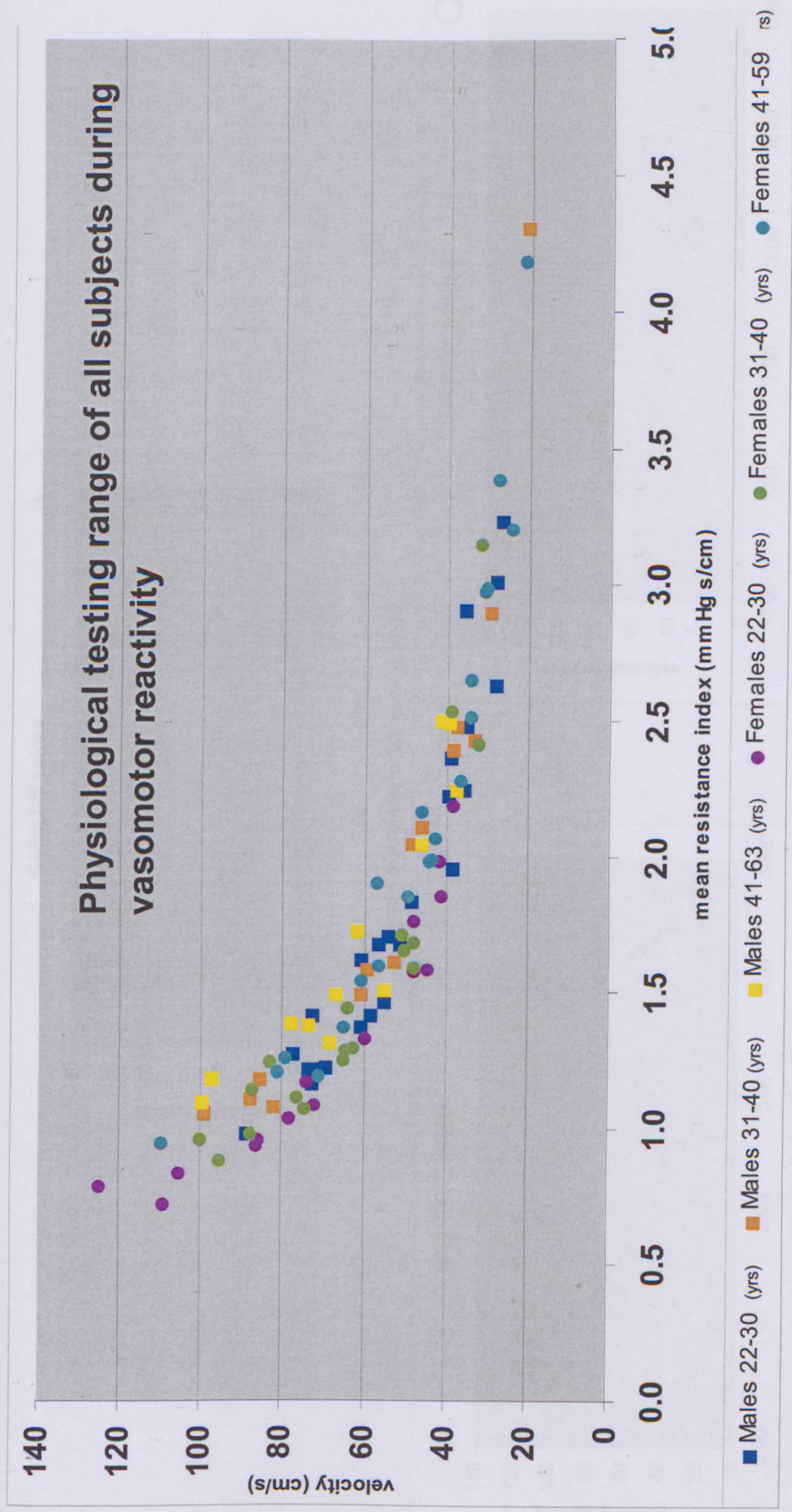


Figure 4.4 This graph represents the physiological testing range induced during our vasoreactivity testing protocol. Each subject is plotted at Baseline, and during Hypocapnia and Hypercapnia. Note that the subjects have been colour-coded by gender and age range to provide the reader with additional information regarding the affect of age on velocity and resistance during vasoreactivity testing.

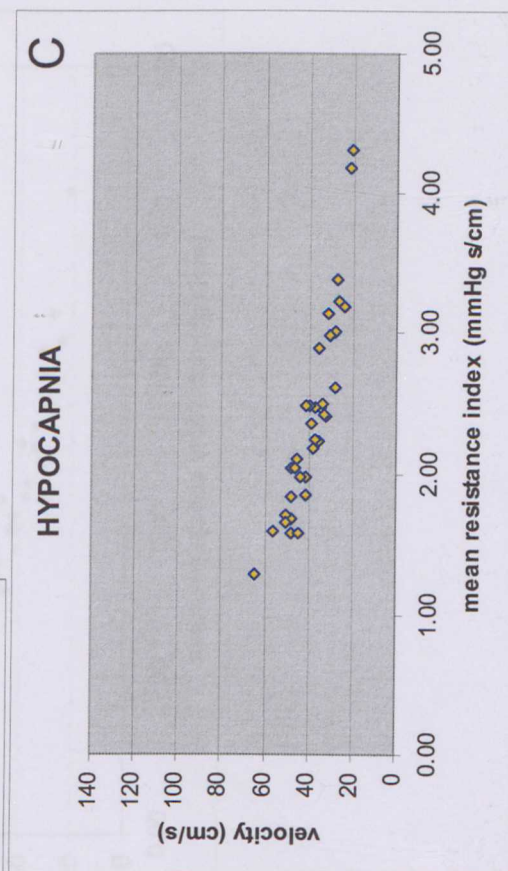
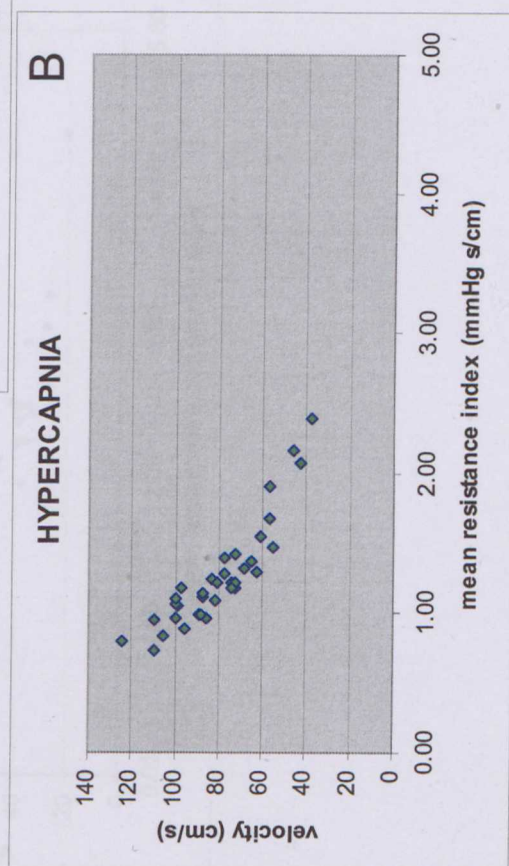
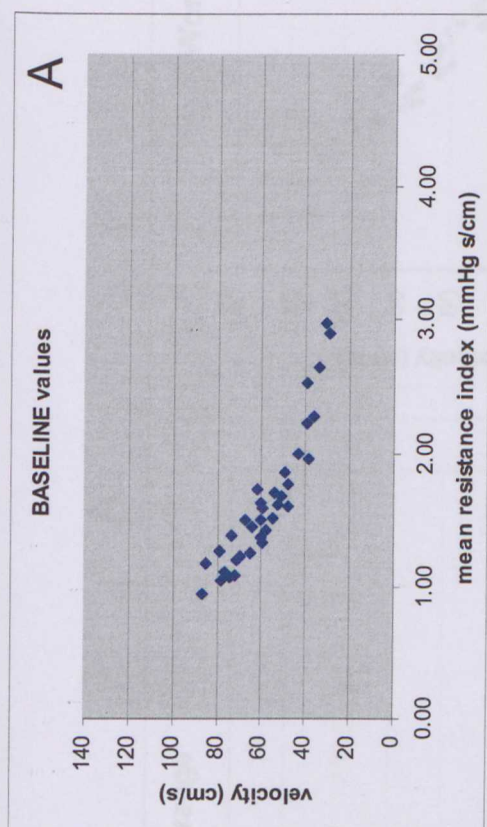
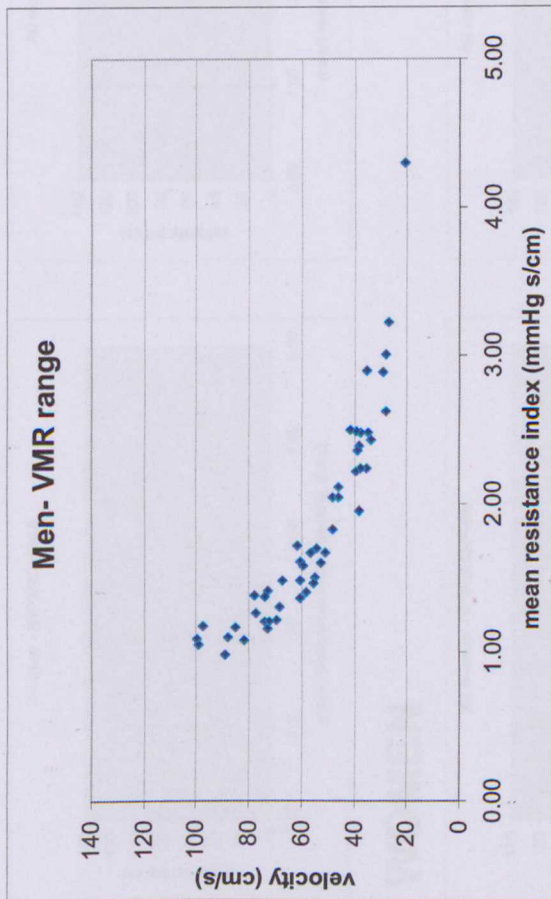
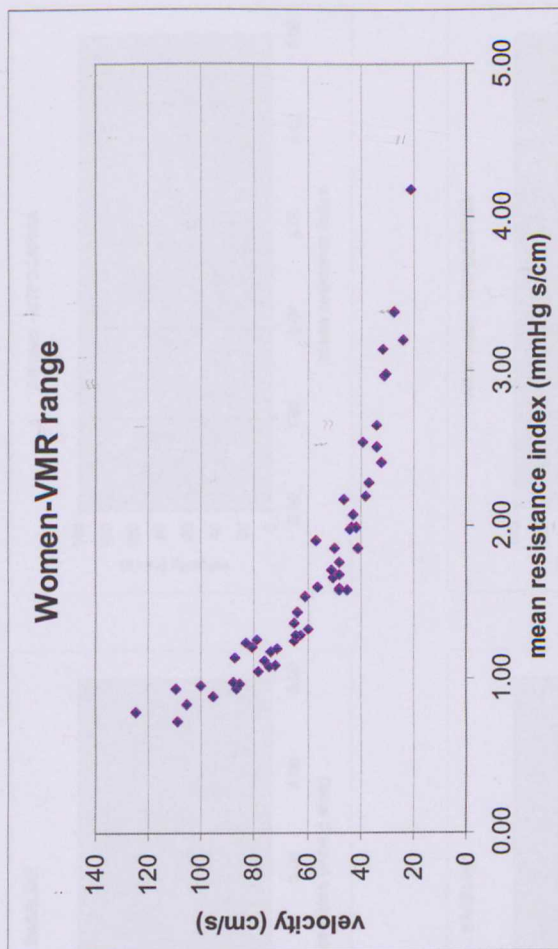


Figure 4.5 (All subjects) These graphs represent the physiological testing range of our subjects at each test: **A)** Baseline, **B)** Hypercapnia and **C)** Hypocapnia. Note that all subjects shift to the left during Hypercapnia, indicating a decrease in the mean resistance index during vasodilatation. Whereas, during Hypocapnia, there is an overall shift towards the right, and an increase in mean resistance index during vasoconstriction.

