MONASH University

Cerebral Oxygenation during Sleep in Preterm Infants

Karinna Lee Fyfe

A thesis submitted for the degree of

DOCTOR OF PHILOSOPHY

May 2014

The Ritchie Centre, MIMR and PHI Institute of Medical Research

Department of Paediatrics, Monash University, Melbourne

mimr-phi institute

the RITCHIE CENTRE

Table of Contents

General Declaration

Monash University

Declaration for thesis based or partially based on conjointly published or unpublished work

In accordance with Monash University Doctorate Regulation 17.2 Doctor of Philosophy and Research Master's regulations the following declarations are made:

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes 1 original paper submitted to a peer reviewed journals and 3 unpublished manuscripts. The core theme of the thesis is cerebrovascular and cardiovascular control in preterm infants across the first six months post-term. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, Karina Fyfe, the candidate, working within the Department of Paediatrics under the supervision of Professor Rosemary Horne

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

In the case of chapters 3, 4, 5 and 6 my contribution to the work involved the following:

Thesis chapter	Publication title	Publication status*	Nature and extent of candidate's contribution
3	Cerebral oxygenation in preterm infants	Accepted	For this chapter I recruited and performed the preterm infant studies and was responsible for analysis of this data. I was responsible for the comparison of term and preterm data, interpretation of all results and writing of the manuscript. My contribution to this chapter was 80%.
4	Preterm infants exhibit greater variability in cerebrovascular control compared to term infants	Unpublished	For this chapter I recruited and performed the preterm infant studies and was responsible for analysis of this data. I was responsible for the comparison of term and preterm data, interpretation of all results and writing of the manuscript. My contribution to this chapter was

			80%.
5	Gestational age at birth affects maturation of baroreflex sensitivity	Unpublished	For this chapter I recruited and performed the preterm infant studies and was responsible for analysis of this data. I was responsible for the comparison of term and preterm data, interpretation of all results and writing of the manuscript. My contribution to this chapter was 80%.
6	The effect of gestational age at birth on post-term maturation of heart rate variability	Unpublished	For this chapter I recruited and performed the preterm infant studies and was responsible for analysis of this data. I was responsible for the comparison of term and preterm data, interpretation of all results and writing of the manuscript. My contribution to this chapter was 80%.

I have renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

Signed: ……

Date: ……

Acknowledgements

Firstly I would like to thank my supervisors Professor Rosemary Horne, Dr Stephanie Yiallourou and Dr Flora Wong whose guidance throughout this process has been invaluable. I would like to express my gratitude for the opportunity to undertake this project which has been an extremely rewarding experience. I owe successful completion of this thesis to the continual support and expertise of my supervisors.

I would like to thank the mothers who kindly gave up their time to allow their babies to participate in this project. It was a pleasure to watch these tiny infants grow into beautiful bubbly little boys and girls.

I would also like to thank Sasha Odoi for her tireless assistance conducting the infant studies that formed the backbone of this thesis. I can't thank you enough for the countless hours spent 'chu chu chu-ing' unsettled infants to sleep. I must also thank Professor Adrian Walker for his input in interpretation of results. I extend my thanks to the whole of the Paediatrics Sleep Research Group including the post-docs and students both past and present. Furthermore, I thank the staff at the Melbourne Children's Sleep Centre for permitting the use of their facilities.

To my fellow PhD students including Anzari, Kristina, Jacqui, Amy, Mel, Dom, Justin, Sam and Maria and most importantly James and Tracey, I thank you for your support. We have endured the trials and tribulations of this PhD together and appreciate more than any the stresses of the journey.

Finally to my partner Ben, who has provided me with unwavering support throughout my PhD, always offering a patient ear and kind words of support and encouragement.

Thank you.

Karinna

Summary

The Sudden Infant Death Syndrome (SIDS) remains the leading cause of death in the post-neonatal period in developed countries (Hauck and Tanabe, 2008). Despite much research, the exact mechanisms underlying SIDS remain unclear, but are thought to involve immature cardiovascular control leading to an uncompensated hypotensive episode, in conjunction with a failure to arouse from sleep (Harper, 2000). The vast majority of SIDS deaths occur within the first six months of life with a distinct peak occurring between 2-3 months of age and the prone sleeping position is well known to be a major risk factor for SIDS (Trachtenberg et al., 2012). This is particularly so amongst infants born preterm who are known to be at significantly increased risk for SIDS (Blair et al., 2006a).

Preterm birth is common and increasing in incidence (Blencowe et al., 2012). Prematurity is associated with multiple consequences including altered cardiovascular control, which has been suggested to underlie their increased risk for SIDS (Trachtenberg et al., 2012), as well as cardiovascular disease later in life (Parkinson et al., 2013). Immaturity of cardiovascular control has been illustrated in studies assessing autonomic control of the cardiovascular system. Preterm infants have been shown to have higher heart rates (HR) and reduced heart rate variability (HRV) (Eiselt et al., 1993, Patural et al., 2004) compared to term infants at term-equivalent age. Furthermore, beyond term-equivalent preterm infants display altered cardiovascular control with impaired maturation of HRV (Yiallourou et al., 2013) and baroreflex sensitivity (Witcombe et al., 2012). However, preterm infants have not previously been studied in the prone sleep position during the period of peak risk for SIDS.

In healthy term infants, prone sleeping has been associated with reduced BP (Yiallourou et al., 2008a) and altered cardiovascular control (Yiallourou et al., 2008b, Yiallourou et al., 2011). More recently, prone sleeping has also been shown to result in reductions in cerebral oxygenation (Wong et al., 2011) and altered cerebrovascular control (Wong et al., 2013) in term infants. Our group have suggested that reduced cerebral oxygenation in the prone position, resulting in brainstem hypoxia, may

contribute to altered brainstem function including impaired autonomic cardiovascular control and reduced arousal.

The aims of this thesis were to assess cerebral oxygenation, cerebrovascular and cardiovascular control during sleep in both the prone and supine positions in preterm infants across the first six months post-term. The studies in Chapter 3 have shown that cerebral oxygenation is reduced in the prone sleeping position in preterm infants until at least 5-6 months post-term age. Furthermore, cerebral oxygenation is reduced in preterm compared to term infants, most prominently at 2-3 months post-term in the prone position. This reduction coincided with a concurrent reduction in BP and HR in preterm infants in the prone position during this period. The studies in Chapter 4 have shown that cerebrovascular control is altered by sleep position in preterm infants. Furthermore, whilst overall cerebrovascular control was similar between term and preterm infants, preterm infants displayed greater variability suggesting immaturity of cerebrovascular control persists beyond term-equivalent age. In Chapter 5 and 6 we have shown that maturation of both baroreflex function and HRV is affected by preterm birth with delayed maturation seen particularly amongst infants born at earlier gestational ages.

The findings of this thesis may have significant implications for SIDS. Infants born preterm have significantly reduced cerebral oxygenation and immature cerebrovascular control, particularly in the prone sleep position, and this may contribute to their increased risk for SIDS. Furthermore, altered maturation of cardiovascular control following preterm birth, particularly in infants born at earlier gestational ages, may predispose these infants to cardiovascular disease later in life.

Abbreviation List

5-HT	Serotonin
ANS	Autonomic nervous system
AS	Active sleep
BOLD	Blood oxygen level-dependent
BP	Blood pressure
BPV	Blood pressure variability
BRS	Baroreflex sensitivity
CA	Corrected age
CBF	Cerebral blood flow
CBV	Cerebral blood volume
$CMRO_2$	Cerebral metabolic rate of oxygen consumption
CNS	Central nervous system
CO_2	Carbon dioxide
DAP	Diastolic arterial pressure
ECG	Electrocardiogram
EEG	Electroencephalogram
EMG	Electro-oculogram
EOG	Electromyogram
GA	Gestational age
Hb	Haemoglobin
HbD	Haemoglobin difference
HbT	Haemoglobin total
HF	High frequency
HHb	Deoxyhaemoglobin
HP	Heart period
HR	Heart rate
HRV	Heart rate variability
IS	Indeterminate sleep
LF	Low frequency

MAP	Mean arterial pressure
MRI	Magnetic resonance imaging
NIRS	Near-infrared spectroscopy
NREM	Non-rapid eye movement
O_2	Oxygen
O_2Hb	Oxyhaemoglobin
PDA	Patent ductus arteriosus
PNA	Postnatal age
PSG	Polysomnography
QS	Quiet sleep
REM	Rapid eye movement
$rScO_2$	Regional cerebral oxygen saturation
SIDS	Sudden infant death syndrome
TOI	Tissue oxygenation index

Units of Measurement

bpm	beats per minute
Hz	Hertz
kPa	Kilopascal
min	minutes
ml	millilitre
mmHg	millimetres of mercury
ms	milliseconds
mo	months
s	seconds
wk	weeks
µV	micro volts
°C	degrees Celsius

Publications

The following papers and book chapters were accepted for publication during my PhD candidature and form the basis for Chapter 1.

Review Articles

FYFE K, YIALLOUROU SR, WONG FY, HORNE RSC. The Development of Cardiovascular and Cerebral Vascular Control in Preterm Infants. Sleep Medicine Reviews 2013 Jul 29. doi:pii: S1087-0792(13)00072-5. 10.1016/j.smrv.2013.06.002. [Epub ahead of print]

Book Chapters

Fyfe K, Yiallourou S, Horne R. (2011) Cardiovascular consequences of preterm birth in the first year of life. *Preterm Birth – Mother and Child,* Dr John Morrison (Ed). InTech.

The following manuscript has been accepted for publication in Pediatrics and is included in this thesis as Chapter 3.

Original Research Articles

Fyfe K, Odoi A, Yiallourou SR, Wong FY, Walker AM, Horne RSC. Cerebral oxygenation in preterm infants. Pediatrics. 2014; 134:435-45 (Chapter 3)

Published Abstracts

Fyfe K, Odoi S, Yiallourou SR, Wong FY, Walker AM, Horne RSC (2014) Parasympathetic activity is reduced during sleep in very preterm infants. *18th Annual Perinatal Society of Australia and New Zealand Congress, Perth, WA, Aus*

Decima P, **Fyfe K**, Odoi S, Yiallourou SR, Wong FY, Horne RSC (2013) The effects of persistent periodic breathing in preterm infants after hospital discharge. *25th Annual Meeting of the Australasian Sleep Association, Brisbane, QLD, Aus*

Fyfe K, Odoi S, Yiallourou SR, Wong FY, Walker A, Horne RSC (2013) Cerebral oxygenation is reduced in preterm infants during sleep. *Pediatric Academic Societies Annual Meeting, Washington, DC, USA*

Fyfe K, Odoi S, Yiallourou S, Wong F, Walker A, Horne R (2013) Cerebral oxygenation is reduced in the prone sleep position in preterm infants: Implications for the Sudden Infant Death Syndrome. *27th Annual Meeting of the Associated Professional Sleep Societies, Baltimore, USA*

**Won prize: Sleep Research Society Abstract Excellence Award*

Fyfe K, Odoi S, Yiallourou S, Wong F, Walker A, Horne R (2013) Prone sleeping alters cerebral vascular control in preterm infants. *27th Annual Meeting of the Associated Professional Sleep Societies, Baltimore, USA*

Fyfe K, Odoi S, Yiallourou S, Wong F, Walker A, Horne R (2013) Preterm birth alters cerebral vascular control during sleep in the prone position. *17th Annual Perinatal Society of Australia and New Zealand Congress, Adelaide, SA*

Fyfe K, Odoi S, Yiallourou S, Wong F, Walker A, Horne R (2013) Preterm infants are more vulnerable to reduced cerebral oxygenation in the prone position. *Fetal and Neonatal Physiology Workshop, Barossa Valley, SA*

Fyfe K, Odoi S, Cohen E, Yiallourou S, Wong F, Horne R (2012) The effects of postnatal age on cerebral oxygenation during sleep in preterm infants. *Fetal and Neonatal Physiology Workshop, Shoal Bay, NSW*

Fyfe K, Odoi S, Yiallourou S, Wong F, Walker A, Horne R (2012) Effects of sleep position on cerebral oxygenation in preterm infants. *Federation of Asia and Oceania Perinatal Societies (FAOPS) and Perinatal Society of Australia and New Zealand (PSANZ) Congress, Sydney, NSW*

**Won prize: New Investigator Award for Neonatology 2012*

Fyfe K, Odoi S, Yiallourou S, Wong F, Walker A, Horne R (2012) Preterm birth results in reduced cerebral oxygenation during sleep. *24th Annual Meeting of the Australasian Sleep Association, Darwin, NT*

**Won prize: New Investigator Award 2012*

Fyfe K, Odoi S, Yiallourou S, Wong F, Walker A, Horne R (2012) The prone sleep position may alter cerebral vascular control in preterm infants. *24th Annual Meeting of the Australasian Sleep Association, Darwin, NT*

Chapter 1

General Introduction

1 Literature Review

Sections of this literature review have previously been published as a review (Appendix A) and book chapter (Appendix B).

1.1 Preterm Birth

1.1.1 Definition and Incidence

Preterm birth is defined as birth before 37 completed weeks of gestation (Beck et al., 2010). The worldwide incidence of preterm birth was 11.1% in 2010 (Blencowe et al., 2012), with Australia seeing an annual rate of preterm birth of approximately 8% of the total live births (Li et al., 2012). In recent years, the number of preterm births has been steadily increasing with a rise of greater than 30% over the past 30 years (Figure 1) (Thilo and Rosenberg, 2010, Ananth et al., 2006). The numbers of both spontaneous and iatrogenic (medically or surgically induced) preterm births (Thilo and Rosenberg, 2010, Mally et al., 2010) are increasing. Iatrogenic preterm birth is on the rise due to changing obstetric practices and a shift towards earlier delivery, whilst the incidence of spontaneous preterm birth is increasing due to greater use of assisted reproductive technology and increases in the number of multiple gestation pregnancies (Voltolini et al., 2013, Blondel et al., 2006).

Preterm birth is commonly classified according to gestational age (GA) at birth; preterm for birth between 32 and 37 weeks gestation, very preterm for birth between 28 and 32 weeks gestation and extremely preterm for birth prior to 28 weeks of gestation (Tucker and McGuire, 2004). Alternatively, preterm infants can be classified as low birth weight (<2500g), very low birth weight (<1500g) or extremely low birth weight (<1000g) (Polin et al., 2011). These clinical definitions generally denote a stepwise increase in the risk of prematurity related morbidity and mortality (Lemons et al., 2001).

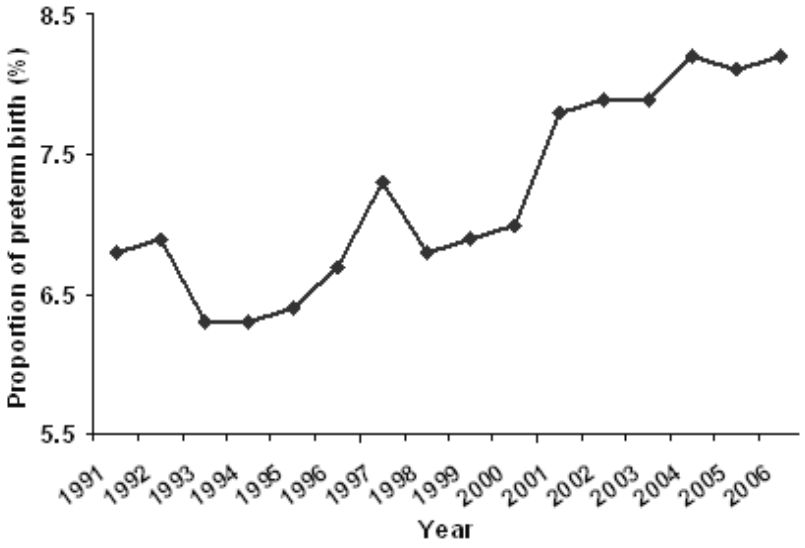


Figure 1: Increasing Incidence of Preterm Birth (Laws and Sullivan, 2010). Preterm birth has been steadily increasing in recent years, rising from approximately 6.5% of the total live births in the early 1990s to over 8% in 2006.

1.1.2 **Consequences of Prematurity**

Infants born prematurely are at risk of a wide range of short and long term complications and these are summarised in Table 1. As such, it is understandable that premature birth and low birth weight are significant contributors to infant mortality, with spontaneous preterm birth being the leading cause of death in the neonatal period (Li et al., 2012). In recent years, the survival rates for preterm birth have significantly improved with infants surviving at much younger GAs. This has been due to improvements in referral to tertiary centres, neonatal resuscitation and neonatal intensive care (Costeloe et al., 2012). More specific interventions responsible for improved survival include antenatal corticosteroids to encourage lung maturation and endogenous surfactant and assisted ventilation to improve the transition to ex-utero life (Lacovidou et al., 2010 , Speer et al., 2013). Evidence suggests that the survival rates of extremely preterm infants increases from approximately 3% at 22 weeks to 40% at 24 weeks and 77% at 25 weeks (Costeloe et al., 2012).

As the number of surviving preterm infants increases it is becoming clear that many infants born prematurely go on to develop either major or minor disabilities (Costeloe et al., 2013). The risk of disability increases considerably with decreasing GA, with infants born at earlier GAs having higher rates of morbidity than infants born at later GA (Dimitriou et al., 2010). Although GA directly

influences the prognosis of preterm infants, adverse events occurring in the neonatal period, such as intraventricular haemorrhage or surgery, are also important predictors of long term outcome, correlating with a higher rate of death or disability and these occur more commonly in infants born at younger GAs (Doyle and Victorian Infant Collaborative Study, 2001). The major disabilities that can occur as a result of preterm birth include cerebral palsy, chronic lung disease and neurosensory deficits such as blindness and deafness (Saigal and Doyle, 2008).

	Short Term	***Long Term***
Respiratory	Respiratory distress syndrome Apnoea of prematurity	Bronchopulmonary dysplasia
Growth and Nutrition	Complications of intrauterine growth restriction Nutritional deficiencies Feeding difficulties	Difficulty with breast feeding Inadequate nutrition and growth
Cardiovascular	Bradycardia of prematurity Patent ductus arteriosus	Persistent patent ductus arteriosus Unstable cardiovascular parameters Cardiovascular remodelling
Gastrointestinal	Need for enteral feeds Necrotizing enterocolitis Direct hyperbilirubinaemia Constipation	Gastroeosphageal reflux Colic Short bowel syndrome
Neurological	Intraventricular haemorrhage Hydrocephalus Periventricular leukomalacia Seizures	Cerebral palsy Delayed neurodevelopment Cognitive impairment Neurobehavioral disorders (Attention Deficit Hyperactivity Disorder, Autism Spectrum Disorder)
Haematological	Anaemia or prematurity Indirect hyperbilirubinaemia	Anaemia of prematurity
Endocrine	Osteopenia of prematurity	Hypothyroidism
Neurosensory	-	Retinopathy of prematurity Hearing loss
Other	Inguinal or umbilical hernia Temperature instability Infection	-

Table 1: Summary of the Consequences of Preterm Birth (Mally et al., 2010, Saigal and Doyle, 2008)

Prematurity related conditions are important contributors to long-term adverse outcomes following preterm birth. Apnoea of prematurity, characterised by prolonged apnoea accompanied by oxygen

desaturation and or bradycardia (Balain and Oddie, 2014), and bronchopulmonary dysplasia, chronic lung disease usually caused by mechanical ventilation (Bowen and Maxwell, 2014), are common following preterm birth and occur with increasing incidence in infants born at earlier GAs. Both conditions potentially expose infants to repetitive hypoxic episodes in the neonatal period which has been associated with an increased risk of adverse neurodevelopmental outcomes (Martin et al., 2011).

Major disability aside, many premature infants go on to develop subtle impairments in areas such as fine and gross motor function, academic performance, attention and executive functioning which are not regarded as disabilities, but nonetheless impact considerably on the child's progress (Saigal and Doyle, 2008). Preterm infants are at an increased risk of re-hospitalisation during infancy and childhood due to prematurity related medical conditions such as jaundice, respiratory and gastrointestinal problems (McLaurin et al., 2009).

In addition, it is now widely recognized that infants born preterm are at increased risk for developing cardiovascular disease in adult life (De Boo and Harding, 2006, Parkinson et al., 2013). Most importantly, preterm birth is associated with a significantly increased risk of developing hypertension in adulthood (Kistner et al., 2005), with the greatest risk seen amongst infants born at earlier GAs (Johansson et al., 2005). Furthermore, there is evidence to suggest that elevated blood pressure (BP) can occur in childhood in infants born extremely preterm (Bonamy et al., 2012). It has been suggested that increased risk of cardiovascular disease in adulthood is due to structural changes to the cardiovascular system (Norman, 2008) occurring as a consequences of preterm birth, whilst altered cardiovascular control may also play a role (Yiallourou et al., 2013).

Premature Infants: Summary

Preterm infants account for approximately 8% of the total live births each year in Australia. Due to the increasing incidence of preterm birth and increases in the survival rates of these infants, the number of preterm infants surviving the neonatal period has significantly increased. Preterm birth is associated with numerous short and long term consequences, ranging from major disability to subtle learning difficulties. The legacies of preterm birth are largely due to immaturity at birth. This affects all the systems of the body and, in particular, the brain. Immaturity of the brain can be illustrated through the developmental differences seen in sleep in both term and preterm infants.

1.2 Sleep

1.2.1 **Adult Sleep**

Sleep is a physiologically important state characterised by altered consciousness, reduced sensory awareness and inhibition of voluntary movement, during which adaptation and repair of the brain and body is thought to occur (Siegel, 2005). Adults spend approximately one-third of their lives asleep, which generally occurs in consolidated 6-8 hour blocks each night. Sleep can be studied through polysomnography which involves the simultaneous recording of electroencephalogram, to monitor brain activity, electro-oculogram, to identify eye movements and electromyogram, to assess muscle tone, as well as cardiovascular and respiratory parameters including but not limited to electrocardiogram, respiratory effort and arterial oxygen saturation (Kryger et al., 2010). Adult sleep is divided into rapid eye movement (REM) sleep and non-REM sleep according to the presence of eye movements. Non-REM sleep is further categorised into stages (Non-REM stages 1-3) according to electroencephalographic and behavioural characteristics (Silber et al., 2007).

1.2.2 **Infant Sleep**

Newborn term infants spend up to 70% of each day sleeping (Pollak et al., 2010) whilst in premature infants this figure can reach up to 90% (Ardura et al., 1995), indicating that sleep is extremely important during this period of accelerated growth and development. Infant sleep consists of two sleep states; quiet sleep (QS) and active sleep (AS), which are considered to be the immature equivalents to adult non-REM and REM sleep respectively. The characteristics of AS and QS are shown in Table 2. In addition, a third state occurs which is known as indeterminate sleep, during which neither the criteria for AS nor QS are met, this is characteristic of the immature infant brain.

Sleep Characteristic	*Quiet Sleep*	*Active Sleep*
EEG pattern	High voltage, low frequency (50-150 µV)	Low voltage, mixed frequency (40-80 µV)
Eye movements	None	Present
Muscle tone	Higher	Lower
Movements	None or seldom	Frequent
Respiration	Regular	Irregular
Heart Rate/Heart Rate Variability	Lower	Higher
Blood Pressure/Blood Pressure Variability	Lower	Higher
Spontaneous Arousals	Few	Common

Table 2: Characteristics of Quiet and Active Sleep (Mirmiran et al., 2003)

Infants under 6 months of age enter sleep through AS and sleep cycles generally last for about 50 minutes. Term infants at birth spend approximately half their sleep time in AS and half in QS which is in contrast to preterm infants who spend up to 80% of the total sleep time in AS (Mirmiran et al., 2003, Shneerson, 2005) and adults who spend only 25% of sleep time in REM sleep while 75% is spent in NREM sleep (Figure 2) (Shneerson, 2005).

Sleep undergoes considerable development during infancy as sleep becomes more adult-like. The major differences between infant and adult sleep are outlined in Table 3. Sleep shifts from being equally distributed across 24 hours, to occurring predominantly at night (Figure 2). Sleep architecture becomes more adult-like with sleep onset transitioning from occurring through AS to through QS (Mirmiran et al., 2003). In addition to this, the sleep cycle length increases and the total sleep duration decreases as sleep patterns become more adult-like (Louis et al., 1997).

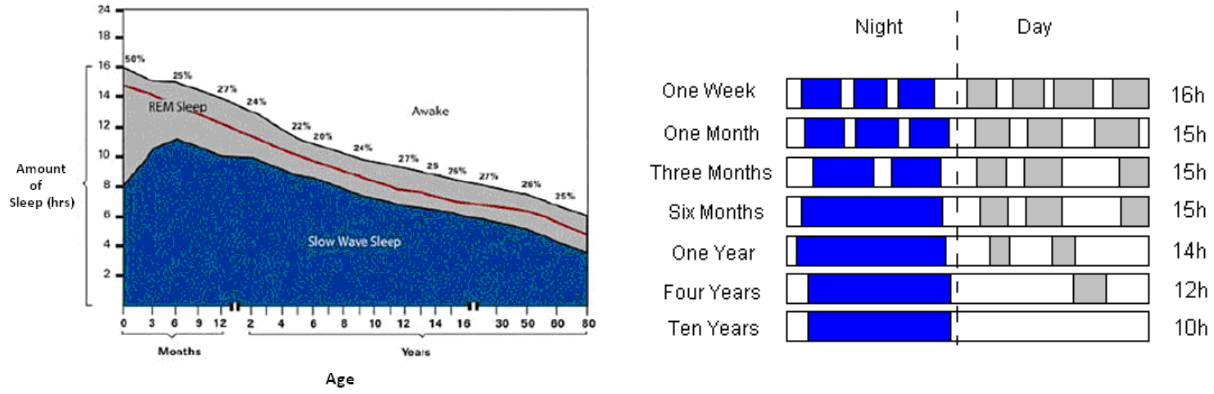


Figure 2: Changes in REM and NREM sleep (left) and the distribution and need for sleep according to age (right) (Chae, 2007, Mindell and Owens, 2010) Left: Term infants spend up to 50% of their total sleep time in active sleep (AS) (Rapid Eye Movement (REM) sleep). During the first few months of life, the proportion of AS decreases whilst the proportion of QS (slow wave sleep or Non-REM sleep) increases until a more adult-like distribution is reached. Right: Newborn infants spend approximately 16 hours a day sleeping, distributed equally throughout 24 hours. In this image, the blue bars represent sleep periods at night, while the grey bars represent sleep periods during the day. Over the first year of life circadian rhythm develops and sleep consolidates to the night with only short naps occurring during the day.

Sleep Characteristic	*Infants*	*Adults*
Sleep states	Quiet Sleep Active Sleep Indeterminate Sleep	NREM stage 1 NREM stage 2 NREM stage 3 REM
Sleep onset	Through AS	Through NREM
Sleep cycle length	45-50mins	90-100minutes
Total sleep duration	16 hours	7-8 hours
Sleep architecture	Equal distribution of AS and QS throughout night	REM sleep occurs predominantly in final third of the night
Sleep distribution	Equal distribution of sleep over entire 24 hour period	Sleep occurs at night
EEG	Tracé alternant (discontinuous EEG pattern seen in QS) 6-8 weeks: high voltage, slow activity of deep sleep 2 months: sleep spindles 6 months: K complexes (Korinthenberg, 1993) > 6months: NREM sleep stages become apparent	NREM stage 1: theta waves 4-7 Hz NREM stage 2: sleep spindles and K complexes NREM stage 3&4: delta waves, 0.5-2Hz REM: rapid, low voltage

Table 3: Summary of the Differences between Infant and Adult Sleep (Mindell and Owens, 2010)

1.2.3 **Arousal from Sleep**

Arousal from sleep refers to a brief interruption of wakefulness during sleep (Halasz et al., 2004). In infants, arousal is classified as either a subcortical activation or cortical arousal depending on polysomnographic variables (Table 4) indicating either partial or complete arousal from sleep (International Paediatric Work Group on Arousals, 2005).

Polysomnographic Variable	***Subcortical Activation***	***Cortical Arousal***
EEG	No Change	Abrupt change in EEG background frequency of at least 1 Hz for a minimum of 3s
	In the presence of at least 2 of the following:	
Heart rate pattern	Change in heart rate; at least 10% higher than baseline values	
Behavioural change	Gross body movement	
EMG amplitude	AS only: Increase in chin EMG amplitude (not associated with sucking)	
Breathing pattern	QS only: Change in breathing pattern (frequency and/or amplitude), may be a single augmented breath	

Table 4: Classification of Arousal in Infants (International Paediatric Work Group on Arousals, 2005)

Arousal results in an increase in heart rate (HR), blood pressure (BP) and ventilation due to an autonomic 'fight or flight' response (Horne et al., 2004). A number of factors influence arousal thresholds, the level at which a stimulus will initiate an arousal response, of an individual at any given age and in particular sleep state. In infants, arousal thresholds are higher in QS than in AS thus infants are more difficult to arouse when in QS (Navelet et al., 1984). This is reflected in numerous reports of increased spontaneous awakenings and more frequent movements occurring in AS compared to QS (Vecchierini-Blineau et al., 1994, Coons and Guilleminault, 1985, Navelet et al., 1984, Horne et al., 2001). This sleep state related change in arousability is less pronounced in neonates and is not seen in preterm infants until 2-3 months post-term age (Horne et al., 2002, Vecchierini-Blineau et al., 1994). In addition to effects on arousability, sleep state has a considerable influence on the cardiovascular system.

1.2.4 **Sleep and the Cardiovascular System**

In infants, cardiovascular parameters are significantly altered during sleep and according to sleep state. AS is associated with sympathetic dominance, thus BP and HR have been reported to be higher in AS than in QS, with greater variability (Figure 3) (Witcombe et al., 2008, Harrington et al., 2001), in both

term and preterm infants (Witcombe et al., 2008). Thus, it is important to take sleep state into consideration when assessing cardiovascular parameters during sleep in infants.

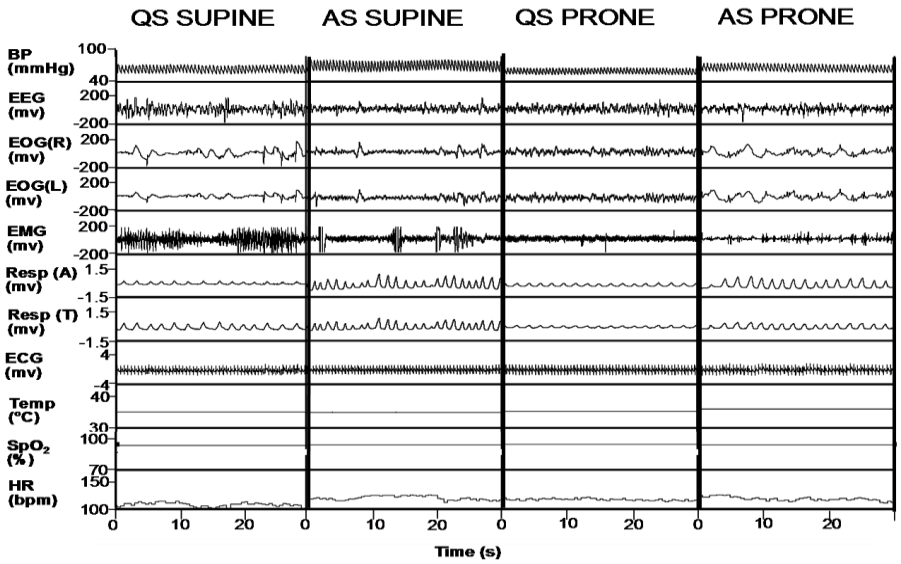


Figure 3: Blood Pressure (BP) and Heart Rate (HR) changes during Active Sleep (AS) and Quiet Sleep (QS) (Witcombe et al., 2008). This polysomnographic trace illustrates that BP is higher during AS in both the prone and supine positions in term infants. It can also be seen that HR is higher and more variable in AS than in QS in both the prone and supine positions.

Sleep: Summary

During infancy, sleep is at a lifetime maximum and significant changes in sleep architecture, duration, onset and arousal occur as sleep patterns mature and become more adult-like. Sleep has a marked effect on the cardiovascular system contributing to instability of cardiovascular control during infancy.

1.3 Cardiovascular Control

Development of the cardiovascular system begins early in embryological life and continues throughout gestation. At term age maturation is not yet complete and the cardiovascular system continues to mature for several weeks after term birth. Mitotic divisions of the myocardium have been found to continue for several weeks after birth and the mechanical performance of the myocardium shows improvement with increasing postnatal age (Friedman, 1972). In addition, the sympathetic nerve supply to the heart is thought to still be immature at term (Larsen et al., 2001). An additional challenge during this period of rapid cardiovascular development is the transition from intrauterine to extra-uterine life which occurs at birth and requires significant circulatory changes. In order to switch from a placental oxygen source to a pulmonary source, critical structural changes must occur, including the closing of circulatory shunts such as the ductus arterious, ductus venosus and foramen ovale (Polin et al., 2011). In infants born prematurely, these shunts often do not close immediately after birth, contributing to cardiovascular instability during this period and placing infants at risk of circulatory complications (Segar, 2011).

1.3.1 **Autonomic Cardiovascular Control**

The cardiovascular system is largely controlled by the autonomic nervous system (ANS). The ANS can be separated into two divisions: the sympathetic nervous system, responsible for increasing HR and BP, and the parasympathetic nervous systems, responsible for reducing HR and BP (Saladin, 2011). Autonomic control of the cardiovascular system undergoes considerable development during fetal life; however the parasympathetic and sympathetic branches develop differently. The sympathetic branch appears to develop most rapidly during the first trimester, developing more slowly thereafter, whilst parasympathetic or vagal control undergoes a period of rapid development between 25 and 32 weeks GA (Wakai, 2004, Schneider et al., 2009). ANS control of cardiovascular parameters involves a complex interaction between the two branches and the degree of input of each branch, known as the sympathovagal balance (Monti et al., 2002, Harper et al., 1976).

The ANS also interacts with the vestibular system in order to maintain cardiovascular parameters, particularly BP, during movement and positional changes (Carter and Ray, 2008). Positional changes such as standing from sitting are detected by the vestibular system and result in rapid adjustment of HR and BP in order to prevent hypotension via the vestibulo-sympathetic reflex (Yates, 1996, Yates and Miller, 1994).

1.3.2 **Heart Rate and Blood Pressure Variability**

HR variability (HRV), the fluctuation in the length of time between consecutive heart beats, and BP variability (BPV) are commonly used tools to assess autonomic cardiovascular control. In adults, altered HRV has been associated with adverse cardiovascular mortality (Malik, 1996). HRV is an indicator of cardiac autonomic modulation whilst BPV is a reflection of peripheral autonomic modulation and reflects changes in vasomotor tone. HRV and BPV can be divided into short term or high frequency (HF) variability and long term or low frequency (LF) variability (Malik, 1996). HF variability reflects parasympathetic vagal tone and is affected by respiratory frequency. LF HRV is influenced by a combination of both parasympathetic and sympathetic inputs and baroreflex mediated HR changes. In contrast, LF BPV predominantly reflects sympathetic activity (Malliani et al., 1991, Leor-Librach et al., 2002, Pagani et al., 1986). The ratio of LF to HF activity (LF/HF ratio) is also commonly presented as this reflects sympathovagal balance. Although spectral divisions have been clearly defined in adults, these cannot be applied to infants due to their much higher heart and respiratory rates. Recently, taking into account these differences and based on previous studies, neonatal spectral divisions have been developed; these are 0.04-0.15Hz for LF and 0.4-1.5Hz for HF (de Beer et al., 2004).

In infancy, control of the cardiovascular system and sympathovagal balance are influenced by a range of factors including sleep state and age. Postnatal age has a considerable influence on ANS cardiovascular control with a significant reduction in HR seen during the first few months of life due to increased parasympathetic input (Harper et al., 1976). At term age, autonomic control is not yet fully mature and alterations in sympathovagal balance continue throughout infancy until at least 6 months of age (Yiallourou et al., 2012). In QS, LF, HF and total HRV power increase and the LF/HF

HRV ratio decreases, reflecting maturation of cardiac autonomic modulation, across the first six months of life in term infants (Yiallourou et al., 2012). AS is associated with a predominance of sympathetic activity particularly in early infancy and as such LF HRV, LF/HF HRV ratio and LF BPV are increased in AS compared to QS up until 2-3 months of age in term infants (Yiallourou et al., 2012).

1.3.3 **The Baroreflex**

The arterial baroreceptors, located in the aortic arch and the carotid sinuses, play an important role in short term regulation of BP. Alterations in BP, detected as changes in vascular stretch, modify the rate of firing of the afferent baroreceptor fibres and this signal is carried via afferent fibres in the vagus and glossopharyngeal nerve primarily to the nucleus tractus solitarius located in the lower brainstem. From here, modulation of efferent sympathetic and parasympathetic activity results in alterations in HR, cardiac contractility and peripheral vascular resistance (Segar, 2011). Increased BP results in decreases in HR, heart contractility and vascular tone, whilst decreased BP stimulates the opposite in order to return BP to normal levels. The effectiveness and functional limits of baroreflex mediated regulation of BP is modelled by the baroreflex function curve (Figure 4). This describes the ability of the baroreflex to induce a change in BP according to the current level of BP and carotid sinus pressure (Kent et al., 1972). When BP is in the linear portion of the baroreflex function curve the capacity for baroreflex mediated compensation for a change in BP is large. In contrast, if BP is at the lower threshold or upper saturation point then the baroreflex will no longer be able to mediate a change in BP.

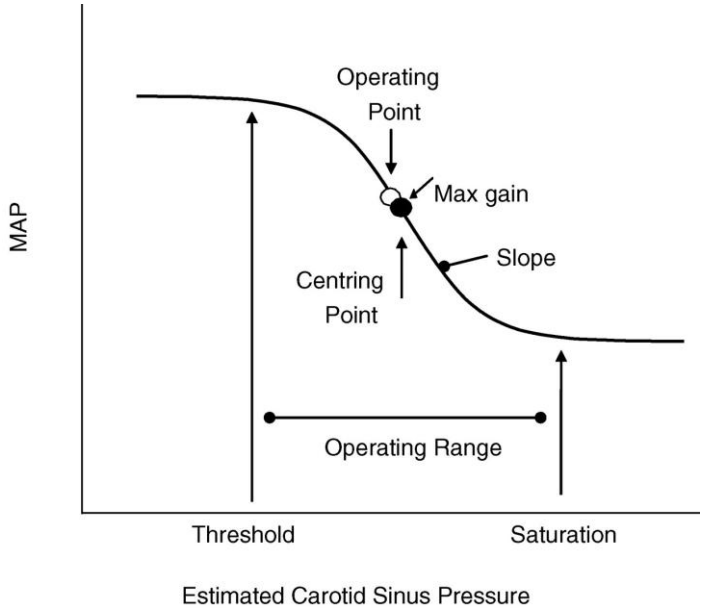


Figure 4: A schematic representation of the baroreflex function curve. The capacity for baroreflex mediated change in blood pressure (BP) is greatest (max gain) when the operating point is the same as the centring point. As BP moves towards the lower threshold or upper saturation point, the capacity for baroreflex mediated change in BP is reduced (Kent et al., 1972, Raven et al., 2006).

The baroreflex is considered the most important autonomic mechanism for short-term regulation of BP. Baroreflex sensitivity (BRS) can be assessed by measuring the change in HR rate caused by a particular change in BP. Whilst historically the techniques for assessing BRS involved manipulation of BP using either vasoactive substances or the physical manoeuvres, more recently it has become possible to assess BRS non-invasively using spontaneous fluctuations in BP (Andriessen et al., 2004). This non-invasive method of assessing BRS makes it feasible to assess BRS in infants. Spontaneous BRS can be assessed using two methods: time-domain or frequency-domain analysis.

Time-domain BRS assessment, otherwise known as the sequence method, involves identifying ramps of increasing or decreasing BP over a minimum of 3 beats that are followed by decreasing or increasing heart period (HP, the duration of the R-R interval). BRS is assessed by calculating the slope of the regression line for BP and HP, this is repeated for multiple BP ramps and the values averaged to generate a single BRS value (La Rovere et al., 2008, Zoccoli et al., 2001, Bertinieri et al., 1988).

Frequency-domain or cross-spectral analysis of BRS is based on the knowledge that spontaneous oscillations in BP induce oscillations in HR of the same frequency via the baroreflex (La Rovere et al., 2008). Therefore, calculation of BRS using cross-spectral analysis involves calculating the transfer function or gain between changes in systolic BP and HP within the LF range of 0.04-0.14 Hz in which baroreflex mediated changes in HR are thought to occur (La Rovere et al., 2008, Pagani et al., 1986).

Sensitivity of the baroreflex can also be tested non-invasively during a cardiovascular challenge using head-up or head-down tilts. In adults, head-up tilting results in a small, transient decrease in arterial BP resulting in a baroreflex mediated increase in HR and peripheral vascular tone (Borst et al., 1982). There is also an increase in the LF component, reflecting sympathetic activity, and a decrease in the HF component, reflecting parasympathetic activity, of HR variability, the magnitude of which corresponds to the degree of the tilt (Montano et al., 1994). In term infants in the supine position, head-up tilting results in a biphasic response with a transient increase and then decrease in BP and HR followed by a return to baseline (Yiallourou et al., 2008b, Harrington et al., 2001, Cohen et al., 2008). In the prone position, BP tends to drop initially following the tilt, while HR displays the biphasic response seen in the supine position (Yiallourou et al., 2008b).

In QS, there is significant maturation of BRS across the first 6 months of life in term infants resulting in significantly greater BRS in QS compared to AS at 5-6 months of age (Yiallourou et al., 2011). Immaturity of cardiovascular control during infancy has been implicated in the pathophysiology of SIDS.

Cardiovascular Control: Summary

The cardiovascular system is controlled primarily by the ANS. Although this system undergoes considerable development during fetal life it is not fully mature when an infant is born, particularly if born prematurely. It is believed that immaturity of autonomic cardiovascular control plays a role in the pathophysiology of the SIDS.

1.4 Sudden Infant Death Syndrome

1.4.1 Definition and Incidence

The Sudden Infant Death Syndrome (SIDS) is currently defined as:

> "*The sudden unexpected death of an infant under one year of age, with onset of the fatal episode apparently occurring during sleep, that remains unexplained after a thorough investigation, including performance of a complete autopsy and review of the circumstances of death and the clinical history*." (Krous et al., 2004)

In developed countries SIDS is a leading cause of infant death (Hauck and Tanabe, 2008), with an annual incidence of 0.5 deaths per 1000 live births in the USA (Sherry L Murphey et al., 2013) or approximately 2000 deaths per year. In Australia, the rate is 0.3 deaths per 1000 live births, equating to approximately 60 deaths each year (Li et al., 2012). Epidemiological studies conducted in the 1980s and 1990s identified the prone sleep position, which is placing the infant on its stomach to sleep, is a significant risk factor for SIDS (Moon et al., 2007, Irgens et al., 1995, Mitchell et al., 1991, Engelberts et al., 1991). As a result, public education campaigns to promote placing infants firstly on their side and more recently in a supine position, on their backs, to sleep in order to reduce the risk of SIDS were instigated (Linacre, 2007). This resulted in 40-80% reductions in the number of SIDS deaths between 1990 and 2005 across a range of countries (Hauck and Tanabe, 2008). Despite this, SIDS remains the leading causes of infant death in the post-neonatal period in developed countries (Mathews and MacDorman, 2010) however, in recent years the incidence of SIDS has plateaued sparking need for further research to eradicate the syndrome (Hauck and Tanabe, 2008).

