



<http://researchspace.auckland.ac.nz>

### *ResearchSpace@Auckland*

#### **Copyright Statement**

The digital copy of this thesis is protected by the Copyright Act 1994 (New Zealand).

This thesis may be consulted by you, provided you comply with the provisions of the Act and the following conditions of use:

- Any use you make of these documents or images must be for research or private study purposes only, and you may not make them available to any other person.
- Authors control the copyright of their thesis. You will recognise the author's right to be identified as the author of this thesis, and due acknowledgement will be made to the author where appropriate.
- You will obtain the author's permission before publishing any material from their thesis.

To request permissions please use the Feedback form on our webpage.

<http://researchspace.auckland.ac.nz/feedback>

#### **General copyright and disclaimer**

In addition to the above conditions, authors give their consent for the digital copy of their work to be used subject to the conditions specified on the Library Thesis Consent Form.

Cerebral Blood Flow Velocity  
Variability in Very Low  
Birthweight Infants

Heather Coughtrey

A thesis submitted in partial fulfilment  
of the requirements for the degree of  
Doctor of Medicine, the University of  
Auckland, 2002.

PHILSON LIBRARY  
Faculty of Medical & Health Sciences  
Park Road, Grafton  
AUCKLAND

## Acknowledgements

All studies were performed by myself.

I would like to thank the following people for their invaluable assistance and guidance

- Paul Scriven and Hugh Dangerfield of BA<sup>e</sup>SEMA for writing software within Labview to enable data analysis
- Tim Cole for his extremely useful statistical advice
- Janet Rennie for her very generous assistance and encouragement with design, analysis and writing
- David Evans for his major input regarding physics and instrument support
- The nursing staff of the Special Care Baby Unit, Rosie Maternity Hospital, Cambridge for their tolerance and cooperation throughout the study
- Ruth Morley for assessing the infants at 18 months

**LIST of ABBREVIATIONS**

<b>ACA</b>	Anterior cerebral artery
<b>AF</b>	Anterior fontanelle
<b>AUTVC</b>	Area under the velocity curve
<b>BWt</b>	Birthweight
<b>BPV</b>	Blood pressure variability
<b>BP</b>	Blood pressure
<b>CBF</b>	Cerebral blood flow
<b>CBFV</b>	Cerebral blood flow velocity
<b>CBFVV</b>	Cerebral blood flow velocity variability
<b>CBV</b>	Cerebral blood volume
<b>CLD</b>	Chronic lung disease
<b>CNS</b>	Central nervous system
<b>CPAP</b>	Continuous positive airway pressure
<b>CSA</b>	Cross-sectional area
<b>CV%</b>	Coefficient of variation expressed as a percentage
<b>CVR</b>	Cerebral vascular resistance
<b>CP</b>	Cerebral palsy
<b>CPP</b>	Cerebral perfusion pressure
<b>CSA</b>	Cross-sectional area
<b>CT</b>	Computerised tomograph
<b>CVP</b>	Central venous pressure
<b>CW</b>	Continuous wave (Doppler)
<b>ECMO</b>	Extracorporeal membrane oxygenation
<b>EDFV</b>	End-diastolic flow velocity
<b>ELBW</b>	Extremely low birthweight

<b>EM</b>	Electromagnetic
<b>FFT</b>	Fast Fourier Transform
<b>GA</b>	Gestational age
<b>HIE</b>	Hypoxic ischaemic encephalopathy
<b>HR</b>	Heart rate
<b>HRV</b>	Heart rate variability
<b>ICH</b>	Intracranial haemorrhage
<b>ICP</b>	Intracranial pressure
<b>IPH</b>	Intraparenchymal haemorrhage
<b>IPPV</b>	Intermittent positive pressure ventilation
<b>IUGR</b>	Intrauterine growth retardation
<b>IVH</b>	Intraventricular haemorrhage
<b>MAP</b>	Mean arterial pressure
<b>MABP</b>	Mean arterial blood pressure
<b>MCA</b>	Middle cerebral artery
<b>MRI</b>	Magnetic resonance imaging
<b>NIRS</b>	Near infra-red spectroscopy
<b>NICU</b>	Neonatal intensive care unit
<b>NMR</b>	Neonatal mortality rate
<b>PaCO<sub>2</sub></b>	Arterial partial pressure of carbon dioxide
<b>PaO<sub>2</sub></b>	Arterial partial pressure of oxygen
<b>PCA</b>	Postconceptional age
<b>PDA</b>	Patent ductus arteriosus
<b>PET</b>	Positron emission tomography
<b>PI</b>	Pulsatility index
<b>PNS</b>	Parasympathetic nervous system
<b>PVH</b>	Periventricular haemorrhage