A

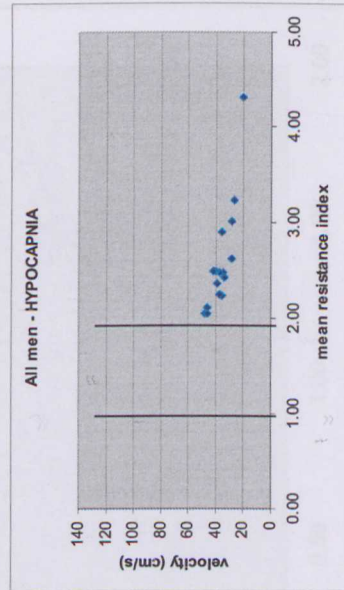
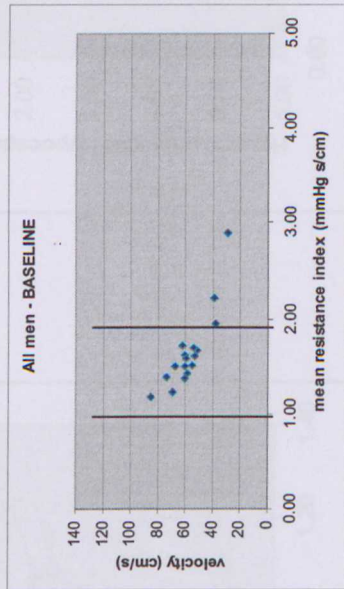
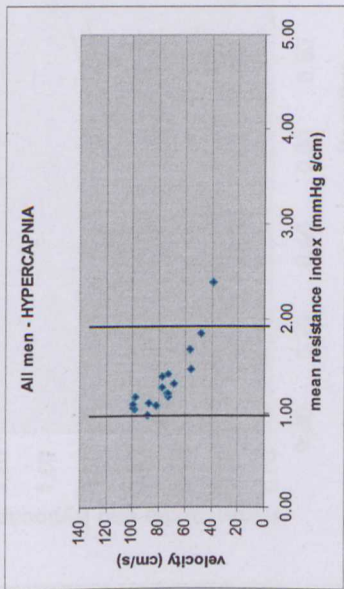


B

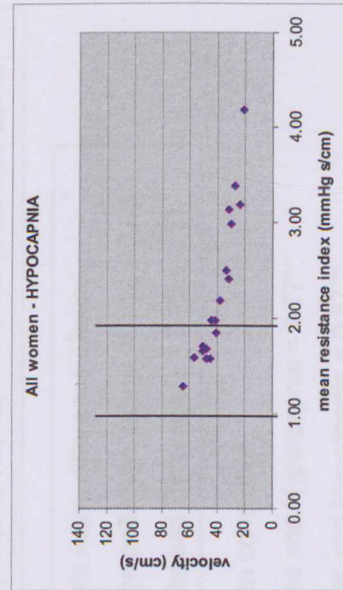
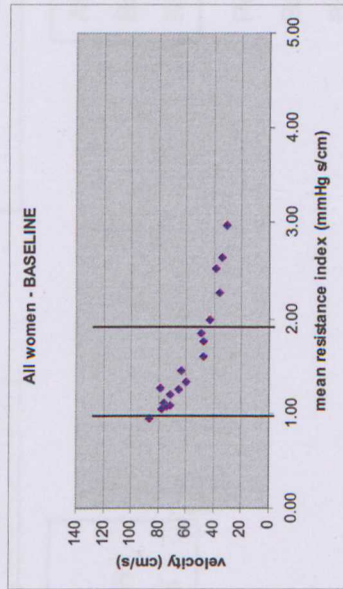
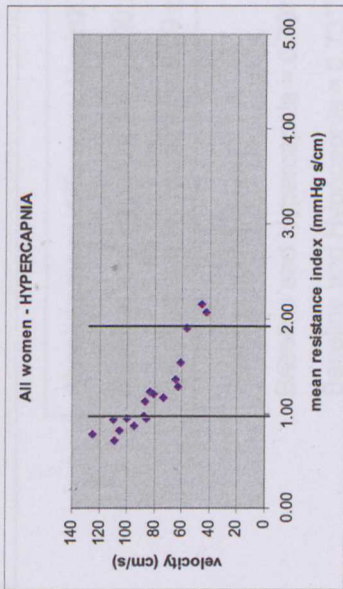


Figures 4.6 A) and B) depict the difference of the VMR testing range (Baseline, Hypercapnia, and Hypocapnia) between men and women. Women appear to have a more extensive range of vasodilatation and vasoconstriction during testing than men.

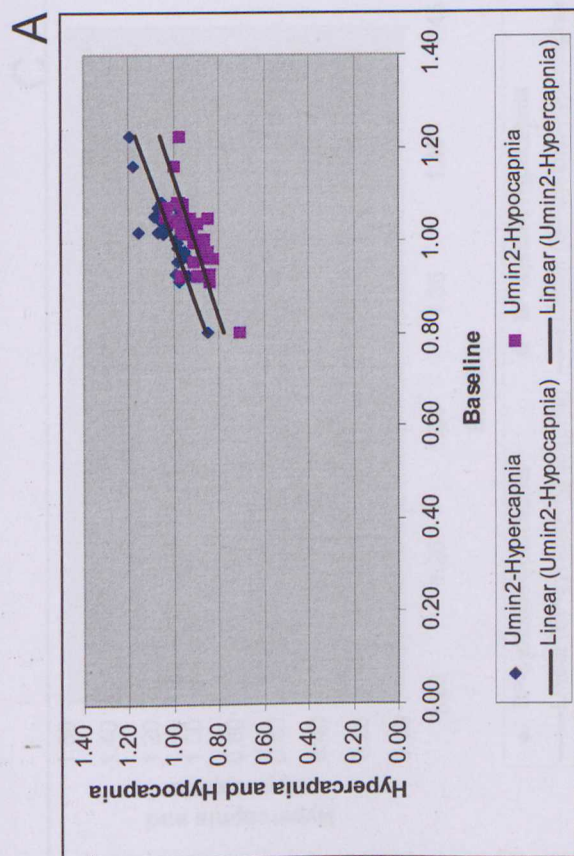
MEN



WOMEN



Figures 4.7 A) Men, and B) Women, show all subjects by gender during vasomotor reactivity testing. Vertical black lines have been arbitrary placed at approximately the 1.00 and 2.00 mean resistance markers, for improved visual clarity of the differences between men and women.



Absolute mean difference: **Umin2'**

Baseline and Hypercapnia = 0.00 ± 0.05

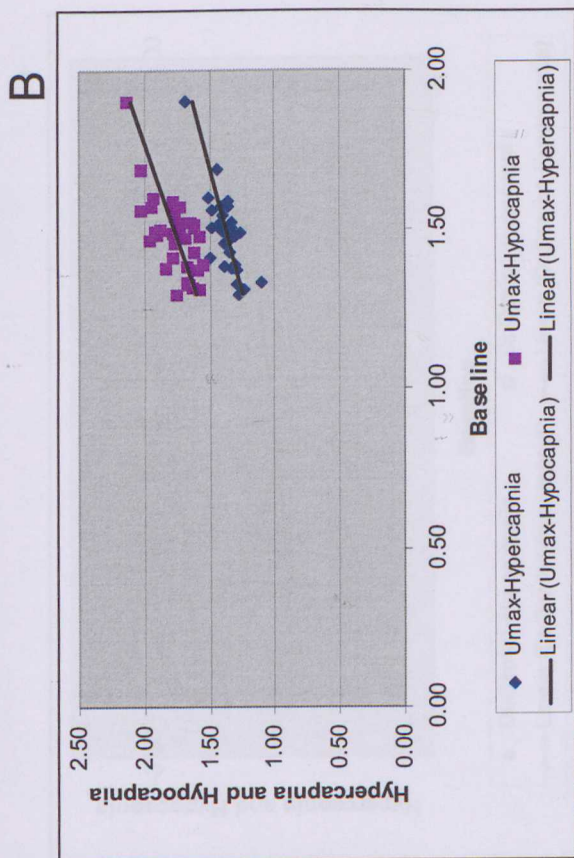
Baseline and Hypocapnia = 0.09 ± 0.05

Pearson correlation:

Baseline and Hypercapnia = 0.79^{**}

Baseline and Hypocapnia = 0.73^{**}

(** $p < .01$)



Absolute mean difference: **Umax'**

Baseline and Hypercapnia = 0.12 ± 0.08

Baseline and Hypocapnia = 0.28 ± 0.11

Pearson correlation:

Baseline and Hypercapnia = 0.77^{**}

Baseline and Hypocapnia = 0.67^{**}

(** $p < .01$)

Figure 4.8 Plot of non-dimensional data (Baseline versus Hypercapnia and Hypocapnia) for Umin2' (A) and Umax' (B), with their corresponding absolute mean difference values, and Pearson correlation.

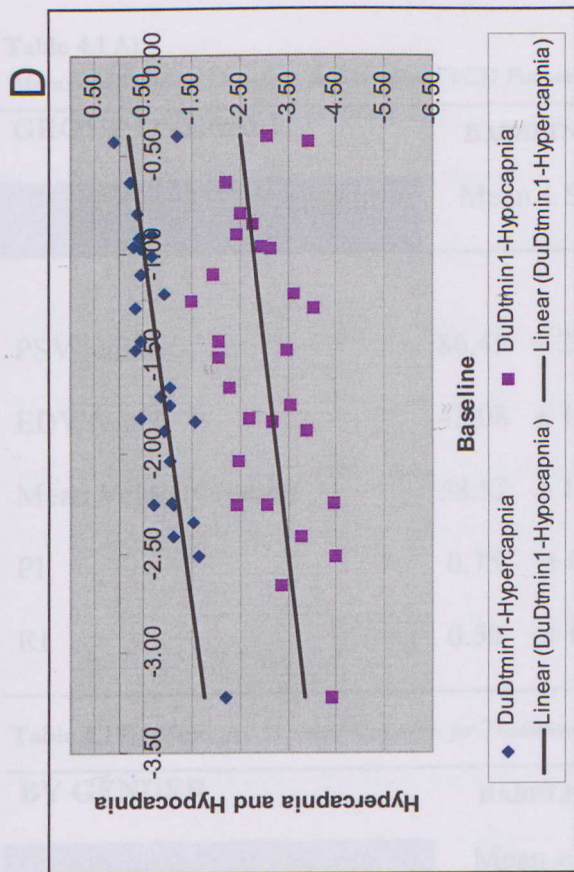
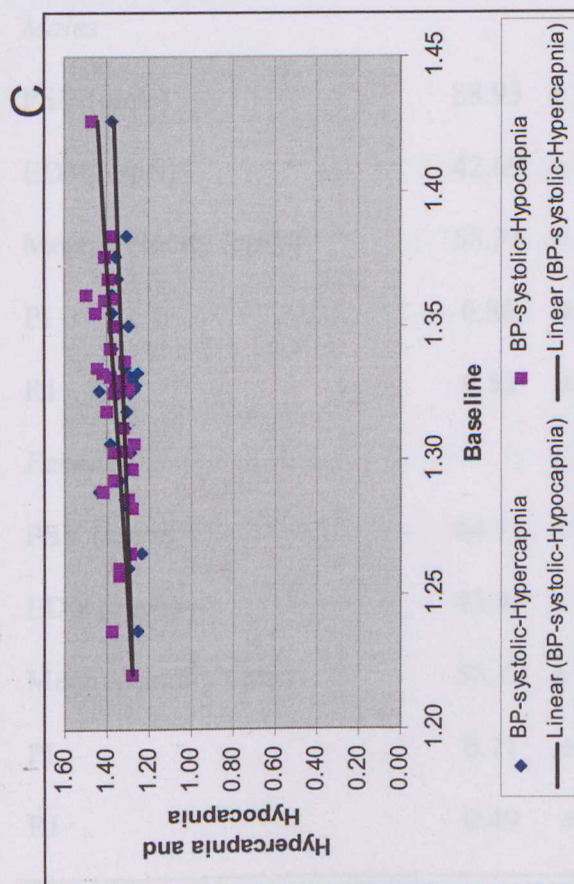


Figure 4.8 cont. Plot of non-dimensional data (Baseline versus Hypercapnia and Hypocapnia) for Blood pressure-systolic' (C) and DuDtm1' (D), with their corresponding absolute mean difference values, and Pearson correlation.

Table 4.1 A)
Means and Standard Deviations for Traditional TCD Parameters for each Test

GROUP OVERALL	BASELINE	HYPERCAPNIA	HYPOCAPNIA
Traditional TCD Parameters	Mean ± SD	Mean ± SD	Mean ± SD
PSV (cm/s)	86.45 ± 22.55	108.07 ± 25.45	69.87 ± 16.33
EDV (cm/s)	43.08 ± 12.69	61.66 ± 16.63	27.08 ± 7.29
Mean Velocity (cm/s)	58.52 ± 15.81	80.36 ± 20.29	39.03 ± 10.19
PI	0.75 ± 0.15	0.59 ± 0.12	1.09 ± 0.17
RI	0.50 ± 0.06	0.43 ± 0.06	0.61 ± 0.05

Table 4.1 B) *Means and Standard Deviations for Traditional TCD Parameters for each Test by Gender*

BY GENDER	BASELINE	HYPERCAPNIA	HYPOCAPNIA
Traditional TCD Parameters	Mean ± SD	Mean ± SD	Mean ± SD

Males

PSV (cm/s)	88.93 ± 22.33	108.04 ± 25.65	71.74 ± 13.77
EDV (cm/s)	42.69 ± 10.68	59.08 ± 13.33	26.17 ± 5.44
Mean Velocity (cm/s)	58.31 ± 14.08	78.56 ± 17.36	37.58 ± 8.57
PI	0.80 ± 0.17	0.63 ± 0.13	1.18 ± 0.18
RI	0.52 ± 0.06	0.45 ± 0.06	0.63 ± 0.05

Females

PSV (cm/s)	84.11 ± 23.14	108.11 ± 26.04	68.11 ± 18.68
EDV (cm/s)	43.45 ± 14.65	64.09 ± 19.33	27.94 ± 8.78
Mean Velocity (cm/s)	58.72 ± 17.71	82.06 ± 23.09	40.39 ± 11.59
PI	0.71 ± 0.11	0.56 ± 0.10	0.99 ± 0.10
RI	0.49 ± 0.05	0.42 ± 0.05	0.59 ± 0.03

Table 4.2 A)

Means and Standard Deviations for Velocity Minima Parameters for each Test

GROUP OVERALL	BASELINE	HYPERCAPNIA	HYPOCAPNIA
Velocity Minima	Mean ± SD	Mean ± SD	Mean ± SD
Umin (cm/s)	43.08 ± 12.69	61.66 ± 16.63	27.08 ± 7.29
Umin 1 (cm/s)	72.62 ± 19.74	98.69 ± 24.48	47.43 ± 11.91
Umin 2 (cm/s)	59.42 ± 16.30	80.76 ± 21.28	36.90 ± 9.82

Table 4.2 B)

Means and Standard Deviations for Velocity Minima for each Test by Gender

BY GENDER	BASELINE	HYPERCAPNIA	HYPOCPANIA
Velocity Minima	Mean ± SD	Mean ± SD	Mean ± SD

Males

Umin (cm/s)	42.69 ± 10.68	59.08 ± 13.33	26.17 ± 5.44
Umin 1 (cm/s)	70.62 ± 18.53	94.61 ± 23.33	43.91 ± 9.19
Umin 2 (cm/s)	57.80 ± 14.29	76.34 ± 17.62	34.24 ± 7.33