1.4.2 Risk Factors

A number of risk factors for SIDS have been identified (Carpenter et al., 2004) and these can be divided into intrinsic or non-modifiable and extrinsic or modifiable risk factors as summarised in Table 5. Intrinsic risk factors are inherent characteristics that place an infant at increased risk for SIDS and include genetic predisposition, male sex, family history of SIDS and particular ethnic groups (Kinney and Thach, 2009, Hunt, 2001). Extrinsic risk factors, including prone sleeping, bed sharing, excessive bedding and smoking are those events or situations which place an infant under

undue homeostatic stress and thus are potential targets for risk reduction campaigns (Hauck et al., 2003). In addition to this, a small number of protective mechanisms have also been identified (Table 5), including pacifier or dummy use (Hauck et al., 2005) and breast feeding (Hauck et al., 2011), however the mechanism by which these factors are protective remains unclear. Evidence suggests that most infants who succumb to SIDS are exposed to more than one risk factor in the final sleep period (Trachtenberg et al., 2012).

There is a distinct peak in the incidence of SIDS occurring between 2 and 4 months of age, representing a developmental window of increased risk, with 90% of SIDS deaths occurring in the first 6 months of life (Moon et al., 2007). As mentioned previously, the prone sleeping position is a major risk factor for SIDS, however as the safe sleeping message has led to improved sleep practices, other risk factors have become more prominent (Hunt and Hauck, 2006).

Risk Factors		**Protective Factors**
Intrinsic	**Extrinsic**	
Genetic – Male sex – Familial SIDS – Polymorphisms in the gene encoding the promoter region of the serotonin transporter – Racial groups: Native American, African American, Aboriginal Australian, Maori **Developmental** – Prematurity/low birth weight – Intrauterine hypoxia or growth restriction – Age (peak 2-4 months) **Environmental** – Exposure to maternal cigarette smoking during pregnancy – Low socioeconomic status – Parental smoking, alcohol and drug use – Increased parity	– Prone sleeping position – Bed sharing – Soft or excessive bedding – Overheating – Mild infection – Extreme parental tiredness* – Overcrowded housing conditions* – Smoking – No pacifier use – Winter, no central heating * = confounding factor	– Pacifier/dummy use (recommended from after the establishment of breast feeding until 12 months of age) – Room sharing but not bed sharing – Breast feeding

Table 5: Summary of Risk and Protective Factors for the Sudden Infant Death Syndrome. Adapted from (Hunt and Hauck, 2006, Kinney and Thach, 2009, Moon et al., 2007, Kitsantas and Gaffney, 2010, Nonnis Marzano et al., 2008, Hauck et al., 2003, Blair et al., 1999, Willinger et al., 1994)

1.4.3 **Pathophysiology of the Sudden Infant Death Syndrome**

1.4.3.1 Mechanisms

The exact mechanisms underlying SIDS remain unclear, however a number of theories have been suggested including asphyxia (Kemp and Thach, 1991, Bolton et al., 1993) or overheating (Oriot et al., 1998, Tuffnell et al., 1995) due to sleeping in the prone position or with excessive bedding. However, although these mechanisms accounted for a small subset of sudden deaths they could not account for all deaths and so alternate theories have been developed. Another suggested mechanism for SIDS is prolonged apnoea and bradycardia (Steinschneider, 1972) however, follow-up studies have failed to confirm any association between respiratory events and SIDS (Committee on Fetus Newborn American Academy of Pediatrics, 2003, Southall et al., 1982, Franks et al., 1980). A large, multi-centre trial involving home infant monitoring identified that apnoeic events occur with a similar incidence in healthy infants and those at risk of SIDS during the period of greatest risk for SIDS (Ramanathan et al., 2001). Furthermore, the incidence of episodes of apnoea and bradycardia declines well before the period of peak risk for SIDS (Hoppenbrouwers et al., 2008). This suggests that apnoea and bradycardia are unlikely to play a causal role in the pathophysiology of SIDS.

Abnormal cardiovascular control has been implicated in the pathophysiology of SIDS and this is supported by recordings of terminal SIDS events on home cardiac monitors which revealed that SIDS deaths result from a severe and prolonged bradycardia (HR <70 beats per minute) leading to circulatory collapse, in conjunction with failure of the infant to arouse from sleep as illustrated in Figure 5 (Kelly et al., 1991). These recordings showed that bradycardia preceded any change in respiration, implicating abnormal control of the cardiovascular system as the primary mechanism of SIDS deaths. It should be noted, however, that these recordings do not include oxygen saturation and thus a potential role of hypoxia as a causal precursor to bradycardia and subsequent hypotension cannot be excluded. Furthermore, since the respiratory tracings are impedance-based, it cannot exclude the contribution of obstructive apnoeas the observed bradycardia. Our group and others, hypothesise that an uncompensated hypotension due to abnormal control of the cardiovascular system coupled with failure of arousal from sleep are the mechanisms that ultimately result in a SIDS death

(Harper, 2000). In order for this to occur, infants who succumb to SIDS must display abnormal control of the cardiovascular system in conjunction with abnormal arousal responses during sleep.

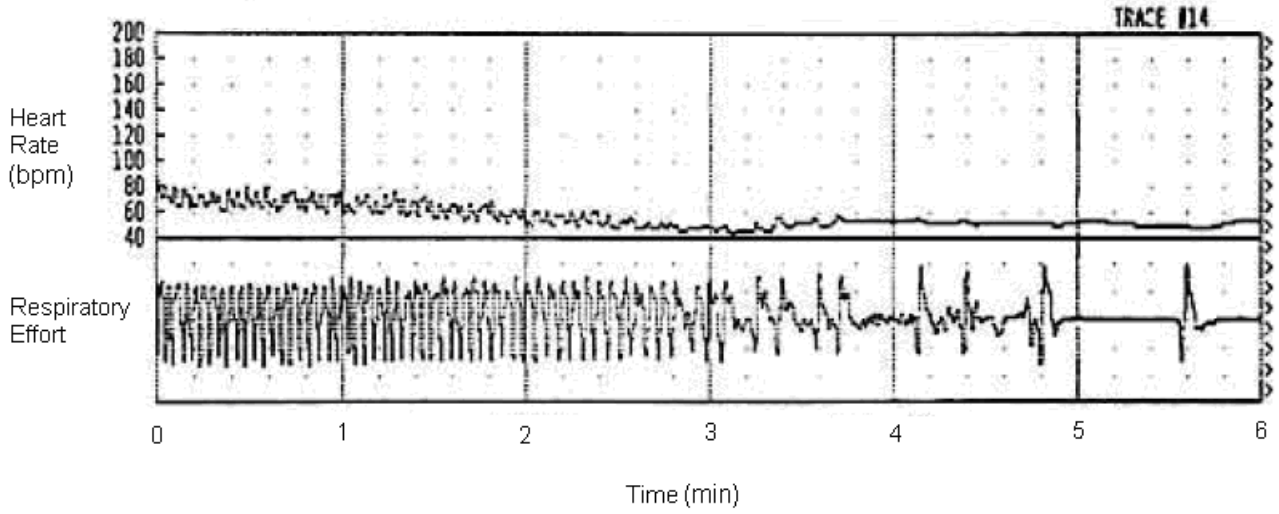


Figure 5: Recording of a SIDS death, adapted from (Kelly et al., 1991). This is a recording from a home monitor of an infant who succumbed to SIDS. It shows initial bradycardia (heart rate < 70 bpm) during which normal respiratory effort continues. After a period of a worsening bradycardia, respiratory effort becomes disrupted and eventually apnoea occurs. This infant was unable to be resuscitated.

1.4.3.2 Abnormal Control of the Cardiovascular System

Autonomic dysfunction has been strongly implicated in the pathogenesis of SIDS through considerable evidence suggesting abnormalities in the cardio-respiratory patterns of SIDS victims (Kluge et al., 1988, Schechtman et al., 1989, Kelly et al., 1986, Schechtman et al., 1990, Schechtman et al., 1988, Harper, 2001). In physiological studies, infants who subsequently died from SIDS were found to have features of autonomic cardiovascular dysfunction in the form of increased HR (Kelly et al., 1986, Wilson et al., 1985) with reduced HRV (Schechtman et al., 1989, Wilson et al., 1985), low parasympathetic tone and high sympathovagal balance (Franco et al., 2003, Kluge et al., 1988); while infants surviving an apparent life threatening event display altered HR responses to a CO_2 challenge (Edner et al., 2002). In addition to this, a number of risk factors for SIDS including the prone sleeping position (Galland et al., 1998), maternal smoking (Franco et al., 2000a) and overheating (Franco et al., 2000b) have been shown to be associated with autonomic dysfunction. This suggests that infants who later succumb to SIDS are less able to maintain cardiovascular homeostasis placing them at risk of bradycardia and hypotension during sleep. SIDS is hypothesised to occur in infants

who not only have abnormal autonomic control of the cardiovascular system but also reduced arousability (Hunt, 1992).

1.4.3.3 Failure to Arouse From Sleep

Arousal from sleep is an important protective mechanism against both endogenous and exogenous stressors. It is particularly important in the presence of a threat to cardiovascular homeostasis such as hypotension, as arousal is associated with increases in HR, BP and ventilation mediated by the ANS (Horner, 1996). Abnormal sleep patterns (Schechtman et al., 1992) and abnormal arousal from sleep are believed to play a role in the mechanism of SIDS deaths (Moon et al., 2007, Kahn et al., 1992) with several studies identifying that future SIDS victims display abnormal arousal processes. In particular, SIDS victims display significantly fewer cortical arousals but more frequent subcortical activations than control infants (Kato et al., 2003, Kato et al., 2006). This suggests that the arousal process of SIDS victims is incomplete with fewer arousals progressing from subcortical activation to a full cortical arousal (Kato et al., 2003). Furthermore, several SIDS risk factors have been found to be associated with reduced arousability including the prone sleeping position (Horne et al., 2001) and maternal smoking (Richardson et al., 2009). Autonomic control has also been shown to be dysfunctional in infants exposed to these risk factors suggesting the brainstem, the region of the brain responsible for regulating both arousal from sleep and the ANS (Kinney, 2009), may be dysfunctional in these infants. Therefore, it is possible that brainstem dysfunction underpins the abnormalities in cardiovascular control and arousal from sleep seen in SIDS victims (Kinney, 2009, Kinney et al., 2001).

1.4.3.4 The Brainstem Hypothesis

The brainstem hypothesis suggests that SIDS deaths occur due to abnormalities in the brainstem resulting in dysfunctional autonomic control of the cardiovascular system and impaired arousal from sleep. This impairs the infant's ability to respond to common cardiovascular events, such as bradycardia and hypotension, which may occur during sleep. Considerable evidence has been produced to support the brainstem hypothesis with the first findings being gliosis, or scarring, of the brainstem in SIDS victims (Naeye, 1976, Takashima et al., 1978, Kinney et al., 1983, Kinney et al.,

2002). This suggests that the infants were exposed to chronic brainstem injury prior to the lethal SIDS event, most likely chronic hypoxia. Following this, neurotransmitter defects were identified in the brainstem's of SIDS victims with the greatest defect being found in the medullary serotonin (5-HT) system (Duncan et al., 2010, Paterson et al., 2006, Kinney et al., 2003), responsible for autonomic control of cardio-respiratory function and regulation of circadian rhythm (Paterson et al., 2006). In addition, a number of structural abnormalities have been identified in SIDS brainstems in regions involved in cardio-respiratory control (Biondo et al., 2003, Filiano and Kinney, 1992, Takashima and Becker, 1991, Machaalani and Waters, 2008). Evidence suggests that brainstem abnormalities are influenced by intrauterine insults (Kinney et al., 2002) as well as exposure to SIDS risk factors including sleeping in the prone position (Machaalani and Waters, 2008).

1.4.3.5 The Prone Sleeping Position

In the past, the prone sleeping position was believed to result in impaired temperature regulation (Oriot et al., 1998, Tuffnell et al., 1995) and rebreathing of expired air (Kemp and Thach, 1991, Bolton et al., 1993), however whilst these factors may contribute to a small number of SIDS deaths they are unlikely to be underlie the majority of cases. Similarly, a large study utilising home infant monitoring has found no increase in extreme respiratory events in the prone compared to the supine sleeping position (Lister et al., 2012). Instead, the increased risk of SIDS in the prone position is widely believed to be due to the influence of prone sleeping on cardiovascular control and arousal from sleep.

A number of studies have suggested the prone sleeping position is associated with altered autonomic control of the cardiovascular system. In term infants, HR has been found to be higher in the prone position in both AS and QS (Tuladhar et al., 2003, Chong et al., 2000), this is likely to be due to peripheral vasodilation in response to increased body temperature in the prone position. At 2-3 months, this increase in temperature is not compensated for by an increase in HR resulting in a drop in BP in term infants (Chong et al., 2000, Yiallourou et al., 2008a). In term infants the prone position results in abnormal cardiovascular responses to head up tilt-induced changes in BP reflecting reduced autonomic responsiveness (Yiallourou et al., 2008b). Furthermore, BRS has been shown to be reduced

in the prone compared to the supine position most prominently at 2-3 months of age (Yiallourou et al., 2011). Thus, sleeping prone places an infant in a position where cardiovascular control is compromised and this is most marked during the period of peak incidence of SIDS.

Our group have recently established that cerebral oxygenation is reduced in the prone sleeping position in term infants (Wong et al., 2011). It is thought that prone sleeping results in impaired flow through the vertebral and basilar arteries as well as the internal jugular vein responsible for providing blood flow to the brainstem (Pamphlett et al., 1999). This impairment in cerebral oxygenation is maximal at 2-4 weeks of age in term infants and improves with age due to anatomical maturation of the infant (Wong et al., 2011). Thus, the addition of a reduction in BP at 2-3 months potentially confounds already impaired blood flow to the brainstem in the prone position.

In addition to the effects on cardiovascular control, the prone position has been associated with altered arousal which may be associated with reduced cerebral oxygenation. Studies have shown that when slept prone healthy term infants display increased total sleep time (Kahn et al., 1993), increased duration of QS (Kahn et al., 1993), fewer spontaneous arousals (Kahn et al., 1993, Ariagno et al., 2006) and reduced overall arousability (Horne et al., 2001, Galland et al., 1998). This reflects a significant reduction in the arousability of term infants slept prone. Similarly, preterm infants display higher arousal thresholds in both AS and QS when prone compared to sleeping supine, most prominently at 2-3 months of age, the age of peak incidence of SIDS (Horne et al., 2002). Prone sleeping is of particular concern in the preterm population as these infants are often slept prone whilst being nursed in hospital and this practice may continue when the infant is discharged home (Grazel et al., 2010), thus contributing to their increased risk of SIDS.

1.4.3.6 The Triple Risk Model

In 1994, Filiano and colleagues proposed the Triple Risk Model in order to combine the various contributing factors in the pathophysiology of SIDS. This model suggests that SIDS deaths occur when three elements of risk interact (Filiano and Kinney, 1994) (Figure 6) including: 1) a vulnerable infant, 2) a critical developmental period and 3) an exogenous stressor. A vulnerable infant, such as

one born preterm, has subtle CNS or systemic impairments leading to altered cardiovascular control and arousal mechanisms that place it at risk of SIDS. The critical developmental period occurs between 2-3 months of age where a distinct peak in the incidence of SIDS occurs. This is thought to be due to rapid changes in physiological systems occurring during this period. Finally, an exogenous stressor, such as the prone sleeping position, places a vulnerable infant under undue homeostatic stress. Filiano and colleagues suggest that an infant's underlying vulnerability will remain dormant until all three elements of risk occur simultaneously, overwhelming the infant's already impaired homeostatic mechanisms and resulting in a SIDS deaths (Filiano and Kinney, 1994).

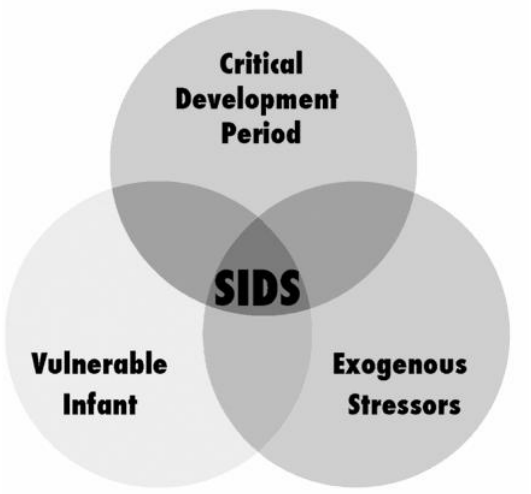


Figure 6: The Triple-Risk Model (Filiano and Kinney, 1994). This model suggests that Sudden Infant Death Syndrome (SIDS) deaths occur when three elements of risk interact including: 1) a vulnerable infant, 2) a critical developmental period and 3) an exogenous stressor. A vulnerable infant (preterm infant) has subtle central nervous system or systemic impairments leading to altered cardiovascular control and arousal mechanisms that place it at risk of SIDS. A critical developmental period (2-3 months of age) occurs when an infant is most vulnerable. An exogenous stressor (prone sleeping position) places a vulnerable infant under undue homeostatic stress.

Sudden Infant Death Syndrome: Summary

SIDS remains a leading cause of death in the post-neonatal period in developed countries. SIDS is thought to occur due to immature cardiovascular control resulting in a hypotensive episode during sleep in combination with a failure of arousal from sleep. Brainstem dysfunction has been implicated in SIDS due to its integral role in both cardiovascular control and arousal. Furthermore, prone sleeping has been associated with alterations in cardiovascular control, reduced cerebral oxygenation and impaired arousal in term infants.

1.5 Preterm Infants and the Sudden Infant Death Syndrome

Evidence suggests that preterm infants have almost 4 times the risk of SIDS when compared to control infants (Blair et al., 2006b), an association that is likely to be multi-factorial in origin. It appears that in preterm infants SIDS deaths occur at a later post-natal age than the peak incidence in term infants (Halloran and Alexander, 2006, Malloy and Hoffman, 1995), which occurs at 2-3 months of age (Figure 7). However, this equates to a similar post-term age in preterm infants of 7-9 weeks post-term corrected age (CA) depending on GA at birth (Malloy, 2013). A number of theories have been postulated to explain the increased incidence of SIDS in the preterm population including immaturity of the ANS and altered arousal responses.

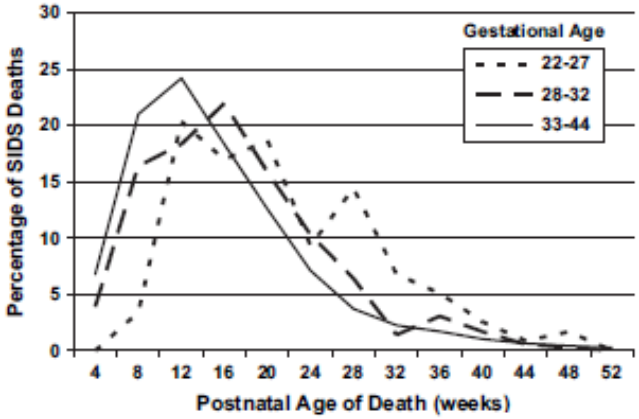


Figure 7: Peak Incidence of Sudden Infant Death Syndrome (SIDS) According to Gestational Age at Birth, adapted from (Halloran and Alexander, 2006). This graph illustrates that the peak incidence for SIDS deaths amongst the preterm population occurs at an older post-natal age than that seen amongst the term or near-term population. However, this results in a more similar post-conceptional age of peak incidence between preterm and term born infants.

1.5.1 Abnormal Arousal

It has been proposed that the increased risk of SIDS amongst preterm infants may be attributed to depressed arousal responses seen in these infants. Prematurity influences both the frequency of spontaneous arousals and the response to stimuli during sleep due to a maturational delay in the arousal process (Franco et al., 2010, Zotter et al., 2008). Furthermore, preterm infants display increased arousal latency, the period of time between an arousing stimulus and when the infant actually arouses, compared to age-matched term infants with greater oxygen desaturation during

hypoxic challenges in both sleep states up to 2-3 months of age (Verbeek et al., 2008). In addition, preterm infants display abnormal HR responses during spontaneous arousals when compared to term infants. During arousal term infants respond with an increase in HR and an increase in the HR-respiratory frequency-ratio whilst preterm infants exhibition a decrease in HR (Hanzer et al., 2007) and no change in HR-respiratory frequency-ratio (Zotter et al., 2009). However, these studies were conducted whilst the infants were sleeping supine and the influence of the prone sleeping position was not examined.

Preterm infants display significantly increased total sleep time and greater sleep efficiency when prone and display more awakenings and arousals when supine (Bhat et al., 2006). Furthermore, when prone, preterm infants experience significantly fewer spontaneous arousals than in the supine position at 1 and 3 months post-term age, coinciding with the period of peak risk for SIDS (Ariagno et al., 2006) with higher arousal thresholds in both sleep states in the prone compared to the supine position at 2-3 months post-term (Horne et al., 2002). While prone sleeping appears to alter arousability in preterm infants, the underlying mechanisms have not yet been elucidated. Potential mechanisms include impaired cerebral perfusion in the prone position possibly related to immature control of both systemic and cerebral vascular control (Wong et al., 2011).

1.5.2 **Immature Cardiovascular Control**

1.5.2.1 Heart Rate

Preterm birth has a considerable effect on cardiovascular parameters including HR and BP. Preterm infants at term-equivalent age have higher resting HRs than infants born at term and this persists up until 7 months of age (Katona et al., 1980, Eiselt et al., 1993). It has been suggested that while HR is primarily dependent on post-conceptional age, fluctuations in HR are also influenced by post-natal age, with HR in both preterm and term infants peaking between 4 and 10 weeks post-natal age (Katona et al., 1980). Similar studies have also found HR to be significantly higher in preterm infants assessed at term-equivalent age than term born control infants (Eiselt et al., 1993); with one study finding preterm infants to have a HR of 155 beats per minute (bpm) versus 117 bpm in term infants (Patural et al., 2008). However, some conflicting studies have found no difference in HR

between preterm and term infants when studied at 2-3 weeks and 2-3 months post-term CA (Tuladhar et al., 2005). Similarly, in preterm infants born between 28 and 32 weeks GA, no difference in HR between preterm and term infants was seen when followed up to 6 months post-term corrected age (Witcombe et al., 2008). These studies also found that the increase in HR from QS to AS due to the increased sympathetic activity in AS, seen in term infants was absent in preterm infants until 5-6 months post-term age, suggesting that impaired autonomic function persists past term-equivalent age in preterm infants, despite finding no baseline difference in HR between preterm and term infants (Witcombe et al., 2008, Tuladhar et al., 2005).

1.5.2.2 Blood Pressure

Only a limited number of studies have assessed BP after term equivalent age in preterm infants. Early studies assessing BP in preterm infants have found that at approximately 12 weeks post-term age there was no difference in BP between preterm and term infants, however these measurements were performed during wakefulness (Greenough and Emery, 1993). A supporting study assessing BP in very low birth weight and low birth weight preterm infants and normal birth weight term infants at 4 months post-term age found no significant difference in BP between groups (Georgieff et al., 1996). More recently, a study assessing BP continuously during sleep in preterm infants has reported BP to be lower in preterm compared to term infants at matched ages up until 5-6 months post-term CA (Witcombe et al., 2008). This study found no difference in HR between the preterm and term infants and the authors concluded that altered vascular regulation, as opposed to impaired cardiac function, was responsible for the discrepancy in BP between groups. This study found BP to be significantly higher in AS compared to QS in preterm infants studied at 2-4 weeks CA, 2-3 months CA and 5-6 months CA (Witcombe et al., 2008). These studies suggest that baseline HR and BP may be altered as a result of preterm birth which implies that preterm birth may have a considerable effect on cardiovascular control.

1.5.2.3 Heart Rate Variability

HR variability (HRV) is commonly used to determine the integrity of ANS control of HR and can provide information about sympathetic and parasympathetic activity (Electrophysiology Task Force of the European Society of Cardiology, 1996). A number of studies have investigated the normal maturation of autonomic HR control. Clairambault et al., compared the HR and HRV parameters of 8 preterm infants (31-36 weeks gestation), 8 intermediate infants (37-38 weeks gestation) and 8 full term infants (38-41 weeks gestation) studied within 11 days of birth, in order to assess normal maturation of the ANS (Clairambault et al., 1992). This study found that all HRV parameters increased from preterm to intermediate to term infants reflecting autonomic maturation. The authors also reported that HF HRV underwent a steep increase from preterm age to intermediate age infants, reaching a plateau thereafter, while LF variability increased steadily from 31 to 41 weeks (Clairambault et al., 1992), thus parasympathetic activity undergoes a period of rapid development in late gestation. Similar results have been reported more recently in a study which compared 39 premature neonates born at 29-35 weeks GA and studied within 1 week of birth with normative data for term infants. Consistent with previous studies, this study revealed preterm infants to have reduced HRV parameters compared to term infants, particularly in the HF variability domain (Longin et al., 2006). Furthermore, when the premature infants were divided into those born prior to 32 weeks and those born after 32 weeks those born at a later gestation had higher HRV parameters, particularly in the HF domain (Longin et al., 2006). In summary, HRV increased across gestation and shortly after birth preterm infants display immature ANS cardiovascular control, particularly the parasympathetic branch, with greater immaturity in infants born at earlier GAs. However, these studies did not follow infants longitudinally to term age and thus do not investigate maturation of cardiovascular control following preterm birth.

Studies assessing the effect of preterm birth on the postnatal maturation of autonomic HR control suggest that preterm birth impairs normal maturation, as preterm infants reaching theoretical term have reduced HRV compared to term infants (Eiselt et al., 1993, Patural et al., 2004, De Rogalski Landrot et al., 2007). One study comparing 12 prematurely born infants studied between 37-41 weeks

post-conceptional age with 16 term born infants studied at < 10 days postnatal age, found the preterm cohort to have reduced HRV and an altered sympathovagal balance with diminished parasympathetic activity (Eiselt et al., 1993). This study also demonstrated that while in the term infants HR and LF variability were higher in AS compared to QS, in preterm infants there was no apparent effect of sleep state. Similar results were found in a study which compared 23 preterm infants born between 25 and 37 weeks GA and studied at term-equivalent age with 8 full term infants studied within the first week of life. HF HRV was found to be significantly lower in the preterm compared to the term born infants, suggesting delayed parasympathetic maturation, with greater prematurity being associated with lower parasympathetic activity at term age (Patural et al., 2004). A recent, study which compared HRV parameters between fetuses at 25-36 weeks GA and premature infants born between 24-36 weeks GA, found lower HF variability in the premature infants, thus supporting previous studies suggesting preterm birth results in delayed maturation of parasympathetic activity (Padhye et al., 2008). Particular vulnerability of the parasympathetic branch to impairment following preterm birth is likely to be due to differing development of the parasympathetic and sympathetic branches of the ANS during gestation. Sympathetic activity is dominant early in gestation whilst the parasympathetic branch undergoes rapid maturation between 25 and 32 weeks of gestation (David et al., 2007, Schneider et al., 2009). Therefore maturation of the parasympathetic branch is vulnerable to disruption from preterm birth occurring during this period of rapid development.

Alterations in cardiovascular control appear to persist beyond term-equivalent age in preterm infants. A recent study assessing HRV and BPV in preterm infants longitudinally between 2-4 weeks and 5-6 months post-term age found a relative plateau in HF, LF and total power HRV activity across the first six months of life in QS in preterm compared to age-matched term infants resulting in significant reductions in all three parameters at 5-6 months post-term age (Yiallourou et al., 2013). The greatest deficit was seen in the HF component of HRV, suggesting impaired maturation of parasympathetic activity contributes to diminished HRV in preterm infants (Yiallourou et al., 2013). Furthermore, studies in preterm infants with persistent apnoea of prematurity have shown a trend towards reduced HRV compared to term infants persisting until approximately 3 months post-term age, with greater

deficits in infants born prior to 30 weeks of gestation (Henslee et al., 1997). Reassuringly, a long-term longitudinal study which found reduced HRV parameters in preterm compared to term infants in the neonatal period, reported no differences in autonomic parameters between term and preterm infants when followed-up at 2-3 years of age (De Rogalski Landrot et al., 2007).

In summary, a number of studies have suggested that preterm delivery is associated with altered autonomic activity with persists beyond term-equivalent age. In particular, suppression of parasympathetic activity may represent an impaired ability to control HR in otherwise healthy, low risk preterm infants. It has been suggested that prematurity impairs parasympathetic maturation, possibly due to prioritization of processes necessary for life, such as breathing and digestion, over the growth and development of less essential systems, such as the nervous system (Eiselt et al., 1993, Padhye et al., 2008). Altered cardiovascular control may place these infants at risk of cardiovascular instability, particularly during sleep, in the first year of life.

1.5.2.4 Baroreflex Mediated Cardiovascular Control

Early studies investigating baroreflex function in preterm infants focused primarily on HR and produced conflicting results. One early study found no significant tachycardia when non-distressed preterm infants aged between 26 and 38 weeks were head-up tilted to an angle of 45° (Waldman et al., 1979). Following on from this study, the same group later reported a significant increase in HR in the first 5 seconds following the tilt, but stated that individual responses varied greatly and concluded that the HR component of the baroreflex was immature in the neonatal period (Holden et al., 1985). Neither of these studies took into account sleep state which significantly affects HR. Similar results were produced from a later study which failed to illicit a significant increase in HR following a 45° head-up tilt in preterm infants born between 27 and 36 weeks (Lagercrantz et al., 1990). In contrast, further studies investigating the effect of tilting on HR in term (Finley et al., 1984, Thoresen et al., 1991) and preterm infants (Finley et al., 1984, Massin et al., 2002) have found significant increases in HR following a head-up tilt in both QS and AS. These differences may be attributed to the varying GAs of the infants studied, a suggestion supported by Mazursky et al., who studied infants born at 28-32 weeks GA longitudinally across the first 5 postnatal weeks. This study revealed an increased HR

response to 45° head-up tilting with increasing postnatal age suggesting that in preterm infants baroreflex control of HR matures with age (Mazursky et al., 1998).

Only a limited number of studies have assessed baroreflex control of BP, due to a paucity of appropriate methods for non-invasively inducing changes in BP and techniques for measuring BP continuously and non-invasively. Drouin et al., validated a method of analysing spontaneous fluctuations in BP and the corresponding changes in HR to assess baroreflex sensitivity (BRS) (Drouin et al., 1997), and found that preterm infants studied prior to term age had lower BRS than term born infants. Using similar methods, postnatal maturation of BRS following preterm birth was assessed in a cohort of preterm infants (mean gestation of 30.6 weeks), studied longitudinally once a week until discharge from hospital. This study revealed significant maturation of BRS with increasing postnatal age, however preterm infants reaching term still had significantly lower BRS than infants born at term (Gournay et al., 2002). Similar results were reported by Andriessen et al., who investigated BRS in two groups of preterm infants born at 28-32 and 32-37 weeks GA and a cohort of term infants, using spontaneous fluctuations in HR and BP. Consistent with previous studies, they found that BRS increased with increasing postnatal age and this was attributed to parasympathetic maturation because vagally mediated HF HRV also increased with age (Andriessen et al., 2005). Furthermore, a recent study following preterm birth up to 5-6 months post-term CA found preterm infants had significantly reduced BRS at 5-6 months CA compared to term infants (Witcombe et al., 2012). This was despite having higher BRS at 2-4 weeks CA suggesting that while term infants undergo considerable maturation during the first 6 months of life, this maturation is significantly altered in preterm infants (Witcombe et al., 2012). Thus, reduced BRS may leave preterm infants vulnerable to both hypotensive and hypertensive episodes due to impaired short term regulation of BP.

BP control in preterm infants has also been assessed using head-up tilts. Witcombe et al., studied preterm infants born between 28 and 32 weeks GA at 2-4 weeks, 2-3 months and 5-6 months post-term age using 15° head-up tilts during QS and AS. They found that although HR responses were comparable between preterm and term infants, the BP response was significantly altered at 2-4 weeks and 2-3 months CA, with BP in the preterm cohort taking significantly more heart beats to return to

baseline following the tilt (Witcombe et al., 2009). Similarly, Cohen et al., found that appropriately grown preterm infants exhibited an exaggerated BP response to a 60° head-up tilt compared to term born control infants, with the exaggeration being much greater in small for GA preterm infants and infants born to smoking mothers (Cohen et al., 2008). Altered BP responses were also found in preterm infants with bronchopulmonary dysplasia compared with term control infants who underwent sideways-motion and 45° head-up tilts at 12 weeks CA (Viskari et al., 2007). These responses have been attributed to sympathetic hyperactivity and may represent early physiological programming in response to adverse circumstances experienced early in development. Whilst this may contribute to an increased risk for SIDS it has also been suggested that this may represent early manifestations of impaired cardiovascular function which can lead to cardiovascular disease later in life.

In summary, studies investigating both HR and BP control have found autonomic cardiovascular control, predominantly parasympathetic activity, to be immature in preterm infants up to and beyond term-equivalent age. This may be because premature birth stunts the development of parasympathetic activity or alternatively, altered ANS activity may have contributed to the premature birth. A number of theories have been suggested to explain ANS immaturity in preterm infants, including cardiac and vessel innervation, neurotransmitter production and receptor efficiency, however, it is possible that ANS immaturity reflects global central nervous system (CNS) immaturity related directly to a reduced gestational period (Patural et al., 2004). Following preterm birth, normal development may be impaired as vital functions previously undertaken by the placenta take precedence over planned maturation. In this case, global CNS immaturity may imply immaturity of other functions, and in the case of very preterm birth, this may even include functions of the vital organs such as control of the cerebral vascular circulation.

Preterm Infants and the Sudden Infant Death Syndrome: Summary

Preterm infants are at significantly increased risk of SIDS. This is thought to be due to immaturity of cardiovascular control with preterm infants displaying immature autonomic control of the cardiovascular system beyond term-equivalent age and during the period of peak risk for SIDS. It has been suggested that immaturity of cardiovascular control may also be seen in the cerebral circulation placing preterm infants at risk of impaired cerebral oxygenation.

1.6 Cerebrovascular Control

The brain is a highly metabolically active organ, requiring 3.5ml of oxygen per 100g of brain tissue per minute which accounts for approximately 15% of the total resting cardiac output. Approximately 60% of the total energy usage of the brain is for generation of continuous electrical activity by neurons (Harper, 1990). The remaining 40% of energy usage is responsible for homeostatic cellular functions undertaken largely by the supporting cells within the brain. The neuronal component of cerebral energy usage is more variable, responding to changes in functional state and arousal, thus the major contributor to changes in cerebral metabolic activity is neuronal activity (Clarke and Sokoloff, 1999).

Consciousness is lost within 10 seconds of complete occlusion of cerebral blood flow (CBF) with corresponding irreversible damage to tissues. Due to this high metabolic activity of the brain, impaired CBF resulting in hypoxia and ischemia or haemorrhage can have catastrophic effects on cerebral tissue (Harper, 1990). Furthermore, the immature brain is particularly susceptible to oxidative stress, thus hyper-perfusion and hyper-oxygenation are major concerns in the context of preterm brain injury (Back et al., 1998, Wong et al., 2009a). Therefore, maintaining relatively constant CBF in the presence of changing systemic variables is essential. In the healthy, adult brain, CBF is influenced by myogenic mechanisms principally cerebral pressure autoregulation; metabolic mechanisms including CBF-metabolism coupling; chemical influences, particularly oxygen (O_2) and carbon dioxide (CO_2) and to a lesser degree neural mechanisms, including efferent vasomotor effects, mechanoreceptors and chemoreceptors (Clarke and Sokoloff, 1999). As such, clinicians and scientists alike have been interested in investigation of cerebral haemodynamics for clinical and research purposes.

1.6.1 Methods of Investigating Cerebral Haemodynamics

When clinicians and scientists initially became interested in the investigation of CBF in preterm neonates the common techniques had a number of limitations. Xenon-133 and positron emission tomography, which involves measurement of xenon-133 clearance to determine CBF, is limited by its

use of ionising radiation and the associated risks. Another commonly used technique, Doppler ultrasound velocimetry is limited by its operator-dependence and the technical difficulty in maintaining angle of insonation for optimal measurement. Furthermore, jugular occlusion plethysmography, which involves complete occlusion of the jugular vein by direct pressure, is potentially risky in small, unstable preterm infants (Cowan et al., 1983).

Thus, the need existed for a simple, non-invasive and safe method of measuring CBF which became available with the introduction of Near-Infrared Spectroscopy (NIRS). NIRS utilises near-infrared light which is capable of penetrating biological tissue and is absorbed in an oxygen-dependent manner by haemoglobin (Hb) (Jobsis, 1977). Near-infrared light passes particularly easily through the thin and soft bone of the neonatal skull, thus enabling NIRS to provide non-invasive measurement of cerebral haemodynamics in neonates (Soul and du Plessis, 1999).

Although a significant improvement on previous techniques, NIRS is not without its own limitations. These include a relatively high signal-to-noise ratio, susceptibility to movement artefact and intra-patient and inter-patient variation (van Bel et al., 2008). Another concern is the non-specific, regional measurement of tissue oxygenation which includes measurement of all tissues between the light source and the detector including skin, bone, cerebrospinal fluid, and brain matter to an unknown depth (Wolf and Greisen, 2009). Furthermore, NIRS provides a weighted average of the saturations within the venous and arterial compartments; this weighting is difficult to determine precisely and may differ over time (Wolf and Greisen, 2009). However, despite these limitations NIRS is currently one of the most widely used technique for assessment of cerebral haemodynamics in infants (van Bel et al., 2008).

The most common prototype of NIRS used in clinical research is the continuous wave NIRS. Continuous wave NIRS provides continuous changes in oxygenated Hb (ΔO_2Hb) and deoxygenated Hb (ΔHHb). Furthermore, total Hb (HbT), calculated by adding ΔO_2Hb and ΔHHb, is an important indicator of cerebral blood volume (CBV)(Volpe, 2008). Continuous wave NIRS can be used to obtain absolute intermittent quantification of CBF and CBV, by employing spontaneous or induced

(by haemodynamic or biochemical manipulation) parameter changes in tissue. Most commonly, measurement of CBF by NIRS utilises a modification of the Fick principle and a purely intravascular and non-diffusable tracer. The tracer can be either endogenous, such as the oxygen bolus technique (Edwards et al., 1988) or exogenous, such as the near infrared dye, indocyanine green, administered intravenously (Patel et al., 1998).

The clinical drive for absolute values of cerebral haemodynamics without the need for biochemical or haemodynamic manipulation has led to the development of "cerebral oximetry" using NIRS techniques. Using multi-distanced sensors and different algorithms (Suzuki et al., 1999, Yoshitani et al., 2007, Nicklin et al., 2003) absolute values of cerebral oxygenation can be calculated from the changes in oxygenated and deoxygenated Hb. This is often expressed as tissue oxygenation index (TOI, %) or regional cerebral oxygen saturation ($rScO_2$, %), depending on the NIRS prototype and algorithms used (Wolf and Greisen, 2009).

HbD, TOI and $rScO_2$ have been used as surrogates of CBF with a few assumptions which include stability of arterial oxygen saturation and cerebral metabolic rate (Wolf and Greisen, 2009). Additional parameters discussed in this review include cerebral metabolic rate of oxygen consumption ($CRMO_2$, ml/100g/min) which refers to the rate at which oxygen is used within the cerebral tissue and thus is a marker of cerebral metabolic activity. Cerebral fractional tissue oxygen extraction (FTOE) refers to the percentage of oxygen being extracted from the arterial blood by the cerebral tissue and can be used to determine the balance between oxygen delivery and consumption. Cerebral oxygen delivery (ml/100g/min) refers to the product of CBF and cerebral arterial oxygen content. Cerebral arterial oxygen content (ml/100ml) can be calculated using the standard formula: arterial oxygen saturation (%) x Hb (g/dL) x 1.39 (stoichiometric oxygen carrying capacity of Hb) + dissolved oxygen (ml/dL) (Wong et al., 2009a).

New technologies for non-invasive assessment of cerebral haemodynamics are under investigation and include techniques such as arterial spin-labelled perfusion magnetic resonance spectroscopy, however this requires the patient to be transported to a magnetic resonance imaging facility and

provides only a cross-sectional snapshot of data, and diffuse optical correlation spectroscopy for which portable devices are currently being developed (Li et al., 2013, Goff et al., 2010).

1.6.2 **Cerebral Autoregulation**

In adults, CBF is tightly controlled in order to ensure that the brain's metabolic requirements are constantly met. CBF is determined by the cerebral perfusion pressure and cerebrovascular resistance. Cerebral perfusion pressure is the pressure gradient which drives blood flow to the brain, which is influenced by systemic arterial pressure and intracranial pressure (Kaiser, 2008). Due to the rigid nature of the skull, intracranial pressure is determined by the contents of the skull and, in the absence of oedema, should remain relatively stable. Systemic arterial pressure, however, can undergo large fluctuations and thus the cerebral vasculature must be capable of protecting the brain against these fluctuations in order to maintain a constant perfusion pressure. This is referred to as cerebral pressure autoregulation and involves changes in cerebrovascular resistance by constriction and dilation of cerebral vessels in the presence of increasing or decreasing arterial pressure in order to ensure CBF remains steady (Kaiser, 2008). In adults, cerebral pressure autoregulation operates within a range of BPs (mean arterial pressure (MAP) between 60 and 150 mmHg (Figure 8)) above and below which CBF becomes pressure passive, changing in direct correlation with changes in BP (Saladin, 2011). Cerebral autoregulation can be divided into 'static' and 'dynamic' with static autoregulation referring to the steady state relationship between MAP and CBF while dynamic autoregulation describes the short term response of CBF to sudden changes in MAP (Greisen, 2005). In infants, especially those born preterm and requiring intensive care, cerebral pressure autoregulation may be immature, may operate within a narrower range of arterial pressures, or be impaired to the extent of having a pressure-passive cerebral circulation (Berger et al., 2002).