<b>PVHI</b>	Periventricular haemorrhagic infarction
<b>PVL</b>	Periventricular leucomalacia
<b>PW</b>	Pulse wave(Doppler)
<b>rCBF</b>	Regional cerebral blood flow
<b>RD</b>	Respiratory distress
<b>RI</b>	Resistance index
<b>RDS</b>	Respiratory distress syndrome
<b>RSA</b>	Respiratory sinus arrhythmia
<b>SD</b>	Standard deviation
<b>sec</b>	seconds
<b>SEH</b>	Subependymal haemorrhage
<b>SNS</b>	Sympathetic nervous system
<b>SPONT RESP</b>	Spontaneous respiration
<b>SPSS</b>	Statistical Package for the Social Sciences
<b>TCD</b>	Transcranial Doppler
<b>VENT</b>	Ventilation
<b>VLBW</b>	Very low birthweight
<b>VMS</b>	Ventrolateral medullary surface
<b>WMD</b>	White matter damage
<b><sup>133</sup>Xe</b>	<sup>133</sup> Xenon

## **Abstract**

Short-term variability in cerebral blood flow velocity (CBFV) in the VLBW infant largely relates to respiratory influence. Extreme variability may be a poor prognostic indicator. Few have studied cohorts of babies in this regard.

I sequentially studied a consecutive cohort of unselected VLBW infants, to determine the frequency of respiratory influence on CBFV and to identify factors associated with its occurrence. Doppler CBFV, arterial BP and respiratory signals were recorded simultaneously and spectral analysis was applied to identify a respiratory signal in BP and CBFV traces.

Respiratory associated variability was present in the cerebral circulation at some time in more than half of the infants studied and was most likely in those of lowest gestational age who were hypotensive. Mortality, and cerebral morbidity as assessed by cerebral ultrasound were more common in those demonstrating a respiratory influence in CBFV.

There was a strong correlation between the coefficient of variation (CV%) of BP and that of CBFV. Babies demonstrating hypotension had higher CV% in CBFV; those who did not survive showed higher variability than survivors, but there was a wide spread of values in both groups. Where the variability in CBFV was high, correlation between CBFV and BP was greater. However, no significant association was found between CV% of CBFV and brain injury, ductal patency, or sedation. Although exaggerated beat-to-beat variability in CBFV was an adverse prognostic indicator, absence of variability carried the worst prognosis.

Slow variations of cerebral blood flow velocity at a frequency of 1-5 cycles per minute, previously described as a normal phenomenon, were also examined. Evolution of this variability was studied amongst those present for a month or more. Slow variations diminished with both increasing postnatal and postconceptional age, perhaps representing maturation of the balance between the two components of the autonomic nervous system. The cycle length of the slow variations was variable suggesting the presence of several low frequency components; longer recordings would be needed to resolve these.

Addition of serial Doppler measurements of CBFV performed in the first week of life, did not improve prediction of an 18-month outcome obtained from ultrasound imaging alone.

## Table of Contents

	Page no
Chapter I. INTRODUCTION	1
I.I. Mortality and morbidity in preterm infants	1
I.I.I. Variations in the reporting of outcome studies	4
I.II. Cerebral injury in the VLBW infant	9
I.II.I. Categories of intracerebral injury in the VLBW infant	9
I.II.II. Detection of intracerebral injury	10
I.II.III. The role of imaging in detection and diagnosis of intracerebral insults in the VLBW infant and relationship to outcome	11
I.II.IV. Incidence of intracerebral injury in the VLBW infant	13
I.II.V. Structural basis of intracerebral injury in the VLBW infant	15
I.II.VI. Clinical situations associated with intracerebral injury	19
I.II.VII. Pathophysiology of intracerebral injury in the VLBW infant	22
I.III. Cerebral blood flow and function-methods of assessment	23
I.III.I. Radioactive microsphere technique	23
I.III.II. <sup>133</sup> Xenon technique	24
I.III.III. Positron Emission Tomography	27
I.III.IV. Kety-Schmidt technique	28
I.III.V. Near-infrared spectroscopy	28