Females

Umin (cm/s)	43.45 ± 14.65	64.09 ± 19.33	27.94 ± 8.78
Umin 1 (cm/s)	74.51 ± 21.18	102.78 ± 25.65	50.74 ± 13.45
Umin 2 (cm/s)	60.96 ± 18.28	84.93 ± 24.02	39.41 ± 11.35

Table 4.3 A)
Means and Standard Deviations for Velocity Maxima for each Test

GROUP OVERALL	BASELINE	HYPERCAPNIA	HYPOCAPNIA
Velocity Maxima	Mean ± SD	Mean ± SD	Mean ± SD
Umax (cm/s)	86.45 ± 22.55	108.07 ± 25.45	69.87 ± 16.33
Umax 1 (cm/s)	75.08 ± 20.74	99.32 ± 24.99	49.50 ± 12.76
Umaxdias (cm/s)	63.91 ± 17.76	85.82 ± 21.86	43.16 ± 10.59

Table 4.3 B)
Means and Standard Deviations for Velocity Maxima for each Test by Gender

BY GENDER	BASELINE	HYPERCAPNIA	HYPOCAPNIA
Velocity Maxima	Mean ± SD	Mean ± SD	Mean ± SD

Males

Umax (cm/s)	88.93 ± 22.33	108.04 ± 25.65	71.74 ± 13.77
Umax 1 (cm/s)	71.87 ± 19.24	92.67 ± 22.39	45.08 ± 9.71
Umaxdias (cm/s)	63.25 ± 15.86	82.00 ± 18.69	42.02 ± 8.12

Females

Umax (cm/s)	84.11 ± 23.14	108.11 ± 26.04	68.11 ± 18.68
Umax 1 (cm/s)	78.12 ± 22.17	105.97 ± 26.37	53.66 ± 14.12
Umaxdias (cm/s)	64.53 ± 19.84	89.63 ± 24.64	44.23 ± 12.65

Table 4.4 A)

Means and Standard Deviations for Acceleration/Deceleration for each Test

GROUP OVERALL	BASELINE	HYPERCAPNIA	HYPOCAPNIA
Acceleration/Deceleration	Mean ± SD	Mean ± SD	Mean ± SD
Dudtmax (cm/s ²)	881.50 ± 240.83	882.01 ± 224.20	943.77 ± 240.68
Dudtmin 1 (cm/s ²)	-257.13 ± 135.90	-189.68 ± 135.79	-379.12 ± 136.09
Dudtmin 2 (cm/s ²)	-283.76 ± 108.60	-310.62 ± 110.38	-231.03 ± 59.49

Table 4.4 B)

Means and Standard Deviations for Acceleration/Deceleration for each Test by Gender

BY GENDER	BASELINE	HYPERCAPNIA	HYPOCAPNIA
Acceleration/Deceleration	Mean ± SD	Mean ± SD	Mean ± SD
<i>Males</i>			
Dudtmax (cm/s ²)	924.35 ± 266.97	932.23 ± 271.03	1016.55 ± 247.00
Dudtmin 1 (cm/s ²)	-319.23 ± 135.53	-241.06 ± 122.10	-424.40 ± 128.00
Dudtmin 2 (cm/s ²)	-274.80 ± 115.20	-313.44 ± 136.61	-232.58 ± 67.65
<i>Females</i>			
Dudtmax (cm/s ²)	841.03 ± 212.95	834.74 ± 163.62	875.26 ± 219.93
Dudtmin 1 (cm/s ²)	-198.48 ± 110.23	-138.30 ± 132.53	-336.50 ± 133.04
Dudtmin 2 (cm/s ²)	-292.23 ± 104.60	-307.96 ± 82.80	-229.57 ± 52.76

Table 4.5 A)

Means and Standard Deviations for Miscellaneous for each Test

GROUP OVERALL	BASELINE		HYPERCAPNIA		HYPOCAPNIA	
Miscellaneous	Mean ± SD		Mean ± SD		Mean ± SD	
Tau	1.04	± 0.24	1.18	± 0.23	0.78	± 0.17
Upulse (cm/s)	43.36	± 12.46	46.53	± 12.17	42.80	± 10.43
Mean blood pressure (mmHg)	88.24	± 7.92	94.46	± 9.23	87.06	± 8.24
Heart rate (bpm)	61.46	± 8.97	65.67	± 9.41	69.10	± 9.42
ETCO ₂ (mmHg)	46.60	± 5.05	58.29	± 3.94	32.89	± 4.24

Table 4.5 B)

Means and Standard Deviations for Miscellaneous for each Test by Gender

BY GENDER	BASELINE		HYPERCAPNIA		HYPOCAPNIA	
Miscellaneous	Mean ± SD		Mean ± SD		Mean ± SD	
<i>Males</i>						
Tau	1.02	± 0.27	1.13	± 0.26	0.75	± 0.17
Upulse (cm/s)	46.24	± 14.33	49.13	± 15.03	45.57	± 9.96
Mean BP (mmHg)	90.41	± 8.60	96.39	± 9.74	90.18	± 8.38
Heart rate (bpm)	61.68	± 8.78	65.40	± 9.10	70.38	± 8.80
ETCO ₂ (mmHg)	48.59	± 4.69	60.12	± 2.69	34.29	± 3.41
<i>Females</i>						
Tau	1.07	± 0.22	1.22	± 0.19	0.81	± 0.18
Upulse (cm/s)	40.63	± 10.06	44.07	± 8.44	40.19	± 10.47
Mean BP (mmHg)	86.19	± 6.83	92.63	± 8.60	84.11	± 7.12
Heart rate (bpm)	61.26	± 9.39	65.92	± 9.97	67.95	± 10.04
ETCO ₂ (mmHg)	44.72	± 4.76	56.56	± 4.20	31.56	± 4.60

Table 4.6 A)
Means and Standard Deviations for Time Measures for each Test

GROUP OVERALL	BASELINE	HYPERCAPNIA	HYPOCAPNIA
Time Measurements	Mean ± SD	Mean ± SD	Mean ± SD
Tmin (s)	0.07 ± 0.02	0.08 ± 0.02	0.07 ± 0.01
Rise Time (s)	0.11 ± 0.02	0.12 ± 0.04	0.09 ± 0.01
Tmin 2 (s)	0.42 ± 0.02	0.43 ± 0.06	0.40 ± 0.03

Table 4.6 B)
Means and Standard Deviations for Time Measures for each Test by Gender

	BASELINE	HYPERCAPNIA	HYPOCAPNIA
Time Measurements	Mean ± SD	Mean ± SD	Mean ± SD
<i>Males</i>			
Tmin (s)	0.07 ± 0.01	0.07 ± 0.01	0.06 ± 0.01
Rise Time (s)	0.11 ± 0.02	0.12 ± 0.05	0.09 ± 0.01
Tmin 2 (s)	0.41 ± 0.02	0.41 ± 0.02	0.38 ± 0.03
<i>Females</i>			
Tmin (s)	0.07 ± 0.02	0.08 ± 0.02	0.07 ± 0.01
Rise Time (s)	0.11 ± 0.03	0.12 ± 0.04	0.09 ± 0.01
Tmin 2 (s)	0.43 ± 0.02	0.45 ± 0.07	0.41 ± 0.02

Table 4.7 A)

Means and Standard Deviations for Indices for each Test

GROUP OVERALL	BASELINE	HYPERCAPNIA	HYPOCAPNIA
Indices	Mean ± SD	Mean ± SD	Mean ± SD
Shape Index 1	0.70 ± 0.16	0.81 ± 0.15	0.49 ± 0.14
Shape Index 2	0.39 ± 0.12	0.42 ± 0.13	0.24 ± 0.08
Velocity Rise Index	0.47 ± 0.35	0.28 ± 0.41	0.73 ± 0.24
Mean Resistance Index	1.63 ± 0.53	1.26 ± 0.38	2.39 ± 0.71

Table 4.7 B)

Means and Standard Deviations for Indices for each Test and Gender

BY GENDER	BASELINE	HYPERCAPNIA	HYPOCAPNIA
Indices	Mean ± SD	Mean ± SD	Mean ± SD
<i>Males</i>			
Shape Index 1	0.62 ± 0.16	0.73 ± 0.13	0.39 ± 0.10
Shape Index 2	0.34 ± 0.10	0.36 ± 0.11	0.18 ± 0.06
Velocity Rise Index	0.63 ± 0.25	0.54 ± 0.28	0.90 ± 0.15
Mean Resistance Index	1.64 ± 0.42	1.29 ± 0.33	2.51 ± 0.61
<i>Females</i>			
Shape Index 1	0.78 ± 0.12	0.89 ± 0.12	0.58 ± 0.10
Shape Index 2	0.44 ± 0.12	0.48 ± 0.12	0.29 ± 0.07
Velocity Rise Index	0.32 ± 0.38	0.03 ± 0.37	0.58 ± 0.20
Mean Resistance Index	1.63 ± 0.62	1.23 ± 0.43	2.28 ± 0.80

Pearson Correlation Coefficients for Age

Parameters Positively Correlated with Age	BASELINE	HYPERCAPNIA	HYPOCAPNIA
Shape Index 1	0.61**	0.63**	0.73**
Shape Index 2	0.58**	0.51**	0.66**
DuDtmin1	0.41*	0.41*	0.50**
Mean blood pressure	NC	0.41*	NC
Mean Resistance Index	NC	0.37*	NC
Parameters Negatively Correlated with Age			
Velocity Rise Index	-0.51**	-0.57**	NC

** $p < .01$, * $p < .05$, NC not correlated with age

Table 4.8 Shows the statistically significant results (Pearson correlation coefficient) for the relationship of age to all parameters during each test: BASELINE, HYPERCAPNIA, and HYPOCAPNIA.

GROUP OVERALL

% Change from BASELINE

<i>per mmCO₂</i>	HYPERCAPNIA		HYPOCAPNIA	
Traditional TCD Parameters	Mean ± SD		Mean ± SD	
	PSV	1.06 ± 0.45	0.71	± 0.28
	EDV	1.80 ± 0.57	1.31	± 0.36
	Mean Velocity	1.58 ± 0.68	1.14	± 0.32
	PI	-0.86 ± 0.42	-1.62	± 0.69
	RI	-0.58 ± 0.27	-0.79	± 0.36

BY GENDER

% Change from BASELINE

<i>per mmCO₂</i>	HYPERCAPNIA		HYPOCAPNIA	
Traditional TCD Parameters	Mean ± SD		Mean ± SD	
<i>Males</i>				
PSV	1.07	± 0.52	0.73	± 0.30
EDV	1.80	± 0.48	1.38	± 0.36
Mean Velocity	1.55	± 0.53	1.21	± 0.31
PI	-0.85	± 0.25	-1.78	± 0.71
RI	-0.54	± 0.19	-0.83	± 0.38
<i>Females</i>				
PSV	1.06	± 0.39	0.68	± 0.26
EDV	1.80	± 0.65	1.24	± 0.35
Mean Velocity	1.60	± 0.80	1.07	± 0.32
PI	-0.87	± 0.54	-1.47	± 0.65
RI	-0.62	± 0.33	-0.76	± 0.34

Table 4.9 Means and standard deviations for the % change from BASELINE values per mmCO₂ during HYPERCAPNIA and HYPOCAPNIA for the group overall and by gender. (Traditional TCD Parameters)

GROUP OVERALL				
% Change from BASELINE				
per mmCO ₂	HYPERCAPNIA		HYPOCAPNIA	
Velocity Minima	Mean ± SD		Mean ± SD	
Umin	1.80	± 0.57	1.31	± 0.36
Umin 1	1.55	± 0.55	1.22	± 0.32
Umin 2	1.50	± 0.61	1.35	± 0.35
BY GENDER				
% Change from BASELINE				
per mmCO ₂	HYPERCAPNIA		HYPOCAPNIA	
Velocity Minima	Means ± SD		Means ± SD	
Males				
Umin	1.80	±0.48	1.38	± 0.36
Umin 1	1.62	±0.56	1.34	± 0.29
Umin 2	1.51	±0.48	1.45	± 0.32
Females				
Umin	1.80	±0.65	1.24	± 0.35
Umin 1	1.49	±0.55	1.10	± 0.30
Umin 2	1.50	±0.73	1.25	± 0.36

Table 4.10 Means and standard deviations for the % change from BASELINE values per mmCO₂ during HYPERCAPNIA and HYPOCAPNIA for the group overall and by gender. (Velocity Minima)

GROUP OVERALL				
% Change from BASELINE				
per mmCO ₂	HYPERCAPNIA		HYPOCAPNIA	
Velocity Maxima	Means ± SD		Means ± SD	
Umax	1.06	± 0.45	0.71	± 0.28
Umax 1	1.37	± 0.69	1.20	± 0.32
Umaxdias	1.42	± 0.81	1.14	± 0.38
BY GENDER				
% Change from BASELINE				
per mmCO ₂	HYPERCAPNIA		HYPOCAPNIA	
Velocity Maxima	Mean ± SD		Mean ± SD	
Males				
Umax	1.07	± 0.52	0.73	± 0.30
Umax 1	1.33	± 0.86	1.32	± 0.30
Umaxdias	1.40	± 0.56	1.17	± 0.40
Females				
Umax	1.06	± 0.39	0.68	± 0.26
Umax 1	1.40	± 0.50	1.08	± 0.30
Umaxdias	1.44	± 1.03	1.11	± 0.37

Table 4.11 Means and standard deviations for the % change from BASELINE values per mmCO₂ during HYPERCAPNIA and HYPOCAPNIA for the group overall and by gender. (Velocity Maxima)

GROUP OVERALL				
% Change from BASELINE				
per mmCO ₂	HYPERCAPNIA		HYPOCAPNIA	
Acceleration/Deceleration	Mean ± SD		Mean ± SD	
Dudtmax	0.12	± 0.58	-0.20	± 0.46
Dudtmin 1	-0.95	± 3.08	-2.30	± 2.74
Dudtmin 2	0.55	± 1.69	0.54	± 0.68