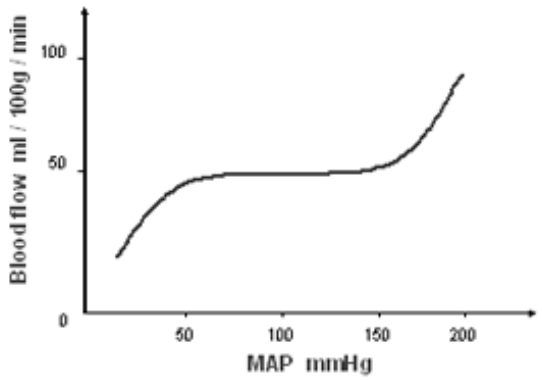


Figure 8: Cerebral Autoregulation (Adapted from (Harper, 1990)) Cerebral autoregulation ensures that cerebral blood flow is maintained at a constant level despite changes in the mean arterial pressure (MAP). In adults it operates within MAP ranging from 60 to 150 mmHg, however in infants this range is believed to be narrower. This is in part due to lower BP in infancy causing the autoregulatory curve to shift to the left.

1.6.3 **Cerebral Blood Flow-Metabolism Coupling**

In addition to BP, CBF is also influenced by cerebral metabolic demand. Cerebral flow-metabolism coupling ensures that regions with increased cerebral metabolism due to increased neuronal activity receive increased CBF. This mechanism is believed to be more linearly related to increased glucose requirements than to increased oxygen demand (Menon, 2000). A number of different substances have been suggested to mediate increased blood flow in the presence of increased neuronal activity including potassium, adenosine and nitric oxide; however the precise interactions between these substances and CBF remain unclear (Menon, 2000).

In the healthy adult brain, increased blood flow actually overshoots the oxygen requirements of activated neurons, resulting in an increase in cerebral oxygenation (Meek et al., 1995). In infants, cerebral flow-metabolism coupling may be immature and so increasing neuronal metabolic requirements are met by increased oxygen extraction which results in a reduction in cerebral oxygenation (Wong et al., 2011). This is evidenced by a decrease in cerebral oxyhaemoglobin concentration following the transition from QS, a state of brain quiescence and low metabolic activity, to AS, a state of increased brain metabolic activity similar to wakefulness (Munger et al., 1998). Furthermore, in infant studies of brain activation following visual stimulation, NIRS detected an increase in CBV suggesting increased blood flow. However, an increase in deoxyhaemoglobin was also seen suggesting that in term infants, increases in oxygen consumption due to neuronal activity

outstrip the haemodynamic response of increased CBF (Meek et al., 1998a). Increased CBF has also been seen during neonatal seizures, an increase that was unrelated to increases in BP and thought to be due to increases in cerebral metabolic demand during seizure activity (Boylan et al., 1999). However, although CBF increases in response to the increased neuronal activity during seizures, the cerebral haemodynamic response appears to be inadequate resulting in reduced cerebral oxygenation and potentially cerebral hypoxia (Silas et al., 2012).

Evidence of maturation of CBF-metabolism coupling after term birth was shown in one study which longitudinally investigated cerebral TOI across the first 6 months of life in term infants during both QS and AS (Figure 9). At 2-4 weeks of age cerebral oxygenation was higher in QS than in AS, this suggests immature cerebral flow-metabolism coupling as the increased metabolic demand of AS is not being met by increased CBF resulting in increased oxygen extraction and a reduction in cerebral oxygenation to meet the brains oxygen requirement. At 2-3 months there was no difference between the sleep states while at 5-6 months cerebral oxygenation was higher in AS than in QS as you would expect to see with effective cerebral flow-metabolism coupling as CBF is increased, exceeding the metabolic requirements of the brain during AS. This suggests that maturation of cerebral flow-metabolism coupling occurs during this period (Wong et al., 2011).

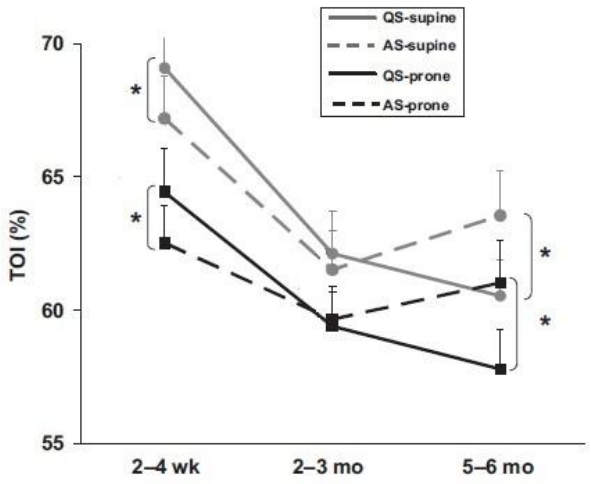


Figure 9: Cerebral Oxygenation in Term Infants (Wong et al., 2011). This image shows the effect of sleep state on tissue oxygenation index (TOI) at three postnatal ages; 2-4 weeks, 2-3 months and 5-6 months. Cerebral TOI is significantly lower in active sleep (AS) than in quiet sleep (QS) at 2-4 weeks, with no difference seen at 2-3 months and cerebral TOI is higher in AS at 5-6 months. * $p<0.05$ QS versus AS

1.6.4 **Influence of Oxygen and Carbon Dioxide on Cerebral Haemodynamics**

CBF is largely influenced by the partial pressure of carbon dioxide ($PaCO_2$) and oxygen (PaO_2) in the arterial circulation and in ventilated patients these variables are easily influenced by altering ventilation parameters. CO_2 is known to be a potent cerebro-vasodilator while increasing arterial O_2 content results in vasoconstriction (Wong et al., 2010, Jones et al., 1981) . These mechanisms aim to protect the brain from hypoxia which will result in neuronal death and hyperoxia which may lead to oxidative stress. In adults, $PaCO_2$ has a linear relationship with CBF resulting in a 2-6% increase in CBF with each Torr increase in $PaCO_2$, this change in CBF in response to changes in $PaCO_2$ is known as cerebral carbon dioxide vasoreactivity. In healthy term newborns, carbon dioxide reactivity is present at birth with a mean CBF-CO_2 reactivity of 25.4%/kPa, thus CBF increased 25.4% per kilopascal (7.5mmHg) increase in $PaCO_2$ (Pryds et al., 1990b). However, in severely asphyxiated term neonates CO_2 reactivity was abolished with a mean CBF-CO_2 reactivity of -8.7%, suggesting that brain injury disrupts normal cerebral vascular control in term infants (Pryds et al., 1990b). Conversely, an inverse relationship exists between PaO_2 and CBF, with increasing arterial oxygen gas tension resulting in reduced CBF (Citerio and Andrews, 2009). This relationship has been illustrated in healthy adults, with hypoxia resulting in increased blood flow velocity and decreased vascular resistance in cerebral vessels (Gupta et al., 1997). The influence of CO_2 and O_2, as well as MAP and cerebral metabolism, on cerebrovascular control is particularly important amongst preterm infants who are at increased risk of brain injury.

Cerebrovascular Control: Summary

Cerebral oxygenation, the product of cerebral oxygen delivery and consumption, is largely controlled by two mechanisms. Cerebral autoregulation ensures that blood flow within the brain remains constant despite fluctuations in systemic BP whilst cerebral blood flow-metabolism coupling ensures areas of increased neuronal activity receive increased blood flow. Furthermore, CBF is largely influenced by changes in the oxygen and carbon dioxide. These mechanisms undergo continuing maturation in infancy, thus infants born prematurely are at risk of significant immaturity of cerebral vascular control.

1.7 Cerebrovascular Control in Preterm Infants

1.7.1 Cerebral Autoregulation in Preterm Infants

With the preterm brain being particularly susceptible to haemorrhage and ischaemia, which may be due to fluctuations in CBF, there has been much interest in the ability of preterm infants to regulate their cerebral haemodynamics. A number of studies have found that cerebral autoregulation is impaired in preterm infants (Wong et al., 2008, Soul et al., 2007, Tsuji et al., 2000). Tsuji et al., found that in 32 infants with GAs ranging from 23-31 weeks, 17 exhibited a high correlation between MAP and Haemoglobin Difference (HbD), a measure of cerebral intravascular oxygenation calculated using NIRS as a surrogate for CBF (Tsuji et al., 2000). These results were supported by Soul et al., in 2007 who found that pressure-passivity in the cerebral circulation, again calculated from the coherence between MAP and HbD, existed in 87 out of 90 preterm infants with birth weight < 1500g (Soul et al., 2007). Furthermore, this study found that pressure-passivity fluctuates over time suggesting that cerebral autoregulation is not simply intact or impaired but changes over time (Soul et al., 2007).

Impaired autoregulation is more common in high-risk preterm infants. Infants born at earlier gestational ages and with lower birth weights are more likely to experience pressure-passivity (Soul et al., 2007). Similarly, very sick preterm infants with higher Clinical Risk Index for Babies (CRIB) scores are associated with impaired autoregulation as shown by greater coherence between MAP and cerebral oxygenation (Wong et al., 2008). Impaired cerebral autoregulation has not been associated with antenatal or postnatal inflammation (Hahn et al., 2012), despite chorioamnionitis being associated with an increased risk of periventricular leukomalacia (PVL) (Perlman et al., 1996). However, cerebrovascular pressure passivity is more likely to occur during episodes of hypotension than during hypertensive episodes suggesting that baseline MAP may rest closer to the lower limit of the cerebral autoregulation plateau in preterm infants (Gilmore et al., 2011). This may explain the increased risk of PVL in infants exposed to chorioamnionitis as infection and inflammation are often associated with hypotension. Hypotension may lead to low CBF due to BP falling below the limit of

the autoregulatory threshold or due to impaired autoregulation secondary to prematurity or adverse clinical conditions.

Impaired cerebral autoregulation has been linked to an increased risk of preterm brain pathology. An early study by Milligan in 1980 found that 4 out of 5 preterm infants who received a blood transfusion which resulted in a significant rise in MAP and CBF measured using jugular vein occlusion plethysmography, developed fatal intraventricular haemorrhages (IVH) (Milligan, 1980). Despite the limitations of the technique used for assessment of CBF in this study, it does suggest that a sudden increase in CBF may have played a causal role in the development of bleeding (Milligan, 1980). In support of this, another study found cerebrovascular pressure passivity due to perinatal stress and the presence of vasoactive substances was present prior to the development of severe intracranial haemorrhage (Pryds et al., 1989). A more recent study found that in a cohort of 32 preterm infants, 8 out of the 10 infants who developed severe brain pathology (germinal matrix haemorrhage, IVH or PVL) had a high correlation between MAP and cerebral oxygenation consistent with impaired cerebral autoregulation (Tsuji et al., 2000). Furthermore, it has been shown that there is a significant correlation between high-magnitude cerebral pressure passivity, greater changes in CBF for a given change in BP, and the development of intracranial haemorrhage (O'Leary et al., 2009).

Most of the studies investigating cerebral autoregulation in the preterm population have been conducted in sick or high-risk preterm infants within the first few days after birth, however there is some evidence to suggest that cerebral autoregulation is impaired even in clinically well preterm infants. Boylan et al., found that cerebral autoregulation was absent in high risk preterm and term infants as well as absent in low risk preterm infants, but was present in low risk term infants (Boylan et al., 2000). This suggests that autoregulation may mature with age in an otherwise healthy preterm infant however; there is a distinct paucity of research investigating the maturation of cerebral autoregulation in otherwise healthy preterm infants up to term age and beyond. Furthermore, a recent study by Verhagen et al., was unable to find a correlation between the absence of cerebral autoregulation, which occurred in 10 out of 25 preterm infants (mean gestation 29.1 weeks) and

clinical parameters in a cohort of relatively healthy preterm infants (Verhagen et al., 2014). Again suggesting that cerebral autoregulation may be absent in clinically well preterm infants.

Despite extensive data suggesting that cerebral autoregulation is absent or impaired in preterm infants, some studies have found cerebral autoregulation to be functional even in very preterm infants. Tyszczuk et al., found no relationship between MAP within the range of 23-39 mmHg and CBF in preterm infants with gestational ages ranging from 24-34 weeks (Tyszczuk et al., 1998). However, this study investigated only steady-state static autoregulation with a single measurement of MAP and CBF per infant, and did not assess dynamic autoregulation. Furthermore, the infants included in the study were of a wide range of gestational and post-natal ages and weights, and importantly, have a wide range of carbon dioxide levels which would significantly influence CBF. Further evidence in support of intact cerebral autoregulation, Caicedo et al. found that preterm infants (mean gestation 28 weeks) with normal outcomes, determined by Bayley's assessment at 12 and 24 months, displayed minimal pressure-passivity in the first 3 days after birth. Conversely, those with poor outcomes and higher CRIB scores were more likely to have spent longer periods with pressure-passive CBF in the first days after birth (Caicedo et al., 2011).

In summary, cerebral autoregulation is likely to be immature in preterm infants with greater impairment displayed by infants who are clinically unwell or of an earlier gestational age. Although the exact arterial pressures within which cerebral autoregulation functions in preterm infants is unclear, it would appear that the autoregulatory curve is narrower and MAP sits closer to the lower end of the autoregulatory plateau in preterm infants. Furthermore, impaired autoregulation is associated with an increased risk of neuropathology including IVH and PVL, leading to poor neurodevelopmental outcomes. Impaired cerebral autoregulation may leave preterm infants vulnerable to reduced cerebral oxygenation and may contribute to their increased risk of SIDS.

1.7.2 **Cerebral Blood Flow-Metabolism Coupling in Preterm Infants**

A number of studies have assessed CBF-metabolism coupling in preterm infants. Despite findings suggestive of immature CBF-metabolism coupling in term infants, there is some evidence that flow-metabolism coupling is intact in preterm infants. Concurrent increases in $CMRO_2$ and CBF have been

reported in preterm infants across the first 3 months of life, prior to term age (Roche-Labarbe et al., 2012). These changes were more closely related to post-menstrual age than chronological age and are thought to be due to increasing cerebral metabolic demands due to increased synaptogenesis (Roche-Labarbe et al., 2012). Similar findings have been reported in very preterm infants with increased CBF in the first 3 days of life (Meek et al., 1998b) and accompanying increases in $CMRO_2$ and decreased cerebral oxygen extraction (Kissack et al., 2005, Meek et al., 1998b), reflecting appropriate increases in CBF to meet the increasing metabolic demands for oxygen associated with the transition to extra-uterine life (Kissack et al., 2005). Greisen et al., found that CBF, assessed using Xenon-133 clearance, increased in response to a change from AS to QS concluding that coupling between blood flow and metabolism was present in the preterm infant brain as early as 32 weeks GA (Greisen et al., 1985). Similarly, Pryds et al., conducted a study assessing CBF using xenon 133 clearance in 24 preterm infants with a mean gestation of 30.8 weeks and found that those infants with hypoglycaemia, blood glucose lower than 1.7mmol/L, had higher CBF which reduced rapidly when blood glucose levels were increased (Pryds et al., 1988). The infants experiencing hypoglycaemia had no change in amplitude-integrated electroencephalogram (EEG) activity during episodes of hypoglycaemia, therefore the authors concluded that increases in CBF met the cerebral metabolic requirements during hypoglycaemia, reflecting intact CBF-metabolism coupling (Pryds et al., 1988). CBF-metabolism coupling has also been reported during seizure activity in preterm infants, with a significant increase in CBF during seizures which is, at least in part, thought to be due to increased neuronal activity (Perlman and Volpe, 1983).

Recent research suggests that the neurovascular coupling is present but the haemodynamic response is immature in preterm infants. Roche-Labarbe et al. used NIRS to assess changes in CBF during somatosensory stimulation in preterm infants (33-34 weeks GA) studied within 2.5 weeks of birth and found significant regional increases in CBF and CBV in response to stimulation (Roche-Labarbe et al., 2014). The authors reported that preterm infants appear to have a greater arterial to venous transit time compared to adult subjects reflecting immaturity of the cerebral vasculature (Roche-Labarbe et al., 2014). Similar results have been produced in MRI studies have found CBF-metabolism coupling

to be present but immature in preterm infants, with maturation of the cerebral haemodynamic response with increasing age. Preterm infants studied prior to term age at 34 weeks GA displayed a significantly delayed haemodynamic response to functional stimulation of the primary motor cortex compared to preterm infants studied at term-equivalent age and adult subjects (Arichi et al., 2012). Furthermore, adult subjects displayed a significantly greater haemodynamic response to stimulation compared to both infant groups, with no difference between term-equivalent and preterm groups (Arichi et al., 2012). This suggests that CBF-metabolism shows maturation with age but remains immature at term-equivalent age. There has been little assessment of CBF-metabolism coupling in preterm infants beyond term-equivalent age.

In contrast, a more recent study conducted by Wong et al. found flow-metabolism coupling to be absent in preterm infants (Wong et al., 2009a). CBF was determined using NIRS and the oxygen bolus technique and $CMRO_2$ was determined using NIRS and jugular venous occlusion in preterm infants with a median gestation of 26 weeks. A lack of correlation between CBF and $CMRO_2$ was found, instead changes in cerebral fractional oxygen extraction, not CBF, occurred to meet changes in $CMRO_2$ (Wong et al., 2009a). This study also found that administration of dopamine clinically indicated to treat hypotension in preterm infants resulted in flow-metabolism coupling more similar to that seen in the mature brain, possibly due to improve microvascular tone (Wong et al., 2009a).

In summary, the evidence describing CBF-metabolism coupling in preterm infants is limited and largely conflicting. Some studies suggest flow-metabolism coupling is intact in preterm infants (Pryds et al., 1988, Greisen et al., 1985, Roche-Labarbe et al., 2012, Kissack et al., 2005), however, recent studies suggest that flow-metabolism coupling remains immature in preterm infants (Arichi et al., 2012), particularly those born very preterm (Wong et al., 2009a). These discrepancies may be due to differences in the techniques used to assess flow-metabolism coupling and further research is needed to fully elucidate the relationship between cerebral metabolism and CBF in preterm infants. However, it is likely that flow-metabolism coupling does function in the preterm infant brain but is immature and thus inadequately meets the cerebral metabolic requirements. This may lead to reduced

cerebral oxygenation in preterm infants, which may be a contributory factor in the increased risk for SIDS amongst infants born preterm.

1.7.3 **Cerebral Vasoreactivity in Preterm Infants**

Intact cerebral CO_2 vasoreactivity in preterm infants has been documented and is associated with improved neurological outcomes. The cerebral vasodilation to CO_2 is thought to be protective of the perinatal brain, especially when there is ventilatory failure with hypoxia and hypercapnia (Mosca et al., 1999, Brucklacher et al., 1995). On the other hand, the cerebral vasoreactivity might also lead to cerebral hypoperfusion and ischemia in the presence of hypocapnia. In support of this, hypocapnia in preterm infants has repeatedly been associated with increased risk of a range of neurological pathologies including IVH, PVL and cerebral palsy (Ikonen et al., 1992, Graziani et al., 1992, Wiswell et al., 1996).

A number of studies have assessed cerebral CO_2 vasoreactivity in preterm infants. One of the earliest studies to describe cerebral CO_2 vasoreactivity in preterm infants was conducted by Leahy et al. in 1980 (Leahy et al., 1980). This study assessed CBF in 24 stable preterm infants with a mean gestation of 34 weeks. Infants were divided into two groups with one group inhaling 2-3% CO_2 and the other inhaling 100% O_2. Inhalation of CO_2 produced a mean increase in CBF of 7.8% per Torr alveolar CO_2 pressure, a value approximately twice that seen in adults, suggesting that CO_2 is an important regulator of CBF in preterm infants. Following on from this work, a study by Greisen et al. investigated cerebral CO_2 vasoreactivity following both ventilator adjustment induced and spontaneous fluctuations in CO_2 in 16 infants of less than 33 weeks gestation undergoing mechanical ventilation and determined that CBF CO_2 reactivity appeared normal in their cohort of stable preterm infants (Greisen and Trojaborg, 1987). A similar study, by Pryds et al., investigated the effects of spontaneous fluctuations in $PaCO_2$ on CBF in 18 healthy, preterm infants with a mean gestation of 30 weeks. They found a mean CO_2 reactivity of 28.9 %/kPa CO_2, a value comparable to that found in term infants and adults, concluding that within the physiological ranges of $PaCO_2$ and MAP, CBF is well controlled in preterm infants (Pryds et al., 1990a).

However, cerebral CO_2 reactivity may be immature or impaired in the very early period after preterm birth and undergoes subsequent improvement with increasing postnatal age. Pryds et al., assessed cerebral CO_2 reactivity using xenon-133 clearance at 2-12, 12-24 and 24-48 hours of life in 57 preterm infants and found that cerebral CO_2 reactivity was significantly attenuated at 2-12 hours (11.2 %/kPa CO_2) and 12-24 hours (11.8 %/kPa CO_2) of life despite normal cranial ultrasounds, while at 24-48 hours (32.6 %/kPa CO_2) cerebral vasoreactivity had reached the hypothesised level of 30 %/kPa CO_2 (Pryds et al., 1989). In further support of impaired cerebral vasoreactivity following preterm birth, Jayasinghe et al., studied cerebral autoregulation and CO_2 reactivity, also using the Xenon-133 clearance technique, in 15 very low birth weight preterm infants within 4 days of life (Jayasinghe et al., 2003). They divided the cohort into normotensive and hypotensive infants and found that the normotensive preterm infants exhibited intact cerebral autoregulation but impaired cerebral CO_2 reactivity in comparison with previous studies conducted in preterm infants of 2 days post-natal age which had reported higher mean CBF-CO_2 reactivity values using the same methodology (11.1 %/kPa CO_2 compared with 32.6 %/kPa CO_2) (Pryds et al., 1989). They also found that hypotensive preterm infants had impaired cerebral autoregulation as well as absent cerebral CO_2 vasoreactivity (Jayasinghe et al., 2003). This may be due to the effect of $PaCO_2$ on cerebral autoregulation as it has been shown in very low birth weight infants that increasing $PaCO_2$ can lead to progressive impairment of cerebral autoregulation (Kaiser et al., 2005). This suggests that carbon dioxide induced vasodilation overrides cerebral autoregulatory mechanisms in the presence of increasing BP, while in the presence of hypotension, maximally dilated vessels have limited capacity for further dilation in order to increase CBF.

Furthermore, impaired cerebral CO_2 vasoreactivity has been associated with adverse neurodevelopmental outcomes. Muller et al., assessed cerebral CO_2 reactivity using xenon-133 clearance in 18 sick, very low birth weight preterm infants (mean gestational age 26 weeks) within 36 hours of birth and assessed cerebral pathology on autopsy in 8 infants and neurodevelopmental outcome in 10 infants at 18 months of age (Muller et al., 1997). They found that the infants with normal development and normal cerebral autopsy had a mean CO_2 reactivity of 24.4 %/kPa CO_2 while

those infants with poor developmental outcome and cerebral pathology on autopsy had a mean CO_2 reactivity of 3.4 %/kPa CO_2. They concluded that reduced cerebral CO_2 reactivity may play a role in the pathology of hypoxic-ischemic encephalopathy and thus be predictive of severe neonatal brain injury (Muller et al., 1997).

A number of animal studies have described the cerebral vascular response to hypoxia in the fetus. Hypoxia is associated with preferential blood supply to the brain with reduced flow to other organs (Peeters et al., 1979) and to the brainstem in preference of other brain regions (Tolcos et al., 2003). In contrast, hyperoxia has been associated with reduced CBF in animal studies. A limited number of studies have assessed O_2 vasoreactivity in human preterm infants. Leahy et al., assessed the effect of inhalation of 100% O_2 in preterm infants born at 34 weeks GA and found a 15% decrease in CBF (Leahy et al., 1980). Similar results were found in a study conducted by Lundstrom et al., in which CBF was assessed using xenon clearance in preterm infants born before 33 weeks GA and assigned to receive either room air or 80% oxygen during resuscitation(Lundstrøm et al., 1995). Those infants who received oxygen had significantly reduced CBF compared to those who received room air (12.2 vs 15.9 ml/100g/min) when assessed at 2 hours of age (Lundstrøm et al., 1995). This suggests hyperoxia produces persistent cerebral vasoconstriction in preterm infants.

In summary, cerebral vasoreactivity to CO_2 and O_2 appears to function in healthy, preterm infants. However, some impairment may be present and those infants with the greatest impairment appear to be at increased risk for cerebral pathology and poor long-term neurodevelopmental outcomes.

Cerebrovascular Control in Preterm Infants: Summary

Preterm infants have immature cerebral vascular control prior to term age. This is particularly prominent in those infants born at earlier GAs or who are clinically unwell. Studies assessing cerebral vascular control in preterm infants have largely been performed prior to term age. We suggest that cerebral vascular control is likely to be impaired in preterm infants beyond term-equivalent age, playing a role in the increased risk of SIDS seen in infants born preterm.

1.8 The Role of Cerebral Haemodynamics in the Sudden Infant Death Syndrome

Current research suggests that cerebral haemodynamics play an important role in the pathogenesis of SIDS. Cerebral hypoperfusion was first postulated as a cause of SIDS in 1978 by Takashima et al., who studied the brains of infants who had died from SIDS. They found that there was a close relationship between brainstem microvasculature and the areas of gliosis. They suggested that cerebral hypoperfusion, resulting in scarring of the brain, is likely to be involved in the pathogenesis of SIDS (Takashima et al., 1978).

We have previously suggested that perhaps low BP and altered systemic cardiovascular control seen in the prone sleeping position is reflected in the cerebral circulation leading to impaired cerebral oxygenation, a theory supported by our findings of reduced cerebral oxygenation in the prone sleeping position in healthy term infants (Wong et al., 2011). We suggest that chronically reduced cerebral oxygenation, which may affect the brainstem region, possibly underlies blunted arousal responses and impaired cardiovascular control in the prone sleep position, thus contributing to SIDS risk (Wong et al., 2011).

1.9 Summary and Rationale for the Study

Increasing rates of preterm birth as well as improvements in survival rates following preterm birth are resulting in increases in the number of preterm infants surviving the neonatal period. Prematurity is associated with a range of consequences including an increased risk of SIDS, which is thought to be due to immature cardiovascular control. Existing evidence suggests that preterm infants have immature systemic vascular control including altered HRV, BPV and baroreflex sensitivity that persists beyond term equivalent age. However, previous studies have assessed cardiovascular control in preterm infants only in the supine position, despite prone sleeping being a major risk factor for SIDS, particularly amongst infants born preterm.

Immature cerebrovascular control has also been implicated in the pathophysiology of SIDS. Previous studies have found areas of gliosis within the brainstem suggestive of hypoxic damage. Furthermore,

our group has recently shown that prone sleeping is associated with a significant reduction in cerebral oxygenation (Wong et al., 2011) in term infants and altered cerebrovascular control (Wong et al., 2013). Preterm infants are known to have immature cerebrovascular control prior to term age, displaying both pressure passivity between BP and CBF and immature CBF-metabolism coupling. However there has been little assessment of cerebral vascular control in preterm infants beyond term-equivalent age.

This thesis aims to address these deficits in the literature by assessing cerebral oxygenation, cerebrovascular and cardiovascular control in both the supine and prone sleeping positions in preterm infants beyond term-equivalent age when SIDS risk is greatest.

1.10 Aims and Hypotheses

Aim 1:

To assess the influence of sleep position, sleep state, post-term age and preterm birth on cerebral oxygenation, BP and HR in preterm infants during sleep across the first 6 months post-term.

Hypothesis 1:

We hypothesise that cerebral oxygenation will be reduced in preterm infants born at earlier gestation, in the prone sleep position, at 2-3 months CA and in preterm compared to term infants and that BP will be reduced in the prone sleep position; in QS compared to AS; that a nadir in BP will occur at 2-3 months CA and that BP will be reduced in preterm compared to term born infants.

Aim 2:

To assess the influence of sleep position, sleep state, post-term age and preterm birth on cerebrovascular control in preterm infants during sleep across the first 6 months of life.

Hypothesis 2:

We hypothesise that cerebrovascular control will be altered in the prone sleep position in preterm infants and in preterm compared to term infants.

Aim 3:

To assess the influence of sleep position, sleep state, post-term age and preterm birth on autonomic cardiovascular control as measured by baroreflex sensitivity in preterm infants during sleep across the first 6 months post-term.

Hypothesis 3:

We hypothesise that baroreflex sensitivity will be impaired in the prone sleep position in preterm infants and in infants born at earlier gestational ages.

Aim 4:

To assess the influence of sleep position, sleep state, post-term age and preterm birth on autonomic cardiovascular control as measured by heart rate variability in preterm infants during sleep across the first 6 months post-term.

Hypothesis 4:

We hypothesise that autonomic cardiovascular control of HR will be impaired in the prone sleep position in preterm infants and in infants born at earlier gestational ages.

Chapter 2

General Methods

2 General Methods

Ethical approval for this project was obtained from the Southern Health and Monash University Human Research Ethics Committees and funding was awarded from the National Health and Medical Research Council (NHMRC) and the Scottish Cot Death Trust.

2.1 Subjects

Preterm infants were recruited from Monash Newborn, a large neonatal unit consisting of 20 Neonatal Intensive Care cots and 30 special care nursery cots, and the special care nursery at Jessie Macpherson Private Hospital.

Healthy preterm infants of varying gestational ages (GAs) ranging from 24 to 36 weeks were recruited. Exclusion criteria were employed to ensure a homogenous group of infants were recruited and to avoid the influence of confounding medical problems, these are summarised in Table 6.

Table 6: Exclusion Criteria

Growth	***Neurological***	***Cardio-Respiratory***	***Risk Factor Exposure***
Intrauterine growth restriction or major congenital abnormalities	Major intracranial abnormalities or significant intraventricular haemorrhage (Grade III or IV)	Chronic lung disease requiring respiratory stimulant medication (caffeine or theophylline), mechanical respiratory support or oxygen therapy at term corrected age, Haemodynamically significant patent ductus arteriosus or pulmonary hypertension	Maternal smoking, family history of SIDS

In addition to the preterm cohort, a group of 17 previously studied term born infants, born between 38 and 42 weeks of gestation, has been included in this PhD for comparison. The term born cohort was studied before commencement of my PhD and the results have been published (Wong et al., 2011, Wong et al., 2013), I played no role in the acquisition or initial analysis of these data. Term infants were all born to non-smoking mothers, were of appropriate birth weight for GA and routinely slept supine at home. Demographic information for the term infants is provided in Appendix C.

2.1.1 Recruitment Protocol

Suitable infants were identified during visits to Monash Newborn, which occurred 2-3 times each week. The parents of infants who met the inclusion criteria for our study were approached and provided with verbal information about the study, together with a detailed plain language parent information statement (Appendix D). Those parents who expressed interest in the study were then contacted by telephone when their infant reached term-equivalent age and an appointment was made for a suitable day to conduct the study.

In total, 118 parents were approached between January 2011 and April 2013 and of these 35 agreed to participate.

2.2 Study Parameters

All infants were studied using daytime polysomnography (PSG) at the Melbourne Children's Sleep Centre. PSG enables continuous, non-invasive monitoring of a number of physiological parameters during sleep. The standard PSG leads we used included: electroencephalogram (EEG), electrooculogram (EOG), electromyogram (EMG), electrocardiogram (ECG), airflow thermistor, respiratory bands, pulse oximeters and a temperature probe. In addition to the standard PSG electrodes, we measured blood pressure using a Finometer^{TM} (FMS, Finapress Medical Systems BV, The Netherlands) and cerebral tissue oxygenation index (TOI, %) using a NIRO-200 spectrophotometer (Hamamatsu Photonics KK, Tokyo, Japan). All signals from the physiological variables were recorded on an E-series Sleep System (Compumedics, Melbourne, VIC, Australia) using the Profusion 2 (Compumedics, Melbourne, VIC, Australia) sleep recording program at a

sampling rate of 512 Hz. In addition, a low light infrared video camera (Compumedics, Melbourne, VIC, Australia) enabled recording and monitoring of the infant's behaviour.

2.3 Standard Polysomnography Measures

2.3.1 Electroencephalogram (EEG)

EEG enables measurement of the electrical activity of the brain and is one of the cardinal features of a polysomnographic recording. EEG is capable of measuring changes in electrical voltage at the scalp, generated by the sum of synchronous post-synaptic potentials within underlying brain tissue. The amplitude of this voltage is very small, generally in the range of tens of microvolts, however appreciable differences are seen between the infant sleep states of AS and QS.

EEG electrodes (Astro-Med, RI, USA) were placed on the infant's head according to the International 10-20 System for electrode placement (Klem et al., 1999), modified for infant use. Four electrodes were used: two central electrodes (CZ and either C3 or C4), an occipital electrode (either O1 or O2) and a reference electrode (either A1 or A2). Electrode placement is shown in Figure 10. Depending on the position of the infant at the time of lead placement, one of two configurations was adopted: CZ, C3, O1 and A2 or CZ, C4, O2 and A1.

The central electrodes are placed with one in the midline (Cz) and the other in either the left (C3) or right (C4) position depending on which side of the head was most easily accessed at the time of electrode placement. The position for Cz is in the midline half way between the nasion and the inion and half way between each ear lobe. The position for C3 or C4 is in line with the tragus of the ear, one-third of the distance between the ear lobe and Cz up from the ear lobe. The occipital electrode was placed on the occipital bone in line with either the left central (C3) or right central (C4) lead, depending on where the lead had been placed. The reference electrode (either A1 or A2) was placed on the opposite side of the head to the occipital and central electrodes on the mastoid bone, just behind the infant's ear. Correct electrode placement enabled recording from C4 and O2 to A1 or from C3 and O1 to A2.

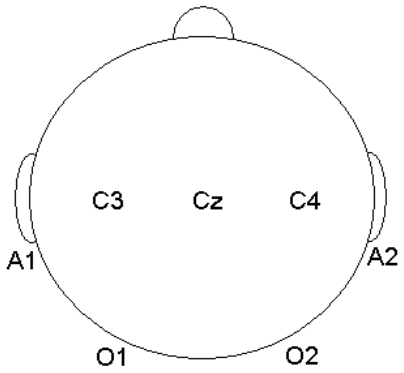


Figure 10: Placement of EEG Leads: This image diagrammatically represents placement of the EEG leads. Cz is placed in the midline half way between the nasion and the inion and half way between each ear lobe. C3 or C4 are placed in line with the tragus of the ear, one-third of the distance between the ear lobe and Cz up from the ear lobe. The occipital electrode is placed on the occipital bone in line with either the left central (C3) or right central (C4) lead. The reference electrode (either A1 or A2) is placed on the opposite side of the head to the occipital and central electrodes on the mastoid bone.

2.3.2 Electro-oculogram (EOG)

EOG tracks eye movements by recording changes in the cornea-retinal potential difference that exists across the globe of the eye. The eye acts as a dipole, with the anterior pole being positive and the posterior pole being negative, the movements of which are measured by the electrode. This ensures that only movements of the eye itself are recorded and not movements of the eye muscles. The EOG recording enables the identification of eye movements which is important for determining sleep state.

Each EOG electrode (Rochester Electro-Medical Inc., Canada) was adhered to the skin using a double-sided adhesive collars (Double Stick Collars, Grass Technologies, Warwick, RI, USA), conductive paste and Mefix adhesive fabric. The EOG electrodes were referenced to A1. Placement of the EOG electrodes is illustrated in Figure 11. The right EOG is placed 0.5cm lateral and slightly superior to the outer canthus of the right eye whilst the left EOG is placed 0.5cm lateral and slightly inferior to the outer canthus of the left eye.

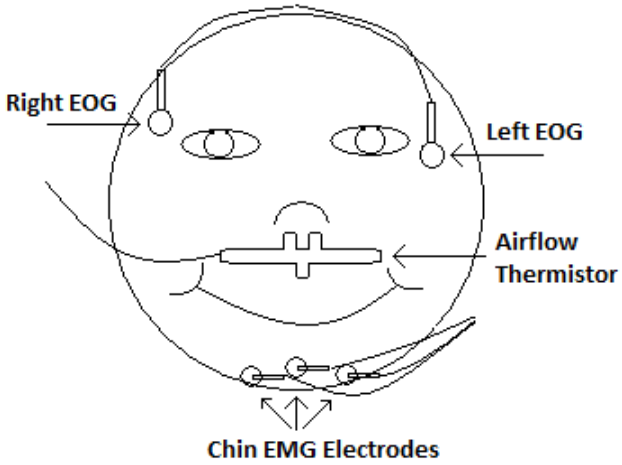


Figure 11: Placement of electro-oculogram (EOG), electromyogram (EMG) and Airflow Thermistor: This image is a diagrammatical representation of the placement of the right and left EOG electrodes, the chin EMG electrodes and the airflow thermistor. The right EOG is placed 0.5cm lateral and slightly superior to the outer canthus of the right eye whilst the left EOG is placed 0.5cm lateral and slightly inferior to the outer canthus of the left eye. The airflow thermistor is placed below the infant's nose. The EMG electrodes were applied beneath the chin in a triangular shape with one central electrode, acting as a reference, and the remaining two electrodes placed 1cm either side of the central electrode

2.3.3 Electromyogram (EMG)

EMG electrodes placed over the submentalis muscle were used to assess electrical activity of the muscle during sleep as an indicator of muscle tone. Three electrodes were applied beneath the chin in a triangular shape with one central electrode, acting as a reference, and the remaining two electrodes placed 1cm either side of the central electrode. Placement of the chin EMG electrodes is shown in Figure 11. Only one EMG electrode signal was recorded at any particular time and the second electrode was used only if the signal was decreased or interrupted for any reason.

2.3.4 Electrocardiogram (ECG)

In order to record heart rate, three self-adhesive, disposable ECG electrodes were applied to the infant's chest and back. Two electrodes were placed on the anterior chest (see Figure 12), one on the right side in the second intercostal space in the mid-clavicular line and the other on the left side just below the nipple in the mid-clavicular line. The third electrode was placed on the infant's back over the spinus process of the first thoracic vertebrae. This lead acted as an earth or 'iso ground' lead. The placement of the two anterior electrodes created a diagonal pathway across the heart which enabled

for the recording of a strong R-wave on the trace. This R wave was then used to determine instantaneous heart rate.

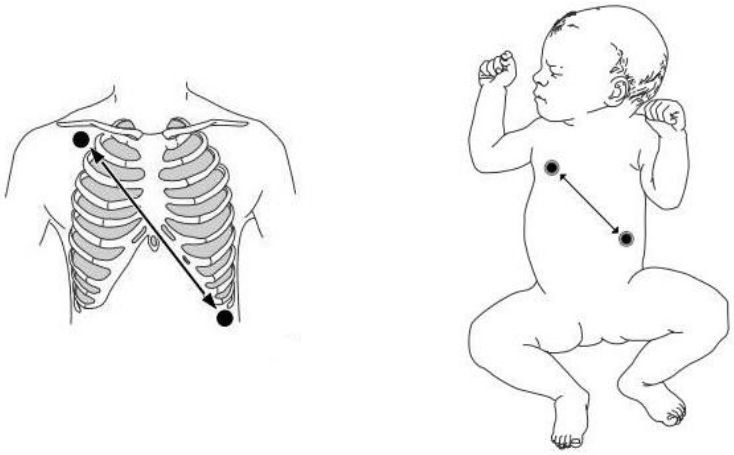


Figure 12: Placement of ECG electrodes. This image is a diagrammatical representation of the placement of the ECG electrodes. One lead is placed lateral to and just above the right nipple in a position that is equivalent to the thoracic placement of the right arm lead in adults. The other lead is place below the left nipple in a position that is equivalent to the thoracic placement of the left leg lead in adults. A third ECG electrode is placed on the infant's back.

2.3.5 Temperature

Abdominal skin temperature was recorded using a probe (Yellow Springs Instruments, Yellow Springs, OH, USA) placed on the infant's abdomen, slightly inferior and lateral to the umbilicus. The probe was covered with a reflective disc (Thermopad, Drager, Lübeck, Germany) and adhered to the skin using Mefix tape. It was important to monitor body temperature throughout the study as temperature may increase when the infant is slept prone. Increased temperature resulting in peripheral dilatation of blood vessels may influence or exacerbate the reduction in arterial blood pressure seen in the prone sleeping position.

2.3.6 Arterial Oxygen Saturation

Oxygen saturation was measured non-invasively throughout the study using pulse oximeter probes (Masimo, Frenchs Forest, NSW, Aus) placed on the infant's foot. Oximetry probes emit near infrared light which passes through tissue and is measured by a photodetector. Alterations in the absorbance pattern of this light correspond to changes in the quantity of oxygenated and deoxygenated haemoglobin in the arterial blood enabling the arterial oxygen saturation to be calculated.

The pulse oximeter probe was attached to the skin using Mefix tape and then covered with a sensor wrap (Nellcor Puritan Bennett Inc., Pleasanton, CA, USA) to prevent external light interfering with the signal.

2.3.7 Airflow Thermistor

To measure airflow through the nose and mouth, an infant airflow thermistor (Breathsensor, Thermal Airflow Sensor, Mortara Instruments Australia, Sydney, NSW, AUS) was placed below the infant's nose (see figure 11). The airflow thermistor detects alterations in temperature associated with exhalation of air thus enabling detection of inhalation, exhalation and absent airflow during apnoea.

2.3.8 Respiratory Bands

To measure breathing movements, two respiratory bands (Resp-ez bands, EPM Systems, Midlothian, VA, USA) were placed around the infant at the level of the abdomen and the thorax (see Figure 22). The thoracic band was placed around the chest, just below the nipples and the abdominal band was placed around the abdomen at the level of the umbilicus. The respiratory bands consist of a centre 'piezo crystal' transducer which detects movement stimuli during respiration and converts this to an electrical potential. Following expansion and depression of the thoracic and abdominal compartments, electrical potential deflections are recorded on the polygraph trace. Recording of respiratory movements is important as regular and irregular breathing patterns are characteristic of QS and AS respectively.

2.4 Blood Pressure

Blood pressure was measured using a Finometer^{TM} (FMS, Finapress Medical Systems BV, The Netherlands) pictured in Figure 13. The Finometer^{TM} provides a non-invasive, continuous method of measuring beat-to-beat BP. The Finometer^{TM} utilises volume-clamp and physiological calibration technology in order to calculate BP using an appropriately sized cuff (Figure 14) placed around the infant's wrist.

Figure 13: The Finometer™. The Finometer™ was used to measure mean arterial pressure (MAP) continuously using a cuff placed around the infant's wrist.

2.4.1 The Volume-Clamp Method

The volume-clamp method involves adjusting the pressure of an inflatable bladder within the cuff to match the intra-arterial pressure creating a transmural pressure across the arterial wall of zero. This is used in conjunction with an in-built infrared plethysmograph which has an infrared light emitter and detector photodiode. Infrared light is absorbed by red blood cells and the increase in arterial diameter during a pulsation creates a concurrent pulsation in the photodiode signal. In order to correct for any movements of the wrist which may change its position in relation to heart level, a fluid-filled height detection device is used. The height detection device is attached at one end to the level of the infant's heart and at the other end to the cuff on the infant's wrist.