I.III.VI.	Magnetic resonance imaging	30
I.III.VII.	Doppler ultrasound	31
I.IV.	Doppler ultrasound technology	31
I.IV.I.	Doppler effect	31
I.IV.II.	Waveform analysis techniques	38
I.IV.III.	Velocity measurements	39
I.V.	Volumetric flow measurement - validation of the pulsed Doppler technique	40
I.VI.	Neonatal intracranial Doppler measurements	44
I.VII.	Intracerebral autoregulation in the VLBW infant	47
I.VII.I.	Vessels involved in intracerebral autoregulation	49
I.VII.II.	Range over which autoregulation is effective	49
I.VII.III.	Regional regulation of cerebral blood flow	51
I.VIII.	Use of Doppler waveform measurements during physiological changes in the newborn infant	52
I.IX.	Clinical studies employing cerebral blood flow velocity measurements	54
I.IX.I.	Patent ductus arteriosus	54
I.IX.II.	Perinatal asphyxia, brain injury and brain death	56
I.IX.III.	Doppler studies in post- haemorrhagic hydrocephalus	57
I.X.	Autoregulation, cerebral blood flow and injury	57

I.X.I.	Arterial hypertension	58
I.X.II.	The cerebral hypoperfusion theory	58
I.XI.	Variability in physiological systems	59
I.XI.I.	Signal analysis- fast Fourier transform and spectral analysis	60
I.XI.II.	Variability of heart rate and blood pressure in neonates	61
I.XI.III.	Mayer waves	62
I.XII.	Cerebral blood flow velocity variability	63
I.XII.I.	Use of spectral analysis in the assessment of cerebral blood flow velocity variability	63
I.XII.II.	Flow studies using Doppler ultrasound in the assessment of cerebral blood flow velocity variability	64
I.XII.III.	Other influences on cerebral blood flow velocity variability	67
<b>Chapter II.</b>	<b>METHODS</b>	<b>69</b>
II.I.	Patients	69
II.II.	Study Design	69
II.II.I.	Acute Phase	70
II.II.II.	Slow fluctuations in CBFV- longterm phase	73
II.II.III.	Follow-up at 18 months corrected age	74
II.III.	Instrumentation	75
II.III.I.	Ultrasound instrumentation	75

II.III.I.I.	Cerebral imaging and recordings	75
II.III.I.II.	Studies of the pulmonary artery	78
II.III.II.	Blood pressure recordings	79
II.III.III.	Respiratory recordings	79
II.IV.	Further analysis of stored recordings	80
II.IV.I.	Acute phase	80
II.IV.I.I.	Signal Analysis	80
II.IV.I.II.	Coefficient of Variation	83
II.IV.II.	Slow fluctuations in CBFV-longterm phase	84
II.IV.III	Follow-up study	87
II.V.	Data collection	87
II.VI.	Statistical analysis	88
Chapter III.	RESULTS	89
III.I.	Description of perinatal factors	89
III.I.I.	Characteristics of babies (a)	89
III.I.II.	Characteristics of babies (b)	89
III.I.III.	Relevant antenatal factors	89
III.I.IV.	Intrapartum factors	90
III.I.V.	Mode of delivery	90
III.I.VI.	Postnatal factors	90
III.I.VII.	Cardiovascular compromise	90
III.I.VIII.	Outcome	91
III.II.	Cerebral blood flow velocity variability in the first week of life	91

III.II.I.	Factors associated with respiration- induced variability in CBFV	91
III.II.I.I.	Factors related to the epoch when respiratory induced variability was noted	94
III.II.I.II.	Factors related to the presence of respiratory variability in cerebral blood flow velocity by baby	96
III.II.II.	The relationship between CBFV and arterial BP, presence or absence of a PDA, cerebral injury and outcome	98
III.II.III.	Ranges of CV% in cerebral blood flow velocity and blood pressure	105
III.III.	Examination of slow variations of CBFV in newborn preterm babies	105
III.III.I.	Association of slow variations with degree of prematurity and outcome	105
III.III.II.	Evolution of slow variations with increasing postconceptional and postnatal age	107
III.IV.	Follow-up study	111
<b>CHAPTER IV. DISCUSSION</b>		116
IV.I.	Study design	116
IV.I.I.	Study validity	116
IV.I.II.	Timing of each study	116
IV.I.III.	Duration of each study	117
IV.II.	Critique	118
IV.III.	Examination of slow variations of CBFV in newborn babies	120