BY GENDER				
% Change from BASELINE				
per mmCO ₂	HYPERCAPNIA		HYPOCAPNIA	
Acceleration/Deceleration	Mean ± SD		Mean ± SD	
<i>Males</i>				
Dudtmax	0.26	± 0.66	-0.29	± 0.62
Dudtmin 1	-0.45	± 2.75	-1.36	± 1.81
Dudtmin 2	0.66	± 1.93	0.45	± 0.68
<i>Females</i>				
Dudtmax	0.00	± 0.47	-0.11	± 0.23
Dudtmin 1	-1.46	± 3.40	-3.19	± 3.19
Dudtmin 2	0.45	± 1.49	0.63	± 0.68

Table 4.12 Means and standard deviations for the % change from BASELINE values per mmCO₂ during HYPERCAPNIA and HYPOCAPNIA. (Velocity Acceleration/Deceleration)

GROUP OVERALL				
% Change from BASELINE				
per mmCO ₂	HYPERCAPNIA		HYPOCAPNIA	
Miscellaneous	Mean ± SD		Mean ± SD	
Tau	0.84	± 0.77	0.83	± 0.44
Upulse	0.39	± 0.64	0.08	± 0.38
Mean blood pressure	0.33	± 0.28	0.06	± 0.15
Heart rate	0.27	± 0.32	-0.42	± 0.37

BY GENDER				
% Change from BASELINE				
per mmCO ₂	HYPERCAPNIA		HYPOCAPNIA	
Miscellaneous	Mean ± SD		Mean ± SD	
<i>Males</i>				
Tau	0.87	± 1.00	0.91	± 0.37
Upulse	0.48	± 0.80	0.08	± 0.48
Mean blood pressure	0.32	± 0.23	0.03	± 0.13
Heart rate	0.23	± 0.35	-0.48	± 0.32
<i>Females</i>				
Tau	0.81	± 0.52	0.75	± 0.50
Upulse	0.29	± 0.46	0.08	± 0.27
Mean blood pressure	0.34	± 0.33	0.08	± 0.17
Heart rate	0.32	± 0.30	-0.37	± 0.41

Table 4.13 Means and standard deviations for the % change from BASELINE values per mm CO₂ during HYPERCAPNIA and HYPOCAPNIA. (Miscellaneous)

GROUP OVERALL				
% Change from BASELINE				
per mmCO ₂	HYPERCAPNIA		HYPOCAPNIA	
Time Measurements	Mean ± SD		Mean ± SD	
Tmin	0.44	± 1.00	0.41	± 1.15
Rise Time	0.62	± 2.47	0.46	± 0.60
Tmin 2	0.09	± 0.39	0.16	± 0.15
BY GENDER				
% Change from BASELINE				
per mmCO ₂	HYPERCAPNIA		HYPOCAPNIA	
Time Measurements	Mean ± SD		Mean ± SD	
Males				
Tmin	0.30	± 0.96	0.22	± 0.69
Rise Time	0.68	± 2.55	0.49	± 0.51
Tmin 2	0.01	± 0.23	0.18	± 0.11
Females				
Tmin	0.58	± 1.06	0.57	± 1.45
Rise Time	0.52	± 2.47	0.42	± 0.71
Tmin 2	0.17	± 0.49	0.13	± 0.18

Table 4.14 Means and standard deviations for the % change from BASELINE values per mmCO₂ during HYPERCAPNIA and HYPOCAPNIA. (Time measurements)

GROUP OVERALL				
% Change from BASELINE				
per mmCO ₂	HYPERCAPNIA		HYPOCAPNIA	
Indices	Mean ± SD		Mean ± SD	
Shape Index 1	17.35	± 15.80	1.01	± 0.34
Shape Index 2	7.56	± 23.66	1.35	± 0.70
Velocity Rise Index	-4.56	± 98.17	-1.05	± 7.12
Mean Resistance Index	-0.88	± 0.37	-1.69	± 0.70
BY GENDER				
% Change from BASELINE				
per mmCO ₂	HYPERCAPNIA		HYPOCAPNIA	
Indices	Mean ± SD		Mean ± SD	
Males				
Shape Index 1	20.62	± 17.94	1.20	± 0.26
Shape Index 2	11.83	± 27.28	1.59	± 0.51
Velocity Rise Index	-9.08	± 56.09	-1.92	± 1.85
Mean Resistance Index	-0.92	± 0.30	-1.94	± 0.75
Females				
Shape Index 1	14.08	± 13.08	0.84	± 0.31
Shape Index 2	3.28	± 19.34	1.12	± 0.80
Velocity Rise Index	0.61	± 133.47	-0.18	± 9.99
Mean Resistance Index	-0.84	± 0.43	-1.45	± 0.56

Table 4.15 Means and standard deviations for the % change from BASELINE values per mmCO₂ during HYPERCAPNIA and HYPOCAPNIA. (Indices)

HYPERCAPNIA		Mean velocity (% change from baseline ± SD) (cm/s)	Mean Resistance Index (% change from baseline ± SD) (mmHg s/cm)
Group overall n = 35 (mean age 35.8 ± 11.3)		39.3 ± 19.9	-21.9 ± 9.9
All men n = 17 (mean age 33.1 ± 11.3)		35.9 ± 13.7	-20.9 ± 7.2
	22- 30 yrs n = 8 (mean age 24.6 ± 2.3)	33.4 ± 11.2	-20.4 ± 6.0
	31- 40 yrs n = 5 (mean age 33.2 ± 1.8)	42.5 ± 18.9	-23.9 ± 9.8
	41-63 yrs n = 4 (mean age 50.0 ± 9.6)	32.8 ± 11.3	-18.3 ± 6.2
All women n = 18 (mean age 38.4 ± 11.1)		42.4 ± 24.4	-22.7 ± 12.0
	23- 30 yrs n = 5 (mean age 26.8 ± 2.8)	46.0 ± 14.6	-26.1 ± 9.2
	31- 40 yrs n = 6 (mean age 33.5 ± 1.9)	45.8 ± 33.7	-23.8 ± 15.0
	41- 59 yrs n = 7 (mean age 50.9 ± 4.8)	37.0 ± 23.3	-19.4 ± 12.1

Table 4.16 This table shows the group results (subdivided by age and gender) for the % change from baseline during Hypercapnia. A side-by-side comparison is made between the commonly reported Mean Velocity, and our Mean Resistance Index. (note: standard deviations are large)

HYPOCAPNIA			Mean velocity (% change from baseline $\pm$ SD) (cm/s)	Mean Resistance Index (% change from baseline $\pm$ SD) (mmHg s/cm)
Group overall n = 35 (mean age 35.8 $\pm$ 11.3)			-32.4 $\pm$ 9.3	48.9 $\pm$ 22.3
All men n = 17 (mean age 33.1 $\pm$ 11.3)			-35.1 $\pm$ 8.0	56.3 $\pm$ 23.5
	22-30 yrs n = 8 (mean age 24.6 $\pm$ 2.3)		-35.3 $\pm$ 9.5	59.5 $\pm$ 31.6
	31-40 yrs n = 5 (mean age 33.2 $\pm$ 1.8)		-34.2 $\pm$ 7.4	54.0 $\pm$ 12.1
	41-63 yrs n = 4 (mean age 50.0 $\pm$ 9.6)		-35.7 $\pm$ 7.2	52.8 $\pm$ 19.0
All women n = 18 (mean age 38.4 $\pm$ 11.1)			-30.0 $\pm$ 10.0	41.8 $\pm$ 19.0
	23-30 yrs n = 5 (mean age 26.8 $\pm$ 2.8)		-36.2 $\pm$ 11.0	52.8 $\pm$ 21.0
	31-40 yrs n = 6 (mean age 33.5 $\pm$ 1.9)		-24.4 $\pm$ 8.0	33.1 $\pm$ 17.4
	41-59 yrs n = 7 (mean age 50.9 $\pm$ 4.8)		-30.3 $\pm$ 9.2	41.5 $\pm$ 17.9

Table 4.17 This table shows the group results (subdivided by age and gender) for the % change from baseline during Hypocapnia. A side-by-side comparison is made between the commonly reported Mean Velocity, and our Mean Resistance Index. (note: standard deviations are large)

VASOMOTOR RESERVE (VMR) (total % change between Hypercapnia and Hypocapnia) <i>Normal VMR (in velocity) is 86 ± 16 % [Ringlstein 1992]</i>		VMR- Velocity (overall % and ± SD)	VMR- Mean Resistance Index (overall % and ± SD)
Group overall		71.7 ± 17.0	70.7 ± 19.4
All men		71.0 ± 11.3	77.2 ± 20.2
	22- 30 yrs	68.8 ± 7.3	79.9 ± 27.3
	31- 40 yrs	76.7 ± 15.5	77.9 ± 8.9
	41-63 yrs	68.4 ± 12.5	71.1 ± 15.9
All women		72.4 ± 21.4	64.6 ± 16.9
	23- 30 yrs	82.0 ± 16.0	78.9 ± 15.9
	31- 40 yrs	70.2 ± 30.7	56.9 ± 18.2
	41-59 yrs	67.2 ± 15.1	60.9 ± 10.8

Table 4.18 VMR is calculated by adding the % changes in Hypercapnia and Hypocapnia. This table shows the calculated VMR for our study group in two ways:
 1) VMR in terms of mean velocity changes, and 2) VMR in terms of Mean Resistance Index changes. (note: standard deviations are large)

In-vivo data Subject #98 (51 yr. old male)		% change from Baseline
Mean velocity (cm/s) Baseline	67.00	
Mean blood pressure (mmHg) Baseline	100.00	
Mean velocity (cm/s) Hypercapnia	99.78	+48.93%
Mean blood pressure (mmHg) Hypercapnia	109.30	+9.30%
Mean velocity (cm/s) Hypocapnia	46.18	-31.07%
Mean blood pressure (mmHg) Hypocapnia	94.67	-5.33%

Mean resistance index- Baseline	1.49	
Mean resistance index- Hypercapnia	1.10	-26.61%
Mean resistance index- Hypocapnia	2.05	+37.36%
VMR (Vasomotor reserve by mean resistance index)	80.00	

Computer Simulations Subject #98 (51 yr. old male)		% change from Baseline
Mean velocity (cm/s) Baseline	63.60	
Mean blood pressure (mmHg) Baseline	100.53	
Mean velocity (cm/s) Hypercapnia	88.74	+39.53%
Mean blood pressure (mmHg) Hypercapnia	104.35	+3.80%
Mean velocity (cm/s) Hypocapnia	47.83	-24.80%
Mean blood pressure (mmHg) Hypocapnia	95.00	-5.50%

Resistance - Baseline	1.58	
Resistance- Hypercapnia	1.18	-25.61%
Resistance- Hypocapnia	1.99	+25.66%
VMR (Vasomotor reserve by resistance)	64.30	

Table 4.19 Tables detail the results of the *in-vivo* data for Subject #98, and the simulations from the computer model of the cerebral circulation. Note that the % change in mean resistance index during Hypercapnia is similar to the model's predictions, but there is a disparity during Hypocapnia.

In-vivo data Subject #73 (33 yr old male)		% change from Baseline
Mean velocity (cm/s) Baseline	29.33	
Mean blood pressure (mmHg) Baseline	85.00	
Mean velocity (cm/s) Hypercapnia	38.28	+30.51%
Mean blood pressure (mmHg) Hypercapnia	91.67	+7.85%
Mean velocity (cm/s) Hypocapnia	20.67	-29.53%
Mean blood pressure (mmHg) Hypocapnia	89.00	-4.71%

Computer simulations Subject #73 (33 yr old male)		% change from Baseline
Mean velocity (cm/s) Baseline	28.75	
Mean blood pressure (mmHg) Baseline	84.92	
Mean velocity (cm/s) Hypercapnia	37.50	+30.43%
Mean blood pressure (mmHg) Hypercapnia	91.40	+7.63%
Mean velocity (cm/s) Hypocapnia	20.35	-29.22%
Mean blood pressure (mmHg) Hypocapnia	89.20	-5.04%

Mean resistance index- Baseline	2.90	
Mean resistance index- Hypercapnia	2.39	-17.37%
Mean resistance index- Hypocapnia	4.31	+48.57%
VMR (Vasomotor reserve by mean resistance index)	60.00	

Resistance - Baseline	2.95	
Resistance- Hypercapnia	2.44	-17.48%
Resistance- Hypocapnia	4.38	+48.40%
VMR (Vasomotor reserve by resistance)	59.70	

Table 4.20 Tables detail the results of the *in-vivo* data for Subject #73, and the simulations from the computer model of the cerebral circulation. Note that the % change in mean resistance index and resistance defined by the model are similar during both Hypercapnia and Hypocapnia.