2.4.2 Physiologic Calibration

Physiologic Calibration (Physiocal) is an automated algorithm that calibrates the arterial size at which the pressure within the cuff equals the arterial blood pressure. Physiocal analyses the amplitude and shape of the plethysmograph signal at two or more pressure levels and thus can determine the unloaded diameter of an artery. Each time the Finometer™ was switched on the cuff would gradually inflate creating a 'start-up staircase' as the pressure incrementally increased. Following this, Physiocal would begin calculating the appropriate pressure for the cuff to achieve the best possible signal quality through a series of 'square wave calibrations'. In order to function, Physiocal requires

constant cuff pressure for a period of a few seconds to occur periodically during a blood pressure measurement. As these periods of constant cuff pressure interrupt a continuous blood pressure measurement, we chose to turn Physiocal off once adequate signal quality had been achieved.

2.4.3 Recording Blood Pressure

Blood pressure was measured only when the Finometer™ was switched on with each measurement lasting for a maximum of two minutes to avoid venous congestion distal to the cuff. After each measurement the Finometer™ remained off for a period of two minutes to allow normal circulation to return.

Figure 14: Finometer™ Cuff. Appropriately sized Finometer™ cuffs were placed around the infant's wrists to measure mean arterial pressure.

The accuracy of the Finometer™ in measuring beat-to-beat BP in infants has previously been validated by our group (Yiallourou et al., 2006). This involved comparing Finometer™ measurements with simultaneously taken measurements from intra-arterial catheters in sick preterm infants requiring intra-arterial catheters for clinical reasons. It was found that the Finometer™ was able to accurately determine mean BP with a mean difference of only 3 mmHg compared with catheter measurements. In addition, the Finometer™ provided an accurate representation of beat-to-beat changes in BP. This study also determined that repeated measurements were important for accurate measurement of BP and calculated that 3-5 measurements provided the most precise estimate of BP when compared to arterial catheter repeated measurements. Following this validation study, our group has used the Finometer™ for continuous, non-invasive measurement of BP in both term (Yiallourou et al., 2008b, Witcombe et al., 2008, Wong et al., 2011, Wong et al., 2013) and preterm (Witcombe et al., 2008, Witcombe et al., 2009) infants.

2.5 Cerebral Oxygenation

2.5.1 Near-Infrared Spectroscopy

In order to assess cerebral oxygenation we used near-infrared spectroscopy (NIRS) which utilises spatially resolved spectroscopy to generate the cerebral tissue oxygenation index (TOI, %). While light above 1300nm is entirely absorbed by water and light of wavelengths less than 700 nm cannot effectively penetrate tissue, near-infrared light, ranging between 700 and 1300nm, is capable of penetrating biological tissues. The primary light-absorbing tissues within the near-infrared wavelength range are chromophores including haemoglobin and cytochrome. Each displays a different absorption spectra with deoxyhaemoglobin displaying a peak from 650 to 1000 nm, oxyhaemoglobin between 700 and 1150 nm (Murkin and Arango, 2009).

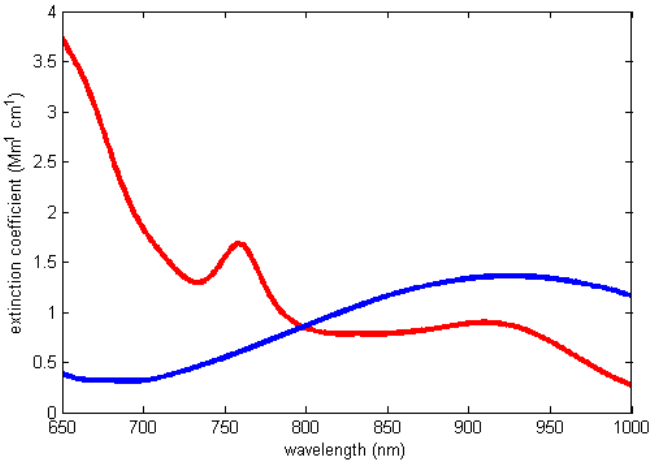


Figure 15: Extinction Coefficients for Oxyhaemoglobin (blue) and Deoxyhaemoglobin (red). Biological tissues display different absorption spectra. Of importance to near-infrared spectroscopy, oxyhaemoglobin displays a peak between 700 and 1150nm whilst deoxyhaemoglobin displays a peak between 650 to 1000nm.

Spectroscopy uses the Beer-Lambert law to compute tissue oxygen saturation based on the degree of light attenuation (A), the different distances of the two photograph-detectors (p) which creates a differential photon path length through tissue (slope = $\partial A/\partial p$) and the absorption coefficient of the chromophore of interest which is determined by the chromophore's extinction coefficient (Figure 15) and the tissue concentration of the chromophore. These data are then inserted into a modified diffusion equation of light transport in tissue to continuously compute the ratio of concentrations of

oxyhaemoglobin (HbO_2) to total haemoglobin (HbT) and thus the absolute average TOI (Figure 16) (Suzuki et al., 1999).

$$TOI = (HbO_2/HbT) \times 100\%$$

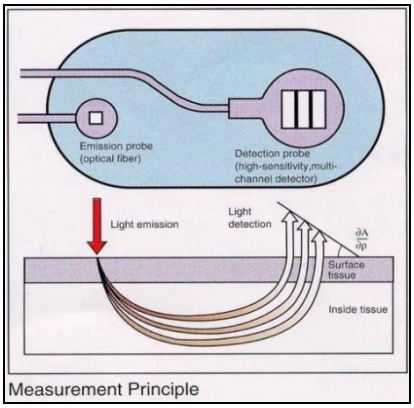


Figure 16: Cerebral Tissue Oxygenation Index (TOI) Measurement Principle (Suzuki et al., 1999). Cerebral TOI is calculated by computation of the ratio of oxyhaemoglobin to total haemoglobin using different absorption spectra generated by near-infrared light passing through biological tissue from an emission probe to a detection probe.

The cerebral circulation is comprised of a multi-compartmental system of arteries, arterioles, capillaries, venules and veins in the brain (Figure 17); each of these compartments has different saturations and volumes. Therefore, cerebral TOI represents a mixed cerebral oxygen saturation of this multi-compartmental system. To simplify the multi-compartmental systems, it is accepted to consider just two compartments, one arterial and one venous, which can be used to create an index of "global" oxygenation in the brain. TOI is therefore dependent on the arterial:venous volume ratio and their relative oxygenations but with a greater sensitivity to the venous oxygenation signal. TOI measurements with relative contributions of the arterial and venous oxygen saturations can be estimated using the cerebral venous volume fraction (Vven) in the equation:

$$TOI = Vven \cdot SvO_2 + (1 - Vven) \cdot SaO_2$$

Previous studies have estimated a cerebral arterial:venous volume ratio of one to three (25% arterial volume, 75% venous volume) (An and Lin, 2002).

Therefore TOI = $0.75.SvO_2 + 0.25.SaO_2$

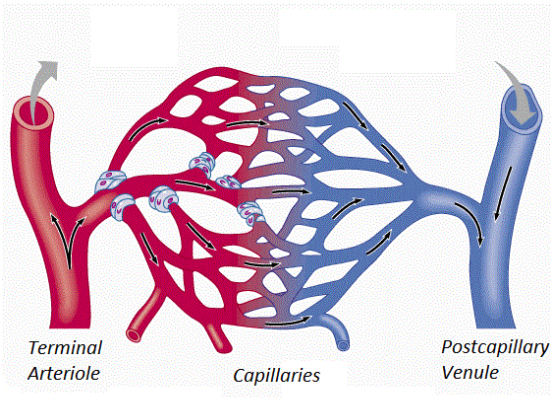


Figure 17: The Vascular Bed. The cerebral circulation is comprised of a multi-compartmental system of arteries, arterioles, capillaries, venules and veins in the brain; each of which has different saturations and volumes.

2.5.2 NIRO-200 Spectrophotometer

The NIRO-200 spectrophotometer (Hamamatsu Photonics KK, Tokyo, Japan; Figure 18) system transmits light within the near-infrared range at three different wavelengths (775, 810 and 850 nm) via a fibre optic bundle which terminates with an emission probe. The light is detected by a detection probe which consists of two aligned photograph-detectors separated by 4 mm, located 4 cm from the emission probe. Both the emission and detection probes were placed on the infant's forehead, thus covering the frontal region of the brain. The probes were covered with a plastic, light-proof casing, attached with strips of transparent dressing (Comfeel Plus, Coloplast, Humlebaek, Denmark) and covered with a self-adherent bandage (3M Coban, St Paul, Minessota, USA) to prevent movement and protect against external light.

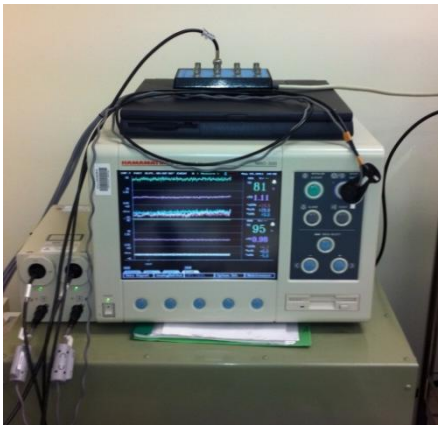


Figure 18: NIRO-200 Spectrophotometer. The NIRO-200 spectrophotometer was used to calculate cerebral tissue oxygenation index (TOI) continuously via a probe placed on the infant's forehead.

Our group has previously validated the use of cerebral TOI, generated by NIRS using the NIRO-200 spectrophotometer, as a surrogate for cerebral blood flow (CBF) as changes in TOI correlate with changes in CBF measured by an ultrasound flow probe positioned around the superior sagittal sinus in a newborn lamb model (Wong et al., 2009b). We have used this technology in a number of previously published human studies (Wong et al., 2011, Wong et al., 2013).

2.6 Study Protocol

Infants were studied longitudinally on three occasions: a) 2-4 weeks, b) 2-3 months and c) 5-6 months post-term corrected age (CA). The design of the study was intended to emulate that used for the previous studies conducted by our group (Yiallourou et al., 2008b, Wong et al., 2011, Witcombe et al., 2008) and enabled comparison between the high and low risk periods for SIDS and between term and preterm infants at similar post-conceptional ages.

Each study consisted of both a morning and afternoon sleep period and the infants were slept in both the supine and prone positions, with the initial sleep position being randomised between infants. This was done to account for differences in sleep quality and duration between the morning and afternoon. Sleep position was generally changed following a midday feed.

2.6.1 Demographic Information

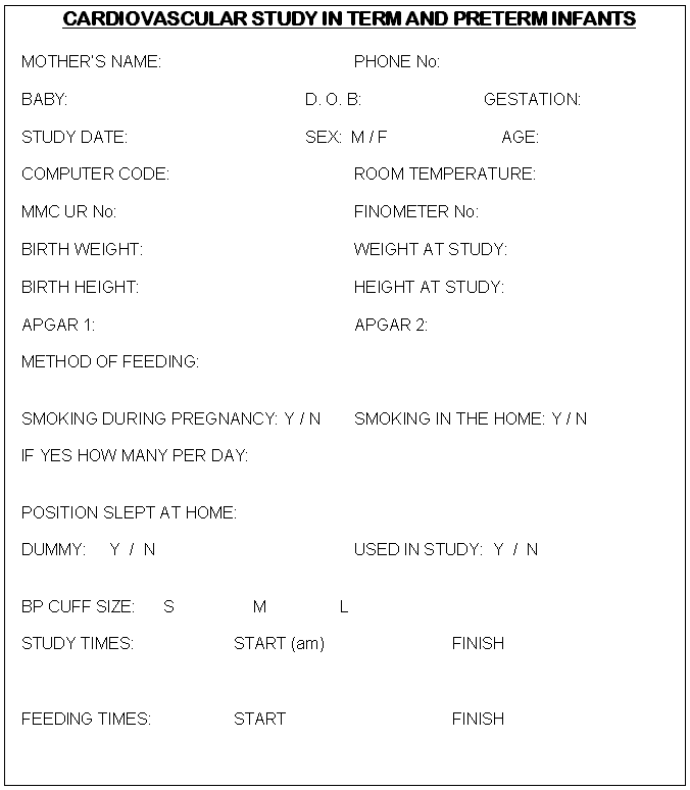
The discharge summary for each infant was obtained which provided information about GA at birth, birth weight, birth length, Apgar scores and neonatal history. Details about each infant's duration of stay in the NICU and/or special care nursery and the duration and modality of ventilation required were noted. It is clinical protocol at Monash Newborn to perform routine cranial ultrasound (CUS) scans on all infants of GA less than 32^{+6} weeks, thus those infants meeting this criterion had CUS results available. In addition, any pertinent features of the neonatal history including apnoea of prematurity, respiratory distress syndrome and anaemia of prematurity were recorded. This information is summarised in appendix E.

Additional demographic information was obtained from the mother on the day of the study. This included current weight and length, method of feeding and dummy use. A summary of this information is provided in Appendix F.

2.6.2 Conducting the Study

2.6.2.1 Setting up for the Study

In order to minimise set-up time on the day of the study some preparation was carried out on the afternoon prior to the study including testing all leads for electrical conductivity using a multimeter, preparing the equipment required for electrode attachment, collecting the linen required for the study and the preparing the appropriate paperwork including the parent information and consent form, study cover sheet (see Figure 19) and sleep diaries. In addition to this, a parking permit was arranged for the parent(s) and two DVDs were collected onto which the completed study would be burned.



CARDIOVASCULAR STUDY IN TERM AND PRETERM INFANTS

MOTHER'S NAME: PHONE No:

BABY: D. O. B: GESTATION:

STUDY DATE: SEX: M / F AGE:

COMPUTER CODE: ROOM TEMPERATURE:

MMC UR No: FINOMETER No:

BIRTH WEIGHT: WEIGHT AT STUDY:

BIRTH HEIGHT: HEIGHT AT STUDY:

APGAR 1: APGAR 2:

METHOD OF FEEDING:

SMOKING DURING PREGNANCY: Y / N SMOKING IN THE HOME: Y / N

IF YES HOW MANY PER DAY:

POSITION SLEPT AT HOME:

DUMMY: Y / N USED IN STUDY: Y / N

BP CUFF SIZE: S M L

STUDY TIMES: START (am) FINISH

FEEDING TIMES: START FINISH

Figure 19: Cover Sheet. Standardised cover sheets were used to document infant details at each study.

On the day of the study, the sleep laboratory was set-up from 7:30-8:00 am, prior to the arrival of the infant between 9 and 10am. All surfaces, including the bed, bench, pram, equipment, pillows and mattresses, were cleaned with HC90 detergent (HC90 Odourless Concentrate Detergent, Agar Cleaning Systems, Preston, Vic, Aus) prior to setting up the study. The electrodes and equipment required for the study were prepared and set out on the bench for easy access (see Figure 20).

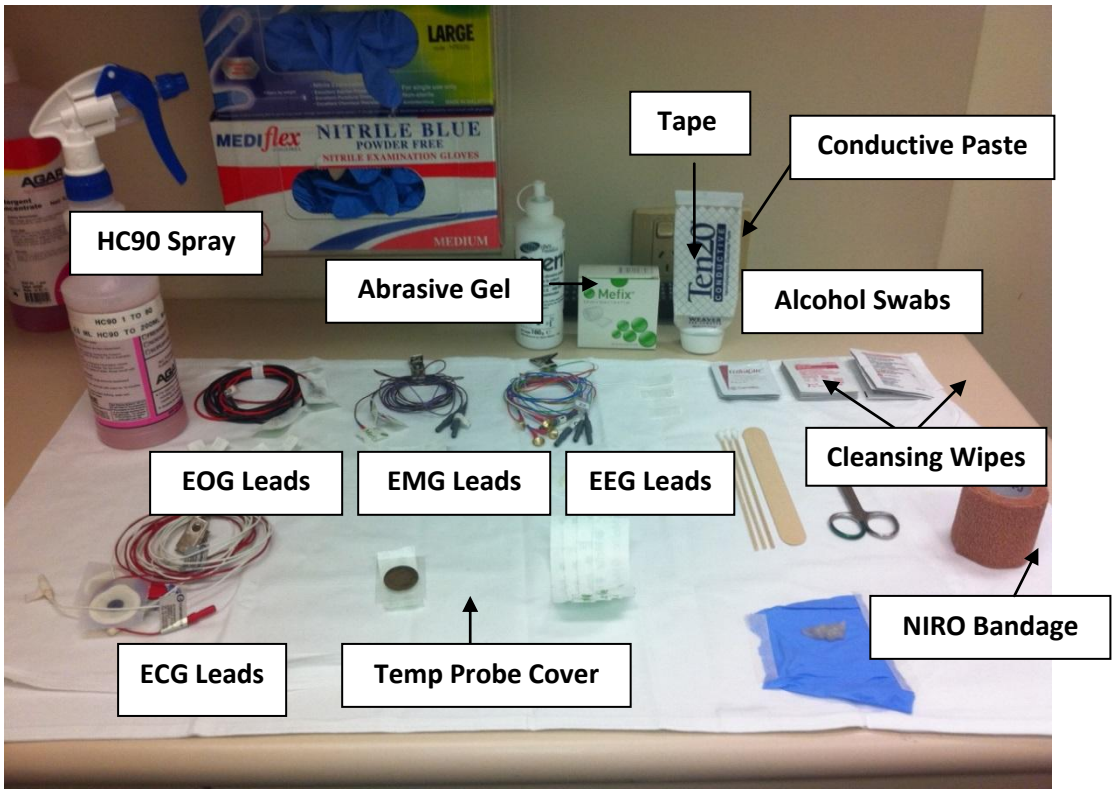


Figure 20: Bench prepared with study equipment. Prior to the arrival of the infant, the bench was prepared with all the necessary equipment for the study. This included the electrocardiogram (ECG), electro-oculogram (EOG), electromyogram (EMG) and electro-encephalogram (EEG) leads, abrasive gel, conductive paste, tape, NIRO bandage, temperature probe cover, cleansing wipes and alcohol swabs.

The pram was prepared for the infant with appropriate linen, blankets and equipment including the respiratory bands, temperature probe and oximetry probes. A nappy change area with all the necessary materials for cleaning the infant after the study was prepared using the adult bed in the study room. The set-up of the room is pictured in Figure 21. In addition to this, a bed was prepared in an adjacent room for the mother to use if she wished.

The recording machines including the NIRO and the Finometer^{TM} were turned on and calibrated.

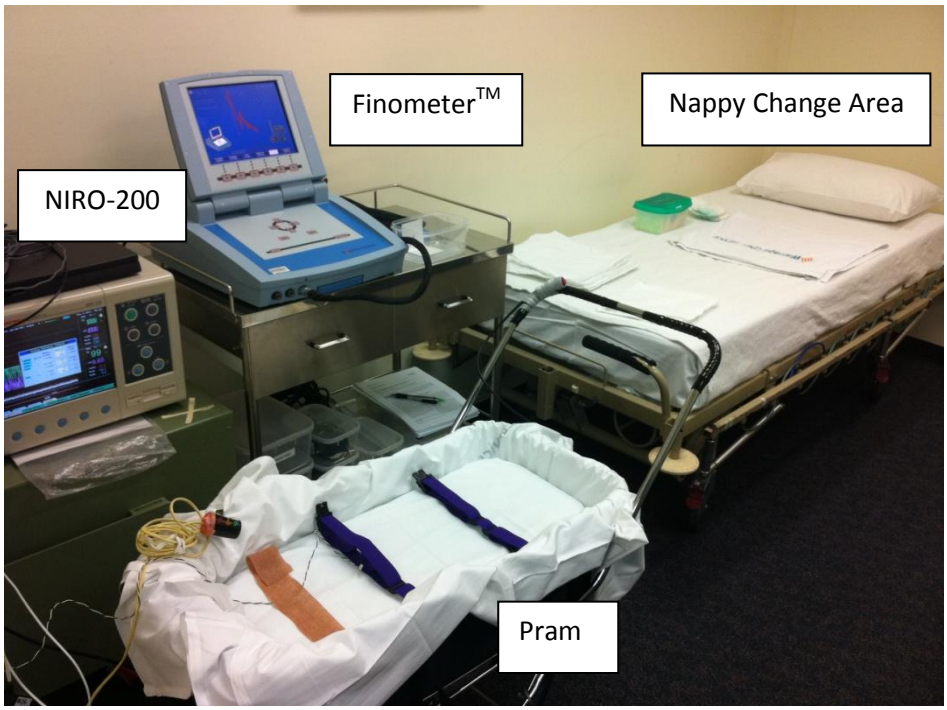


Figure 21: Room Set-Up. Prior to the arrival of the infant, the room was set up with the necessary equipment for the study. This included the NIRO-200, the Finometer™, a pram with sheets and blankets, temperature probe, oxygen saturation probes, NIRO bandage and respiratory bands and a nappy change area with sheets, blankets, towels, cloths, baby wipes and nappies.

2.6.2.2 Commencement of Study

The parent(s) and infant arrived at a time that suited the infant's sleeping and feeding patterns, usually between 9 and 10 am. Upon arrival, the parent(s) were oriented to the sleep laboratory facilities and introduced to the staff and students present. The parent(s) were asked to sign the consent form and the infant's current demographic details were recorded in the laboratory book.

Attachment of the EEG, EOG and EMG electrodes was usually carried out whilst the infant was feeding. In order to achieve the best possible signal quality, the area of the infant's skin in contact with electrodes was cleaned prior to electrode attachment. This involved cleaning the area with an alcohol swab (Skin Cleansing Alcohol Wipe, Kendall Webcol, Mansfield, MA, USA), to remove any oil from the skin surface, followed by a mild abrasive skin preparation gel (Everi Conductive and Abrasive Paste, Spes medica, Battipaglia, Italy) to remove any dead skin cells.

The electrodes were attached to the skin using conductive paste (Ten20 Conductive Paste, D.O. Weaver and Co, Colorado, USA) to facilitate signal conduction. They were then covered with either a

small piece of gauze or Mefix adhesive fabric (Mefix, Mölnlycke Health Care, NSW, Australia). This combination ensured the electrodes had good contact with the skin whilst enabling them to be easily moved and reattached if necessary. This method of electrode attachment was used for all EEG, EMG and EOG leads.

Once attached, the leads were tied together at the crown of the head to keep them out of the way of the infant's fingers and to prevent lead rock and movement artefact. The ECG leads were usually attached whilst the infant's nappy was being changed and these leads were grouped separately to prevent ECG artefact. The infant was then placed in the pram and the pulse oximeter, temperature probe, respiratory bands, airflow thermistor, Finometer^{TM} cuff and NIRO probe were attached (Figure 22). Once all leads were attached they were plugged into a head box which connected to the E-series recording system. From the monitoring room, the signal quality was assessed and adjusted to ensure all signals were clear and correct and when this was achieved the recording was initiated. The entire process of attaching the leads took approximately 1 hour.

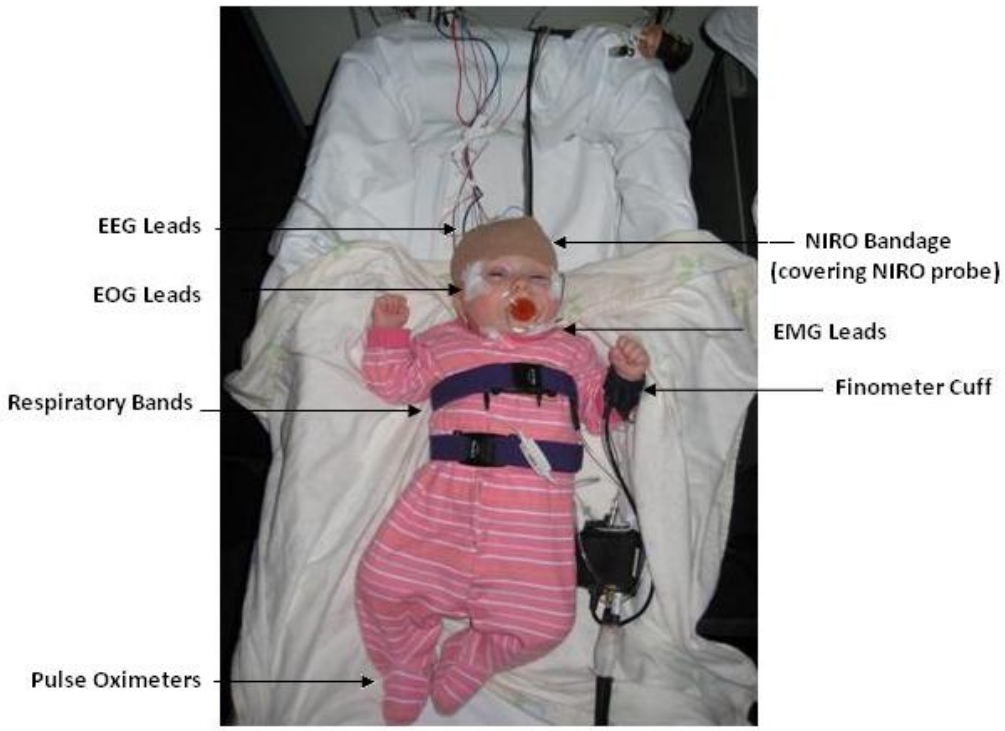


Figure 22: Infant set-up for study. This image shows an infant set-up for a study. It shows the placement of the left and right electro-oculogram (EOG) leads, the chin electromyogram (EMG) leads, the abdominal and thoracic respiratory bands, the NIRO probe and the Finometer^{TM} cuff. The airflow thermistor is not shown in this picture. (Image used with permission)

2.6.2.3 During the Study

The infant slept in a pram in a darkened, quiet room at constant temperature 22-23 degrees. Throughout the recording, one researcher was located at the recording station whilst the second researcher was in the room with the sleeping infant. The researcher at the recording station indicated to the researcher in the room when to begin Finometer^{TM} recordings and perform head-up tilts via a small light. The study was documented by entering detailed notes about events such as sleep state, movements, interruptions and wake or feeding times into the computer.

2.6.2.4 Baseline Recordings

In order to obtain baseline data for cardiovascular and cerebral variables we conducted two minute control recordings with the Finometer^{TM} switched on, with a two minute rest period between each measurement (Figure 24). During these recordings the infant and the signals were closely monitored for any movement artefact, arousal, sigh or apnoea which, if present, were noted in the study notes. If insufficient artefact free data was recorded (i.e. less than one minute) then the control recording was repeated, this occurred frequently in AS. We conducted three successful control recordings in each sleep state and in each sleep position for every infant, with a minimum duration of two minutes between each recording.

2.6.2.5 Head-Up Tilt Recordings

In order to induce a change in BP, HR and cerebral TOI, 15° head-up tilts (HUTs) were performed. The HUT is a commonly used manoeuvre to present a non-invasive cardiovascular challenge resulting in a change in HR, BP and TOI. Tilting an infant is an arousing stimulus; therefore, we used an angle of 15° in order to compromise between causing a significant change in cardiovascular variables whilst reducing infant arousal responses at the tilt. The 15° angle was achieved by tilting the pram as shown in Figure 23.

Figure 23: Head-Up Tilt (HUT). Head-up tilts were performed by raising the head of the pram to an angle of 15°. This non-invasively induces a change in blood pressure and heart rate.

HUT recordings involved a one minute baseline period, the pram was then tilted over a 2-4 second period and the angle maintained for a further one minute (Figure 24). During the tilt the infant was closely monitored for movement or respiratory changes. At the completion of two minutes the Finometer™ was switched off and the pram was lowered. If the infant moved, sighed or aroused at the HUT then the HUT was repeated. A minimum of two minutes recovery was allowed between HUT tests. We aimed to achieve three successful HUTs in each sleep state and in each sleep position.

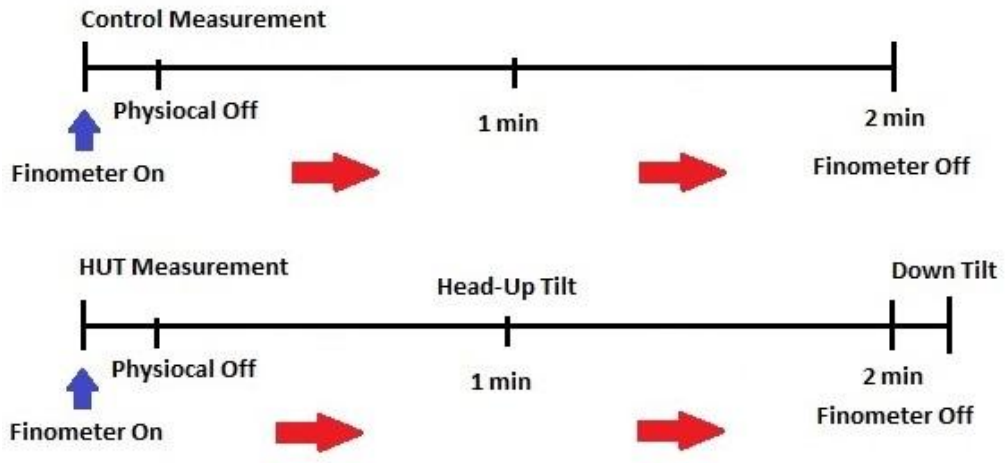


Figure 24: Control and Head-Up Tilt (HUT) Measurement Protocols. Control recordings involved a two-minute period of continuous recording during which the blood pressure cuff was inflated. HUT recordings involved a one minute baseline period, the pram was then tilted over a 2-4 second period and the angle maintained for a further one minute

2.6.2.6 Study Conclusion

The study was concluded when adequate data had been collected which usually took 4-5 hours. If possible, leads were removed whilst the infant was in QS or was feeding. Leads were removed using adhesive removal wipes (ConvaCare, ConvaTec, Uxbridge, Middlesex, UK and Universal Remover Wipes, Hollister Inc, Libertyville, Illinois, USA) and baby oil (Johnson and Johnson, Sydney, Aus). The infant's face and head were then washed to remove any residue and the infant's nappy was changed before returning home.

All the leads, electrodes and equipment were carefully cleaned with alcohol swabs and HC90 solution and the linen used was cleaned by the hospital linen service. All surfaces were wiped down using HC90 solution.

Finally, two copies of the study were burned onto DVD. One was used for analysis and one for archiving purposes.

2.7 Data Analysis

2.7.1 Preparing the Data

Physiological data were analysed offline at the completion of the sleep studies. Data were transferred from Profusion via European Data Format to LabChart analysis software (LabChart 7, ADInstruments, Sydney, Australia). Once the data had been transferred to LabChart, the comments created during the study were manually entered into the LabChart file.

It was important to stringently identify and exclude any movement artefact, sighs or apnoeas from the data. Sighs were identified as any breaths that were greater than two times the amplitude of a normal breath and apnoeas were defined as periods of cessation of breathing for greater than 3 seconds or two regular breathing cycles (Yiallourou et al., 2010). Sighs and apnoeas are both likely to result in a change in HR, BP and TOI and so are excluded from the data prior to analysis.

Only BP epochs containing at least 2 square wave calibrations at the start of the measurement and of greater than 30 seconds in length after the removal of movement artefacts etcetera were included. In

acknowledgement of the fact that the Finometer™ occasionally gives a BP reading that is higher than would be expected for a particular age a histogram of all BP epochs was produced for each sleep state and position at each age (Appendix G). Any epochs that lay 1.5 x inter-quartile range outside of the 1st and 3rd quartiles were excluded as outliers (Yiallourou et al., 2008a).

2.7.2 Sleep State Analysis

The sleep state of the infant was scored during the recording of the study and documented as quiet sleep (QS), active sleep (AS) or in determinant sleep (IS), however, to ensure accuracy the sleep states were reanalysed in LabChart according to accepted paediatric criteria (Mirmiran et al., 2003). Determination of sleep state involved examination of the EEG, EOG and EMG traces, respiratory and heart rate patterns and behavioural observations. QS is characterised by a high voltage, low frequency EEG trace, absence of eye movements, increased muscle tone, regular respiratory and heart rate patterns and an absence of body movements. In contrast, AS is characterised by a low voltage, high frequency EEG trace, the presence of eye movements, reduced muscle tone, irregular respiration and heart rate and frequent body movements (Stern et al., 1969). Where neither the criteria for QS or AS were met, sleep was classified as IS and removed from further analysis. In addition to sleep states, periods where the infants were awake, moving, feeding or crying were noted. Dummy use throughout the study was also documented.

2.7.3 Data Analysis

We conducted a beat-to-beat analysis of the data using programmed analysis functions (Macros) in LabChart which enabled us to extract the cardiovascular data for each heart period (HP) recorded. Creating a macro involved programming LabChart to calculate the average value of the data in the period between two consecutive heart beats (determined by the R wave), for a prescribed number of heart beats. This information was then placed into the data pad which had been manually set up to collect the relevant data as shown in Figure 25. Beat-to-beat analysis was performed on all measurements from the point at which the Physiocal of the Finometer™ was switched off until the conclusion of the measurement.

A Selection Start	B Selection End	C Selection Duration s	D	E ECG1-ECG2 Avg Cyc Rate BPM	F Fimometer BP 1/3 Max + 2/3 Min mmHg	G Fimometer BP Maximum Value mmHg	H Fimometer BP Minimum Value mmHg	I emperature Abd Mean %	J INT SAO2 Mean %	K External SpO2 Mean mmHg	L OxyHB (N1) Mean Um.CM	M DeOxyHB (N2) Mean uM.cm	N TOI (N3) Mean %	O THI (N4) Mean Index	P Comment Text

Figure 25: Data Pad. This is an example of how the data pad was set up for data acquisition in LabChart. Column A – time at the start of the heart beat; Column B – time at the end of the heart beat; Column C – duration of the heart beat; Column E – mean cyclical rate for the ECG during the heart beat; Column F – mean arterial pressure; Column G – systolic blood pressure; Column H – diastolic blood pressure; Column I – mean abdominal temperature; Column J – mean internal oxygen saturation; Column K – mean external oxygen saturation; Column L – mean oxygenated haemoglobin; Column M – mean deoxygenated haemoglobin; Column N – mean TOI (TOI); Column O – mean tissue haemoglobin index (THI); Column P – comments. Note: internal oxygen saturation refers to the oximeter that is built-in to the Profusion polysomnography software, while external oxygen saturation is measured using a standalone Masimo oximeter.

From LabChart, data were copied into Microsoft Office Excel® (2003) for statistical and graphical analysis. Once in Excel, data were manually checked to ensure that each individual heart beat had been correctly identified by checking that the duration of each beat or the heart period (HP) was appropriate. If the macro inaccurately identified a beat then the HP would be inappropriately long or short, where this occured it was necessary to manually extract these data from the LabChart file and insert it into the Excel file at the appropriate time.

In Excel, HR was calculated from the HP using the following equation: HR = 60/HP.

2.7.4 Baseline Data

Baseline data included the 2 minute control recordings, of which there were usually 3 in each sleep state and sleep position, and the 1 minute baseline recordings prior to each HUT, of which there were usually 3 or more in each sleep state and position.

A beat-to-beat analysis was conducted for the cardiovascular variables including HR and BP (including MAP, SAP and DAP), oxygen saturation, temperature and cerebral TOI. The mean values for each recording were then aggregated for each infant according to sleep state and sleep position and the mean and SEM were calculated and displayed graphically.

The averages for each infant were then grouped according to post-term age, sleep state and sleep position and the mean and SEM was again calculated for the grouped data.

2.7.5 Head Up Tilt (HUT) Analysis

For the HUTs, analysis involved calculating the beat-to-beat percentage change from baseline of HR, BP and cerebral TOI following a HUT. The baseline for comparison was the average of the 30 beats prior to the HUT and the percentage change from this baseline was then calculated for the 30 beats prior to and the 90 beats following each HUT. This analysis enabled fluctuations in cardiovascular variables and cerebral oxygenation in response to a HUT to be visualised in graph form. An example of the graph generated from each individual tilt is illustrated in Figure 26.

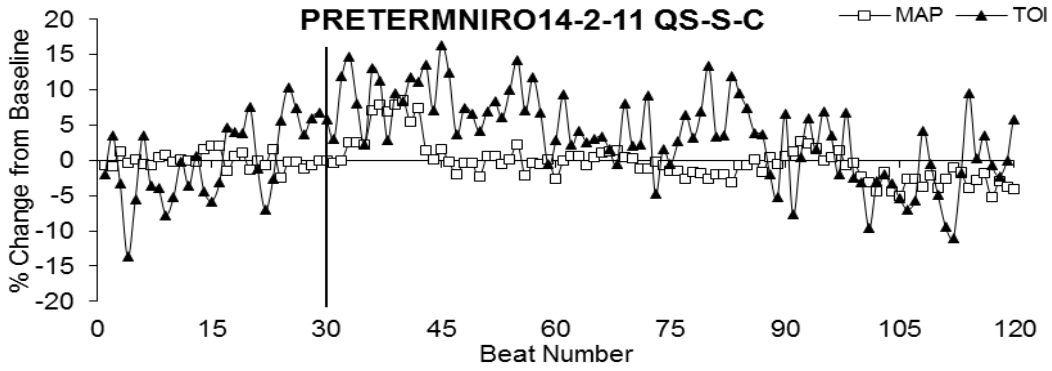


Figure 26: Percentage Change from Baseline during a Head-Up Tilt Recording. This is an example of a graph generated from a HUT recording illustrating the percentge change from baseline for MAP and TOI during a HUT. The tilt occurred at 30 beats (indicated by a line) and the 30 beats prior to this are the baseline. The graph is labeled with the infant's computer code (PRETERMNIRO14-2-11) followed by the tilt label (QS-S-C) indicating the sleep state (QS), position (supine) and tilt number (C, indicating the third tilt performed).

The data from each tilt were grouped according to sleep state and sleep position at each post-term age and the mean and SEM were calculated for each infant. The averages for each infant were grouped for each sleep state and sleep position enabling the grouped mean and SEM to be calculated.

In order to quantify the HUT response, three phases were identified according to previously published cerebral TOI and MAP HUT responses (Wong et al., 2013). These phases, illustrated in Figure 27, consisted of:

1) Baseline: beats 1-30
2) Early Phase: beats 31-60
3) Middle Phase: beats 61-90
4) Late Phase: beats 91-120

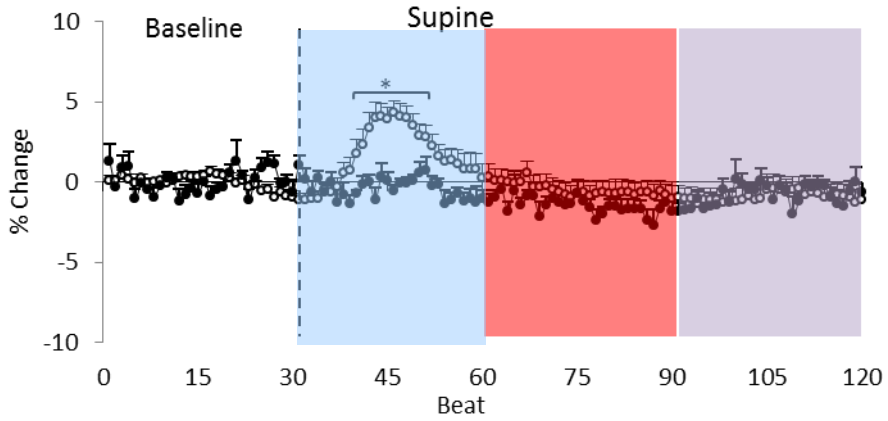


Figure 27: Head Up Tilt Phases. In order to quantify the HUT response, three phases were identified: baseline (beats 1-30), early phase (beats 31-60) illustrated in blue, middle phase (beats 61-90) illustrated in red and late phase (beats 91-120) illustrated in purple. The open circles represent mean arterial pressure while the closed circles represent cerebral tissue oxygenation index.

2.7.6 Analysis of Autonomic Parameters

In order to assess autonomic cardiovascular control we assessed baroreflex sensitivity (BRS) and heart rate variability (HRV). Artefact free epochs of baseline data greater than 1 minute in duration during which systolic BP, HR and respiratory effort were simultaneously recorded were selected from the LabChart file. Epochs were analysed using a specially developed program in MATLAB (Mathworks, Natick, MA) analysis software to generate BRS and HRV (Yiallourou et al., 2011, Yiallourou et al., 2010). Systolic BP and heart period (HP) were calculated using automated peak detection and each epoch was manually checked to ensure that each individual peak was correctly identified. Epochs containing ectopic beats were excluded from further analysis. Beat-to-beat data for systolic BP and HP were resampled at 200Hz (cubic interpolation) to create a continuous, evenly spaced time series for further analysis.

2.7.6.1 Frequency-Domain Baroreflex Sensitivity

BRS was calculated using cross-spectral analysis of BP and HP. This involves calculation of a transfer function, which characterizes the gain (ms/mmHg), coherence and phase lag between spontaneous or induced oscillations in systolic BP with respect to those in HP. The gain quantifies BRS by representing the expected amplitude of oscillation in systolic BP that results in an oscillation in HP of 1ms. The phase lag describes the time delay (delay = [phase lag/360°]/frequency) between oscillations in systolic BP and HP. The coherence between these oscillations was also calculated to quantify the strength of the frequency dependent relationship between systolic BP and HP oscillations. Coherence values fall between 0 and 1 with 0 representing no relationship and 1 representing a perfect correlation. Coherence values of less than 0 represent a change in HP that occurred prior to the change in systolic BP and thus is unlikely to be due to the baroreflex. Therefore, spectral BRS values with a corresponding negative coherence value were excluded. The values for gain and phase lag (delay) were taken at the frequency at maximum coherence within the specific LF range (0.04-0.15Hz) at which baroreflex mediated oscillations in BP and HP are thought to primarily occur (Yiallourou et al., 2011, Yiallourou et al., 2010). Cross-spectral analysis of BRS provides detailed description of frequency-dependent changes in BRS gain and sensitivity, however, it cannot differentiate between central and baroreflex changes therefore cannot exclude that some changes may be centrally mediated.

2.7.6.2 Time-Domain Baroreflex Sensitivity

Spontaneous sequence analysis of BRS calculated using methods adapted from Bertinieri and Zoccoli (Zoccoli et al., 2001, Bertinieri et al., 1988) was used as it is capable of distinguishing between central-command driven and BRS mediated changes in HR. Respiratory sinus and variations in intra-thoracic pressure during respiration can influence BRS values. Therefore, a second-order 2 Hz low-pass filter was passed over the continuous HR and systolic BP traces in order to minimise the influence of respiration (Zoccoli et al., 2001). Increasing or decreasing BP ramps were identified in each individual epoch as increases or decreases of greater than 0.5mmHg during each of three or more BP oscillations. Baroreflex sequences were identified where a positive correlation occurring between the slope of BP and the slope of HR i.e. both were moving in the same direction. Spontaneous

sequence analysis was performed using two methods; variable heart period delay (BRS_{var}) and fixed 1 beat heart period delay (BRS_1).