IV.III.I.	Association of slow variations with degree of prematurity and outcome	120
IV.III.II.	Evolution of slow variations with increasing postconceptional and postnatal age	122
IV.IV.	Cerebral blood flow velocity variability in the first week of life	125
IV.IV.I.	Respiration induced variability in cerebral blood flow velocity variability	125
IV.IV.II.	Cerebral autoregulation	130
IV.IV.III.	Relationship between CBFVV and arterial BP, cerebral injury and outcome	134
IV.IV.IV.	Relationship between variability of CBFV, presence or absence of a patent duct, cerebral injury and outcome	137
IV.V.	Predictive value of cerebral blood flow velocity in VLBW infants	138
IV.VI.	Conclusions	140
IV.VI.I.	Key messages	140
IV.VI.II.	Summary of publications and presentations resulting from this research	141
IV.VI.II.I.	Publications	141
IV.VI.II.II.	Presentations at meetings	142
	Bibliography	143
	Appendix 1. Data sheet	175

LIST OF TABLES

	Page no
Table 1. Follow-up data for preterm infants	6
Table 2. Incidence of IVH/PVH in preterm infants	14
Table 3. Incidence of PVL in preterm infants	14
Table 4. Cases of bilateral occipital PVL and their outcome (Rennie JM:Neonatal Cerebral Ultrasound 1997 p225)	18
Table 5. Measurement of cerebral blood flow/volume in the newborn human infant	26
Table 6. Doppler ultrasound measurements of pulsatility index, mean flow velocity and end-diastolic flow velocity, and correlation to CBF-Xe (Greisen et al 1984)	46
Table 7. Factors recorded prospectively and used in univariate and multivariate analysis	95
Table 8. Factors related to the presence of respiratory variability in CBFV by epoch	96
Table 9. Factors related to the presence of respiratory variability in CBFV by baby	97
Table 10. Correlation between CV% in CBFV v BP	99
Table 11. Ranges of CV% in CBFV and BP	105
Table 12. Characteristics of babies in longitudinal study	106
Table 13. Comparison of visual inspection compared with measured amplitude of slow variation	107

Table 14. Characteristics of infants followed to 18 months, mean cerebral blood flow velocity and mean arterial blood pressure measurements 112

Table 15. Results of measures of diagnostic performance for prediction of an abnormal neurological outcome 114

### LIST OF FIGURES

Figure 1	The path of an ultrasound beam in tissue (Rennie JM:Neonatal Cerebral Ultrasound 1997 p225)	32
Figure 2	Real-time spectrum with aliasing	34
Figure 3	Aliasing	35
Figure 4	Pourcelot's index of resistance	38
Figure 5	Doppler measured flow versus true flow in artificial blood vessels	41
Figure 6	Colour Doppler identification of the anterior cerebral artery	45
Figure 7	Stable and fluctuating patterns of CBFV and simultaneously recorded arterial BP	65
Figure 8	A recording of 4-channel raw data	72
Figure 9	A recording of 4-channel raw data	73
Figure 10	Colour Doppler of the ACA on the left and a simultaneous 4-channel recording in Labview on the right	77
Figure 11	A recording of cerebral Doppler being made on An infant in the study	79

Figure 12	Spectral analysis of raw data Respiratory-induced variability present in CBFV	81
Figure 13	Spectral analysis of raw data Respiratory-induced variability absent in CBFV	82
Figure 14	Evolution of cyclical variations	85
Figure 15	Evolution of cyclical variations	86
Figure 16	Number of observations made on each infant	92
Figure 17	Distribution of responses over the first week of life	93
Figure 18	Maximum CV% in CBFV versus BP	98
Figure 19	Minimum CV% in CBFV versus BP	100
Figure 20a	Raw data and CV% of both CBFV and BP showing the mirroring which occurs	101
Figure 20b	Raw data and CV% of both CBFV and BP showing the mirroring which occurs	102
Figure 21	CV% of CBFV in normotensive versus hypotensive babies	103
Figure 22	CV% of CBFV on day 1 versus outcome	104
Figure 23	Presence of slow variability in CBFV related to postconceptional age	108
Figure 24	Presence of slow variability in CBFV related to PCA, showing percentage incidence and 95% confidence intervals	109

- Figure 25 Presence of slow variability in CBFV related to postnatal age, showing percentage incidence and 95% confidence intervals 110
- Figure 26 Cerebral blood flow velocity during the first 3 days of life shown in 3 groups according to outcome at 18 months 113
- Figure 27 Percentage change in cerebral blood flow velocity between the third and first days of life: comparison between normal and handicapped infants 114