Summary Table

Hypercapnia					Hypocapnia			
Absolute mean difference	SD	Non-dimensional parameter			Absolute mean difference	SD	Non-dimensional parameter	
0.00	0.05	systolic BP'			0.00	0.06	Tmin'	
0.00	0.05	Umin2'			0.00	0.06	Tmin2'	
0.00	0.03	diastolic BP'			0.01	0.09	Umaxdias'	
0.01	0.06	Umin1'			0.02	0.02	diastolic BP'	
0.02	0.08	Umaxdias'			0.04	0.06	Umax1'	
0.02	0.04	Tmin'			0.04	0.05	systolic BP'	
0.02	0.09	Rise Time'			0.05	0.05	Umin1'	
0.02	0.09	Umax1'			0.06	0.04	EDV'	
0.04	0.03	EDV'			0.06	0.04	Umin'	
0.04	0.03	Umin'			0.09	0.05	Umin2'	
0.06	0.22	Tmin2'			0.27	0.34	DuDtmin2'	
0.12	0.08	PSV'			0.28	0.11	PSV'	
0.12	0.08	Umax'			0.28	0.11	Umax'	
0.15	0.08	Upulse'			0.34	0.14	Upulse'	
0.18	0.47	DuDtmin2'			1.50	0.85	DuDtmin1'	
0.73	0.46	DuDtmin1'			2.26	0.43	Rise Time	
1.08	1.21	DuDtmax'			2.49	1.10	DuDtmax'	

Table 4.22 This set of summary tables are derived from Table 4.21 and show the parameters by order of absolute mean differences for both Hypercapnia and Hypocapnia. Note that the parameters coloured in yellow show very little difference between the Baseline and Hypercapnia/Hypocapnia. This indicates that there is little change during vasoreactivity for these parameters. Now look at the orange section, the mean differences are greater suggesting that these parameters do undergo a change during vasoreactivity. However, the parameters in the pink section, show much more change and may indicate parameters which are affected by alterations in cerebral vascular resistance. Also note that there is a difference between the parameters during Hypercapnia and Hypocapnia. (N.b. some standard deviations are large)

Parameter		Baseline vs. Hypercapnia			
	Pearson Correlation (r value)	p value	positive or negative correlation	ANOVA (F value)	p value
Traditional TCD Parameters					
PSV'	.77	p < .01	+	73.74	p < .001
EDV'	.66	p < .01	+	43.28	p < .001
Velocity Minima					
Umin'	.66	p < .01	+	43.28	p < .001
Umin1'	.74	p < .01	+	0.40	NS (p=.532)
Umin2'	.79	p < .01	+	0.79	NS (p=.928)
Velocity Maxima					
Umax'	.77	p < .01	+	73.74	p < .001
Umax1'	.71	p < .01	+	2.12	NS (p=1.55)
Umaxdias'	.44	p < .01	+	1.56	NS (p=.222)
Acceleration/Deceleration					
DuDtmax'	.59	p < .01	+	67.50	p < .001
DuDtmin1'	.76	p < .01	+	70.57	p < .001
DuDtmin2'	.51	p < .01	+	4.11	NS (p=.052)
Miscellaneous					
Upulse'	.83	p < .01	+	104.49	p < .001
Blood pressure-systolic'	.38	p < .05	+	0.04	NS (p=.844)
Blood pressure-diastolic'	.38	p < .05	+	0.04	NS (p=.844)
Time Measurements					
Tmin'	.63	p < .01	+	4.72	p < .05
Rise Time'	-.07	NS (p=.757)	NC	1.34	NS (p=.259)
Tmin2'	.63	p < .01	+	4.72	p < .05

Table 4.23 Results of Pearson correlation and ANOVA for Baseline and Hypercapnia by parameter. (NS non-significant, NC not correlated)

Parameter	Baseline vs. Hypocapnia			
	Pearson Correlation (r value)	p value	positive or negative correlation	ANOVA (F value)
<i>Traditional TCD Parameters</i>				
PSV'	.67	$p < .01$	+	198.08
EDV'	.45	$p < .01$	+	66.89
<i>Velocity Minima</i>				
Umin'	.45	$p < .01$	+	66.89
Umin1'	.86	$p < .01$	+	25.47
Umin2'	.73	$p < .01$	+	94.53
<i>Velocity Maxima</i>				
Umax'	.67	$p < .01$	+	198.08
Umax1'	.89	$p < .01$	+	13.44
Umaxdias'	.29	NS ($p=0.98$)	+	.50
<i>Acceleration/Deceleration</i>				
DuDtmax'	.50	$p < .001$	+	142.87
DuDtmin1'	.41	$p < .001$	+	90.91
DuDtmin2'	.69	$p < .001$	+	18.21
<i>Miscellaneous</i>				
Upulse'	.63	$p < .001$	+	193.06
Blood pressure-systolic'	.60	$p < .001$	+	26.08
Blood pressure-diastolic'	.60	$p < .001$	+	26.08
<i>Time Measurements</i>				
Tmin'	.32	NS ($p=0.96$)	+	0.15
Rise Time'	.16	NS ($p=.437$)	NC	677.13
Tmin2'	.32	NS ($p=0.96$)	+	0.15

Table 4.24 Results of Pearson correlation and ANOVA for Baseline and Hypocapnia by parameter. (NS non-significant, NC not correlated)

Chapter 5

Discussion and conclusions

This Chapter begins with an overview of the thesis and a discussion of the results from Chapter 4. We examine the four major concepts which arise from the work in this thesis: the language of Doppler waveforms; how Transcranial Doppler may be used in conjunction with cerebral perfusion studies; the use of mean resistance index in TCD studies; and finally Cerebrovascular set-point theory.

5.1 Overview

The understanding of human physiology was once based on the simple concepts of Galen of Pergamus (130-201 AD) who believed that veins and arteries were separate and unconnected. By the 17th century, a more sophisticated understanding of blood flow and the cerebral circulation had been achieved, and physiological experiments could begin to take place. In terms of the cerebral circulation, the scientific revolution of the late 20th century lead to significant advances in methods and techniques for the evaluation of cerebral blood flow and perfusion. Today, a clinician has an array of tests available to assess the cerebral circulation, and needs to consider which test is to be most appropriate to answer the clinical questions involved in each individual patient's management; is it SPECT, PET, XeCT, PCT, or perhaps Doppler ultrasound?

The problem may be likened to a car (blood flow) and its arrival at the destination (the brain). If the observer needs only to know that the car has arrived, then he may select a test which simply tells of the car's arrival. A scan revealing adequate cerebral perfusion shows that the blood flow has reached its destination (locations in the brain), hence the clinical question has been answered. But perhaps the observer wishes to know how long the car took to reach its destination? In this case he may choose tests that can track the time the car takes to make its journey. These could be likened to cerebral blood flow studies, where the tests give information regarding the blood flow in ml/100 g of brain/min; this may be helpful if there is carotid stenosis, for example. However, there may be another circumstance; the observer (or clinician) may need to know how fast the car was travelling, what roads it was taking, and whether there were any delays along the way. This is the niche of Transcranial Doppler ultrasound. TCD may not be able to document the car's arrival at its destination (cerebral perfusion); but it can tell you the speed (velocity), the highway (arterial path), and the direction of travel (flow direction) it

was likely to have reached the destination in good time. TCD has been used prior to interventional or surgical planning such carotid endarterectomy, or balloon occlusion of the internal carotid artery. But this thesis is about answering a further question. Is TCD capable of giving additional information over and above what it is currently being utilised for?

In Chapter 2, we described the hardware and software system we designed to address the problem. It was not enough simply to combine the parts of commercially available hardware; we also needed a specialised software program to synchronise it, and to analyse the information. A total of 28 different versions of the software were developed before our goal was achieved. We took care to include many waveform shape parameters for analysis, since there was limited research in this area with TCD. In addition, we included 4 different ways to view the results: numerical; graphical or 2-D (using an ensemble-averaged waveform shape); 3-D (where each cardiac cycle in the sample is shown); and waveform shape comparison software (allowing comparison of shapes during interventions or over time). Along with our new waveform shape parameters, we chose to include the Traditional TCD measurements that are found in the literature, as reference values.

We did extensive repeatability and reproducibility testing to assess our new system and to understand the inherent variability of cerebral blood flow itself which could affect our measurements (Chapter 3). We addressed the repeatability/reproducibility issue in three ways: by assessing potential sources of error with the *input*; the effect on the *output*; and what may cause *drift* in the measurements. We considered repeatability (measurements that were repeated within a short time-frame, a few minutes apart), and also reproducibility (measurements that were taken months apart). We described potential sources of measurement *drift*; such as the waves, or natural oscillations

occurring in the cerebral circulation. Our results produced the foundation, on which we based a methodology for testing the cerebral circulation. We conducted a study on a small group of subjects using, Hypercapnia and Hypocapnia, and analysed our findings. These results gave us insight into which waveform parameters were most reproducible, and least reproducible; at rest and under vasoreactivity testing conditions (Chapter 3, section 3.7).

Finally we were ready to perform a study on a larger group of subjects, and perform Doppler waveform shape analysis with our system. We selected 35 healthy subjects of different ages (22-62 years), and gender. We presented our results in five ways: **1)** Waveform shape parameter measurements for each test (Baseline, Hypercapnia and Hypocapnia), for the group overall and then sub-divided by gender. We also examined the relationship of each parameter with age (Chapter 4, section 4.2). **2)** Doppler waveform shape results – graphically presented (2-D). This allowed us to view the ensemble-averaged waveform shape changes which took place in each individual we tested. This is important because Doppler ultrasound interpretation has been based on pattern recognition for many years. **3)** We examined further information which could be derived from our initial analysis. For instance, we wanted to know the percentage change from Baseline in velocity *per mmCO₂*. This particular derived data helped to set up a common term by which TCD velocity studies and cerebral blood flow studies can be related. **4)** In Chapter 4, section 4.4.2, we used our velocity measurements and some physiologic principles, to understand how changes in cerebral resistance vessels can affect our velocity measurements. We identified an important point, that TCD velocity changes and cerebral resistance changes are *not* proportional to each other. **5)** One of the problems of this study was that the parameters were measured in several different units (cm/s, cm/s², seconds, mmHg). This made statistical comparison difficult. To address this problem, we chose to non-dimensionalise the data, or perform a scaling

process (Chapter 4, section 4.4.3). This technique allowed us to see if we could gain additional insight into the cerebral circulation from our new parameters.

The intriguing question was whether some of our waveform shape parameters were simply shifting upwards or downwards on the scale during Hypercapnia, and Hypocapnia? Were there other parameters that simply did not change, even while the cerebral resistance vessels were altering their diameters? Or perhaps, could we identify which waveform shape parameters underwent large changes during these resistance alterations, thereby giving us key indicators (by Doppler ultrasound) of cerebral resistance changes? This may have the potential to be a very useful clinical tool.

5.2 Discussion of results in Chapter 4

Results from Section 4.2 - parameter measurements

Traditional TCD parameters - (from Table 4.1 A, B)

As expected, velocities rise during Hypercapnia, and decrease from Baseline during Hypocapnia. The Traditional TCD indices, PI and RI, decrease during Hypercapnia (vasodilatation), and increase during Hypocapnia (vasoconstriction), as expected. Mean velocities are similar between men and women in the group for all three tests (Baseline, Hypercapnia and Hypocapnia). However, females consistently have lower PI and RI. Although standard deviations are large in this Table and others in this section, we could still see significant changes in many of the parameters.

Velocity Minima - (from Table 4.2 A, B)

Velocity minima increases during Hypercapnia, and decrease with Hypocapnia in both males and females. The data shows that females have higher Umin, Umin1, and Umin2 values in comparison to male subjects for all three tests.

Velocity Maxima - (from Table 4.3 A, B)

Velocity maxima also increase with Hypercapnia, and decrease with Hypocapnia. There is no clear pattern with Umax values between males and females. However, Umax1 and Umaxdias values are higher in females than males in all three tests.

Acceleration/Deceleration - (from Table 4.4 A, B)

For the group overall, DuDtmax remains unchanged during Hypercapnia, but increases during Hypocapnia. DuDtmin1 decreases during Hypercapnia (vasodilatation), but increases over Baseline during Hypocapnia. In contrast, DuDtmin2 increases during Hypercapnia, and decreases during Hypocapnia.

This table also shows that females have markedly lower velocity deceleration immediately after peak velocity (DuDtmin1), in comparison with male subjects. This is consistent for all three tests. Females also show decreased DuDtmax values, indicating lower acceleration at the systolic upstroke. No clear pattern is seen with DuDtmin2. In addition, this table demonstrates that the acceleration DuDtmax is most increased during Hypocapnia (vasoconstriction), over Baseline and Hypercapnia values. It is similar with DuDtmin1: deceleration after peak systole is fastest during Hypocapnia, over Baseline and Hypercapnia for the group. DuDtmin1 is slowest during Hypercapnia, (vasodilatation).

Miscellaneous - (from Table 4.5 A, B)

This table shows that for the group overall, Tau becomes longer during Hypercapnia, and shorter during Hypocapnia. Mean blood pressure rises during Hypercapnia, but remains essentially unchanged during Hypocapnia. Heart rate increases during both Hypercapnia and Hypocapnia. ETCO₂ rises for Hypercapnia and decreases during

Hypocapnia, as expected. Mean blood pressure is higher in males than females for all three tests.

Time measurements - (from Table 4.6 A, B)

For the group overall, Tmin remains essentially unchanged between the three tests. Rise Time decreases during Hypocapnia. Tmin2 decreases with Hypocapnia. Females have longer times for Tmin2 than males overall.

Indices - (from Table 4.7 A, B)

For the group overall, Shape Index 1 $((U_{min1}-U_{min})/(U_{max}-U_{min}))$, increases with Hypercapnia and decreases with Hypocapnia; there are similar findings with Shape Index 2 $((U_{min2}-U_{min})/(U_{max}-U_{min}))$, and Velocity Rise Index $((U_{max}-U_{max1})/(U_{max}-U_{maxdias}))$. Mean resistance index $((mean\ BP/mean\ velocity))$ shows a decrease during Hypercapnia (vasodilatation), and an increase during Hypocapnia (vasoconstriction), at which point it is nearly double the measurement during Hypercapnia. Females have higher values of Shape Index 1 and 2, across all three tests. However, males have a higher Velocity Rise Index in all three tests. Females show a decreased mean resistance index in comparison to male subjects during all three tests.

Relationship with age (from Table 4.8)

Shape Index 1 characterises the first velocity plateau (U_{min1}), and U_{max} and U_{min} (Figure 5.1); while Shape Index 2 (Figure 5.2) characterises the second velocity plateau which is the result of aortic valve closure (U_{min2}), and U_{max} and U_{min} . Both of these indices show a positive correlation with age at Baseline, and during Hypercapnia and Hypocapnia. DuDtmin1 is the first deceleration measurement after peak velocity, and we believe it is linked to wave reflection from the peripheral cerebral circulation. This

was also positively correlated with age over all three tests. Mean blood pressure and mean resistance during Hypercapnia are positively correlated with age.