Fixed heart period delay was assessed by performing linear regression on each ramp sequence between the slopes of BP and HP changes using a fixed heart period delay of 1 beat. The regression coefficient was calculated for each sequence and only those with a sufficiently high coefficient of determination ($R^2 > 0.8$) were included for further analysis. $BRS_1$was calculated from the slope of the blood pressure-heart period regression equation and the mean BRS_1 for each epoch was determined and then grouped according to sleep state and position within each infant and means calculated.

Variable heart period delay was calculated by performing linear regression, calculating the R^2 and regression coefficients, on the slope of BP and HP changes for each BP ramp identified for beat delays of 0 through to 13. The optimal heart period delay was selected as the regression with the highest R^2 value. To ensure only BRS mediated changes in HR were included any regression with a negative R^2, an R^2 >0.8 or with the greatest R^2 occurring at beats 0 or 13 were excluded. Again, BRS_{var} was calculated from the slope of the blood pressure-heart period regression equation for the optimal heart period delay. The mean BRS_{var} and optimal heart period delay were calculated for each infant within each sleep state and position.

Time-domain measures of BRS produced similar results to frequency-domain measures and for simplicity have not been discussed in the manuscript, however a summary of this information can be found in Appendix H.

2.7.6.3 Heart Rate Variability

Fast Fourier transformations were used to calculate the spectral power for HP. Each epoch was detrended and divided into 4 overlapping segments with 75% overlap. A Hamming window was used to reduce spectral leakage and the halving of measured power caused by windowing was corrected for. Power spectra were calculated for HRV within two frequency bands: low frequency (LF) (0.04-0.15 Hz) reflecting slow oscillations attributed to the baroreflex which occur maximally at a frequency of approximately 0.1 Hz and high frequency (HF) which is calculated for each infant based on

respiratory frequency and is defined by the 10^{th} and 90^{th} centiles of the respiratory rate. Total power (TP) and the LF/HF ratio, reflecting sympathovagal balance, were also calculated. The power values represent the square of the amplitude of an oscillatory signal in the identified frequency range. HRV was presented as ms^2 (Yiallourou et al., 2012, Andriessen et al., 2003).

All data were then transferred into excel and grouped according to sleep state and position within each infant.

2.8 Statistical Analysis

Statistical analysis was performed in SigmaPlot 12.0 (Systat Software Inc, Chicago, Illinois, USA).

2.8.1 Baseline Data

Baseline parameters included cerebral TOI, MAP, HR, temperature and oxygen saturation as well as BRS and HRV (including LF, HF, LF/HF and total power). To determine the effect of gestational age (GA) on baseline parameters we used linear regression within each sleep state and position at each post-term age. Where an effect of GA at birth was identified, the preterm infant group was divided into two groups for following analysis; very preterm infants born prior to 32 weeks GA and preterm infants born between 32 and 36 weeks GA. Please note, the graphs for the relationship between GA and cerebral TOI and MAP, where no effect of GA at birth was identified, are included in Appendix I.

To determine the effect of sleep state and position on baseline data including BP, HR, cerebral TOI and autonomic parameters we used two-way repeated measures (RM) analysis of variance (ANOVA) within each post-term age. To determine the effect of increasing post-term age we used two-way RM ANOVA with sleep state and post-term age as factors.

To determine the effects of prematurity on baseline data we compared the grouped means for BP, HR and cerebral TOI for each sleep state and position for the preterm infants against those for the previously studied cohort of term infants. Statistically significant differences were determined using two-way ANOVA with sleep state and birth (preterm or term) as factors within each post-term age.

Where a statistically significant difference was identified with ANOVA ($p<0.05$) Student-Newman-Keuls post-hoc analysis was used to determine where the difference occurred.

2.8.2 Head-Up Tilt Data

Statistically significant change from baseline for each phase was determined using a one-way RM ANOVA. Where data failed normality, a one-way RM ANOVA on ranks was performed with Dunnett's Method post-hoc analysis. The effect of preterm birth was determined using one-way ANOVA within each phase. Data that failed normality was transformed in order to achieve normality. Where a statistically significant difference was detected on ANOVA ($p<0.05$) Student-Newman-Keuls post-hoc analysis was used to determine where the difference occurred. Variability was assessed by comparing the standard deviations for each beat within each phase between term and preterm infants using one-way ANOVA.

Chapter 3

Cerebral Oxygenation in Preterm Infants

3 Cerebral Oxygenation in Preterm Infants

This chapter is presented in manuscript form as it has been accepted for publication in Pediatrics.

Karinna L Fyfe, Stephanie R Yiallourou, Flora Y Wong, Alexsandria Odoi, Adrian M Walker, Rosemary SC Horne

3.1 Declaration for Chapter 3

Monash University

In the case of Chapter 3, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
For this chapter I recruited and performed the preterm infant studies and was responsible for analysis of this data. I was responsible for the comparison of term and preterm data, interpretation of all results and writing of the manuscript.	80%

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Stephanie R Yiallourou	Dr Yiallourou assisted with data collection, interpretation of results and writing of the manuscript.	N/A
Flora Y Wong	Dr Wong assisted with recruitment, interpretation of results and writing of the manuscript.	N/A
Alexsandria Odoi	Miss Odoi assisted with data collection and writing of the manuscript	N/A
Adrian M Walker	Professor Walker assisted with interpretation of the results and writing of the manuscript	N/A
Rosemary SC Horne	Professor Horne aided in recruitment and data collection, interpretation of results and writing of the manuscript	N/A

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work*.

Candidate's Signature		**Date**
Main Supervisor's Signature		**Date**

3.2 Introduction to Chapter 3

Preterm birth, defined as birth before 37 completed weeks of gestation, is increasing in incidence and now accounts for over 10% of live births worldwide annually (Blencowe et al., 2012). Preterm infants are at increased risk for a range of complications, including a significantly increased risk for the Sudden Infant Death Syndrome (SIDS), with greater risk seen in those infants born at earlier gestational ages (Malloy, 2013).

SIDS remains the leading cause of infant death in the post-neonatal period in developed countries (Sherry L Murphey et al., 2013, Li et al., 2012). Despite years of research the exact mechanisms underlying SIDS remain unclear, but it is widely believed that SIDS occurs due to immature cardiovascular control leading to a hypotensive episode during sleep, in combination with a failure of the life-saving arousal response (Harper, 2000). Ninety percent of SIDS deaths occur during the first 6 months of life with a distinct peak in incidence between 2-3 months. Prone sleeping is recognised as a major risk factor for SIDS, particularly amongst infants born preterm (Blair et al., 2006a) .

Previous studies in term infants have established that prone sleeping is associated with reduced blood pressure (BP) (Yiallourou et al., 2008a), decreased cerebral oxygenation (Wong et al., 2011) and impaired arousal (Horne et al., 2001). Our group has previously suggested that reduced cerebral oxygenation affecting the brainstem may contribute to blunted arousal responses thought to play a role in the pathophysiology of SIDS.

Earlier studies by our group have shown that preterm infants born at 28-32 weeks of gestation have reduced BP (Witcombe et al., 2008) and immature cardiovascular control (Witcombe et al., 2009) compared to term infants over the 6 months beyond term-equivalent age when they sleep in the supine position. To date, the effects of prone sleeping on BP and cerebral oxygenation have not been investigated during the period of peak risk for SIDS in preterm infants. Furthermore, the effects of gestational age on these variables have not been assessed.

Therefore, the aim of the following chapter was to investigate BP and cerebral oxygenation during sleep in both the supine and prone positions in preterm infants across the first six months of life. We hypothesised that cerebral oxygenation and BP would be reduced in the prone position in preterm infants and in preterm compared to term infants. Furthermore, we hypothesised that the greatest deficits would be seen at 2-3 months post-term age and in preterm infants born at earlier gestational ages.

Title: Cerebral Oxygenation in Preterm Infants

Authors: Karinna L Fyfe BMedSc[1,2], Stephanie R Yiallourou PhD[1,2], Flora Y Wong MBBS PhD[1,2,3], Alexsandria Odoi BNS (Hons)[1], Adrian M Walker PhD[1], Rosemary SC Horne PhD[1,2]

Affiliations:

[1]The Ritchie Centre, Monash Institute of Medical Research and Prince Henry's Institute and Monash University, Melbourne, Australia;

[2]Department of Paediatrics, Monash University, Melbourne, Australia.

[3]Monash Newborn, Monash Medical Centre, Melbourne, Australia;

Address correspondence to: Professor Rosemary SC Horne, [redacted], The Ritchie Centre, Level 5 Monash Medical Centre, 246 Clayton Road, PO Box 5418, Clayton, Victoria, Australia 3168; [redacted]

Short title: Cerebral Oxygenation in Preterm Infants

Abbreviations: ANOVA – analysis of variance; AS – active sleep; CA – corrected age; CBF – cerebral blood flow; GA – gestational age; Hb – hemoglobin; HR – heart rate; MAP – mean arterial pressure; QS – quiet sleep; RM – repeated measures; SEM – standard error of the mean; SIDS – Sudden Infant Death Syndrome; SpO_2 – arterial oxygen saturation; TOI – Tissue Oxygenation Index

Key words: preterm birth, Sudden Infant Death Syndrome, prone sleeping position, cerebral oxygenation, blood pressure

Funding Source: The National Health and Medical Research Council of Australia and the Victorian Government Infrastructure Program.

Financial Disclosure: The authors have no financial relationships relevant to this article to disclose.

Potential Conflicts of Interest: The authors have no conflicts of interest relevant to this article to disclose.

What's Known on This Subject

Prone sleeping is a major risk factor for the sudden infant death syndrome (SIDS). Cerebral oxygenation and blood pressure are reduced in the prone sleeping position in healthy term infants. Preterm infants are at significantly increased risk of SIDS.

What This Study Adds

Preterm infants display reduced cerebral oxygenation compared to term infants, most prominently at 2-3 months corrected age in the prone position when blood pressure is concurrently reduced. This may contribute to the increased risk for SIDS amongst infants born preterm.

Abstract

Background: Prone sleeping is a major risk factor for the Sudden Infant Death Syndrome (SIDS) and preterm infants are at significantly increased risk. In term infants prone sleeping is associated with reduced mean arterial pressure (MAP) and cerebral tissue oxygenation index (TOI). However, little is known about the effects of sleeping position on TOI and MAP in preterm infants. We aimed to examine TOI and MAP in preterm infants after term-equivalent age, during the period of greatest SIDS risk.

Methods: 35 preterm and 17 term infants underwent daytime polysomnography, including measurement of TOI (NIRO-200 spectrophotometer, Hamamatsu Photonics KK, Japan) and MAP (Finapress Medical Systems, Amsterdam, The Netherlands) at 2-4 weeks, 2-3 months and 5-6 months post-term age. Infants slept prone and supine in active and quiet sleep. The effects of sleep state and position were determined using two-way RM ANOVA and of preterm birth using two-way ANOVA.

Results: In preterm infants, TOI was significantly lower when prone compared to supine in both sleep states at all ages ($p<0.05$). Notably, TOI was significantly lower in preterm compared to term infants at 2-4 weeks, in both positions ($p<0.05$), and at 2-3 months when prone ($p<0.001$), in both sleep states. MAP was also lower in preterm infants in the prone position at 2-3 months ($p<0.01$).

Conclusion: Cerebral oxygenation is reduced in the prone position in preterm infants and is lower compared to age-matched term infants, predominantly in the prone position when MAP is also reduced. This may contribute to their increased SIDS risk.

Introduction

Preterm birth is increasing in incidence and now accounts for over 10% of live births annually worldwide.[1] Preterm infants are at significantly increased risk of the Sudden Infant Death Syndrome (SIDS),[2,3] with 29% of SIDS victims being born preterm.[4] SIDS peaks in incidence at 2-4 months of age[5,6] and is believed to involve an uncompensated cardiovascular event presumed to occur during sleep, in conjunction with failure of the life-saving arousal response.[7-11] Preterm infants exhibit immature cardio-respiratory control which persists past term-equivalent age,[12] is related to gestational age (GA) at birth,[13,14] and may contribute to their heightened risk for SIDS.[15]

Prone sleeping is a major risk factor for SIDS, particularly amongst infants born preterm.[2,16] Term infants sleeping prone have alterations in cardiovascular control[17-21] and we have previously demonstrated that this is reflected in the cerebral circulation, expressed as reduced cerebral oxygenation and altered cerebrovascular control.[22,23] It has been suggested that reduced cerebral oxygenation may contribute to impaired arousal[22] which is seen in the prone position in both term[18,24] and preterm infants[25-27] and is likely to be significant in the pathophysiology of SIDS.[10,28]

Preterm infants display immature cerebrovascular control prior to term-equivalent age,[29-32] the severity of which is related to their GA at birth.[30] However, little is known about cerebral oxygenation in preterm infants during the period of greatest SIDS risk. We measured cerebral oxygenation and blood pressure during sleep in both the prone and supine positions in preterm infants across the first 6 months post-term. We hypothesized that cerebral oxygenation would be lower in infants born at earlier GA, in the prone position, at 2-3 months post-term corrected age (CA) and in preterm compared to term infants and that perturbations in cerebral oxygenation would be associated with alterations in systemic cardiovascular parameters.

Subjects and Methods

Ethical approval was obtained from the Monash Health and Monash University human research ethics committees. Written parental consent was obtained and no monetary incentive was provided for participation.

Subjects

35 preterm infants born at 26-36 weeks GA and 17 term infants born at 38-42 weeks GA were studied with daytime polysomnography (Table 1). All infants were appropriately grown for GA, born to non-smoking mothers, had no family history of SIDS and routinely slept supine at home. In the preterm cohort, exclusion criteria included intrauterine growth restriction, major congenital abnormalities, hemodynamically significant patent ductus arteriosus, significant intraventricular hemorrhage (grade III or IV) and chronic lung disease requiring ongoing respiratory stimulant medication or oxygen therapy at term-equivalent age.

Of the preterm infants, 24 were studied on 3 occasions at 2-4 weeks, 2-3 months and 5-6 months post-term CA; 7 were studied at only 2-4 weeks CA and 4 were studied only at 2-3 months and 5-6 months CA. Term infants were all studied at three ages; 2-4 weeks, 2-3 months and 5-6 months chronological age, and data from this study have previously been published.[22,23]

Study Protocol

Daytime polysomnography was performed in a sleep laboratory with constant temperature (22-23°C), dim lighting and quiet conditions. Infants slept both prone and supine, with the initial sleep position randomized. Sleep position was changed following a midday feed.

Electrodes required for determining sleep state were applied during a morning feed; these included electroencephalogram, electrooculogram, submental electromyogram,

electrocardiogram and abdominal and thoracic respiratory belts (Resp-ez bands, EPM Systems, Midlothian, VA, USA). Arterial oxygen saturation (SpO_2) (Masimo, Frenchs Forest, NSW, Australia) and abdominal skin temperature (ADInstruments, Sydney, NSW, Australia) were also recorded.

Cerebral Oxygenation

Cerebral tissue oxygenation index (TOI %) was measured continuously using near-infrared spectroscopy (NIRO-200 spectrophotometer, Hamamatsu Photonics KK, Tokyo, Japan). Near-infrared spectroscopy enables calculation of cerebral TOI using continuous-wave light emission and detection measured over the frontal region of the infant's brain, with the detection probe placed 4cm away from the emission probe. TOI was computed at 6 Hz using a spatially resolved spectroscopy algorithm[33] and represents mixed oxygen saturations of all cerebral vascular compartments.

Mean Arterial Pressure

Mean arterial pressure (MAP) was measured using a photoplethysmographic cuff (Finapress Medical Systems, Amsterdam, The Netherlands) placed around the infant's wrist, using a technique previously validated by our group.[34] Data were collected in 1-2 minute epochs with at least 2 minutes between inflations to prevent venous pooling in the infants' hands.

All physiological variables were recorded with a sampling rate of 512 Hz using an E-series sleep system with Profusion software (Compumedics, Abbotsford, VIC, Australia).

Data Analysis

At the completion of each study, data were transferred to LabChart7 software (ADInstruments, Sydney, NSW, Australia) for analysis. Sleep state was defined as either quiet sleep (QS) or active sleep (AS).[35] Beat-to-beat values were calculated for cerebral TOI,

MAP, heart rate (HR), SpO_2 and temperature during each 1-2 minute epoch; data were averaged for each epoch and pooled for each sleep state and position within each infant. An average of 6 epochs was analyzed in each sleep state and position for each infant. Data containing movement artifact and epochs where MAP data lay more than 1.5 times the interquartile range outside the first and third quartiles were excluded from further analysis.[36]

Statistical Analysis

Statistical analysis was performed using SigmaPlot 12.0 software (Systat Software Inc, IL, USA). Linear regression was used to determine the relationships between GA at birth and cerebral TOI and between GA at birth and MAP. The effects of sleep state and position were determined using two-way repeated measures (RM) analysis of variance (ANOVA) at each CA. The effect of increasing CA was determined using two-way RM ANOVA with CA and sleep state as factors. The effect of preterm birth was determined using two-way ANOVA with birth and sleep state as factors. When a significant difference was indicated on ANOVA, the specific source of the difference was identified with Student-Newman-Keuls post-hoc analysis. Results are presented as mean ± standard error of the mean (SEM) with significance taken at $p<0.05$.

Results

Effects of Gestational Age at Birth in Preterm Infants

No significant correlation was found between cerebral TOI and GA at birth or between MAP and GA at birth at any age studied in either sleep state or position (data not shown).

Effects of Sleep Position in Preterm Infants (Figure 1)

Cerebral Tissue Oxygenation Index

In preterm infants cerebral TOI was affected by sleep position at all three ages, with TOI being lower in the prone compared to the supine position in both sleep states at 2-4 weeks ($p<0.05$), 2-3 months ($p<0.01$) and 5-6 months CA ($p<0.01$).

Mean Arterial Pressure and Heart Rate

MAP was not significantly affected by sleep position at any age, although a trend towards lower MAP was evident in the prone position at 2-3 months CA, in both QS and AS. Overall, HR was higher in the prone compared to the supine position at both 2-4 weeks ($p<0.05$) and 5-6 months CA ($p<0.01$) and post-hoc analysis revealed that this reached significance in QS (2-4 weeks CA $p<0.05$; 5-6 months CA $p<0.01$). In AS, HR tended to be higher in the prone position at 2-4 weeks ($p=0.085$) and 5-6 months CA ($p=0.069$). At 2-3 months CA there was no effect of position on HR.

Temperature and Arterial Oxygen Saturation

Abdominal skin temperature (Figure 1) was higher in the prone compared to the supine position in both sleep states at 2-4 weeks, 2-3 months and 5-6 months CA ($p<0.001$ for all). SpO_2 (data not shown) was higher in the supine compared to the prone position in AS at 2-4 weeks CA and in QS at 5-6 months CA ($p<0.05$), however differences were within 1% and unlikely to be of clinical significance.

Effects of Sleep State in Preterm Infants (Table 2)

Cerebral Tissue Oxygenation Index

TOI was higher in QS compared to AS in both the supine and prone positions ($p<0.01$) at 2-4 weeks CA. At 2-3 months CA cerebral TOI was not affected by sleep state in either position. At 5-6 months CA cerebral TOI was lower in QS compared to AS in both the supine and prone ($p<0.01$) positions.

Mean Arterial Pressure and Heart Rate

MAP was higher in AS compared to QS at 2-4 weeks CA ($p<0.001$) and 2-3 months CA ($p<0.05$) in both the prone and supine positions, and at 5-6 months CA ($p<0.05$) in the supine position. HR tended to be higher in AS compared to QS, reaching significance at 2-3 months CA in the supine position ($p<0.05$) and at 5-6 months CA in both the supine ($p<0.001$) and prone ($p<0.001$) positions.

Skin Temperature and Oxygen Saturation

Abdominal skin temperature and SpO_2 were not affected by sleep state at any age in either position.

Effects of Post-Term Corrected Age in Preterm Infants (Table 2)

Cerebral Tissue Oxygenation Index

In the supine position in QS, TOI was higher at 2-4 weeks compared to 2-3 months CA ($p<0.05$) and 5-6 months CA ($p<0.05$), with no difference between 2-3 months and 5-6 months CA. In the supine position in AS, TOI was lower at 2-3 months compared to 5-6 months CA ($p<0.05$). In the prone position, in both QS and AS, TOI was higher at 2-4 weeks compared to 2-3 months CA ($p<0.05$) and higher at 5-6 months compared to 2-3 months CA ($p<0.05$). In AS in the supine position and in both sleep states in the prone position there was no difference in TOI between 2-4 weeks and 5-6 months CA, so that an age-related nadir in TOI was evident at 2-3 months CA.

Mean Arterial Pressure and Heart Rate

Age-related differences in MAP were evident in QS in the supine position, where MAP was higher at 5-6 months CA compared to 2-4 weeks CA ($p<0.01$), and in both QS and AS in the

prone position where MAP was higher at 5-6 months CA compared to both 2-4 weeks ($p<0.001$) and 2-3 months CA ($p<0.01$). HR declined significantly in both sleep states and in both sleep positions with increasing post-term CA ($p<0.05$ for all).

Temperature and Oxygen Saturation

There was no effect of post-term CA on abdominal skin temperature. SpO_2 was higher (approximately 1%) at 2-4 weeks compared to 5-6 months CA in QS in the supine position ($p<0.05$), a difference unlikely to be of clinical significance.

Effects of Preterm Birth

There were no differences between term and preterm infants for age, weight and length at any of the three studies (Table 1).

Cerebral Tissue Oxygenation Index and Mean Arterial Pressure (Figure 2)

At 2-4 weeks CA cerebral TOI was lower in preterm compared to term infants in both sleep states in the prone ($p<0.01$ for both) and supine ($p<0.05$ for both) sleep positions. At 2-3 months CA, there was no difference in cerebral TOI between term and preterm infants in the supine position. However, in the prone position cerebral TOI was lower in preterm compared to term infants in both QS and AS ($p<0.001$ for both). At 5-6 months there was no effect of preterm birth on TOI.

In the supine position at all three ages, and in the prone position at 5-6 months CA, there was no effect of preterm birth on MAP (Figure 2). In the prone position, there was an overall effect of preterm birth on MAP at 2-4 weeks CA, with MAP being lower in the preterm cohort ($p<0.05$), although post-hoc analysis did not identify whether the difference lay in AS or QS. At 2-3 months CA, MAP was lower in the preterm cohort in both QS ($p<0.01$) and AS ($p<0.01$).

Heart Rate, Temperature and Arterial Oxygen Saturation (Table 3)

In both the supine and prone positions there was no effect of preterm birth on HR at 2-4 weeks CA and 5-6 months CA, in either sleep state. At 2-3 months CA, HR was lower in the preterm cohort in QS in the supine position ($p<0.05$) and in both QS ($p<0.01$) and AS ($p<0.01$) in the prone position.

Temperature was higher in term compared to preterm infants ($p<0.05$) in all sleep states and positions except AS in the supine position at 5-6 months. SpO_2 was higher in preterm compared to term infants in both QS and AS in the prone and supine position at 2-4 weeks ($p<0.001$ for all) and 5-6 months CA ($p<0.05$ for all). At 2-3 months CA there was no effect of preterm birth on SpO_2.

Discussion

To our knowledge, this is the first study to assess the effects of sleeping position on cerebral TOI in preterm infants during the period of greatest SIDS risk. We found cerebral TOI to be consistently lower in the prone compared to the supine position, with the maximal difference at 2-3 months CA. Furthermore, we found cerebral TOI to be lower in preterm infants compared to term-born infants at similar post-term ages, most prominently at 2-3 months in the prone position, coinciding with a reduction in MAP and HR.

Effects of Gestational Age at Birth

In contrast to our hypothesis, we found no association between GA at birth and cerebral TOI amongst this cohort of preterm infants born at 26-36 weeks GA. Any potential effect of GA may have been obscured by studying the infants at similar post-conceptional ages, when brain maturation may have been similar regardless of GA at birth. Furthermore, our strict exclusion of infants with significant intracranial pathology ensured a low-risk cohort.

Previous MRI studies assessing brain maturation in low-risk preterm infants have found only subtle effects of GA.[37] Similarly, we found no association between GA at birth and MAP, probably because infants had reached normal weight by the time of study, a strong predictor of MAP,[38] with no differences in weight between term and preterm infants.

Effects of Sleep Position

Cerebral TOI was consistently reduced in the prone compared to the supine position in preterm infants, a finding similar to our previous study in term-born infants.[22] Cerebral TOI reflects the ratio of oxygenated to deoxygenated haemoglobin (Hb) in the cerebral vasculature and is largely influenced by changes in the cerebral venous compartment due to its greater volume relative to the arterial compartment. Thus impaired cerebral venous drainage, resulting in venous congestion, may contribute to the reduction in cerebral TOI seen in the prone position. Additionally, impaired cerebral blood flow (CBF) may be an important contributor. Previous studies have found blood flow to be impaired through the internal jugular vein[39] and the vertebral and basilar arteries[40,41] of infants in the prone position with their heads turned to the side. Furthermore, in preterm infants these prone-related deficits in vertebral artery flow were found to be maximal at 1 month CA compared to the newborn period,[42] suggesting position-dependent changes in CBF may be aggravated with advancing age.

We found the maximal effect of sleep position on cerebral TOI to occur at 2-3 months CA, with cerebral TOI averaging 51% in prone sleeping. Whilst the lower threshold for safe cerebral TOI in infancy remains unclear,[43] in animal studies cerebral TOI falls below 40% during imposed hypoxic-ischemic insults.[44] With cerebral TOI values approaching this level in the prone position, preterm infants may be at risk of critically impaired cerebral TOI during hypoxic or hypotensive episodes occurring during sleep.

The effect of prone sleeping in preterm infants may be maximal at 2-3 months CA due to impaired cardiovascular control during this period. It is well established that prone sleeping is associated with an increase in temperature and peripheral vasodilation in infancy.[20,45,46] This reduction in peripheral vascular resistance stimulates a baroreflex-mediated increase in HR in order to maintain MAP.[19,45] This reflex response is consistent with our observations at 2-4 weeks and 5-6 months CA, where HR and temperature were increased in the prone position and MAP was maintained. In contrast, we found no increase in HR in the prone position at 2-3 months CA, despite the observed increase in temperature; this coincided with a tendency for MAP to be lower in the prone compared to the supine position. This suggests that baroreflex-mediated HR responses may be impaired during this period, resulting in a reduced ability to maintain MAP in the prone position and suggestive of reduced cardiac output. This is consistent with findings of reduced cardiac index, a measure of cardiac output relative to body surface area, in adults[47,48] and children[49] in the prone compared to the supine position. Reduced cardiac output may explain why the greatest deficit in cerebral oxygenation is seen in the prone position during this period.

Although still present at 5-6 months CA, the effect of position on cerebral TOI lessens with age. This is likely to be due to maturation of cardiovascular control, anatomical maturation allowing improved blood flow through position-affected vessels and a reduced head-to-body ratio with growth of the infant.[22]

Effects of Sleep State

Consistent with our findings in term infants, cerebral TOI was also influenced by sleep state in the preterm cohort.[22] At 2-4 weeks CA cerebral TOI was lower in AS compared to QS, at 2-3 months no effect of sleep state was observed and at 5-6 months CA cerebral TOI was higher in AS compared to QS. We suggest that this age-related progression is due to

maturation of CBF-metabolism coupling during this period. AS is a state of increased brain activity, similar to wakefulness, and CBF normally increases from the level in QS to meet the heightened metabolic demands.[50,51] In the mature brain, CBF usually overshoots the metabolic demands of AS resulting in an increase in oxygenated Hb relative to deoxygenated Hb and therefore an increase in cerebral TOI.[52] At 2-4 weeks CA the CBF-metabolism coupling response appears to be relatively immature with an inadequate increase in CBF[22] resulting in increased oxygen extraction, increased deoxygenated Hb and a decrease in TOI in AS. The reversal of this observation at 5-6 months CA suggests that there is continuing maturation of CBF-metabolism coupling occurring during this period.

Effects of Post-Term Corrected Age

Consistent with previous findings in term infants,[22] increasing age had a considerable influence on cerebral TOI in preterm infants. TOI reached a nadir at 2-3 months CA, most consistently in AS. We speculate that immature CBF-metabolism coupling at 2-3 months CA in combination with continuing growth of the brain and accompanying increases in cerebral oxygen requirements result in a mismatch between cerebral metabolic demands and the capacity for cerebral oxygen delivery during this period. Furthermore, physiological anemia peaks at approximately 10 weeks of age in term infants with the nadir in Hb being more severe and earlier in onset in preterm infants.[53] Anemia is associated with reduced cerebral TOI due to increased oxygen extraction necessitated by a reduced oxygen carrying capacity.[54] Although Hb was not measured in our study, it is likely that Hb concentrations would be relatively low at 2-3 months CA, contributing to reduced cerebral TOI.

Furthermore, in preterm infants in the prone position we saw a plateau in MAP between 2-4 weeks and 2-3 months CA, followed by a significant increase between 2-3 months and 5-6 months CA. Relative depression of MAP at 2-3 months is similar to the nadir in MAP seen

in term infants.[20] When coupled with the peak in physiological anemia during this period,[55] lower MAP may represent vulnerability of the preterm infant to impaired oxygen delivery to vital organs including the brain during the period of greatest risk for SIDS.

Our data suggest that cerebral oxygen delivery relative to consumption improves by 5-6 months CA, with increased cerebral TOI most notably in AS. This is likely to be due to maturation of CBF-metabolism coupling in combination with improvements in Hb concentration.

Effects of Preterm Birth

We found cerebral TOI to be lower in preterm compared to term infants until 2-3 months CA. In order to exclude differences in arterial SpO_2 as a cause for the difference in cerebral TOI we assessed arterial SpO_2 and found higher SpO_2 in preterm infants at 2-4 weeks CA and no difference at 2-3 months CA. The differences in SpO_2 were within 2% and therefore unlikely to be either clinically significant or underlie the differences in cerebral TOI. Therefore we can assume that the difference in cerebral TOI is due to increased oxygen extraction in the preterm infant brain, resulting in increased deoxygenated Hb and reduced cerebral TOI. A limited number of previous studies have assessed cerebral TOI in preterm and term infants with conflicting findings.[56-59] However, these studies failed to match infants according to post-conceptional or term-equivalent age, so age-related differences were likely to be obscured by the range of developmental stages.[56-59]

Lower cerebral TOI in preterm infants compared to term infants may be due to inadequate cerebral oxygen delivery relative to consumption.[22] Impaired oxygen carrying capacity due to anemia, which is likely to be more severe in preterm infants, as mentioned previously, may contribute to this mismatch.[53] Furthermore, it is well established that prematurity and a period of neonatal intensive care can result in altered brain maturation as evidenced by MRI

studies at term-equivalent age assessing cerebral volumes,[60,61] cortical folding[62] and neural networks.[63] Although few data exist on brain development in preterm infants after term-equivalent age, we suggest that the preterm infant brain undergoes significant 'catch-up' growth resulting in an increased cerebral metabolic rate for oxygen compared to term infants, a maturational difference which appears to resolve by 5-6 months CA.

Interestingly, the effect of preterm birth was greatest in the prone position at 2-3 months CA, with a cerebral TOI deficit of approximately 10%. We attribute this to our finding of significantly reduced MAP and HR in preterm compared to term infants in the prone position during this period. We suggest preterm infants may have altered cardiovascular regulatory responses to prone sleeping at 2-3 months CA, as they appear not to increase HR in order to maintain MAP. Previous studies in the supine position have found alterations in the development of autonomic cardiovascular control in preterm compared to term infants during the first six months of life.[64,65] Specifically, high frequency HR variability reflecting parasympathetic cardiac modulation has been found to be lower in preterm compared to term infants at term-equivalent age.[14] At 2-3 months CA, altered peripheral vasomotor tone is seen in preterm compared to term infants in the supine position.[64] Moreover, preterm infants, assessed at term-equivalent age, displayed a diminished HR response to a cardiovascular stress compared to term infants.[66] Our data provide evidence that impaired autonomic cardiovascular control seen in preterm infants in the supine position may be exacerbated in the prone sleep position at 2-3 months CA, manifesting as significant differences in MAP and HR between term and preterm infants.

Implications for SIDS

Our findings of reduced cerebral TOI in preterm infants, particularly in the prone position, in conjunction with reduced MAP in preterm compared to term infants in the prone position at

2-3 months CA, have significant implications for SIDS. We speculate that reduced cerebral TOI in the prone position may reflect impaired oxygen delivery to the brainstem and contribute to deficient autonomic activation and blunted arousal responses in the prone position. Furthermore, lower baseline cerebral TOI in preterm infants may represent an increased vulnerability for critically impaired cerebral TOI during a hypotensive or hypoxemic event occurring during sleep. Our data suggest that deficits in cerebral oxygenation are exacerbated by immature systemic cardiovascular control as periods during which cerebral oxygenation was lowest were associated with concomitant reductions in MAP and HR.

It is important to note that epidemiological studies have identified that the peak in SIDS deaths occurs at a slightly earlier post-term CA (7-9 weeks CA depending on GA at birth) for preterm compared to term infants.[6] In this study we chose to investigate term and preterm infants at similar post-term CAs to enable comparison at equivalent developmental ages. It may be that the cerebral oxygenation and cardiovascular differences we observed were in fact underestimated, as our infants were studied at a slightly older age than that of peak SIDS risk in preterm infants.

Conclusions

Cerebral oxygenation is depressed in the prone sleep position in preterm infants until at least 5-6 months CA. In addition, cerebral oxygenation is reduced in preterm compared to term infants until approximately 2-3 months CA, predominantly in the prone position. The greatest deficit in cerebral oxygenation between term and preterm infants was seen at 2-3 months CA in the prone position, when MAP and HR were concurrently reduced in preterm infants. We suggest preterm infants may be particularly vulnerable to critically impaired

cerebral oxygenation in the prone position, particularly in the presence of cardiovascular instability, contributing to their heightened risk of SIDS.

Acknowledgements

The authors wish to thank the parents and infants who participated in this study and the staff of the Melbourne Children's Sleep Centre where these studies were carried out.

References

1. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller A-B, Narwal R, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. *The Lancet*. 2012;379(9832):2162-2172.
2. Blair PS, Platt MW, Smith IJ, Fleming PJ, Group CSR, Platt MW. Sudden infant death syndrome and sleeping position in pre-term and low birth weight infants: an opportunity for targeted intervention. *Arch Dis Child*. 2006;91(2):101-106.
3. Blair PS, Sidebotham P, Berry PJ, Evans M, Fleming PJ. Major epidemiological changes in sudden infant death syndrome: a 20-year population-based study in the UK. *The Lancet*. 2006;367(9507):314-319.
4. Trachtenberg FL, Haas EA, Kinney HC, Stanley C, Krous HF. Risk Factor Changes for Sudden Infant Death Syndrome After Initiation of Back-to-Sleep Campaign. *Pediatrics*. 2012;129(4):630-638.
5. Halloran DR, Alexander GR. Preterm delivery and age of SIDS death. *Ann Epidemiol*. 2006;16(8):600-606.
6. Malloy MH. Prematurity and sudden infant death syndrome: United States 2005-2007. *J Perinatol*. 2013;33(6):470-475.
7. Schechtman VL, Harper RM, Kluge KA, Wilson AJ, Hoffman HJ, Southall DP. Heart rate variation in normal infants and victims of the sudden infant death syndrome. *Early Hum Dev*. 1989;19(3):167-181.
8. Kelly DH, Pathak A, Meny R. Sudden severe bradycardia in infancy. *Pediatr Pulmonol*. 1991;10(3):199-204.
9. Harper RM. Sudden infant death syndrome: a failure of compensatory cerebellar mechanisms? *Pediatr Res*. 2000;48(2):140-142.
10. Kato I, Franco P, Groswasser J, Scaillet S, Kelmanson I, Togari H, et al. Incomplete Arousal Processes in Infants Who Were Victims of Sudden Death. *Am J Respir Crit Care Med*. 2003;168(11):1298-1303.
11. Paterson D, Trachtenberg FL, Thompson EG, et al. Multiple serotonergic brainstem abnormalities in sudden infant death syndrome. *J Am Med Assoc*. 2006;296(17):2124-2132.
12. Witcombe NB, Yiallourou SR, Walker AM, Horne RSC. Blood pressure and heart rate patterns during sleep are altered in preterm-born infants: implications for sudden infant death syndrome. *Pediatrics*. 2008;122(6):e1242-e1248.
13. Katona PG, Frasz A, Egbert J. Maturation of cardiac control in full-term and preterm infants during sleep. *Early Hum Dev*. 1980;4(2):145-159.
14. Eiselt M, Curzi-Dascalova L, Clairambault J, Kauffmann F, Medigue C, Peirano P. Heart-rate variability in low-risk prematurely born infants reaching normal term: A comparison with full-term newborns. *Early Hum Dev*. 1993;32(2-3):183-195.
15. Horne RS. Effects of prematurity on heart rate control: implications for sudden infant death syndrome. *Expert Rev Cardiovasc Ther*. 2006;4(3):335-343.
16. Syndrome TFoSID. SIDS and Other Sleep-Related Infant Deaths: Expansion of Recommendations for a Safe Infant Sleeping Environment. *Pediatrics*. 2011;128(5):1030-1039.
17. Tuladhar R, Harding R, Cranage SM, Adamson TM, Horne RSC. Effects of sleep position, sleep state and age on heart rate responses following provoked arousal in term infants. *Early Hum Dev*. 2003;71(2):157-169.
18. Galland BC, Reeves G, Taylor BJ, Bolton DP. Sleep position, autonomic function, and arousal. *Archives of Disease in Childhood Fetal & Neonatal Edition*. 1998;78(3):F189-194.
19. Chong A, Murphy N, Matthews T. Effect of prone sleeping on circulatory control in infants. *Arch Dis Child*. 2000;82(3):253-256.
20. Yiallourou SR, Walker AM, Horne RS. Effects of sleeping position on development of infant cardiovascular control. *Arch Dis Child*. 2008;93(10):868-872.
21. Yiallourou SR, Walker AM, Horne RS. Prone sleeping impairs circulatory control during sleep in healthy term infants: implications for SIDS. *Sleep*. 2008;31(8):1139-1146.

22. Wong FY, Witcombe NB, Yiallourou SR, Yorkston S, Dymowski AR, Krishnan L, et al. Cerebral Oxygenation Is Depressed During Sleep in Healthy Term Infants When They Sleep Prone. *Pediatrics*. 2011;127(3):e558-e565.
23. Wong F, Yiallourou SR, Odoi A, Browne P, Walker AM, Horne RSC. Cerebrovascular control is altered in healthy term infants when they sleep prone. *Sleep*. 2013;36(12):1911-1918.
24. Horne RS, Ferens D, Watts AM, Vitkovic J, Lacey B, Andrew S, et al. The prone sleeping position impairs arousability in term infants. *J Pediatr*. 2001;138(6):811-816.
25. Ariagno RL, van Liempt S, Mirmiran M. Fewer spontaneous arousals during prone sleep in preterm infants at 1 and 3 months corrected age. *J Perinatol*. 2006;26(5):306-312.
26. Bhat RY, Hannam S, Pressler R, Rafferty GF, Peacock JL, Greenough A, et al. Effect of prone and supine position on sleep, apneas, and arousal in preterm infants. *Pediatrics*. 2006;118(1):101-107.
27. Horne RS, Bandopadhayay P, Vitkovic J, Cranage SM, Adamson TM. Effects of age and sleeping position on arousal from sleep in preterm infants. *Sleep*. 2002;25(7):746-750.
28. Moon RY, Horne RS, Hauck FR. Sudden infant death syndrome. *Lancet*. 2007;370(9598):1578-1587.
29. Wong FY, Leung TS, Austin T, Wilkinson M, Meek JH, Wyatt JS, et al. Impaired autoregulation in preterm infants identified by using spatially resolved spectroscopy. *Pediatrics*. 2008;121(3):e604-611.
30. Soul JS, Hammer PE, Tsuji M, Saul JP, Bassan H, Limperopoulos C, et al. Fluctuating pressure-passivity is common in the cerebral circulation of sick premature infants. *Pediatr Res*. 2007;61(4):467-473.
31. Tsuji M, Saul JP, du Plessis A, Eichenwald E, Sobh J, Crocker R, et al. Cerebral intravascular oxygenation correlates with mean arterial pressure in critically ill premature infants. *Pediatrics*. 2000;106(4):625-632.
32. Hahn GH, Maroun LL, Larsen N, Hougaard DM, Sorensen LC, Lou HC, et al. Cerebral autoregulation in the first day after preterm birth: no evidence of association with systemic inflammation. *Pediatr Res*. 2012;71(3):253-260.
33. Suzuki S, Takasaki S, Ozaki T, Kobayashi Y. Tissue oxygenation monitor using NIR spatially resolved spectroscopy. 1999:582-592.
34. Yiallourou SR, Walker AM, Horne RS. Validation of a new noninvasive method to measure blood pressure and assess baroreflex sensitivity in preterm infants during sleep. *Sleep*. 2006;29(8):1083-1088.
35. Anders T, Emde RN, Parmelee AH, University of California LABIS. *A Manual of Standardized Terminology, Techniques and Criteria for Scoring of States of Sleep and Wakefulness in Newborn Infants*: UCLA Brain Information Service; 1971.
36. Brase CH, Brase CP. *Understandable Statistics: Concepts and Methods*: Cengage Learning; 2011.
37. Mewes AU, Huppi PS, Als H, Rybicki FJ, Inder TE, McAnulty GB, et al. Regional brain development in serial magnetic resonance imaging of low-risk preterm infants. *Pediatrics*. 2006;118(1):23-33.
38. Georgieff MK, Mills MM, Gomez-Marin O, Sinaiko AR. Rate of change of blood pressure in premature and full term infants from birth to 4 months. *Pediatr Nephrol*. 1996;10(2):152-155.
39. Watson GH. Effect of head rotation on jugular vein blood flow. *Arch Dis Child*. 1974;49(3):237-239.
40. Gabai N, Cohen A, Mahagney A, Bader D, Tirosh E. Arterial blood flow and autonomic function in full-term infants. *Clin Physiol Funct Imaging*. 2006;26(2):127-131.
41. Pamphlett R, Raisanen J, Kum-Jew S. Vertebral artery compression resulting from head movement: a possible cause of the sudden infant death syndrome. *Pediatrics*. 1999;103(2):460-468.
42. Eichler F, Ipsiroglu O, Arif T, Popow C, Heinzl H, Urschitz M, et al. Position dependent changes of cerebral blood flow velocities in premature infants. *Eur J Pediatr*. 2001;160(10):633-639.