Velocity Rise Index (Figure 5.3) characterises all of the velocity maxima (U_{max} , U_{max1} , and $U_{maxdias}$) of the waveform. This index is negatively correlated with age at Baseline and during Hypercapnia.

Results from Section 4.3

Doppler waveform shape results - (from Figures 4.1 Males)

These figures depict the waveform shape changes at Baseline and during Hypercapnia and Hypocapnia in our male subjects. It is clear from these figures that all subjects have an overall 'upward shift' (or increase) in the velocity waveform during inhalation of CO_2 (vasodilatation). In contrast, there appears to be a 'downward shift' of the waveform during hyperventilation (vasoconstriction). It can be seen that each individual has a distinctive waveform shape or 'print'. During vasoreactivity, this waveform shape is altered, but nevertheless remains characteristic of the individual. An important alteration of the waveform shape occurs immediately after peak systole, as the velocity decelerates ($DuDt_{min1}$). It is readily identifiable even with the naked eye, that this deceleration is reduced during Hypercapnia, when the distal vascular bed becomes dilated. In contrast, we see that this deceleration is increased in most individuals during Hypocapnia, when vasoconstriction has occurred.

Doppler waveform shape results - (from Figures 4.2 Females)

Females follow similar patterns to males in the aspects discussed above. However, there is one striking difference. If one examines the waveform shape during Hypercapnia when the vascular bed is dilated, it can be seen that the waveform can take on a distinctly different shape from the original waveform 'print'. This could be qualitatively

described as being more ‘rounded at the top’. In many instances U_{max1} exceeds U_{max} . There appears to be no deceleration occurring after the point we term U_{max} , but rather a further increase in velocity. Since this portion of the waveform shape has been linked previously in this thesis to wave reflections from the peripheral cerebral vascular bed, we hypothesise that this means there is little wave reflection occurring in these individuals due to marked vasodilatation.

From Section 4.4 – derived results

4.4.1 % Change per mmCO₂

Traditional TCD parameters - (from Table 4.9)

For the group overall, this table shows that PSV, EDV, and mean velocity have a greater change for Hypercapnia than Hypocapnia. Whereas, if we look at the indices of PI and RI; they show a larger percentage change per mmCO₂ during Hypocapnia than Hypercapnia.

In females, the percentage change per mmCO₂ is less than males in PSV, EDV, and mean velocity during Hypocapnia. Both indices, PI and RI, also reflect this difference between females and males.

Velocity Minima - (from Table 4.10)

For the group overall, Hypercapnia creates a larger change in all velocity minima parameters (U_{min} , U_{min1} , U_{min2}) than does Hypocapnia. Hypercapnia appears to have the most effect on U_{min} ($\Delta U_{min} = 1.80 \pm 0.57$ AU/mmCO₂), with consecutive decreases from U_{min} found in U_{min1} ($\Delta 1.55 \pm 0.55$ AU/mmCO₂), and U_{min2} ($\Delta 1.50 \pm 0.61$ AU/mmCO₂). However, this same relationship does not hold true for Hypocapnia.

For Umin1 (the first plateau after peak velocity), females appear to have less of a change per mmCO₂ than males during both interventions.

Velocity Maxima - (from Table 4.11)

In the group overall for Hypercapnia, we can see that the largest change in velocity maxima ($\Delta 1.42 \pm 0.81$ AU/mmCO₂) occurs in Umaxdias (the velocity rise after closure of the aortic valve). In the other parameters there is a decrease with Umax1 ($\Delta 1.37 \pm 0.69$ AU/mmCO₂), and Umax ($\Delta 1.06 \pm 0.45$ AU/mmCO₂). Again, the pattern does not hold for Hypocapnia.

During Hypercapnia, females have a greater change in Umax1 (velocity rise after the first velocity plateau) than males. This finding is readily apparent by visual inspection of the Doppler waveform shapes we showed in Figure 4.2. During Hypocapnia, males appear to have a greater change in all the Velocity Maxima parameters than females.

Acceleration/Deceleration - (from Table 4.12)

For the group overall, the parameter most affected by Hypercapnia and Hypocapnia appears to be DuDtmin1 (first velocity deceleration after peak velocity, which is linked to the first reflected wave returning from the peripheral cerebral circulation.) There are large standard deviations in this measurement. However, we believe this may be due to the difference between males and females, and we have also shown that there is an effect with age (Table 4.8). DuDtmax (systolic acceleration) shows an increase per mmCO₂ during Hypercapnia, but a decrease during Hypocapnia. However, DuDtmin2 shows a similar change during both interventions.

By gender, for DuDtmin1, we can see that females show a much larger decrease from Baseline per mmCO₂ in both Hypercapnia and Hypocapnia than males.

Miscellaneous - (from Table 4.13)

For the group overall, we see that Tau is similarly affected by both Hypercapnia and Hypocapnia. In Upulse and Mean Blood Pressure there is a greater increase during Hypercapnia than Hypocapnia.

By gender, the percentage change per mmCO₂ in Upulse is less in females than males. Mean Blood Pressure is more affected in females than males during both interventions.

Time Measurements - (from Table 4.14)

For the group overall, Tmin shows a similar result during both Hypercapnia and Hypocapnia. However, Rise Time appears to be more affected by Hypercapnia, than by Hypocapnia. In contrast, Tmin2 shows a greater percentage change per mmCO₂ during Hypocapnia.

By gender, males appear to have a greater change in Rise Time for both interventions than females. For Tmin2, females appear to experience a larger change during Hypercapnia. Conversely, male subjects show more change during Hypocapnia.

Indices - (from Table 4.15)

For the group overall, Shape Index 1 shows a very large change per mmCO₂ (17.35 ± 15.80), but only during Hypercapnia. This reflects the changes in the relationship of Umin, Umax, and Umin1 to each other. We have seen from our visual inspections of the waveform shapes in Figures 4.1 and 4.2, that the waveform undergoes a shape change during Hypercapnia, mainly driven by the rise in Umin1 during vasodilatation. Whereas for Hypocapnia, Umin1 is not as affected, and the index shows a change of only 1.01 ± 0.34 . Shape Index 1 and Velocity Rise Index also show a greater change

during Hypercapnia, than Hypocapnia. In contrast, Mean Resistance Index shows a greater change per mmCO₂ during Hypocapnia, rather than Hypercapnia; and suggests that there may be greater diameter changes during this portion of the vasoreactivity test.

By gender, male subjects appear to show a higher percentage change per mmCO₂ in Shape Index 1 than females in both interventions. This also holds true for Shape Index 2, Velocity Rise Index and Mean Resistance Index.

5.3 Conclusions

5.3.1 The language of Doppler waveform shape

The shape of the Doppler waveform is *encoded* with physiological information. Each parameter we measure (velocity, acceleration/deceleration, or even time points such as aortic valve closure) tells us important information about the arterial vasculature. Once understood or *decoded*, these ‘sentences’ reveal physiological information can then be used towards directing best patient management. Doppler ultrasound is quick, non-invasive, portable and cost-effective. However, characterising and measuring Doppler waveform shapes have been always been difficult. Doppler waveform analysis (pattern recognition) can be likened to learning a new language. First, one needs to understand the variation of possible shapes (or the alphabet) and then how a sentence is formed. In this thesis we take the simple alphabet (PSV, EDV, mean velocity) already defined by other researchers, and build on it by defining further characters (our new parameters) in the alphabet.

Our early work focused on techniques that could measure the waveform shape (analysis software). We followed this by utilising vasoreactivity testing, to produce changes in the cerebral resistance vessels so we could measure the associated waveform shape changes.

Our results have shown that one parameter undergoes remarkable changes during the alteration of resistance vessels during vasoreactivity testing. This is DuDtmin1 (the first velocity deceleration after peak velocity). Studies of wave intensity analysis have shown that shortly after the large compression wave passes, due to cardiac contraction; the first reflected wave occurs (a backward moving compression wave). This wave drives down the velocity while increasing the pressure. The parameter, DuDtmin1, characterises this occurrence by measuring the rate of velocity deceleration after peak systole. Since vasodilatation (Hypercapnia) decreases the impedance mismatch between the MCA and the small regulating vessels; the reflected wave from the periphery of the cerebral circulation is also diminished. Duddtmin1 has been shown to also reduce. Whereas, during the vasoconstriction produced by Hypocapnia the impedance mismatch becomes even greater than at Baseline. This creates a strong reflected wave, and in turn we see Duddtmin1 increase. Interestingly, Duddtmin1 is positively correlated with age. Therefore, our study shows that the wave reflections from the cerebral periphery, which is driving this parameter, increases in strength as we age. We believe DuDtmin1 to be one of the important parameters for recognising changes in cerebral resistance.

Interestingly, our reproducibility study in Chapter 3 (Figure 3.23A) showed this parameter (DuDtmin1) to have a poor reproducibility score. This would not be surprising, if it is a sensitive indicator to constant resistance changes in the cerebral circulation. Overall, we have learned that a specific segment of the Doppler waveform shape, between peak velocity (U_{max}) to aortic valve closure (U_{min2}), contains valuable information about relative changes in cerebral vascular resistance. Further work will be required to *decode* the full amount of physiological information contained in this segment.

This thesis has pointed out the differences in waveform shape between males and females, and what parameters are affected by age. Most interestingly, we have found that each individual has a distinctive cerebral flow ‘print’. We believe this ‘print’ represents the *encoded* physiological data at the time of testing; in addition it appears remarkably reproducible in both the short and the long time frame, as described within Chapter 3.

We can only speculate that the differences in the cerebral flow ‘print’ (Figure 5.4), seen at Baseline in a young woman 70 days apart, may be driven by changes in oestrogen levels. Kochanowicz et al. [2005] investigated blood flow velocities in the internal carotid arteries over 10 different days within the menstrual cycle. They found the blood flow velocities increased considerably in all subjects with increasing plasma concentrations of oestrogen. The end-diastolic blood flow velocities rose most significantly, on average by 16%, but in some cases 24%. They also noted that the PI decreased from baseline value, suggesting a decrease in vascular resistance. Interestingly, they also noted a decrease in the flow velocity in the external carotid artery during the increases in the internal carotid artery flow, like a ‘steal’ effect. Since oestrogen acts as a cerebral vasodilator, this may be a possibility. The waveform shape changes ($DuDt_{min1}$, U_{min1} , U_{max1}) between two repeated examinations in Subject C (Figure 5.4), are consistent with the changes we have seen during vasodilatation (Hypercapnia) in our female subjects, however, this particular subject was not undergoing any intervention at the time. However, the subject was in a different part of her menstrual cycle during each of the two tests. (This was also discussed in Chapter 3, Section 3.6.1.2.)

One of the unknown aspects of the cerebral flow 'print' is how it may change over an individual's lifespan, or with disease. This would be an important area for future research.

5.3.2 Cerebral blood flow velocity and blood volume flow rate

If Transcranial Doppler is to survive as a technique in the world of sophisticated technology, and powerful computer generated imagery, it must reaffirm its utility for the assessment of real-time cerebral haemodynamics. The first step may be to establish a common language so TCD can work in conjunction with other cerebral blood flow techniques. This issue has not been adequately addressed in the past.

One simple link between the methods has been provided by this thesis. This is addressing the issue of how blood flow velocity (cm/s) and blood flow (ml/100 gm brain/min) are related. We believe this may be best accomplished by looking at the changes in both methods for every *1 mmHg change in CO₂*. We use Table 5.1 to review what has been presented in this thesis about CBF, and compare it to our new Doppler waveform parameters. This table illustrates that whether using CBF or mean blood flow velocity, the percentage change for every *1 mmHg change in CO₂* are remarkably similar. (We are aware there is always the variation between authors on CBF measurements; however, this is simply a representative sample and not an exhaustive review.) When we compare this to our new waveform parameters to what is already known in the literature; we see that Velocity Minima, Velocity Maxima, and Acceleration/Deceleration all fall into a similar range as CBF, and mean velocity. However, our other categories such as Miscellaneous (Tau, Upulse, Mean Blood Pressure, and Heart) showed a much lesser change. This represents the rather smaller effect the changes in CO₂ have to more systemic based parameters such as blood pressure. For Time Measurements we can see that they undergo only a 1.06% change

for every 1 mmHg change in CO_2 . These parameters are related to more cardiac based physiology, for instance, in a closure of the aortic valve as detected in the cerebral circulation. This study has shown that changes in CO_2 mainly affect the cerebral circulation, and can be used to gain a better understanding into cerebral resistance changes.

5.3.3 Mean resistance index

Changes in arterial resistance are an important aspect in the regulation of cerebral blood flow. We spend considerable time in this attempting to understand the relationship between resistance changes, and velocity changes. We proposed the ‘mean resistance index’ and demonstrated its link to changes in vascular resistance as clearly as our methods would allow. We believe this to be an important take away message from this thesis. Velocity changes are not directly proportional to changes in resistance (mean resistance index). However, understanding how velocity and resistance relate to each other is central to interpretation of transcranial Doppler studies. Mean resistance index helps the observer understand this concept. In addition it is a simple index, requires only the additional measurement of blood pressure at the time of the examination, and can be calculated at any vascular laboratory without special equipment or software. We believe this would be a useful index for every TCD examination.

5.3.4 Cerebrovascular set-point theory

A final concept that we would like to introduce in this thesis is ‘Cerebrovascular set-point theory’. This theory simply states that every individual has a ‘set-point’ or resting level of tone in the cerebral resistance vessels. This ‘set-point’ is on a scale between maximal vasodilatation and maximal vasoconstriction, but *within the zone of normal autoregulation*. We assumed at the beginning of our work, that if there were a ‘set-point’, it would likely be in the middle between the two extremes (a maximal vasodilatation and

maximal vasoconstriction). We use Figure 5.5 to illustrate the idea. This simple schematic shows two red circles representing the two extremes of resistance; and we use the blue box in the centre to represent the resting or 'set-point' of the resistance vessels. In our study group, we did not measure the maximal vasodilatation or vasoconstriction possible; however, we did measure the percentage change from Baseline during vasodilatation (from Hypercapnia -Table 4.16), and vasoconstriction (from Hypocapnia -Table 4.17) in mean resistance index with our vasoreactivity protocol. We added these two results together to tell us the overall vasomotor testing range for the group (from VMR -Table 4.18). We will use these results to demonstrate our theory. First, we would like to re-introduce our graph showing the physiological testing range of our group (from Figure 4.4), but this time include our cerebrovascular set-point schematic (see Figure 5.6). You can see that if we have an individual with a 'set-point' to the far right-hand side of the graph; according to this testing range they would have little ability left to vasoconstrict, since their resistance vessels would already be largely constricted. In contrast, they would have a large ability left to vasodilate (or move left on the graph).

However, the opposite is true if the individual has a 'set-point' on the far left-hand side of the graph. This subject could make only small changes towards vasodilatation before they reached the maximum testing range, whereas, they would have a much greater ability to vasoconstrict if necessary. We reviewed some of our data as it relates to cerebrovascular set-point theory, and found some interesting results.

In the final Figure, (Figure 5.7) we show some examples. The data has been normalised since our various groups showed different ranges of VMR (an interesting point in itself). These diagrams show the relative capacity to vasodilate and to vasoconstrict according to our results. We have placed the coloured box, representing the 'set-point', based on the VMR range. Our data would suggest that the resting level (arteriolar dilatation) of

cerebral resistance vessels at Baseline **do not** reside in the centre of the VMR range. In fact, they are always in a state of vasodilatation, therefore their capacity to *further* vasodilate is somewhat restricted. However, this does suggest that the cerebral circulation has a large capacity to vasoconstrict, from its normal resting state. We speculate that this is because rapid rises in blood pressure and heart rate (forcing cerebral vasoconstriction) or more likely to occur in everyday life, than sudden falls in blood pressure (requiring vasodilatation). Therefore the system has offset itself. The other interesting point is that different groups apparently have different 'set-points'. It is important to remember that our data is an average of our subjects, and therefore the true variation in individual 'set-points' are somewhat obscured. For completeness, we have included three individual subjects (#76, #70, #72) so the variation can be appreciated (at the bottom of Figure 5.7).

Cerebrovascular 'set-point' theory suggests that every person has an individual 'set-point' or resting level of precapillary arteriolar dilatation. This level may dictate the remaining capacity to vasodilate, or vasoconstrict, should the need arise. What we do not know is how this level is set by the cerebral circulation, or what may force it to change (perhaps chronic hypertension, or arterial obstruction). Although we are using a surrogate measure of resistance to discuss this theory; we have shown in that mean resistance index has the highest reproducibility score of all the Indices over the three tests (Baseline, Hypercapnia, and Hypocapnia). In addition, it can be easily calculated in any vascular laboratory.

5.4 Summary

The aim of this thesis was to create a comprehensive analysis of cerebral Doppler waveform shapes in normal subjects, and to track the waveform shape changes during

alterations in vascular resistance (vasoreactivity testing) in an effort to ‘decode’ additional physiological information about the cerebral circulation.

We found out that the cerebral Doppler waveform shape is sensitive enough to reflect subtle changes within the stream of blood flow. In the future, Doppler waveform shape analysis may be a real-time indicator of how quickly and precisely this complex and finely tuned system meets the ever changing demands of the brain.

We believe the work in this thesis adds to the technical aspects of TCD waveform analysis (waveform shape analysis software, and new waveform parameters); provides practical benefits (the repeatability and reproducibility of parameters); establishes a set of ‘normal values’ at Baseline and during vasoreactivity testing); and makes a theoretical contribution to TCD (relationship of Doppler flow velocity and resistance changes; cerebrovascular set-point theory).

Our work may have provided a few answers and helped to build onto several foundations; but more importantly, it may have opened new doors for further research into the cerebral circulation.

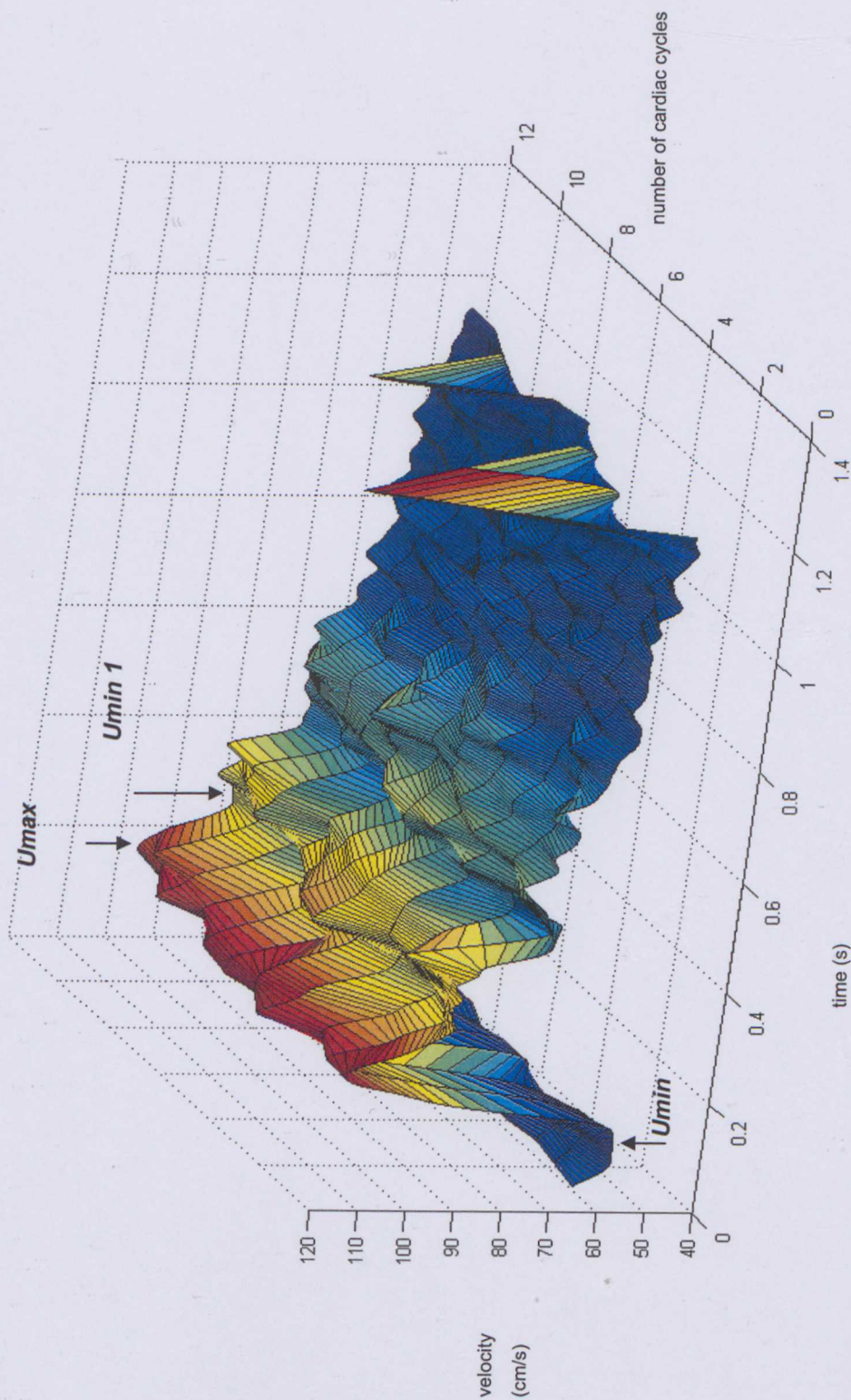


Figure 5.1 Visual representation of Shape Index 1, a relationship of the minimum velocity, maximum velocity and the *first* velocity plateau (systolic notch created by wave reflection). Shape Index 1 is positively correlated with age.

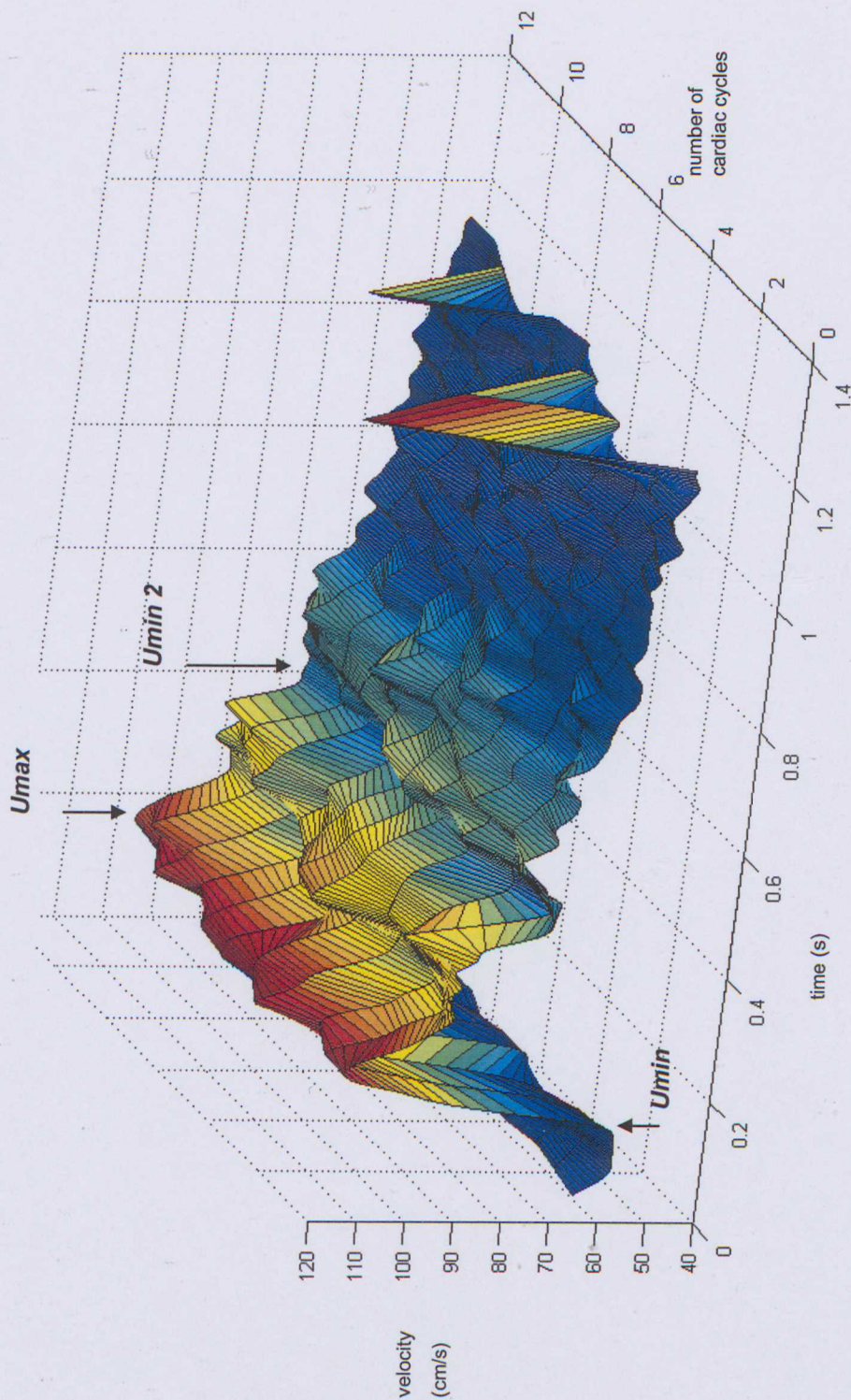


Figure 5.2 Shape Index 2, a relationship of the minimum velocity, maximum velocity and the *second* velocity plateau (dicrotic notch created by aortic valve closure). Shape Index 2 is positively correlated with age.