43. van Bel F, Lemmers P, Naulaers G. Monitoring neonatal regional cerebral oxygen saturation in clinical practice: Value and pitfalls. *Neonatology*. 2008;94(4):237-244.
44. Ioroi T, Peeters-scholte C, Post I, Leusink C, Groenendaal F, van Bel F. Changes in cerebral haemodynamics, regional oxygen saturation and amplitude-integrated continuous EEG during hypoxia-ischaemia and reperfusion in newborn piglets. *Exp Brain Res*. 2002;144(2):172-177.
45. Skadberg BT, Markestad T. Behaviour and physiological responses during prone and supine sleep in early infancy. *Arch Dis Child*. 1997;76(4):320-324.
46. Sahni R, Schulze KF, Ohira-Kist K, Kashyap S, Myers MM, Fifer WP. Interactions among peripheral perfusion, cardiac activity, oxygen saturation, thermal profile and body position in growing low birth weight infants. *Acta Pædiatrica*. 2010;99(1):135-139.
47. Poon K-S, Wu K-C, Chen C-C, Fung S-T, Lau AW-C, Huang C-C, et al. Hemodynamic Changes During Spinal Surgery in the Prone Position. *Acta Anaesthesiologica Taiwanica*. 2008;46(2):57-60.
48. Yokoyama M, Ueda W, Hirakawa M, Yamamoto H. Hemodynamic effect of the prone position during anesthesia. *Acta Anaesthesiol Scand*. 1991;35(8):741-744.
49. Brown ZE, Görges M, Cooke E, Malherbe S, Dumont GA, Ansermino JM. Changes in cardiac index and blood pressure on positioning children prone for scoliosis surgery. *Anaesthesia*. 2013;68(7):742-746.
50. Munger DM, Bucher HU, Duc G. Sleep state changes associated with cerebral blood volume changes in healthy term newborn infants. *Early Hum Dev*. 1998;52(1):27-42.
51. Meek JH, Elwell CE, Khan MJ, Romaya J, Wyatt JS, Delpy DT, et al. Regional changes in cerebral haemodynamics as a result of a visual stimulus measured by near infrared spectroscopy. *Proc R Soc Lond B Biol Sci*. 1995;261(1362):351-356.
52. Khadra MA, McConnell K, VanDyke R, Somers V, Fenchel M, Quadri S, et al. Determinants of Regional Cerebral Oxygenation in Children with Sleep-disordered Breathing. *Am J Respir Crit Care Med*. 2008;178(8):870-875.
53. Strauss RG. Anaemia of prematurity: Pathophysiology and treatment. *Blood Rev*. 2010;24(6):221-225.
54. van Hoften JC, Verhagen EA, Keating P, ter Horst HJ, Bos AF. Cerebral tissue oxygen saturation and extraction in preterm infants before and after blood transfusion. *Archives of Disease in Childhood Fetal & Neonatal Edition*. 2010;95(5):F352-358.
55. Widness JA. Pathophysiology of Anemia During the Neonatal Period, Including Anemia of Prematurity. *NeoReviews*. 2008;9(11):e520.
56. Arri SJ, Muehlemann T, Biallas M, Bucher HU, Wolf M. Precision of cerebral oxygenation and hemoglobin concentration measurements in neonates measured by near-infrared spectroscopy. *Journal of Biomedical Optics*. 2011;16(4):047005-047005-047006.
57. Bokiniec R, Zbiec A, Seliga J, Sawosz P, Liebert A, Klosinska I, et al. Assessment of brain oxygenation in term and preterm neonates using near infrared spectroscopy. *Adv Med Sci*. 2012;57(2):348.
58. Wijbenga RG, Lemmers PM, van Bel F. Cerebral oxygenation during the first days of life in preterm and term neonates: differences between different brain regions. *Pediatr Res*. 2011;70(4):389-394.
59. Tina LG, Frigiola A, Abella R, Artale B, Puleo G, D'Angelo S, et al. Near Infrared Spectroscopy in healthy preterm and term newborns: correlation with gestational age and standard monitoring parameters. *Curr Neurovasc Res*. 2009;6(3):148-154.
60. Inder TE, Warfield SK, Wang H, Huppi PS, Volpe JJ. Abnormal cerebral structure is present at term in premature infants. *Pediatrics*. 2005;115(2):286-294.
61. Inder TE, Huppi PS, Warfield S, Kikinis R, Zientara GP, Barnes PD, et al. Periventricular white matter injury in the premature infant is followed by reduced cerebral cortical gray matter volume at term. *Ann Neurol*. 1999;46(5):755-760.
62. Dubois J, Benders M, Borradori-Tolsa C, Cachia A, Lazeyras F, Ha-Vinh Leuchter R, et al. Primary cortical folding in the human newborn: An early marker of later functional development. *Brain*. 2008;131(8):2028-2041.

63. Smyser CD, Inder TE, Shimony JS, Hill JE, Degnan AJ, Snyder AZ, et al. Longitudinal Analysis of Neural Network Development in Preterm Infants. *Cereb Cortex*. 2010;20(12):2852-2862.
64. Yiallourou SR, Witcombe NB, Sands SA, Walker AM, Horne RS. The development of autonomic cardiovascular control is altered by preterm birth. *Early Hum Dev*. 2013;89(3):145-152.
65. Witcombe NB, Yiallourou SR, Sands SA, Walker AM, Horne RS. Preterm birth alters the maturation of baroreflex sensitivity in sleeping infants. *Pediatrics*. 2012;129(1):e89-96.
66. Cohen G, Lagercrantz H, Katz-Salamon M. Abnormal circulatory stress responses of preterm graduates. *Pediatr Res*. 2007;61(3):329-334.

Table 1: Neonatal History and Characteristics at the Time of Study of Preterm and Term Infants.

Clinical Feature		Preterm Infants (n=35)	Term Infants (n=17)
Gestational Age (wks)		31.2 (0.4)***	40.1 (0.3)
Birth Weight (g)		1697 (92)***	3666 (105)
Male/Female (% male)		21/14 (60%)	9/8 (53%)
Apgar Scores	1st minute	6 (2-9)***	9 (7-9)
	5th minute	9 (5-9)**	9 (9-10)
Received respiratory stimulant during hospitalization, n (%)		20 (57%)†	0
Antenatal Steroids, n (%)		25 (71%)	0
Anemia of Prematurity, n (%)		14 (40%)	0
2-4 Weeks	Age (wks)‡	3.2 (0.1)	3.4 (0.1)
	Weight (g)	3742 (103)	3956 (148)
	Length (cm)	51.9 (0.5)	53.3 (0.6)
2-3 Months	Age (wks) ‡	10.6 (0.2)	10.6 (0.2)
	Weight (g)	5323.9 (165)	5214 (179)
	Length (cm)	56.9 (0.7)	57.8 (0.4)
5-6 Months	Age (wks) ‡	22.7 (0.3)	22.3 (0.3)
	Weight (g)	7179 (209)	6964 (200)
	Length (cm)	63.7 (0.5)	64.3 (0.5)

Values are presented as mean (SEM) with the exception of Apgar scores which are presented as median (range).

† 19 preterm infants received caffeine before discharge, 1 infant received theophylline and aminophylline; no infants were receiving respiratory stimulant medication at the time of study

‡ Corrected age for preterm infants, post-natal age for term infants

*** $p<0.001$ term vs preterm

** $p<0.01$ term vs preterm

Table 2: Effect of sleep state and increasing corrected age on cerebral tissue oxygenation index (TOI), mean arterial pressure (MAP), heart rate (HR), abdominal skin temperature (Temp) and oxygen saturation (SpO_2).Values are presented as mean (SEM).

			TOI (%)	**MAP (mmHg)**	**HR (bpm)**	**Temp (°)**	**SpO_2 (%)**
2-4 Weeks CA	Supine	QS	63.2 (0.4) *** #‡	63.1 (1.6) ** ‡	136.3 (0.6) ###‡‡‡	35.7 (0.2) ‡	98.8 (0.1) ‡‡
		AS	59.9 (0.5)	70.1 (1.6)	137.1 (0.6) ###‡‡‡	35.8 (0.2)	98.6 (0.1)
	Prone	QS	58.0 (0.5)* #	61.8 (1.7)*** ‡‡‡	139.3 (0.6) ###‡‡‡	36.7 (0.2)	99.0 (0.1)
		AS	56.2 (0.4) #	70.3 (1.6) ‡‡	139.2 (0.6) ###‡‡‡	36.6 (0.2)	98.8 (0.1)
2-3 Months CA	Supine	QS	59.6 (0.5)**	67.6 (1.8)* †	126.8 (0.5)* †††	35.6 (0.1)	98.1 (0.1)
		AS	57.1 (0.6) †	73.1 (1.9)	128.7 (0.5) ††	35.6 (0.1)	98.2 (0.1)
	Prone	QS	50.9 (0.5) †	64.7 (1.9)** †††	128.5 (0.5) ††	36.2 (0.1)	98.3 (0.1)
		AS	51.9 (0.6) †	70.4 (2.0) †††	129.6 (0.5)	36.3 (0.1)	98.4 (0.1)
5-6 Months CA	Supine	QS	56.6 (0.5)***	72.0 (2.5)*	117.2 (0.4)***	35.0 (0.1)	97.7 (0.10
		AS	60.8 (0.5)	76.3 (2.8)	121.2 (0.5)	35.0 (0.1)	98.0 (0.1)
	Prone	QS	53.3 (0.5)**	75.5 (2.8)	120.4 (0.4)***	36.1 (0.1)	98.3 (0.1)
		AS	57.4 (0.6)	78.6 (3.1)	123.5 (0.5)	36.2 (0.1)	98.5 (0.1)

* p <0.05; ** p < 0.01; *** p < 0.001 QS vs AS

# p <0.05; ## p < 0.01; ### p < 0.001 2-4 weeks vs 2-3 months

† p < 0.05; †† p < 0.01; ††† p < 0.001 2-3 months vs 5-6 months

‡ p < 0.05; ‡ ‡ p < 0.01; ‡ ‡ ‡ p < 0.001 2-4 weeks vs 5-6 months

Table 3: Effect of preterm birth on oxygen saturation, heart rate and temperature. Values are mean (SEM).

			Oxygen Saturation (%)		Heart Rate (bpm)		Temperature (°C)	
			Preterm	**Term**	**Preterm**	**Term**	**Preterm**	**Term**
2-4 Weeks	Supine	QS	98.8 (0.2)***	97.3 (0.3)	135.8 (1.3)	137.8 (1.8)	35.7 (0.2)***	36.8 (0.2)
		AS	98.6 (0.2)***	97.0 (0.4)	136.9 (1.4)	139.5 (1.9)	35.8 (0.2)***	36.8 (0.2)
	Prone	QS	98.9 (0.2)***	96.9 (0.3)	139.2 (1.6)	141.2 (2.0)	36.7 (0.2)*	37.3 (0.2)
		AS	98.8 (0.2)***	96.9 (0.3)	139.2 (1.6)	141.4 (2.0)	36.6 (0.1)*	37.2 (0.2)
2-3 Months	Supine	QS	98.1 (0.2)	97.8 (0.3)	126.8 (1.9)*	133.2 (2.5)	35.6 (0.1)***	36.6 (0.1)
		AS	98.2 (0.2)	97.6 (0.3)	129.3 (1.9)	135.2 (2.6)	35.7 (0.1)***	36.6 (0.1)
	Prone	QS	98.3 (0.2)	98.2 (0.2)	128.5 (1.8)*	136.1 (2.3)	36.2 (0.1)***	37.2 (0.1)
		AS	98.4 (0.2)	98.3 (0.2)	129.4 (1.8)**	137.4 (2.3)	36.3 (0.1)***	37.1 (0.1)
5-6 Months	Supine	QS	97.8 (0.2)**	96.8 (0.3)	117.9 (1.7)	121.4 (1.9)	35.0 (0.3)*	36.1 (0.3)
		AS	98.1 (0.2)***	96.9 (0.3)	122.2 (1.8)	125.1 (1.9)	35.0 (0.3)	35.4 (0.3)
	Prone	QS	98.3 (0.2)*	97.4 (0.3)	122.2 (1.9)	125.1 (2.1)	36.1 (0.1)***	36.9 (0.2)
		AS	98.4 (0.2)**	97.4 (0.3)	124.5 (2.0)	128.8 (2.1)	36.2 (0.1)***	37.0 (0.2)

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ preterm versus term

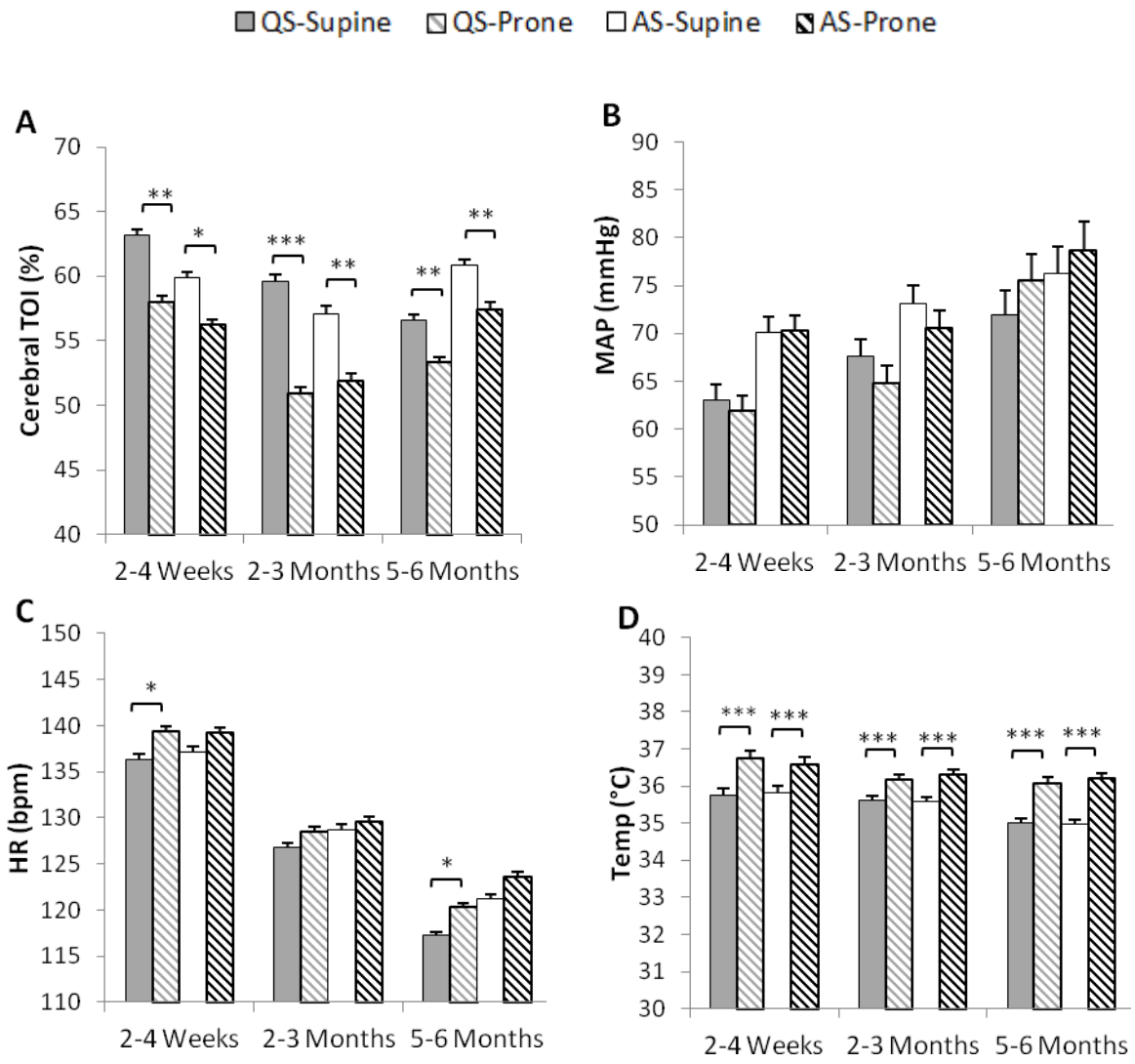


Figure 1: Effect of sleep position on (A) cerebral tissue oxygenation index (TOI) (B) mean arterial pressure (MAP), (C) heart rate (HR) and (D) abdominal skin temperature (Temp) in preterm infants. Results are mean ± SEM.
* $p<0.05$;** $p<0.01$; *** $p<0.001$ prone versus supine

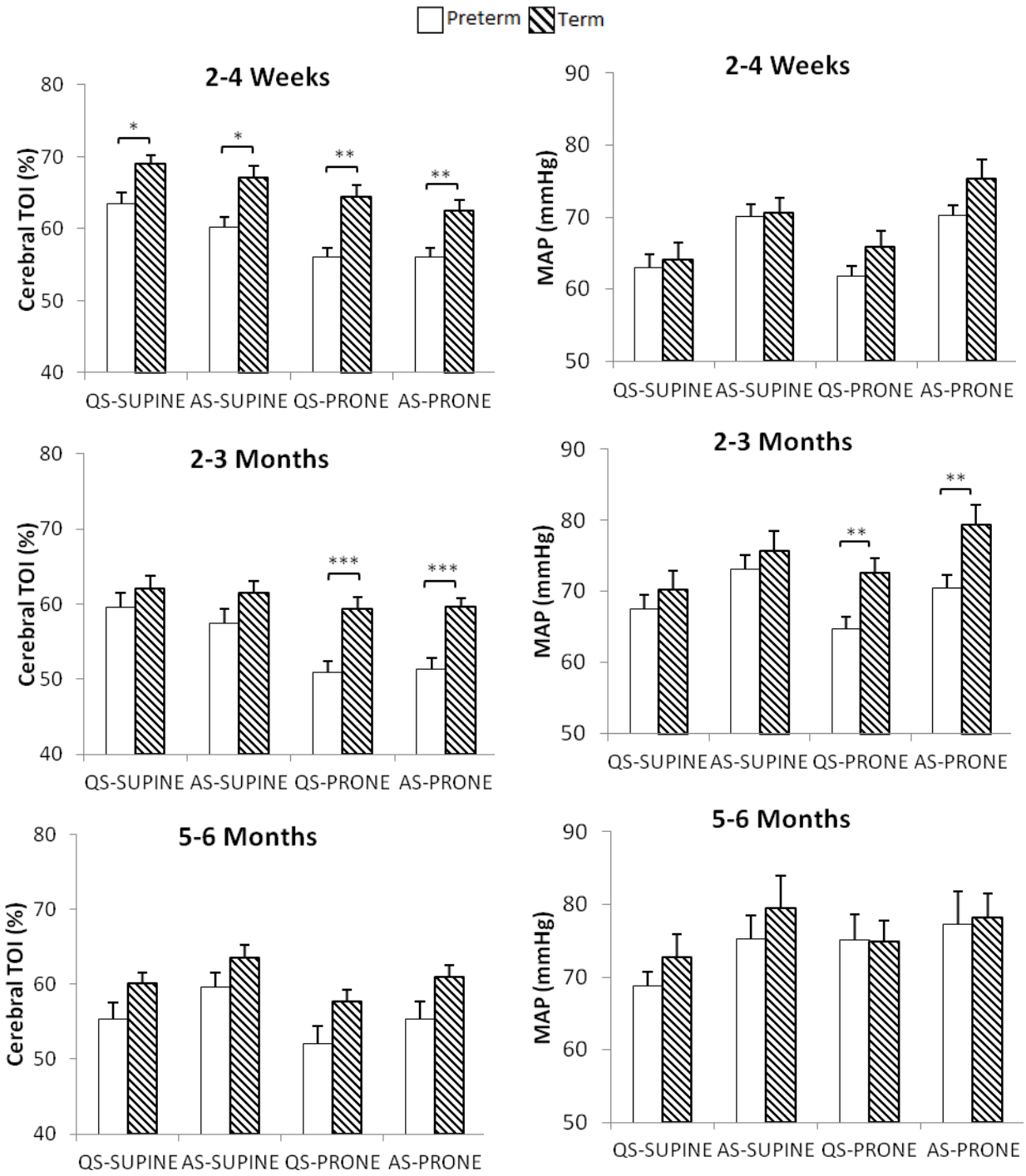


Figure 2. Effect of preterm birth on cerebral tissue oxygenation index (TOI) (left) and mean arterial pressure (MAP) (right) at: 2-4 weeks (upper), 2-3 months (middle) and 5-6 months post-term age (lower). Results are mean ± SEM.
*p<0.05; ** p<0.01; *** p<0.001 term versus preterm.

Chapter 4

Preterm infants exhibit greater variability in cerebrovascular control compared to term infants

4 Preterm infants exhibit greater variability in cerebrovascular control compared to term infants

This chapter is presented in manuscript form in preparation for submission to Sleep.

Karinna L Fyfe, Alexsandria Odoi, Stephanie R Yiallourou, Flora Y Wong, , Adrian M Walker, Rosemary SC Horne

4.1 Declaration for Chapter 4

Monash University

In the case of Chapter 4, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
For this chapter I recruited and performed the preterm infant studies and was responsible for analysis of this data. I was responsible for the comparison of term and preterm data, interpretation of all results and writing of the manuscript.	80%

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Alexsandria Odoi	Miss Odoi assisted with data collection and writing of the manuscript	N/A
Stephanie Yiallourou	Dr Yiallourou assisted with data collection, interpretation of results and writing of the manuscript.	N/A
Flora Y Wong	Dr Wong assisted with recruitment, interpretation of results and writing of the manuscript.	N/A
Adrian M Walker	Professor Walker assisted with interpretation of the results and writing of the manuscript	N/A
Rosemary SC Horne	Professor Horne aided in recruitment and data collection, interpretation of results and writing of the manuscript	N/A

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work*.

Candidate's Signature		**Date**
Main Supervisor's Signature		**Date**

4.2 Introduction to Chapter 4

In Chapter 3 we identified that cerebral oxygenation is reduced in the prone sleep position in preterm infants until at least 5-6 months post-term corrected age (CA) and reduced in preterm compared to term infants until 2-3 months CA. The greatest deficit in cerebral oxygenation between term and preterm infants occurred in the prone position at 2-3 months CA, where there was a concomitant decrease in heart rate (HR) and blood pressure (BP) in preterm compared to term infants.

In chapter 4 we seek to explain why cerebral oxygenation is reduced in preterm compared to term infants across the first six months post-term. In order to do this, we have assessed cerebrovascular control during sleep in both the prone and supine sleep positions. Control of the cerebral vasculature is mediated by a number of mechanisms including cerebral autoregulation, cerebral blood flow-metabolism coupling and cerebral vasoreactivity (Volpe, 2008). In the following chapter we will investigate cerebral autoregulation in preterm infants beyond term-equivalent age and compare responses to control infants born at term.

Cerebral autoregulation ensures cerebral blood flow (CBF) remains constant despite fluctuations in systemic arterial pressure. Control of CBF involves a myogenic mechanism by which stretch of the blood vessel walls results in reflex vasoconstriction and conversely, reduced BP results in vasodilation (Volpe, 2008). This ensures constant CBF within a range of systemic arterial pressures. Preterm infants have immature cerebral autoregulation prior to term-equivalent age (Wong et al., 2008, Soul et al., 2007, Tsuji et al., 2000), however there has been little assessment of cerebrovascular control in preterm infants beyond this age.

In this chapter we aimed to investigate cerebrovascular control in preterm infants during sleep in both the prone and supine sleep positions. We hypothesised that cerebrovascular control would be altered in preterm compared to term infants, particularly in the prone sleeping position at 2-3 months CA, thus underlying the deficits in cerebral oxygenation seen in preterm infants during this period.

Title: Preterm infants exhibit greater variability in cerebrovascular control compared to term infants

First author's surname: Fyfe

Short Title: Cerebrovascular Control in Preterm Infants

Authors: Karinna Fyfe[1,2] BMedSc, Alexsandria Odoi[1] BNS (Honours), Stephanie R Yiallourou[1,2] PhD, Flora Wong[1, 2 3] MBBS, PhD, Adrian M Walker PhD[1], Rosemary SC Horne[1,2] PhD

[1] The Ritchie Centre, MIMR and PHI Institute of Medical Research, Melbourne, Victoria, Australia

[2] Department of Paediatrics, Monash University, Melbourne, Victoria, Australia

[3] Monash Newborn, Monash Medical Centre, Melbourne, Victoria, Australia

Miss Fyfe wrote the first draft of the manuscript and no payment was given to anyone to produce the manuscript

Financial Disclosure: The authors have no financial relationships to disclose.

Conflicts of Interest: The authors have no conflicts of interest to disclose.

Correspondence:
Professor Rosemary SC Horne, PhD
The Ritchie Centre
Level 5, Monash Medical Centre, 246 Clayton Rd, Clayton, VIC, Australia
Email: [redacted]
Telephone: [redacted] Facsimile: +61 3 9594 6811

Keywords: preterm birth, cerebrovascular circulation; cerebral blood flow; blood pressure; cerebral oxygenation

Abstract

Study Objectives: Sudden Infant Death Syndrome (SIDS) remains an important cause of infant death, particularly amongst infants born preterm. Prone sleeping is a major risk factor for SIDS and it has recently been shown that prone sleeping alters cerebrovascular control in term infants. As preterm infants are at greater risk for SIDS, we hypothesized that cerebrovascular control would be reduced in preterm infants in the prone position and in preterm compared to term infants.

Patients or Participants: 35 preterm (mean gestation 31.2±0.4wk) and 17 term (mean gestation 40.1±0.3wk) infants.

Design: Infants underwent daytime polysomnography at 2-4 weeks, 2-3 months and 5-6 months post-term age. Infants slept both prone and supine and were presented with cardiovascular challenges in the form of 15° head-up tilts (HUT).

Measurements and Results: Cerebral tissue oxygenation index (TOI) was recorded using near-infrared spectroscopy (NIRO-200 spectrophotometer, Hamamatsu Photonics KK, Japan) and mean arterial pressure (MAP) was recorded using a Finometer^{TM} cuff (Finapress Medical Systems, Amsterdam, The Netherlands). The percentage change from baseline following HUT was calculated. In the prone position TOI increased following the HUT in contrast to no change seen in the supine position. The response of TOI to HUT was similar but more variable in preterm compared to term infants.

Conclusions: Cerebrovascular control is altered in the prone position in preterm infants. Whilst overall the response to HUT was similar between term and preterm infants, greater variability in preterm infants suggests persistent immaturity of cerebrovascular control which may contribute to their increased risk of SIDS.

Keywords: preterm birth, cerebrovascular circulation, cerebral blood flow, blood pressure, cerebral oxygenation

Introduction

Sudden Infant Death Syndrome (SIDS) remains the leading cause of death in the post-neonatal period in developed countries.[1] Although the exact mechanisms are yet to be fully elucidated, SIDS is thought to occur due to immature cardiovascular control allowing an uncompensated hypotensive episode during presumed sleep, in combination with a failure to arouse from sleep.[2,3] It is currently unclear in which of the two infant sleep states, active sleep (AS) or quiet sleep (QS) SIDS deaths occur. Approximately 90% of SIDS deaths occur within the first 6 months of life, with the incidence peaking between 2-3 months of age,[4,5] a period that is associated with developmental changes in both cardiovascular[6,7] and cerebrovascular control.[8,9]

Prone sleeping has been established as a major SIDS risk factor.[4,10] Term infants sleeping prone have reduced cerebral oxygenation,[8] altered cerebrovascular control[9] and depressed arousal responses,[11] particularly at 2-3 months of age. Most recently we have also identified that preterm infants have lower cerebral oxygenation than infants born at term and this is most marked when they sleep prone[12]. We have previously suggested that reduced cerebral oxygenation in the prone position may contribute to dysfunctional brainstem reflexes, including blunted arousal responses, implicated in the pathophysiology of SIDS.[8]

Infants born preterm are at significantly increased risk for SIDS and this risk is increased when they are slept prone.[10,13] Cerebrovascular control is immature in preterm infants prior to term-equivalent age with deficits in cerebral autoregulation[14-17] and cerebral blood flow-metabolism coupling.[18] Furthermore, we have recently reported that this cohort of preterm infants exhibited reduced cerebral oxygenation in the prone compared to the supine position and in comparison to term infants.[12] However, the effects of sleeping position on cerebrovascular control have not previously been assessed in preterm infants beyond term-equivalent age. To address this deficit in the literature, we assessed cerebrovascular control in preterm infants in both AS and QS in the prone and supine sleep positions across the first 6 months post-term. We hypothesized that cerebrovascular control would be

altered in preterm infants in the prone position and in preterm compared to term infants, particularly in the prone position at 2-3 months corrected age (CA), when SIDS risk is greatest.

Patients and Methods

Ethical approval was obtained from the Monash Health and Monash University human research ethics committees. Written parental consent was obtained prior to the commencement of each study. No monetary incentive for participation was provided.

Subjects

35 healthy preterm infants (21M/14F) born between 26-36 weeks of gestational age (GA) (mean gestation 31.2±0.4, mean birth weight 1697±92g) and 17 healthy term infants (9M/8F; mean gestation 40.1±0.3; mean birth weight 3666±105g) were recruited. Data from the term infants has previously been published.[8,9] All infants were appropriately grown for GA, born to non-smoking mothers, had no family history of SIDS and were routinely slept supine at home. For the preterm cohort, exclusion criteria included significant intra-cerebral pathology, congenital abnormalities, hemodynamically significant patent ductus arteriosus and chronic lung disease requiring ongoing oxygen therapy or respiratory stimulant medication at term-equivalent age. Where twins were included only one twin was studied. All infants were discharged home prior to the first study.

Study Protocol

Infants underwent daytime polysomnography at 2-4 weeks, 2-3 months and 5-6 months post-term corrected age (CA). Studies were conducted between 0900 and 1700 in the Melbourne Children's Sleep Centre, Monash Medical Centre under constant temperature (22-24°C) and dim lighting and quiet conditions. Recording electrodes were applied during a morning feed, following which the infants were allowed to sleep naturally in a pram and feed on demand. Infants were slept in both the prone and supine sleep positions with the initial sleep position randomized between infants and studies. Sleep position was usually changed following a midday feed and data were collected in both QS and AS.

Data Collection

Polysomnography electrodes included two channels of electroencephalogram (EEG; C4/A1; O2/A1), electrooculogram (EOG), submental electromyogram (EMG), electrocardiogram (ECG), abdominal and thoracic respiratory belts (Resp-ez Piezo-electric sensor, EPM Systems, Midlothian, VA, USA), arterial oxygen saturation (Masimo Radical Oximeter, French's Forest, NSW, Australia) and abdominal skin temperature (ADInstruments, Sydney, NSW, Australia). In addition, mean arterial pressure (MAP) was recorded using a photoplethysmographic cuff (Finapress Medical Systems, Amsterdam, The Netherlands) placed around the infant's wrist as previously validated.[19] Cerebral tissue oxygenation index (TOI) was also recorded using near-infrared spectroscopy (NIRS) (NIRO-200 photospectrometer, Hamamatsu Photonics KK, Tokyo, Japan).[8,9] Infants were continuously monitored via an infra-red camera located above the pram.

Physiological data were recorded using an E series sleep recording system with Profusion 2 polysomnography software (Compumedics, Abbotsford, VIC, Australia) at a sampling rate of 512 Hz. Sleep state was determined using electroencephalographic, heart rate and breathing patterns together with behavioural changes according to recognized guidelines.[20-22]

Cardiovascular Challenge

Whilst sleeping, infants were presented with a cardiovascular challenge in the form of a 15° head-up tilt (HUT). This involved raising the head of the pram to a 15° angle over a period of 2-3 s, which has been shown to produce a small but significant change in MAP and heart rate (HR)[7] without an associated arousal from sleep. HUTs were performed following a 1 minute baseline period, during which the blood pressure cuff was inflated, and infants remained in the tilted position for a further 1 minute following the HUT. We aimed to perform a total of 3 HUTs in each sleep state and in each sleep position. HUTs were performed when the infants were physiologically stable and free of movement and a minimum two minute rest period was allowed between HUTs for stabilization of physiological variables.

Data Analysis

At the conclusion of each study, data were transferred via European Data Format to LabChart 7 analysis software (ADInstruments, Sydney, NSW, Australia). Beat-beat averages for HR, cerebral TOI and MAP were calculated for the 1 minute baseline period and the 1 minute HUT. HUTs containing movement, arousals, sighs or apneic pauses within the baseline or HUT periods were excluded from further analysis. The response to the HUT was determined by calculating the percentage change (Δ%) from baseline for cerebral TOI and MAP following each HUT, with the baseline being the 30 beats preceding each HUT. The HUT response period was divided into four phases: baseline (beats 1-30), early (beats 31-60), middle (beats 61-90) and late (beats 91-120) according to methods used in our previous studies.[7,9,23] This enables quantification of the typical biphasic infant response to a HUT which consists of an initial increase to a peak in MAP and HR, followed by a decrease either to or below baseline, following which HR returns to baseline and MAP either returns to or remains below baseline. HUT responses were averaged for each infant in each sleep state and sleeping position.

Effect of Gestational Age on the HUT Response

We assessed the effect of GA on the HUT response in two ways. Firstly, we performed linear regression between GA at birth and the peak in MAP in the early phase of the tilt response as well as the maximum and minimum change from baseline during any phase for cerebral TOI and found no significant correlations (data not shown). Secondly, we grouped infants into very preterm (<32 weeks GA) and preterm (32-36 weeks GA). As the response of both MAP and TOI to a HUT was similar between very preterm and preterm infants (data not shown), data have been pooled and will be presented as a single preterm group.

Statistical Analysis

Statistical analysis was performed using SigmaPlot analysis software (Systat Software Inc, IL, USA). The effect of sleep position and preterm birth on baseline data was determined using two-way analysis of variance (ANOVA) with Student-Newman Keuls post-hoc analysis. A statistically significant

change in MAP and cerebral TOI from baseline was determined within each phase (early, middle and late) using one-way repeated measures ANOVA. For data that did not pass normality, repeated measures ANOVA on ranks was performed with Dunnett's Method post-hoc analysis.

To assess the effect of preterm birth on the HUT we used two-way ANOVA within each phase, with beat number and birth (preterm or term) as factors, non-normal data was transformed to achieve normality. To assess variability of the HUT response, the mean standard deviation for each beat was determined for term and preterm infants within each phase and compared using two-way ANOVA within each sleep state and position.

Results

Infant Characteristics

There were no differences in age or weight between term and preterm infants at the 2-4 week (preterm vs term: 3.2±0.1 vs 3.3±0.2 weeks; 3.7±0.1 vs 3.9±0.1 kg), 2-3 month (preterm vs term: 10.7±0.2 vs 10.6±0.2 weeks; 5.2±0.1 vs 5.2±0.2 kg) or 5-6 month studies (preterm vs term: 22.7±0.3 vs 22.4±0.3 weeks; 7.2±0.2 vs 7.0±0.2 kg).

Baseline MAP and TOI

The effects of sleep position in term and preterm infants and the effect of preterm birth on baseline MAP and TOI are shown in Table 1.

Sleep position had no effect on MAP at any age in either AS or QS in either the preterm or term cohorts. In preterm infants cerebral TOI was significantly lower in the prone compared to the supine position in both sleep states at 2-4 weeks and 2-3 months CA ($p<0.05$ for all). In term infants cerebral TOI was significantly lower when prone in AS at 2-4 weeks ($p<0.05$). At 5-6 months CA in preterm infants and at 2-3 months and 5-6 months in term infants there was no effect of sleep position on baseline cerebral TOI.

Preterm infants had lower MAP compared to term infants in both sleep states in the prone position at 2-3 months CA ($p<0.05$ for both). No differences were seen at either 2-4 weeks or 5-6 months. Cerebral TOI was significantly lower in preterm compared to term infants in both sleep states and positions at 2-4 weeks CA ($p<0.01$ for all) and in both sleep states in the prone position at 2-3 months CA ($p<0.05$ for both). There was no effect of preterm birth on baseline cerebral TOI at 5-6 months CA.

Preterm Infant Responses of MAP and TOI to a HUT in the Supine Position (Figure 1)

In preterm infants, in both sleep states and at all three ages, MAP showed a characteristic surge in the early phase of the HUT response. Following the initial surge, MAP fell below baseline in both sleep states at 2-4 weeks (middle phase $p<0.05$) and 2-3 months CA (late phase $p<0.05$). At 5-6 months CA, following the initial surge, in both sleep states MAP remained at baseline for the remainder of the HUT response.

In the supine position in QS, there was a small, but statistically significant fall in TOI below baseline at 2-4 weeks CA (early phase $p<0.05$; middle phase $p<0.05$), 2-3 months (early phase $p<0.05$) and 5-6 months CA (early phase $p<0.05$ and middle phase $p<0.05$), at 2-3 months TOI fell below baseline only in the early phase of the HUT response. In AS, TOI remained at baseline for the duration of the HUT response at 2-4 weeks CA and 5-6 months CA but fell below baseline at 2-3 months CA (early phase $p<0.05$).

Preterm Infant Responses of MAP and TOI to a HUT in the Prone Position (Figure 2)

In preterm infants in the prone position MAP also showed a characteristic surge in the early phase of the HUT response in both sleep states at all three ages. In QS, following the initial surge, MAP fell below baseline at 2-4 weeks (late phase $p<0.05$), 2-3 months (late phase $p<0.05$) and at 5-6 months (middle phase $p<0.05$ and late phase $p<0.05$). In AS, following the initial surge MAP fell below baseline at 2-4 weeks CA (late phase $p<0.05$), rose above baseline at 2-3 months (middle phase $p<0.05$) and remained at baseline at 5-6 months CA.

In the prone position in QS, TOI rose above baseline at 2-4 weeks (late phase, $p<0.05$), 2-3 months CA ($p<0.05$) and 5-6 months (early phase, $p<0.05$ and middle phase, $p<0.05$). In the prone position in AS, TOI also rose above baseline at 2-4 weeks CA (early phase $p<0.05$ and middle phase $p<0.05$), 2-3 months CA (early phase $p<0.05$ and middle phase $p<0.05$) and at 5-6 months CA (early phase $p<0.05$).

Comparison of the TOI Response to a HUT between Preterm and Term Infants

The response of cerebral TOI to a HUT was generally similar between term and preterm infants however small (~ 1-2%) but significant differences were observed.

In QS (Figure 3) at 2-4 weeks, there were no differences in the TOI response to a HUT between term and preterm infants in either sleep position. At 2-3 months in the prone position, there was a greater increase in TOI in preterm infants compared to term infants (late phase $p< 0.05$). At 5-6 months in the supine position, TOI fell lower in preterm compared to term infants (middle phase $p<0.05$ and late phase $p<0.05$), but there were no differences between the term and preterm infant groups in the prone position.

In AS (Figure 4) at 2-4 weeks, there was also no differences in the TOI response to a HUT between term and preterm infants in either sleep position. At 2-3 months in the supine position, there was a smaller fall in TOI in preterm infants compared to term infants (middle phase $p<0.05$) and a greater increase in TOI in the prone position (late phase $p<0.05$). At 5-6 months in the supine position, TOI fell in term infants, but not preterm infants (early phase $p<0.05$), and there was no differences in the TOI response between the infants groups in the prone position.

Comparison of Variability of Responses to HUT between Preterm and Term Infants

Table 2 compares the variability of the cerebral TOI response to a HUT between preterm and term infants. In both sleeping positions, the response of cerebral TOI to a HUT was significantly more variable in preterm compared to term infants in all three phases at all three ages studied ($p<0.001$ for all except early phase, QS-supine at 5-6 months $p<0.05$), with the exception of the middle phase of the response in AS in the prone position at 2-3 months.

Discussion

Our study provides novel data on cerebrovascular control in preterm infants beyond term-equivalent age. Consistent with findings in term infants, in the supine position cerebral oxygenation is tightly controlled even in the presence of a surge in MAP. In contrast, in the prone position, an orthostatic challenge results in increase in cerebral oxygenation possibly due to cerebral vasodilation. Whilst the response to a HUT was similar between term and preterm infants, preterm infants showed significantly greater variability in their responses compared to term infants, suggesting cerebrovascular control is less mature in preterm infants at matched post-term ages.

There is evidence to suggest that cerebral autoregulation is immature in preterm infants prior to term-equivalent age resulting in pressure passivity between systemic blood pressure and cerebral blood flow.[14-16] This is particularly true amongst unwell preterm infants, but there is evidence to suggest that cerebral autoregulation is also impaired in clinically stable preterm infants.[24] However, to our knowledge cerebral autoregulation in preterm infants has not previously been assessed beyond term-equivalent age. Our data suggest that cerebral autoregulation is functioning effectively in preterm infants at 2-4 weeks CA. In the supine position and in the prone position in QS, cerebral TOI was maintained despite a surge in MAP suggesting an autoregulatory increase in cerebral vascular resistance prevents a concomitant increase in cerebral blood flow. In QS cerebral TOI tended to fall below baseline approximately 15-20 beats after the HUT (20 beats at 2-4 weeks and 2-3 months CA, 15 beats at 5-6 months CA), coinciding with a fall in MAP. This is a similar pattern to that seen in term infants,[9,24] and is likely to be due to the response time required for autoregulation-mediated cerebral vasodilation resulting in a temporary and minor decrease in cerebral blood flow in the presence of falling MAP.[25,26] In the prone position in QS at both 2-4 weeks and 2-3 months CA, cerebral TOI increased in the late phase of the HUT response when MAP fell. This suggests increased cerebral blood flow due to cerebral vasodilation in response to reduced MAP. This increase

in cerebral blood flow appears to slightly overshoot cerebral metabolic requirements leading to increased cerebral TOI.

In contrast, in the prone position in QS at 5-6 months CA and at all three ages in AS, cerebral TOI increased immediately in response to the HUT. The increase in cerebral TOI preceded the surge in MAP induced by the HUT, consistent with findings in term infants.[9,27] This suggests that changes in cerebral blood flow occur due to a vestibular-mediated response to a change in position and not in response to changing MAP. A previous study in preterm infants assessed at 36 weeks GA, sleeping in the supine position, found immature vestibular responses to side-ways shifts compared to healthy term infants assessed at 3 months of age. The authors reported diminished heart rate and blood pressure responses to side-ways motion tests in preterm infants and concluded that vestibular-mediated cardiovascular control is immature in preterm infants between 34 to 39 weeks post-conceptional age.[28] Our data suggest improvement in vestibular responses to a positional change by 42-44 weeks post-conceptional age in healthy preterm infants, particularly in AS. However, failure of this immediate increase in cerebral oxygenation in response to a HUT in the prone position at 2-4 weeks and 2-3 months in QS may represent immaturity of the vestibular response during the period of peak risk for SIDS.

Contrary to our hypothesis, we found that the response of cerebral oxygenation to a HUT was generally similar between term and preterm infants and there was no effect of gestational age at birth, however, we believe that preterm infants may still be at risk of cerebral hypoxia. We have previously suggested in term infants,[9] that the observed increase in cerebral oxygenation in response to a HUT in the prone position may be a protective response to safeguard against critically reduced cerebral oxygenation in a position where baseline cerebral oxygenation is already reduced. Consistent with our previously reported results, baseline cerebral oxygenation was significantly lower in preterm compared to term infants, with the difference approaching 10 percentage points at both 2-4 weeks and 2-3 months CA in the prone position. Thus, in preterm infants, in whom baseline cerebral oxygenation sits significantly lower, a greater increase in cerebral oxygenation following a change in position would be required to protect against cerebral hypoxia. Studies in both humans and animals

suggest that cerebral hypoxic damage occurs with cerebral oxygenation levels below 40%.[29,30] Preterm infants with a baseline cerebral TOI of approximately 50% are dangerously close to pathologically impaired cerebral oxygenation in the prone position at 2-3 months CA. Therefore, despite no overall difference in the response between term and preterm infants, preterm infants may still be at greater risk due to their lower baseline cerebral oxygenation levels.