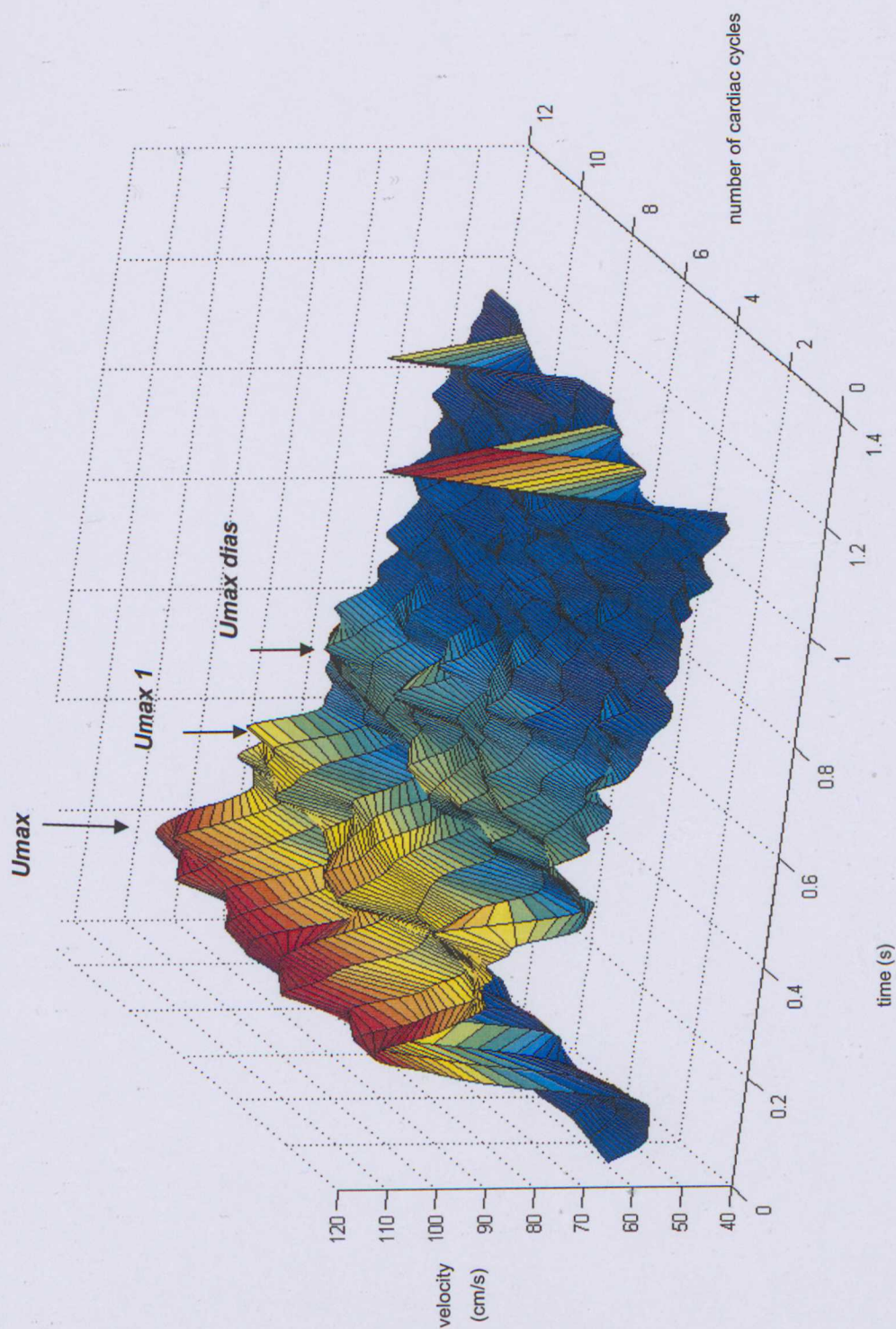
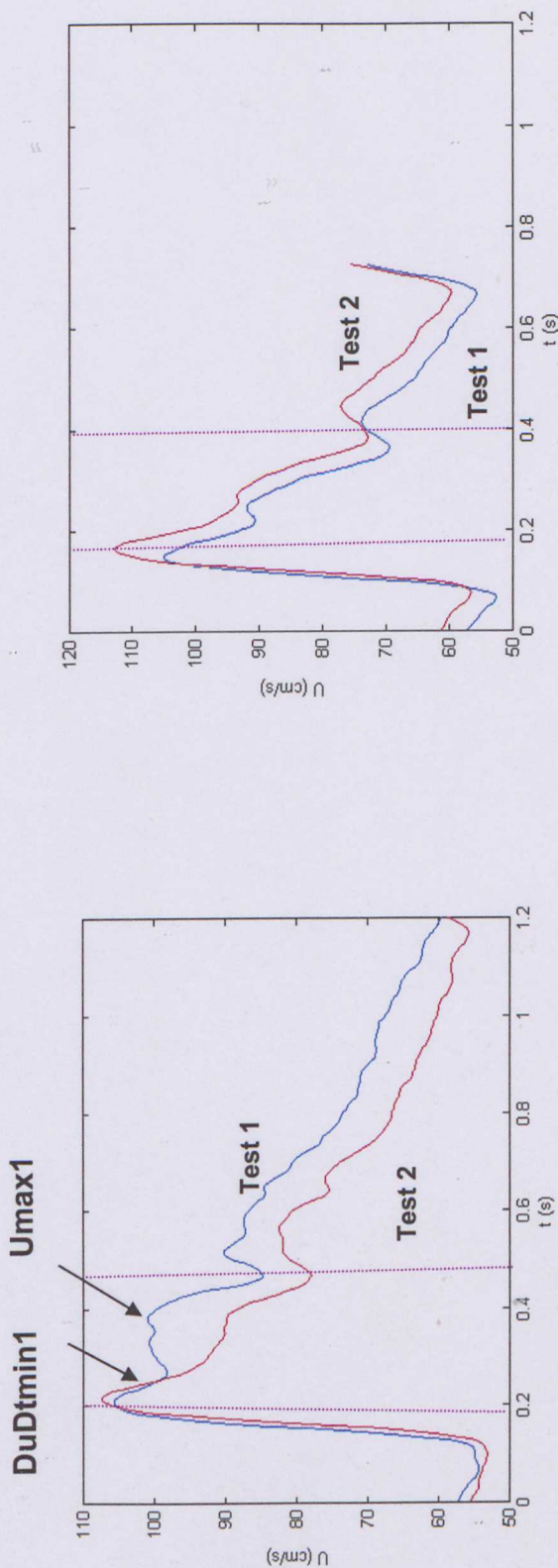


Figure 5.3 Visual representation of the Velocity Rise Index, a relationship between of all of the velocity maxima along the waveform which is negatively correlated with age.



Subject C (from Chapter 3.4.1.2)

Female, 30 yrs, time between tests = 70 days

Mean blood pressure (mmHg):

Test 1= 78

Test 2= 78

Subject B (from Chapter 3.4.1.2)

Female, 34 yrs, time between tests = 85 days

Mean blood pressure (mmHg):

Test 1= 88

Test 2= 85

Figure 5.4 Subject C demonstrates a change in waveform shape between Baseline Test 1 and Baseline Test 2 (as discussed in the text); as compared with Subject B. The segment of the waveform shape between peak velocity and the diastolic notch (pink lines) reflects changes in vascular resistance during our vasoreactivity testing as our results have shown.

Cerebrovascular set-point theory

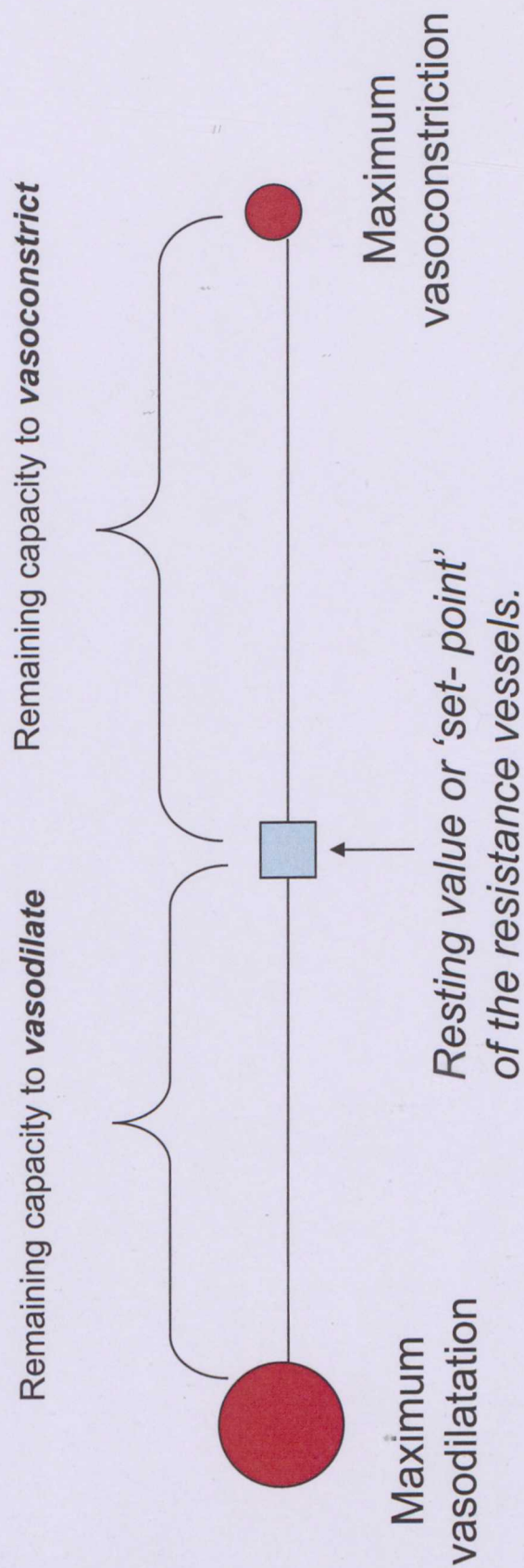


Figure 5.5 This schematic represents the basis for the cerebrovascular set-point theory. The blue box signifies the resting value or 'set-point' of the resistance vessels which is represented here as being in the centre between maximal vasodilatation and maximal vasoconstriction.

Cerebrovascular set-point theory

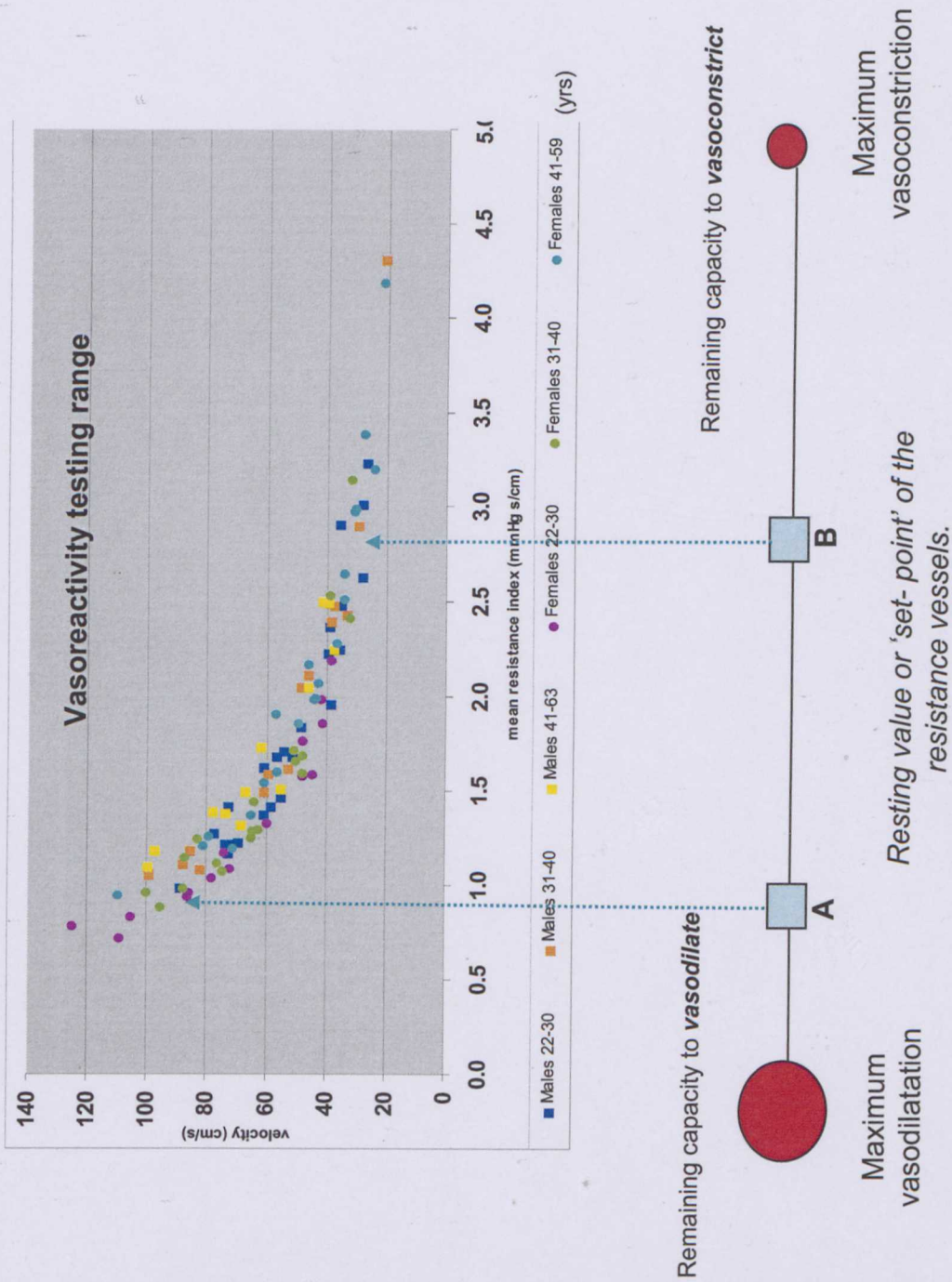


Figure 5.6 This figure shows the vasoreactivity testing range from our group, along with the cerebrovascular set-point schematic. For subject **A**, you can see this individual already is vasodilated, and therefore the remaining capacity, according to the curve, would be limited. However, their ability to vasoconstrict would be much larger. Whereas, subject **B** can vasodilate much more than constrict.



Figure 5.7 Cerebrovascular 'set-points' of groups and individuals in our study.

% Change from Baseline <i>per 1 mmCO₂</i>		
Blood <i>flow</i> results		
CBV	1-2 ml/100 g brain/min	Sato et al. [1984] Reivich M [1964]
CBF	3-5 % (ml/100 g brain/min)	Yonas H [1987]
	2-3% (ml/100 g brain/min)	Brian J [1998]
Blood flow <i>velocity</i> results		
	5 % (cm/s)	Ringlestein and Otis [1992]
	2-4 % (cm/s)	Clinical Neurovascular lab (Newell-Univ.of WA)
Our study		
Mean Velocity	2.72 % (cm/s)	Overall results- Hypercapnia + Hypocapnia
Velocity Minima	3.15 % (cm/s)	
Velocity Maxima	2.62 % (cm/s)	
Acceleration/ Deceleration	2.85 % (cm/s ²)	
Miscellaneous	1.67 % (includes mmHg, cm/s, bpm)	
Time Measurements	1.06 % (s)	

Table 5.1 This table shows the results of our new parameters with previous information presented regarding CBF, and CBV from the literature for comparison. (Note the similarity between the measurements.)

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