Despite generally similar responses between preterm and term infants of cerebral TOI to a HUT, we found significantly greater variability in the responses of the preterm cohort, suggesting that cerebrovascular control remains immature in preterm infants. Greater variability in the cerebrovascular response to a HUT has previously been suggested to reflect immaturity of cerebrovascular control.[31] The response of cerebral blood flow to a HUT has been shown to become more uniform with increasing gestational age in preterm infants assessed at <26 weeks, 27-32 weeks and >32 weeks of gestation, with the pattern in older preterm infants being similar to that in term infants.[31] We found no significant correlation between gestational age at birth and the TOI response to a HUT, suggesting that post-conceptional age influences cerebrovascular control regardless of gestational age at birth in preterm infants.

Implications for the Sudden Infant Death Syndrome

Preterm infants are at significantly increased risk for SIDS[13,32], the underlying mechanism for which is commonly believed to be due to immaturity of cardiovascular control.[33] We have recently identified that preterm infants have significantly reduced cerebral oxygenation compared to term infants, particularly in the prone sleeping position during QS.[12] Greater variability in the cerebral vascular response to a HUT suggests that cerebral vascular control is immature in preterm compared to term infants across the first six months after term-equivalent age. Furthermore, in preterm infants, the presumed protective increase in cerebral oxygenation in response to a postural change in the prone position[9] is absent in QS at 2-4 weeks and 2-3 months CA. We suggest that these factors could denote a greater risk of cerebral hypoxia during sleep in preterm infants, particularly during QS, which could contribute to their heightened risk for SIDS.

Conclusions

To our knowledge this is the first study to assess cerebrovascular control in preterm infants beyond term-equivalent age. We have shown that control of cerebral oxygenation in response to a cardiovascular challenge is similar to that of term infants at matched post-conceptional ages across the first six months post-term. However, preterm infants display greater variability in their responses, suggesting immaturity of cerebrovascular control persists beyond term-equivalent age. Consistent with findings in term infants, the prone sleeping position is associated with an altered cerebrovascular response to HUT, possibly to protect against cerebral hypoxia in a condition when baseline cerebral oxygenation is low.

Acknowledgements

We would like to thank the parents and infants involved in this study and the staff at the Melbourne Children's Sleep Centre.

References

1. Sherry L Murphey, Jiaquan Xu, Kochanek KD. Deaths: Final Data for 2010. Hyattsville, MD: National Centre for Health Statistics; 2013.
2. Harper RM. Sudden infant death syndrome: a failure of compensatory cerebellar mechanisms? *Pediatr Res*. 2000;48(2):140-142.
3. Kato I, Franco P, Groswasser J, Scaillet S, Kelmanson I, Togari H, et al. Incomplete Arousal Processes in Infants Who Were Victims of Sudden Death. *Am J Respir Crit Care Med*. 2003;168(11):1298-1303.
4. Moon RY, Horne RS, Hauck FR. Sudden infant death syndrome. *Lancet*. 2007;370(9598):1578-1587.
5. Halloran DR, Alexander GR. Preterm delivery and age of SIDS death. *Ann Epidemiol*. 2006;16(8):600-606.
6. Yiallourou SR, Walker AM, Horne RS. Effects of sleeping position on development of infant cardiovascular control. *Arch Dis Child*. 2008;93(10):868-872.
7. Yiallourou SR, Walker AM, Horne RS. Prone sleeping impairs circulatory control during sleep in healthy term infants: implications for SIDS. *Sleep*. 2008;31(8):1139-1146.
8. Wong FY, Witcombe NB, Yiallourou SR, Yorkston S, Dymowski AR, Krishnan L, et al. Cerebral Oxygenation Is Depressed During Sleep in Healthy Term Infants When They Sleep Prone. *Pediatrics*. 2011;127(3):e558-e565.
9. Wong F, Yiallourou SR, Odoi A, Browne P, Walker AM, Horne RSC. Cerebrovascular control is altered in healthy term infants when they sleep prone. *Sleep*. 2013;36(12):1911-1918.
10. Blair PS, Platt MW, Smith IJ, Fleming PJ, Group CSR, Platt MW. Sudden infant death syndrome and sleeping position in pre-term and low birth weight infants: an opportunity for targeted intervention. *Arch Dis Child*. 2006;91(2):101-106.
11. Richardson HL, Walker AM, Horne RSC. Sleep position alters arousal processes maximally at the high-risk age for sudden infant death syndrome. *J Sleep Res*. 2008;17(4):450-457.
12. Fyfe KL, Yiallourou SR, Wong FY, Odoi A, Walker AM, Horne RS (in press). Cerebral oxygenation in preterm infants. *Pediatrics*. 2014.
13. Trachtenberg FL, Haas EA, Kinney HC, Stanley C, Krous HF. Risk Factor Changes for Sudden Infant Death Syndrome After Initiation of Back-to-Sleep Campaign. *Pediatrics*. 2012;129(4):630-638.
14. Tsuji M, Saul JP, du Plessis A, Eichenwald E, Sobh J, Crocker R, et al. Cerebral intravascular oxygenation correlates with mean arterial pressure in critically ill premature infants. *Pediatrics*. 2000;106(4):625-632.
15. Soul JS, Hammer PE, Tsuji M, Saul JP, Bassan H, Limperopoulos C, et al. Fluctuating pressure-passivity is common in the cerebral circulation of sick premature infants. *Pediatr Res*. 2007;61(4):467-473.
16. Wong FY, Leung TS, Austin T, Wilkinson M, Meek JH, Wyatt JS, et al. Impaired autoregulation in preterm infants identified by using spatially resolved spectroscopy. *Pediatrics*. 2008;121(3):e604-611.
17. Gilmore MM, Stone BS, Shepard JA, Czosnyka M, Easley RB, Brady KM. Relationship between cerebrovascular dysautoregulation and arterial blood pressure in the premature infant. *J Perinatol*. 2011;31(11):722-729.
18. Wong FY, Barfield CP, Horne RS, Walker AM, Wong FY, Barfield CP, et al. Dopamine therapy promotes cerebral flow-metabolism coupling in preterm infants. *Intensive Care Med*. 2009;35(10):1777-1782.

19. Yiallourou SR, Walker AM, Horne RS. Validation of a new noninvasive method to measure blood pressure and assess baroreflex sensitivity in preterm infants during sleep. *Sleep*. 2006;29(8):1083-1088.
20. Grigg-Damberger M, Gozal D, Marcus CL, Quan SF, Rosen CL, Chervin RD, et al. The visual scoring of sleep and arousal in infants and children. *J Clin Sleep Med*. 2007;3(2):201-240.
21. Anders T, Emde RN, Parmelee AH, University of California LABIS. *A Manual of Standardized Terminology, Techniques and Criteria for Scoring of States of Sleep and Wakefulness in Newborn Infants*: UCLA Brain Information Service; 1971.
22. Iber C, Ancoli-Israel S, Chesson AL, Quan SF for the American Academy of Sleep Medicine. *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications*. 1st ed. Westchester, IL, USA: American Academy of Sleep Medicine; 2007.
23. Witcombe NB, Yiallourou SR, Walker AM, Horne RSC. Delayed blood pressure recovery after head-up tilting during sleep in preterm infants. *J Sleep Res*. 2009;19(1-Part-I):93-102.
24. Boylan GB, Young K, Panerai RB, Rennie JM, Evans DH. Dynamic cerebral autoregulation in sick newborn infants. *Pediatr Res*. 2000;48(1):12-17.
25. Aaslid R, Lindegaard KF, Sorteberg W, Nornes H. Cerebral autoregulation dynamics in humans. *Stroke*. 1989;20(1):45-52.
26. Aaslid R, Newell DW, Stooss R, Sorteberg W, Lindegaard KF. Assessment of cerebral autoregulation dynamics from simultaneous arterial and venous transcranial Doppler recordings in humans. *Stroke*. 1991;22(9):1148-1154.
27. Wilson TD, Cotter LA, Draper JA, Misra SP, Rice CD, Cass SP, et al. Effects of postural changes and removal of vestibular inputs on blood flow to the head of conscious felines. *J Appl Physiol*. 2006;100(5):1475-1482.
28. Viskari-Lahdeoja S, Hytinantti T, Andersson S, Kirjavainen T, Viskari-Lahdeoja S, Hytinantti T, et al. Acute cardiovascular responses in preterm infants at 34-39 weeks of gestational age. *Early Hum Dev*. 2012;88(11):871-877.
29. Kurth CD, Levy WJ, McCann J. Near-Infrared Spectroscopy Cerebral Oxygen Saturation Thresholds for Hypoxia-Ischemia in Piglets. *J Cereb Blood Flow Metab*. 2002;22(3):335-341.
30. Silas R, Sehgal A, Walker AM, Wong FY. Cerebral oxygenation during subclinical seizures in neonatal hypoxic-ischaemic encephalopathy. *Eur J Paediatr Neurol*. 2012;16(3):304-307.
31. Anthony MY, Evans DH, Levene MI. Neonatal cerebral blood flow velocity responses to changes in posture. *Arch Dis Child*. 1993;69(3 Spec No):304-308.
32. Malloy MH. Prematurity and sudden infant death syndrome: United States 2005-2007. *J Perinatol*. 2013;33(6):470-475.
33. Horne RSC, Witcombe NB, Yiallourou SR, Scaillet S, Thiriez Gr, Franco P. Cardiovascular control during sleep in infants: Implications for Sudden Infant Death Syndrome. *Sleep Med*. 2010;11(7):615-621.

Table 1: Effects of sleep position and preterm birth on baseline MAP and cerebral TOI Results are presented as mean (SEM)

			MAP (mmHg)		Cerebral TOI (%)	
			Preterm	**Term**	**Preterm**	**Term**
2-4 Weeks	Supine	QS	63.8 (1.9)‡‡‡	64.6 (2.7)	62.7 (1.2)*** †††‡‡	68.5 (1.5)
		AS	70.9 (1.8)	69.5 (2.7)	60.3 (1.3)* †††	68.3 (1.9)*
	Prone	QS	62.2 (1.8) ‡‡‡	65.2 (2.6) ‡	56.4 (1.2) ††‡‡	65.7 (1.5) ‡
		AS	71.8 (1.7)	73.9 (2.8)	55.6 (1.2) ††	62.7 (1.9)
2-3 Months	Supine	QS	68.6 (2.0)	69.8 (2.5) ‡	58.5 (1.6)*	62.7 (2.0)
		AS	72.6 (2.0)	74.5 (3.4)	57.5 (1.6)*	62.6 (2.9)
	Prone	QS	64.1 (2.0) †‡‡	71.2 (2.7) ‡	53.1 (1.5) ††	61.2 (2.1)
		AS	70.0 (2.1) †	79.4 (3.2)	51.7 (1.6) †	59.9 (2.6)
5-6 Months	Supine	QS	72.5 (2.7)	73.7 (3.3)	57.9 (1.7) ‡‡	60.2 (2.2)
		AS	77.8 (3.3)	72.6 (4.4)	61.1 (1.8)	63.2 (2.6)
	Prone	QS	76.3 (3.0)	73.8 (3.4)	53.6 (1.9) ‡‡	57.8 (2.3)
		AS	78.7 (3.5)	76.2 (4.2)	56.3 (1.9)	60.8 (2.5)

* p<0.05, ** p<0.01, *** p<0.001 supine versus prone

† p<0.05, †† p<0.01, ††† p<0.001 preterm versus term

‡p<0.05, ‡‡p<0.01, ‡‡‡p<0.001 quiet sleep versus active sleep

Table 2: Effect of preterm birth on variability in the response of TOI to a HUT in the prone and supine positions. Values are mean standard deviation (SEM)

			2-4 Weeks		2-3 Months		5-6 Months	
			QS	AS	QS	AS	QS	AS
Supine	Early	Preterm	3.0 (0.2)***	4.0 (0.3)***	3.1 (0.2)***	4.5 (0.2)***	4.0 (0.1)*	3.6 (0.2)***
		Term	1.2 (0.0)	1.7 (0.1)	1.7 (0.1)	2.5 (0.2)	3.5 (0.2)	1.8 (0.1)
	Middle	Preterm	3.3 (0.2)***	4.3 (0.2)***	3.9 (0.1)***	4.7 (0.1)***	3.5 (0.1)***	5.0 (0.2)***
		Term	1.2 (0.0)	2.0 (0.1)	1.8 (0.0)	3.8 (0.1)	3.0 (0.2)	2.2 (0.1)
	Late	Preterm	3.4 (0.2)***	5.4 (0.3)***	4.0 (0.1)***	5.5 (0.1)***	4.0 (0.1)***	4.3 (0.2)***
		Term	1.3 (0.0)	2.2 (0.1)	2.1 (0.1)	4.0 (0.1)	3.2 (0.1)	2.2 (0.1)
Prone	Early	Preterm	5.5 (0.3)***	4.2 (0.2)***	4.4 (0.2)***	6.1 (0.3)***	6.1 (0.2)***	5.2 (0.3)***
		Term	2.1 (0.1)	1.9 (0.1)	2.8 (0.2)	4.1 (0.3)	2.7 (0.1)	3.4 (0.2)
	Middle	Preterm	6.1 (0.2)***	5.1 (0.1)***	5.6 (0.1)***	5.8 (0.2)	5.9 (0.1)***	6.5 (0.3)***
		Term	2.6 (0.0)	2.5 (0.1)	3.5 (0.1)	5.7 (0.0)	3.2 (0.1)	4.0 (0.1)
	Late	Preterm	7.6 (0.2)***	6.3 (0.1)***	6.2 (0.1)***	7.6 (0.2)***	6.9 (0.2)***	7.0 (0.2)***
		Term	2.7 (0.0)	2.4 (0.1)	3.8 (0.1)	4.1 (0.1)	3.1 (0.0)	4.0 (0.1)

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ preterm versus term

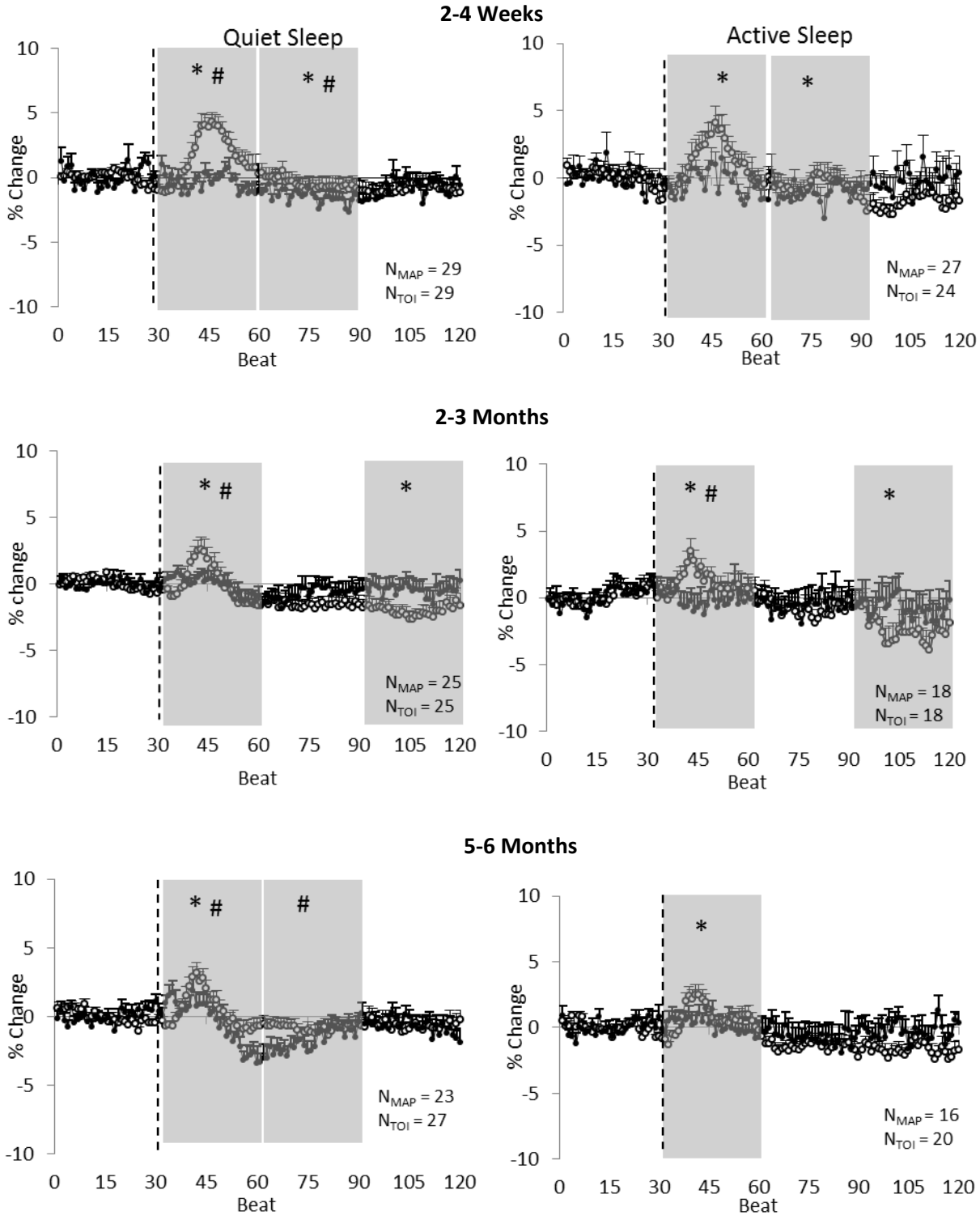


Figure 1: Mean arterial pressure (MAP) (open circles) and cerebral tissue oxygenation index (TOI) (closed circles) responses to a head-up tilt (HUT) (indicated by the dashed line) in preterm infants in quiet sleep (left) and active sleep (right) in the supine position at 2-4 weeks (top), 2-3 months (middle) and 5-6 months (bottom) corrected age (CA). Results are mean ± SEM. Shaded areas represent the early, middle and late phases of the tilt response, shown only when there was an overall significant difference between term and preterm infants detected on ANOVA. N_{MAP} and N_{TOI} refer to the number of infants in which MAP and TOI data respectively was included in each age and sleep state. * $p<0.05$ MAP versus baseline; # $p<0.05$ TOI versus baseline.

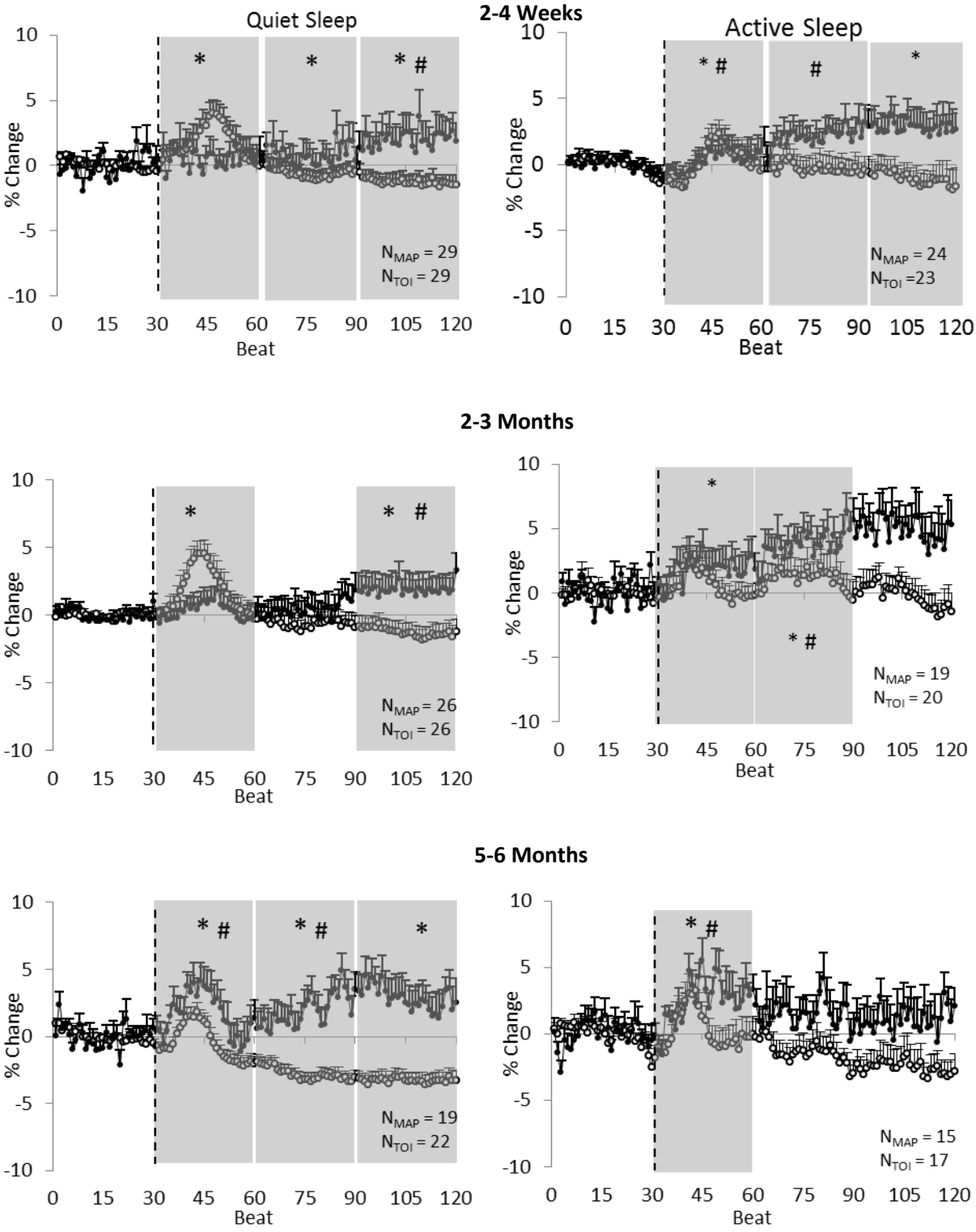


Figure 2: Mean arterial pressure (MAP) (open circles) and cerebral tissue oxygenation index (TOI) (closed circles) responses to a head-up tilt (HUT) (indicated by the dashed line) in preterm infants in quiet sleep (left) and active sleep (right) in the prone position at 2-4 weeks (top), 2-3 months (middle) and 5-6 months (bottom) corrected age (CA). Results are mean ± SEM. Shaded areas represent the early, middle and late phases of the tilt response, shown only when there was an overall significant difference between term and preterm infants detected on ANOVA. N_{MAP} and N_{TOI} refer to the number of infants in which MAP and TOI data respectively was included in each age and sleep state. * $p<0.05$ MAP versus baseline; # $p<0.05$ TOI versus baseline

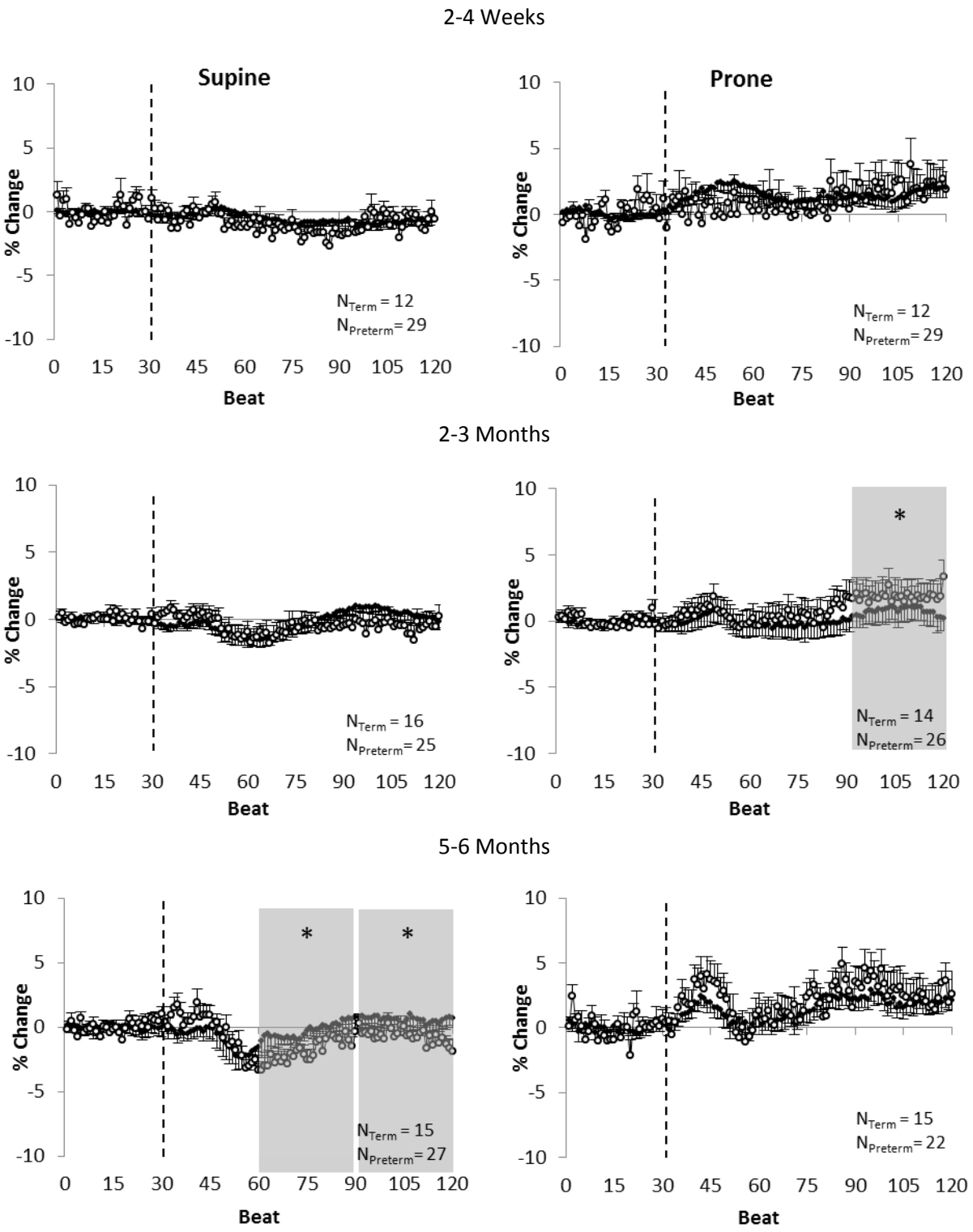


Figure 3: Comparison between term (closed circles) and preterm (open circles) infants of the response of cerebral tissue oxygenation index (TOI) to a head-up tilt (HUT) in quiet sleep in the supine position (left) and prone position (right) at 2-4 weeks (top), 2-3 months (middle) and 5-6 months (bottom). Shaded areas represent the early, middle and late phases of the tilt response, shown only when there was an overall significant difference between term and preterm infants detected on ANOVA. N_{term} and $N_{preterm}$ refer to the number of term and preterm infants respectively included in analysis for each age and sleep position. *$p<0.05$ term versus preterm

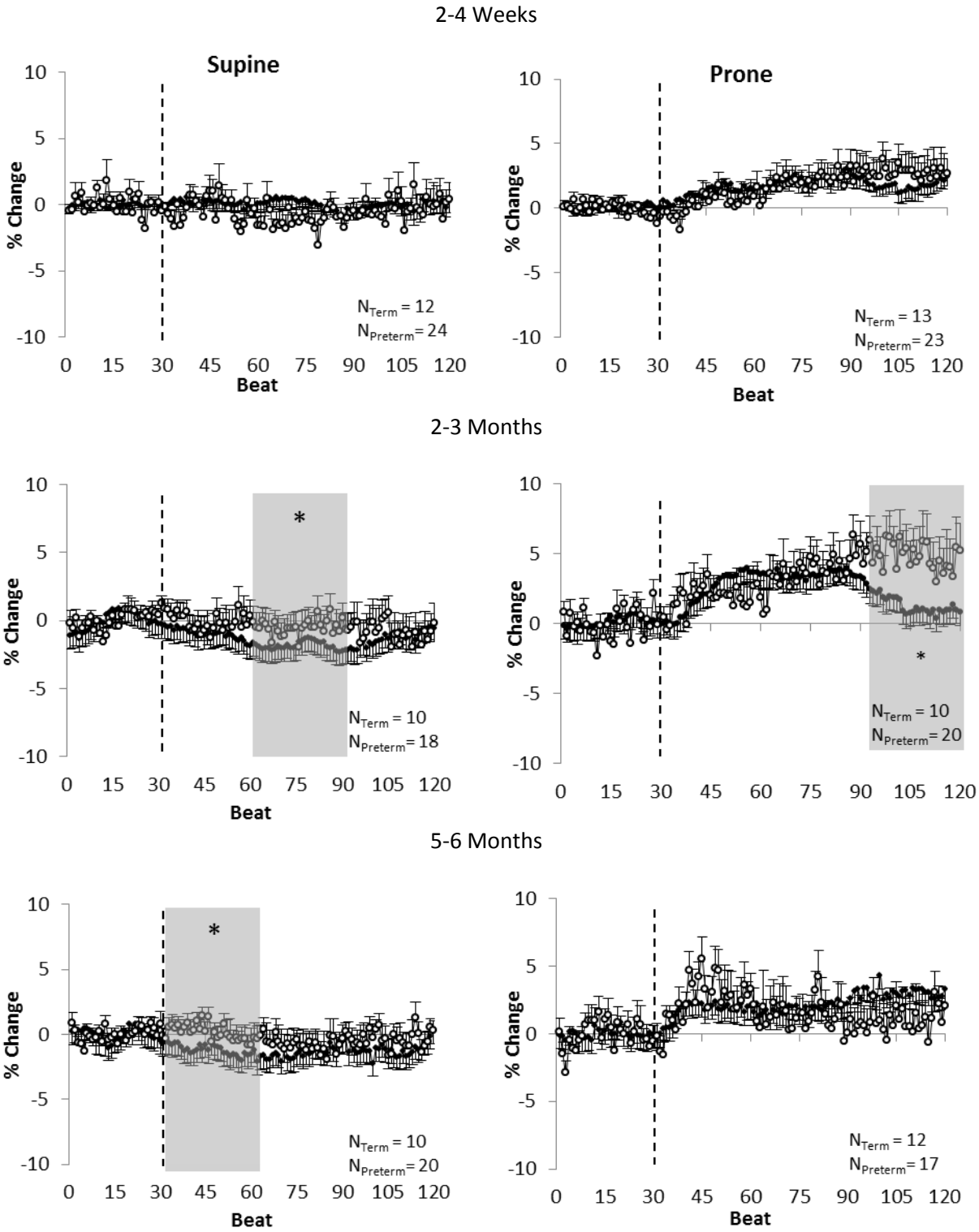


Figure 4: Comparison between term (closed circles) and preterm (open circles) infants of the response of cerebral tissue oxygenation index (TOI) to a head-up tilt (HUT) in active sleep in the supine position (left) and prone position (right) at 2-4 weeks (top), 2-3 months (middle) and 5-6 months (bottom). Shaded areas represent the early, middle and late phases of the tilt response, shown only when there was an overall significant difference between term and preterm infants detected on ANOVA. N_{term} and $N_{preterm}$ refer to the number of term and preterm infants respectively included in analysis for each age and sleep position. *p<0.05 term versus preterm

Chapter 5

Gestational age at birth affects maturation of baroreflex sensitivity

5 Gestational age at birth affects maturation of baroreflex sensitivity

This chapter is presented in manuscript form in preparation for submission to the Journal of Pediatrics.

Karinna L Fyfe, Stephanie R Yiallourou, Flora Y Wong, Alexsandria Odoi, Adrian M Walker, Rosemary SC Horne

5.1 Declaration for Chapter 5

Monash University

In the case of Chapter 5, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
For this chapter I recruited and performed the preterm infant studies and was responsible for analysis of this data. I was responsible for the comparison of term and preterm data, interpretation of all results and writing of the manuscript.	80%

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Stephanie R Yiallourou	Dr Yiallourou assisted with data collection, interpretation of results and writing of the manuscript.	N/A
Flora Y Wong	Dr Wong assisted with recruitment, interpretation of results and writing of the manuscript.	N/A
Alexsandria Odoi	Miss Odoi assisted with data collection and writing of the manuscript	N/A
Adrian M Walker	Professor Walker assisted with interpretation of the results and writing of the manuscript	N/A
Rosemary SC Horne	Professor Horne aided in recruitment and data collection, interpretation of results and writing of the manuscript	N/A

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work*.

Candidate's Signature		**Date**
Main Supervisor's Signature		**Date**

5.2 Introduction to Chapter 5

In Chapter 3 we identified that cerebral oxygenation is reduced in preterm compared to term infants until at least 2-3 months post-term corrected age (CA). Maximal differences were seen in the prone sleeping position at 2-3 months CA, coinciding with significantly reduced blood pressure (BP) in preterm compared to term infants in the prone position during this period. In Chapter 3, we also observed an altered cardiovascular response to prone sleeping in preterm infants at 2-3 months CA, with a failure of the normal increase in heart rate (HR) and a tendency towards reduced BP. This finding suggests that cardiovascular control is altered in preterm infants in the prone sleeping position at 2-3 months CA and the resulting perturbations to systemic BP may exacerbate impaired cerebral oxygen delivery in preterm infants.

In this chapter, we aimed to examine autonomic control of BP in preterm infants sleeping in both the supine and prone positions across the first six months post-term. The baroreflex is primarily responsible for short-term regulation of BP and baroreflex sensitivity (BRS) can be assessed using cross-spectral analysis of spontaneous fluctuations in BP and HR. BRS has been shown to be reduced in term infants in the prone position during the period of peak risk for SIDS (Yiallourou et al., 2011) and in preterm infants compared to term infants prior to term-equivalent age (Drouin et al., 1997, Gournay et al., 2002). Beyond term-equivalent age maturation of BRS appears to be altered in infants born between 28-32 weeks of gestation when they sleep supine, with a plateau in maturation between 2-4 weeks and 5-6 months CA (Witcombe et al., 2012). To date, BRS has not been assessed in the prone position in preterm infants, nor has the effect of gestational age at birth been examined.

In Chapter 5, we aimed to assess BRS in both the prone and supine sleeping positions in preterm infants born across a range of gestational ages. We hypothesised that BRS would be reduced in preterm infants in the prone position and in preterm compared to term infants, particularly in the prone position during the period of peak risk for SIDS, and with greater deficits seen in those infants born at younger gestational ages.

Title: Gestational age at birth affects maturation of baroreflex sensitivity

Authors: Karinna L Fyfe BMedSc[1,2], Stephanie R Yiallourou PhD[1,2], Flora Y Wong MBBS PhD [1,2,3], Alexsandria Odoi BNS(Hons)[1], Adrian M Walker PhD[1], Rosemary SC Horne PhD[1,2]

Affiliations

1. The Ritchie Centre, MIMR-PHI, Melbourne, VIC
2. The Department of Paediatrics, Monash University, Melbourne, VIC
3. Monash Newborn, Monash Health, Melbourne VIC

Short Title: Baroreflex Sensitivity in Preterm Infants

Financial Disclosure: The authors have no financial conflicts to disclose.

Conflicts of Interest: The authors have no conflicts of interest to disclose.

Corresponding Author:

Professor Rosemary SC Horne, PhD

The Ritchie Centre

Level 5, Monash Medical Centre, 246 Clayton Rd, Clayton, VIC, Australia

Email: [redacted]

Telephone: [redacted] Facsimile: +61 3 9594 6811

Key Words: autonomic nervous system, baroreflex sensitivity, Sudden Infant Death Syndrome, preterm birth

Abbreviations: AS – active sleep; BP- blood pressure; BRS – baroreflex sensitivity; CA – corrected age; HR – heart rate; QS – quiet sleep; SIDS – Sudden Infant Death Syndrome;

Abstract

Study Objectives: Preterm birth is associated with increased risk of the Sudden Infant Death Syndrome (SIDS) and cardiovascular disease in adulthood, which may be due to impaired cardiovascular control. The baroreflex is the primary mechanism by which autonomic control of blood pressure (BP) occurs. Baroreflex sensitivity (BRS) has been shown to be altered by preterm birth. In term infants it is reduced in the prone position, the major risk factor for SIDS. To date, the effect of prone sleeping on BRS in preterm infants has not been assessed. Therefore, we aimed to determine the effect of prone sleeping on BRS in preterm infants born across a range of gestational ages.

Design: Daytime polysomnography was performed at 2-4 weeks, 2-3 months and 5-6 months post-term age.

Patients or Participants: 21 very preterm (mean gestation 29.4±0.3wk), 14 preterm (mean gestation 33.1±0.3wk) and 17 term (mean gestation 40.1±0.3wk).

Measurements and Results: Blood pressure was measured using a Finometer^{TM} cuff (Finapress Medical Systems, Amsterdam, The Netherlands). Data were recorded in both the supine and prone positions. BRS was calculated using cross spectral analysis of spontaneous fluctuations in BP. BRS was lower in the prone position in very preterm infants at 2-4 weeks in AS ($p<0.05$). Maturation of BRS was delayed in very preterm compared to preterm and term infants.

Conclusions: Maturation of BRS after term-equivalent age is altered in very preterm infants. Although this is unlikely to contribute to increased SIDS risk, it may predispose very preterm infants to cardiovascular disease in adulthood.

Introduction

With modern intensive care techniques more infants are surviving preterm birth at younger gestational ages[1]. Over the past 10 years there has been an increase in the rate of preterm birth of more than 30%, so that 5-18% of all births are before 37 weeks of gestation worldwide[2]. Preterm birth is associated with a range of consequences, including an increased risk of the Sudden Infant Death Syndrome (SIDS)[3,4] and a susceptibility to cardiovascular disease in adult life[5]. It has been suggested that both morbidities may be due to alterations in the development of cardiovascular control following preterm birth[6] and that this may be exacerbated in those individuals born at younger gestational ages [4].

The baroreflex is primarily responsible for short-term autonomic control of blood pressure (BP) and minimizes fluctuations in BP by increasing or decreasing heart rate (HR) and arterial vascular resistance. Baroreflex sensitivity (BRS), defined as the reflex-induced change in interbeat R-R interval per unit change of BP (ms/mmHg), is used to assess baroreflex function[7]. In healthy term born infants, the baroreflex is immature at birth and a significant increase in BRS occurs across the first six months of life[8]. This immaturity of baroreflex function may play a role in the underlying mechanism of SIDS, which is theorised to involve circulatory failure, in association with a failure to arouse from sleep[9]. Previously, in term born infants, we have shown that prone sleeping, the major risk factor for SIDS, reduces BP[10] and BRS[11,12], particularly at 2-3 months of age which is the period of peak risk for SIDS.

Soon after birth, infants born preterm display reduced BRS compared to term infants[13], and there is evidence to suggest that greater deficits are seen in infants born at earlier gestational ages[14,15]. Furthermore, preterm birth alters the normal maturation of BRS, with reduced BRS in preterm infants at term-equivalent age compared to newborn term infants[14]. Previously, in a cohort of preterm infants born between 28-32 weeks of gestation and sleeping in the supine position, we have shown that maturation of BRS in quiet sleep (QS) is impaired after term equivalent age, which results in significantly reduced BRS at 5-6 months corrected age (CA) compared to term-born infants[16]. However, to date the effect of prone sleeping on BRS in preterm infants has not been assessed nor

have the effects of gestational age at birth on the maturation of BRS been examined beyond term-equivalent age.

Thus, we aimed to assess the effect of prone sleeping and gestational age at birth on BRS across the first six months of life when the majority of infants die from SIDS. We hypothesized that BRS would be reduced in the prone compared to the supine sleep position in preterm infants and in preterm compared to term infants, with the greatest deficit seen in those infants born at earlier gestational ages.

Methods

Ethical approval for this study was obtained from the Monash University and Monash Health human research ethics committees. Written parental consent was obtained prior to the commencement of each study.

Subjects

Thirty-five preterm infants (21M/14F) born between 26-36 weeks of gestation were recruited. Initial analysis revealed a significant effect of gestational age, therefore infants were divided into a very preterm group of infants, born prior to 32 weeks of gestation (n=21; 13M/8F; mean gestation: 29.4±0.3wk (SEM); mean birth weight: 1366±62g (SEM)) and a preterm group, born between 32 and 36 weeks gestational age (N=14; 8M/6F; mean gestation 33.5±0.3wk (SEM); mean birth weight: 2221±109g (SEM). Data were compared to that of 17 term infants born between 38 and 42 weeks of gestation (9M/8F; mean gestation: 40.1±0.3wk (SEM); mean birth weight: 3666±105g (SEM)).

Exclusion criteria for all infants included maternal smoking, family history of SIDS and intrauterine growth restriction. For the preterm infants exclusion criteria also included significant intraventricular hemorrhage (Grade III or IV), clinically significant patent ductus arteriosus, major congenital abnormalities and chronic lung disease requiring respiratory stimulant medication, ventilatory support or oxygen therapy at term-equivalent age. All preterm infants were discharged home prior to the first study. All infants routinely slept supine at home and were born to non-smoking mothers. Where twins were included only one infant was studied.

Infants underwent daytime polysomnography at three post-term ages; 2-4 weeks, 2-3 months and 5-6 months (post-term CA for preterm infants). Analyzable data were obtained in 16 very preterm, 12 preterm and 15 term infants at 2-4 weeks, 16 very preterm, 10 preterm and 17 term infants at 2-3 months and 14 very preterm, 10 preterm and 15 term infants at 5-6 months (post-term CA for preterm infants).

Daytime Polysomnography

Polysomnography electrodes were applied during a morning feed and included electroencephalogram, electrooculogram, submental electromyogram, electrocardiogram (ECG), abdominal and thoracic respiratory belts (Resp-ez bands, EPM Systems, Midlothian, VA, USA) arterial oxygen saturation (SpO_2) (Masimo, Frenchs Forest, NSW, Australia) and abdominal skin temperature (ADInstruments, Sydney, NSW, Australia). BP was recorded continuously using a Finometer (Finometer Medical Systems, Amsterdam, The Netherlands) photoplethysmographic cuff placed around the infants wrist using a technique previously validated by our group[17]. Cerebral tissue oxygenation index was also recorded using near-infrared spectroscopy (NIRO-200 spectrophotometer, Hamamatsu Photonics KK, Tokyo, Japan) however data has been published previously[18] and are not be reported in this paper.

Studies were performed between 0900 and 1700 hours, in a quiet and dimly lit sleep laboratory kept at constant temperature (22-24°). Infants were slept in both the prone and supine sleep position. The initial sleep position was randomized between infants and studies and sleep position was usually changed following a midday feed. Data were recorded in both QS and active sleep (AS).

Data were analyzed from 1-2 minute epochs when the BP cuff was inflated. A minimum of 3 epochs was recorded in each sleep state and position in each infant at each study. A rest period of 2 minutes duration was observed between cuff inflations to prevent venous pooling in the hand.

Physiological variables were recorded with a sampling rate of 512 Hz using an E-series sleep system with Profusion software (Compumedics, Abbotsford, VIC, Australia).

Data Analysis

Our methods for analysis of BRS have been described previously[8,12,16,17]. Briefly, artifact free epochs of 1-2 minutes duration were selected from LabChart (ADInstruments, Sydney, NSW, Australia) and transferred to MATLAB (Mathworks, Natick, MA)[12,19] for analysis. Systolic BP and heart period (HP, the duration of the R-R interval) were calculated using automated peak detection and beat-to-beat data for systolic BP and HP were resampled at 200 Hz (cubic interpolation) to create a continuous, evenly spaced time series for further analysis.

Cross Spectral Analysis

BRS was calculated using cross-spectral analysis of systolic BP and HP. This involves calculation of a transfer function, which characterizes the gain (ms/mmHg), coherence and phase lag (delay) between spontaneous oscillations in systolic BP with respect to those in HP. The gain quantifies BRS by representing the expected amplitude of oscillation in systolic BP that results in an oscillation in HP of 1ms. The coherence between these oscillations was calculated to quantify the strength of the frequency dependent relationship between systolic BP and HP oscillations. The phase lag describes the time delay (delay = [phase lag/360°]/frequency) between oscillations in systolic BP and HP. Spectral BRS values with a corresponding negative delay were excluded as these HR changes precede the associated BP change and are unlikely to be caused by the baroreflex. The values for gain and phase lag (delay) were taken at the frequency at maximum coherence within the specific low frequency range (0.04-0.15Hz) at which baroreflex mediated oscillations in systolic BP and HP are thought to primarily occur[20].

Statistical Analysis

Statistical analysis was performed using Sigmaplot (Systat Software Inc, IL, USA) analysis software. The effect of gestational age at birth was determined using linear regression. The effects of sleep state and position were determined using two-way analysis of variance (ANOVA) within very preterm, preterm and term infant groups. The effects of post-term age and gestational age at birth (very preterm, preterm or term) were determined using two-way ANOVA within each sleep state and

position. Where normality failed, data was transformed to achieve normality. Where an overall significant difference was detected ($p<0.05$) on ANOVA, Student-Newman-Keuls post-hoc analysis was used to determine where the difference occurred.

Results

There were no differences in age or weight between very preterm, preterm or term infants at the 2-4 week (Age: very preterm 3.1±0.2wks; preterm 3.2±0.1wks; term 3.4±0.1wks. Weight: very preterm 3.6±0.1kgs; preterm 3.9±0.2kgs; term 4.0±0.1kgs), 2-3 month (Age: very preterm 10.6±0.1wks; preterm 10.6±0.4wks; term10.6±0.2wks. Weight: very preterm 5.0±0.2kgs; preterm 5.8±0.3kgs; term 5.2±0.2kgs) or 5-6 month (Age: very preterm 23.0±0.3wks; preterm 22.4±0.4wks, term 22.3±0.3wks. Weight: very preterm 6.9±0.2kgs; preterm 7.6±0.4kgs, term 7.0±0.2kgs) studies.

Effect of Sleep Position and Sleep State

The effect of sleep position and sleep state on systolic BP and HP in preterm, very preterm and term infants is shown in Table 1. There was no effect of sleep position on systolic BP at any age. HP was higher in the supine position in QS at 5-6 months in preterm infants ($p<0.05$). There was no effect of sleep position on HP at 2-4 weeks or 2-3 months CA. There was no effect of sleep state on systolic BP in any of the three cohorts or on HP in very preterm or preterm infants at any age. HP was significantly higher in QS compared to AS in term infants at 5-6 months in both sleep positions.

The effect of sleep position and sleep state on BRS is shown in Figure 1. BRS tended to be lower in the prone sleep position at 2-4 weeks CA in very preterm infants, reaching statistical significance in AS ($p<0.05$), with a similar trend in preterm infants in QS at 5-6 months CA ($p=0.085$). There was no effect of sleep state on BRS in either very preterm, preterm or term infants at any age.

Effects of Gestational Age at Birth

The effects of gestational age at birth on systolic BP and HP are also shown in Table 1. Systolic BP was lower in very preterm ($p<0.01$) and preterm ($p<0.05$) infants compared to term infants in QS and lower in very preterm compared to term infants in AS ($p<0.05$) in the prone position at 2-3 months

CA. There was no effect of gestational age at birth on systolic BP at any other age. There was no effect of gestational age at birth on HP at any age. When compared at each age studied there was no difference in BRS between very preterm, preterm and term infants in either sleep position or sleep state (Figure 2), although there was a trend towards reduced BRS in very preterm compared to both term and preterm infants at 5-6 months post-term age ($p=0.06$).

Gestational age at birth altered the maturation of BRS across the first six months post-term (Figure 2). When sleeping in the supine position in QS, BRS increased significantly between 2-4 weeks and 5-6 months CA in both preterm and term infants ($p<0.01$ for both). In contrast, in very preterm infants BRS did not increase between 2-4 weeks and 5-6 months CA. When sleeping in the supine position in AS, preterm and term infants showed no significant maturation of BRS between 2-4 weeks and 5-6 months post-term. In contrast, BRS tended to decrease in very preterm infants.

When sleeping in the prone position in QS, BRS increased between 2-4 weeks and 5-6 months ($p<0.001$) in term infants. In contrast, in both groups of preterm infants there was no significant maturation across the first 6 months. When sleeping in the prone position in AS, there was no change in BRS with post-term age in any of the three groups of infants.

Discussion

Our study provides new information on the effects of prone sleeping and of gestational age at birth on BRS during the first 6 months after term-equivalent age. We have shown that BRS is lower in the prone position in very preterm infants in AS at 2-4 weeks CA, with no other significant effects of sleeping position. Although we did not find any statistically significant differences in BRS between very preterm, preterm or term infants at each of the study ages, we found that very preterm birth resulted in altered maturation of BRS during the first six months post-term.

Prone sleeping, the major risk factor for SIDS, is associated with reduced BP[10] and BRS[12] in term infants, and this is most marked at 2-3 months of age, during the period of peak risk for SIDS. As infants born preterm are at greater risk for SIDS, particularly those born at earlier gestational ages[4], we had hypothesized that BRS would also be reduced in very preterm and preterm infants in the prone

position. BRS was lower in the prone compared to the supine position in AS in very preterm infants at 2-4 weeks CA, however, at 2-3 months CA, the period of peak risk for SIDS during which we predicted the greatest effect of prone sleeping would occur, we found no significant effect of prone sleeping on BRS. This may be due to the age at which our preterm infants were studied, as in preterm infants the post-conceptional age of peak risk for SIDS occurs 2-4 weeks earlier than in term infants. Our preterm infants were studied between 2-3 months post-term age to enable age-matched comparison with term infants, however, as a result we may have missed the period of peak risk for SIDS and possibly underestimated the effect of prone sleeping on BRS. Furthermore, whilst our findings are similar to those previously published in term infants[12], the effects of sleeping position on BRS are considerably less marked in our cohort of term infants than those previously described. In the previous cohort of term infants, BP was reduced in the prone sleeping position, coinciding with reduced BRS[10]. It is important to note that we found no decrease in systolic BP in the prone compared to the supine position in either very preterm, preterm or term infants. Thus in the prone position, a fall in BP to below the linear portion of the baroreflex function curve may underlie reduced BRS[21,22]. In our cohorts of infants, where BP was not reduced in the prone position, BRS was maintained.

Our second hypothesis was that BRS would be reduced in preterm compared to term infants, particularly in those born at earlier gestational ages. Previous studies prior to term-equivalent age have shown BRS is reduced in preterm compared to term infants[13]. Studies examining the effect of gestational age on BRS function shortly after birth have produced conflicting results, with some studies finding greater immaturity in infants born at earlier gestational ages[14,15], whilst others have reported no correlation between gestational age at birth and baroreflex function[23,24]. At term-equivalent age, a trend towards lower BRS in preterm compared to term infants has been demonstrated, but only in those infants born prior to 33 weeks of gestation[14].

Beyond term-equivalent age, our studies in a different cohort of preterm infants sleeping in the supine position only found higher BRS in preterm infants at 2-4 weeks CA, followed by a plateau in the maturation of BRS, which results in significantly reduced BRS in preterm compared to term infants at

5-6 months post-term age in QS[16]. In the current study we observed a similar pattern of reduced maturation of BRS in infants born preterm, particularly very preterm. In very preterm infants in the supine position BRS tended to be higher at 2-4 weeks CA (QS: very preterm 9±1 versus term 7±2 ms/mmHg; AS: very preterm 12±2 versus term 9±2 ms/mmHg) and lower BRS at 5-6 months CA (QS: very preterm 11±1 versus term 13±1 ms/mmHg; AS: very preterm 8±1 versus term 12±2 ms/mmHg) compared to term infants in the supine position. A significant effect of preterm birth on maturation of BRS was also seen in the prone position in QS with reduced maturation of BRS in both very preterm and preterm infants compared to term infants. This delayed maturation of BRS in very preterm and to a lesser extent preterm infants may be driven by reduced parasympathetic activity which has been shown in preterm infants at term-equivalent age[25-27], particularly in those born at younger gestational ages[28].

An interesting effect of gestational age at birth on the maturational pattern of BRS was seen in the supine position in AS. In the very preterm cohort, BRS tended to decrease between 2-4 weeks and 5-6 months CA, in contrast in preterm and term infants there was no change in BRS during the same period. This decrease in BRS with age in AS in very preterm infants was not seen in the prone position, nor was a decrease in BRS with age in AS reported in the previous study of preterm infants sleeping in the supine position[16]. It is important to note that all infants were routinely slept supine at home, so this is not an effect of sleep position on maturation of BRS. Furthermore, the effect of position on BRS in very preterm infants in AS at 5-6 months CA did not reach significance suggesting that, although intriguing, this pattern does not indicate any deleterious effect of supine sleeping in infants born very preterm.

Our results differ from those previously reported in preterm infants studied in the supine position in two ways; firstly, in QS no significant differences were seen between very preterm, preterm or term infants at 2-4 weeks or 5-6 months CA and secondly, in AS BRS tended to decline with age in very preterm infants. A number of factors may have contributed to our differing observations; in our preterm cohorts all infants were appropriately grown for gestational age and we observed no difference in weight between our cohorts of term and preterm infants at the time of each study. This

is in contrast to the previous study where the preterm cohort consistently weighed less at the time of each study, a finding which may have been influenced by the inclusion of three infants who were born small for gestational age[16]. Importantly, preterm infants in the previous cohort were all born between 28 and 32 weeks of gestation thus falling into the very preterm category[29].

Previous studies have identified that other consequences of preterm birth, including bronchopulmonary dysplasia and apnea of prematurity, can influence the maturation of BRS beyond term-equivalent age[30-32]. These conditions occur much more commonly in infants born at younger gestational ages[33,34]. In particular, exposure to intermittent hypoxia in the early postnatal period, as is often experienced by infants with apnea of prematurity, can have long-lasting effects on the cardiovascular system[31,35,36]. Animal models investigating the effect of intermittent hypoxia on BRS have found an approximately 50% reduction in BRS in rats exposed to intermittent hypoxia compared to control animals at 3.5-5 months of age. This decrease was associated with reductions in vagal efferent projections to cardiac ganglia in rats, suggesting remodelling of vagal efferent inputs to the heart which may contribute to long-term cardiovascular impairment[31]. Human infants exposed to intermittent hypoxia in the early postnatal period due to bronchopulmonary dysplasia have altered BP control, with greater variability in response to a head-up tilt than control infants when assessed at 2-3 months post-term age[30]. However, it is currently unclear how exposure to hypoxia and preterm birth interact and further research is required to determine if very preterm birth alone results in similar perturbations to vagal maturation.

Our data suggest that infants born very preterm develop long-term alterations in BRS resulting in reduced BRS at 5-6 months CA, while maturation of BRS in preterm infants is relatively preserved. Reduced BRS may result in an impaired ability of very preterm infants to respond to cardiovascular stress during infancy and may predispose them to cardiovascular disease later in life. Reduced BRS is associated with greater short-term fluctuations in BP with an impaired ability to recover from sudden falls in BP[37]. Furthermore, altered baroreflex function has been associated with a range of cardiovascular diseases in adults including hypertension[38,39] and is an established negative prognostic factor for cardiac mortality following myocardial infarction[40,41]. It is thought that impaired baroreflex

function may occur due to alterations in symaptho-vagal outflow to the heart with a predominance of sympathetic activity and diminished parasympathetic activity, as is seen in a range of cardiovascular diseases including hypertension. Long-term exposure to greater sympathetic activity and impaired baroreflex function can contribute to the progression of cardiovascular disease and exacerbate end-organ damage[40]. Thus, infants born very preterm may be exposed to reduced BRS from as young as six months CA, potentially contributing to their increased risk of cardiovascular disease later in life[42-44].

Conclusions

In our otherwise healthy cohorts of preterm infants we found BRS was reduced in the prone position in very preterm infants at 2-4 weeks post-term CA but found no effect of sleep position on BRS during the period of maximal risk for SIDS. We found no significant effect of gestational age at birth on BRS; however, maturation of BRS beyond term-equivalent age appears to be significantly altered in infants born very preterm. Failure of the normal post-term increase in BRS results in reduced BRS at 5-6 months CA and may predispose very preterm infants to cardiovascular disease in adolescence and adulthood.

Acknowledgements

We would like to thank the parents and infants involved in this study and the staff at the Melbourne Children's Sleep Centre.

References

[1] Horbar JD, Carpenter JH, Badger GJ, Kenny MJ, Soll RF, Morrow KA, et al. Mortality and neonatal morbidity among infants 501 to 1500 grams from 2000 to 2009. Pediatrics. 2012;129:1019-26.
[2] Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller A-B, Narwal R, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. The Lancet. 2012;379:2162-72.
[3] Trachtenberg FL, Haas EA, Kinney HC, Stanley C, Krous HF. Risk Factor Changes for Sudden Infant Death Syndrome After Initiation of Back-to-Sleep Campaign. Pediatrics. 2012;129:630-8.
[4] Malloy MH. Prematurity and sudden infant death syndrome: United States 2005-2007. J Perinatol. 2013;33:470-5.
[5] Parkinson JR, Hyde MJ, Gale C, Santhakumaran S, Modi N. Preterm birth and the metabolic syndrome in adult life: a systematic review and meta-analysis. Pediatrics. 2013;131:e1240-63.
[6] De Boo HA, Harding JE. The developmental origins of adult disease (Barker) hypothesis. Aust N Z J Obstet Gynaecol. 2006;46:4-14.
[7] Oosting J, Struijker-Boudier HA, Janssen BJ. Validation of a continuous baroreceptor reflex sensitivity index calculated from spontaneous fluctuations of blood pressure and pulse interval in rats. J Hypertens. 1997;15:391-9.
[8] Yiallourou SR, Sands SA, Walker AM, Horne RS. Postnatal development of baroreflex sensitivity in infancy. J Physiol. 2010;588:2193-203.
[9] Harper RM. Sudden infant death syndrome: a failure of compensatory cerebellar mechanisms? Pediatr Res. 2000;48:140-2.
[10] Yiallourou SR, Walker AM, Horne RS. Effects of sleeping position on development of infant cardiovascular control. Arch Dis Child. 2008;93:868-72.
[11] Yiallourou SR, Walker AM, Horne RS. Prone sleeping impairs circulatory control during sleep in healthy term infants: implications for SIDS. Sleep. 2008;31:1139-46.
[12] Yiallourou SR, Sands SA, Walker AM, Horne RS. Baroreflex sensitivity during sleep in infants: impact of sleeping position and sleep state. Sleep. 2011;34:725-32.
[13] Drouin E, Gournay V, Calamel J, Mouzard A, Roze J-C. Assessment of spontaneous baroreflex sensitivity in neonates. Archives of Disease in Childhood - Fetal and Neonatal Edition. 1997;76:F108-F12.
[14] Gournay V, Drouin E, Roze JC. Development of baroreflex control of heart rate in preterm and full term infants. Archives of Disease in Childhood Fetal & Neonatal Edition. 2002;86:F151-4.
[15] Zhang Y, Chan GS, Tracy MB, Lee QY, Hinder M, Savkin AV, et al. Spectral analysis of systemic and cerebral cardiovascular variabilities in preterm infants: relationship with clinical risk index for babies (CRIB). Physiol Meas. 2011;32:1913-28.
[16] Witcombe NB, Yiallourou SR, Sands SA, Walker AM, Horne RS. Preterm birth alters the maturation of baroreflex sensitivity in sleeping infants. Pediatrics. 2012;129:e89-96.
[17] Yiallourou SR, Walker AM, Horne RS. Validation of a new noninvasive method to measure blood pressure and assess baroreflex sensitivity in preterm infants during sleep. Sleep. 2006;29:1083-8.
[18] Fyfe KL, Yiallourou SR, Wong FY, Odoi A, Walker AM, Horne RS (in press). Cerebral oxygenation in preterm infants. Pediatrics. 2014.
[19] Yiallourou SR, Sands SA, Walker AM, Horne RSC. Postnatal development of baroreflex sensitivity in infancy. The Journal of Physiology. 2010;588:2193-203.
[20] Robbe HW, Mulder LJ, Ruddel H, Langewitz WA, Veldman JB, Mulder G. Assessment of baroreceptor reflex sensitivity by means of spectral analysis. Hypertension. 1987;10:538-43.
[21] Segar JL, Hajduczok G, Smith BA, Merrill DC, Robillard JE. Ontogeny of baroreflex control of renal sympathetic nerve activity and heart rate. Am J Physiol. 1992;263:H1819-26.
[22] DiCarlo SE, Bishop VS. Central baroreflex resetting as a means of increasing and decreasing sympathetic outflow and arterial pressure. Ann N Y Acad Sci. 2001;940:324-37.
[23] Golder V, Hepponstall M, Yiallourou SR, Odoi A, Horne RSC. Autonomic cardiovascular control in hypotensive critically ill preterm infants is impaired during the first days of life. Early Hum Dev. 2013;89:419-23.

[24] Holden K, Morgan JS, Krauss AN, Auld PA. Incomplete baroreceptor responses in newborn infants. Am J Perinatol. 1985;2:31-4.
[25] De Rogalski Landrot I, Roche F, Pichot V, Teyssier G, Gaspoz J-M, Barthelemy J-C, et al. Autonomic nervous system activity in premature and full-term infants from theoretical term to 7 years. Auton Neurosci. 2007;136:105-9.
[26] Patural H, Barthelemy JC, Pichot V, Mazzocchi C, Teyssier G, Damon G, et al. Birth prematurity determines prolonged autonomic nervous system immaturity. Clin Auton Res. 2004;14:391-5.
[27] Andriessen P, Oetomo SB, Peters C, Vermeulen B, Wijn PFF, Blanco CE. Baroreceptor reflex sensitivity in human neonates: the effect of postmenstrual age. The Journal of Physiology. 2005;568:333-41.
[28] Patural H, Pichot V, Jaziri F, Teyssier G, Gaspoz J-M, Roche Fdr, et al. Autonomic cardiac control of very preterm newborns: A prolonged dysfunction. Early Hum Dev. 2008;84:681-7.
[29] Tucker J, McGuire W. Epidemiology of preterm birth. Br Med J. 2004;329:675-8.
[30] Viskari S, Andersson S, Hytinantti T, Kirjavainen T, Viskari S, Andersson S, et al. Altered cardiovascular control in preterm infants with bronchopulmonary dysplasia. Pediatr Res. 2007;61:594-9.
[31] Soukhova-O'Hare GK, Cheng ZJ, Roberts AM, Gozal D. Postnatal intermittent hypoxia alters baroreflex function in adult rats. American Journal of Physiology - Heart & Circulatory Physiology. 2006;290:H1157-64.
[32] Prabhakar NR, Peng Y-J, Kumar GK, Pawar A. Altered carotid body function by intermittent hypoxia in neonates and adults: Relevance to recurrent apneas. Respir Physiol Neurobiol. 2007;157:148-53.
[33] Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. The Lancet. 2008;371:261-9.
[34] Theobald K, Botwinski C, Albanna S, McWilliam P. Apnea of prematurity: diagnosis, implications for care, and pharmacologic management. Neonat Netw. 2000;19:17-24.
[35] Martin RJ, Wang K, Koroglu O, Di Fiore J, Kc P. Intermittent hypoxic episodes in preterm infants: do they matter? Neonatology. 2011;100:303-10.
[36] Pozo ME, Cave A, Koroglu OA, Litvin DG, Martin RJ, Di Fiore J, et al. Effect of postnatal intermittent hypoxia on growth and cardiovascular regulation of rat pups. Neonatology. 2012;102:107-13.
[37] Cowley AW, Jr., Liard JF, Guyton AC. Role of baroreceptor reflex in daily control of arterial blood pressure and other variables in dogs. Circ Res. 1973;32:564-76.
[38] Gribbin B, Pickering TG, Sleight P, Peto R. Effect of age and high blood pressure on baroreflex sensitivity in man. Circ Res. 1971;29:424-31.
[39] Honzíková N, Fiser B. Baroreflex Sensitivity and Essential Hypertension in Adolescents. Physiol Res. 2009;58:605-12.
[40] La Rovere MT, Pinna GD, Raczak G. Baroreflex Sensitivity: Measurement and Clinical Implications. Annals of Noninvasive Electrocardiology. 2008;13:191-207.
[41] La Rovere MT, Bigger JT, Jr., Marcus FI, Mortara A, Schwartz PJ. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. Lancet. 1998;351:478-84.
[42] Kistner A, Celsi G, Vanpée M, Jacobson SH. Increased systolic daily ambulatory blood pressure in adult women born preterm. Pediatr Nephrol. 2005;20:232-3.
[43] Bonamy AK, Kallen K, Norman M, Bonamy A-KE, Kallen K, Norman M. High blood pressure in 2.5-year-old children born extremely preterm. Pediatrics. 2012;129:e1199-204.
[44] Johansson S, Iliadou A, Bergvall N, Tuvemo T, Norman M, Cnattingius S. Risk of high blood pressure among young men increases with the degree of immaturity at birth. Circulation. 2005;112:3430-6.

Table 1: Effect of sleep position, sleep state and gestational age at birth on systolic blood pressure (SBP) and heart period (HP). Values are mean (SEM)

			Systolic BP (mmHg)			HP (ms)		
			Very Preterm	Preterm	Term	Very Preterm	Preterm	Term
2-4 Weeks	QS	Supine	83 (3)	80 (4)	79 (3)	444 (8)	439 (6)	432 (7)
		Prone	81 (3)	78 (4)	80 (3)	436 (8)	442 (7)	426 (7)
	AS	Supine	84 (4)	82 (5)	83 (5)	439 (11)	450 (8)	427 (10)
		Prone	83 (4)	88 (5)	89 (4)	432 (10)	451 (8)	421 (8)
2-3 Months	QS	Supine	83 (3)	81 (4)	87 (3)	469 (10)	480 (14)	454(9)
		Prone	79 (3)**	78 (4) Δ	92 (3)	465 (10)	474 (14)	447 (6)
	AS	Supine	80 (5)	91 (4)	93 (4)	441 (14)	472 (17)	452 (9)
		Prone	81 (4)*	88 (4)	97 (4)	471 (14)	463 (15)	444 (8)
5-6 Months	QS	Supine	89 (4)	90 (4)	88 (3)	511 (9)	513 (8)†	500 (10)‡
		Prone	88 (5)	92 (5)	88 (3)	516 (11)	485 (8)	485 (9) ‡
	AS	Supine	91 (7)	89 (6)	90 (6)	501 (12)	496 (9)	470 (5)
		Prone	93 (9)	88 (5)	91 (4)	497 (14)	476 (10)	461 (8)

* $p < 0.05$; ** $p < 0.01$ very preterm versus term
Δ $p<0.05$ preterm versus term
† $p<0.05$ supine versus prone
‡ $p<0.05$ quiet sleep versus active sleep

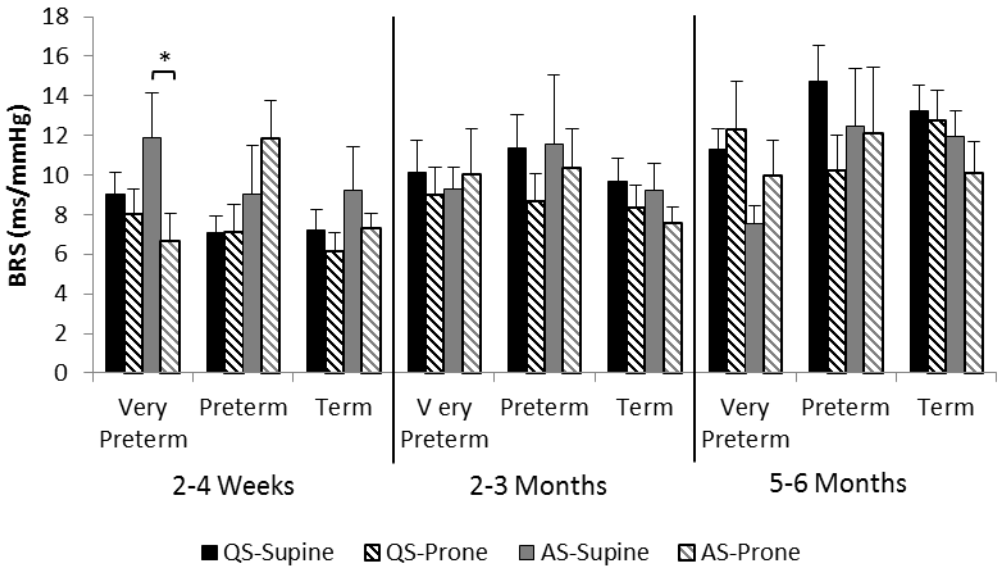


Figure 1: Effect of sleeping position on BRS in preterm, very preterm and term infants. *p<0.05 supine versus prone

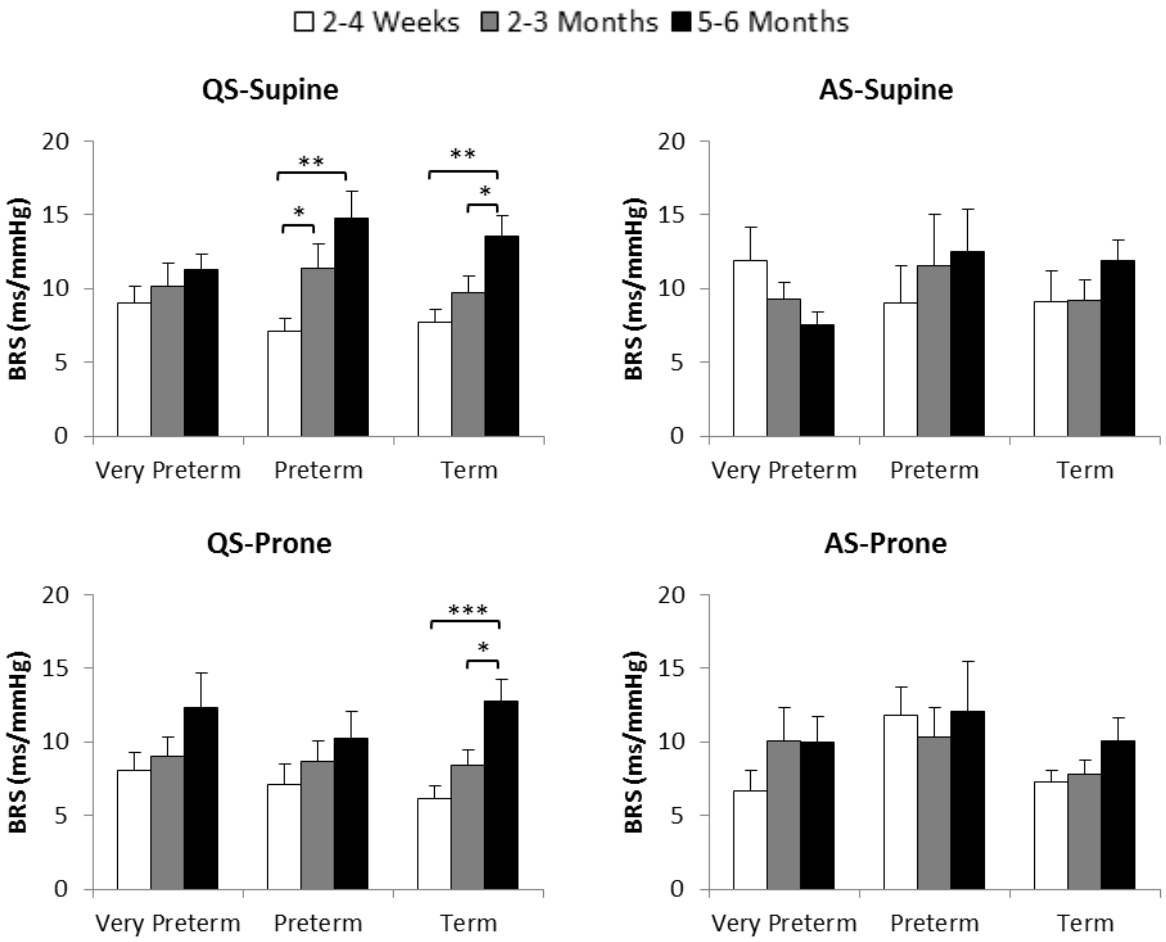


Figure 2: Effect of post-term age on BRS in very preterm, preterm and term infants in both quiet sleep (QS) and active sleep (AS) in the supine and prone positions. Values are mean ± SEM. *p<0.05, ** p<0.01, ***p<0.001

Chapter 6

The Effect of Gestational Age at Birth on Post-Term Maturation of Heart Rate Variability

6 The Effect of Gestational Age at Birth on Post-Term Maturation of Heart Rate Variability

This chapter is presented in manuscript form in preparation for submission to Pediatrics.

Karinna L Fyfe, Stephanie R Yiallourou, Flora Y Wong, Alexsandria Odoi, Adrian M Walker, Rosemary SC Horne

6.1 Declaration for Chapter 6

Monash University

In the case of Chapter 6, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
For this chapter I recruited and performed the preterm infant studies and was responsible for analysis of this data. I was responsible for the comparison of term and preterm data, interpretation of all results and writing of the manuscript.	80%

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Stephanie R Yiallourou	Dr Yiallourou assisted with data collection, interpretation of results and writing of the manuscript.	N/A
Flora Y Wong	Dr Wong assisted with recruitment, interpretation of results and writing of the manuscript.	N/A
Alexsandria Odoi	Miss Odoi assisted with data collection and writing of the manuscript	N/A
Adrian M Walker	Professor Walker assisted with interpretation of the results and writing of the manuscript	N/A
Rosemary SC Horne	Professor Horne aided in recruitment and data collection, interpretation of results and writing of the manuscript	N/A

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work*.

Candidate's Signature		**Date**
Main Supervisor's Signature		**Date**

6.2 Introduction to Chapter 6

In Chapter 3 we identified that significantly reduced cerebral oxygenation in preterm infants compared to term infants at 2-3 months in the prone position was associated with a concurrent reduction in blood pressure (BP) and heart rate (HR) in the prone position. In Chapter 4 we identified that cerebrovascular control is similar, but more variable in preterm compared to term infants. While this may contribute to impaired cerebral oxygenation, it is unlikely to be the sole cause of the differences we have observed. Thus, in Chapter 5 we assessed autonomic control of BP and identified that sensitivity of the baroreflex is not reduced in preterm compared to term infants in the prone position at 2-3 months post-term, suggesting that autonomic control of BP does not underlie the differences in BP and cerebral oxygenation reported in Chapter 3. Therefore, in the following chapter we investigated autonomic control of HR in preterm infants across the first six months post-term in preterm infants.

Assessment of heart rate variability (HRV), defined as fluctuations in the duration of the beat-beat interval of HR, has been established as a non-invasive method of assessing autonomic cardiovascular control. Using fast-Fourier transforms, HRV can be stratified into two frequency ranges; the low frequency range (LF) of 0.04-0.15 Hz and the high frequency range (HF) of 0.4-1.5 Hz (de Beer et al., 2004). LF HRV reflects a mixture of sympathetic and parasympathetic activity whilst HF HRV is thought to primarily reflect parasympathetic activity (Pagani et al., 1986). Previous studies have identified delayed maturation of HRV, particularly HF HRV, in preterm infants across the first six months post-term (Yiallourou et al., 2013). However, the effect of sleeping position and decreasing gestational age at birth has not previously been investigated.

Therefore, in this chapter we aimed to examine HRV parameters in preterm infants in the prone and supine sleep positions across the first six months post-term. We hypothesised that in preterm infants HRV parameters would be reduced in the prone position and reduced in comparison to term infants, with greater deficits seen in infants born at earlier gestational ages.

Title: The Effect of Gestational Age at Birth on Post-Term Maturation of Heart Rate Variability

Authors: Karinna L Fyfe[1,2], Stephanie R Yiallourou[1,2], Flora Y Wong[1,2,3], Alexsandria Odoi[1], Adrian M Walker[1], Rosemary SC Horne[1,2]

Affiliations:

[1]The Ritchie Centre, Monash Institute of Medical Research and Prince Henry's Institute and Monash University, Melbourne, Australia;

[2]Department of Paediatrics, Monash University, Melbourne, Australia.

[3]Monash Newborn, Monash Medical Centre, Melbourne, Australia;

Address correspondence to: Professor Rosemary SC Horne, [redacted] The Ritchie Centre, Level 5 Monash Medical Centre, 246 Clayton Road, PO Box 5418, Clayton, Victoria, Australia 3168; Telephone: [redacted] Fax: +61 3 9594 6811.

Short title: Heart Rate Variability in Preterm Infants

Abbreviations: ANOVA – analysis of variance; AS – active sleep; CA – corrected age; GA – gestational age; HF – high frequency; HR – heart rate; HRV – heart rate variability; LF – low frequency; QS – quiet sleep; SEM – standard error of the mean; SIDS – Sudden Infant Death Syndrome; TP – total power

Key words: preterm birth, Sudden Infant Death Syndrome, prone sleeping position, heart rate variability, autonomic nervous system

Funding Source: The National Health and Medical Research Council of Australia and the Victorian Government Infrastructure Program.

Financial Disclosure: The authors have no financial relationships relevant to this article to disclose.

Conflict of Interest: The authors have no conflicts of interest relevant to this article to disclose.

What's Known on This Subject

Preterm infants are at significantly increased risk of SIDS, with greater risk in those born very preterm. Preterm birth is associated with alterations in cardiovascular control which is thought to contribute to their increased risk for SIDS.

What This Study Adds

Maturation of HF HRV is significantly reduced in very preterm compared to both preterm and term infants resulting in significantly altered sympathovagal balance during the period of peak risk for SIDS.

Abstract

Background: Preterm birth delays maturation of autonomic cardiovascular control, reflected in reduced heart rate variability (HRV), in preterm compared to term infants at term-equivalent age. It has been suggested that immature cardiovascular control contributes to the increased risk for the Sudden Infant Death Syndrome (SIDS) in preterm infants. However, the effect of prone sleeping, the major SIDS risk factor, and of gestational age (GA) at birth on HRV have not been assessed in preterm infants beyond term-equivalent age.

Methods: Very preterm (n=21; mean GA 29.4±0.3wk), preterm (n=14; mean GA 33.5±0.3wk) and term (n=17; mean GA 40.1±0.3wk) infants were recruited and underwent daytime polysomnography at 2-4 weeks, 2-3 months and 5-6 months post-term corrected age (CA). Infants slept both supine and prone. HRV was assessed in the low frequency (LF) and high frequency (HF) ranges.

Results: There was no effect of prone sleeping on HRV parameters in either preterm group. In term infants LF/HF was significantly elevated in the prone position in AS at 2-4 weeks ($p<0.05$). HF HRV was significantly reduced ($p<0.05$) and LF/HF increased ($p<0.05$) in very preterm compared to both preterm and term infants at 2-3 months CA.

Conclusion: Prone sleeping did not significantly impact on HRV in preterm infants. However, reduced maturation of HF HRV in very preterm infants resulted in significantly altered sympathovagal balance at 2-3 months CA, the age of peak SIDS risk. This may contribute to the increased risk of SIDS in infants born at earlier gestational age.

Introduction

Preterm birth (birth <37 weeks of gestation) is common and increasing in incidence, with rates ranging from 5-18% of live births worldwide.[1] Prematurity is associated with a range of complications including an increased risk of the Sudden Infant Death Syndrome (SIDS),[2] with infants born at earlier gestational ages (GA) are at an even greater risk.[2,3] SIDS occurs with a peak incidence between 2 and 3 months of age[4] and is theorised to occur due to impaired cardiovascular control leading to an uncompensated hypotensive episode during sleep.[5] Prone sleeping is a major risk factor for SIDS and there is evidence to suggest that cardiovascular control is diminished in the prone position in both term[6,7] and preterm infants.[8,9]

Autonomic control of the cardiovascular system can be assessed non-invasively through spectral analysis of spontaneous beat-to-beat changes in heart rate (HR), known as heart rate variability (HRV).[10] Spectral divisions of HRV reflect the relative contributions of the two branches of the autonomic nervous system; low frequency (LF; 0.04-0.15Hz) reflects mixed sympathetic and parasympathetic activity, high frequency (HF; 0.4-1.5Hz) reflects parasympathetic activity whilst the ratio of LF to HF (LF/HF) reflects sympathovagal balance.[11] Alterations in HRV have been reported in infants born preterm[12-17] and in adults with cardiovascular disease.[18]

Autonomic function matures across gestation before term-equivalent age.[19-21] At term-equivalent age, preterm infants have a higher HR[22] and lower HRV compared to term infants,[13,17] suggesting preterm birth delays the normal maturation of cardiovascular control.[12,14] Maturation of HF HRV, reflecting parasympathetic activity is primarily affected,[13,15] resulting in alterations in sympathovagal balance in preterm infants at term-equivalent age. One study has shown that these alterations in HRV persist beyond term-

equivalent age, with delayed maturation of both LF and HF HRV resulting in significant reductions in these parameters at 5-6 months post-term age compared to term infants in the supine position.[23]

However, despite preterm infants born at earlier GA being at greater risk for SIDS, the effect of GA at birth on maturation of HRV beyond term-equivalent age in healthy preterm infants has not been assessed. Furthermore, it is unclear if prone sleeping has greater effects on HRV in infants born at earlier GAs. In this study we aimed to assess 1) the effect of GA at birth on HRV within the first six months after term-equivalent age and 2) the effect of prone sleeping in preterm infants on HRV. We hypothesized that HRV would be reduced in infants born at earlier GA and in preterm infants in the prone sleep position, particularly those infants born at younger GA.

Methods

Ethical approval for this study was obtained from the Monash University and Monash Health human research ethics committees. Written parental consent was obtained prior to the commencement of each study.

Subjects

Thirty-five preterm infants (21M, 14F) born between 26-36 weeks of gestational age (GA) were recruited. As we initially identified an effect of GA at birth on HRV parameters, infants were subsequently divided into a very preterm group of infants born prior to 32 weeks GA (n=21) and a preterm group, born between 32 and 36 weeks GA (n=14). Data were compared to that of 17 term infants born between 38 and 42 weeks GA. Exclusion criteria for all infants included maternal smoking, family history of SIDS and intrauterine growth restriction. For the preterm infants exclusion criteria also included significant intraventricular

hemorrhage (Grade III or IV), clinically significant patent ductus arteriosus, major congenital abnormalities and chronic lung disease requiring respiratory stimulant medication or oxygen therapy at term-equivalent age. In the instance that twins were recruited only one infant was studied. All preterm infants were discharged home prior to the first study and all infants routinely slept supine at home.

Infants underwent daytime polysomnography at three post-term ages; 2-4 weeks, 2-3 months and 5-6 months (post-term corrected age (CA) for preterm infants). 15 very preterm and 9 preterm infants were studied at all 3 ages, 2 very preterm and 3 preterm infants were studied at only 2-4 weeks CA and 2 very preterm and 2 preterm infants were studied only at 2-3 months and 5-6 months CA. Term infants were all studied at three ages.

Daytime Polysomnography

Polysomnography electrodes were applied during a morning feed and included electroencephalogram, electrooculogram, submental electromyogram, electrocardiogram and abdominal and thoracic respiratory belts (Resp-ez bands, EPM Systems, Midlothian, VA, USA). In addition to the standard polysomnography measures arterial oxygen saturation (SpO_2) (Masimo, Frenchs Forest, NSW, Australia) and abdominal skin temperature (ADInstruments, Sydney, NSW, Australia) were also recorded. Blood Pressure (BP) was recorded continuously using a Finometer (Finometer Medical Systems, Amsterdam, The Netherlands) BP photoplethysmographic cuff placed around the infants wrist using a technique previously validated by our group.[24] Cerebral tissue oxygenation index (TOI) was also recorded using near-infrared spectroscopy (NIRO-200 spectrophotometer, Hamamatsu Photonics KK, Tokyo, Japan). BP and cerebral TOI data have been reported previously[25] and are not presented in this paper.

Daytime polysomnographic studies were performed in a quiet and dimly lit sleep laboratory kept at constant temperature (22-24°). Sleep duration averaged 3.4±0.2 hours at 2-4 weeks, 3.0±0.2 hours at 2-3 months and 2.3±0.2 hours at 5-6 months CA. Infants were slept in both the prone and supine sleep position with the initial sleep position randomized between studies. Sleep position was usually changed following a midday feed. Data were recorded in both quiet sleep (QS) and active sleep (AS).

Data were recorded in 1-2 minute epochs during which the BP cuff was inflated with a minimum of 2 minutes rest period between cuff inflations to prevent venous pooling in the hand. A minimum of 3 epochs was recorded in each sleep state and position in each infant.

Physiological variables were recorded with a sampling rate of 512 Hz using an E-series sleep system with Profusion software (Compumedics, Abbotsford, VIC, Australia).

Data Analysis

Data analysis was performed offline at the completion of each study. Our methods for analysis of HRV have been described previously.[7,24,26,27] Briefly, artifact free epochs of ECG data of 1-2 minutes in duration were selected from LabChart (ADInstruments, Sydney, NSW, Australia) and transferred to MATLAB (Mathworks, Natick, MA)[7,28] for analysis. Heart period (HP, the duration of the R-R interval) and respiratory rate (RR) were calculated using automated peak detection and beat-to-beat data were resampled at 200Hz (cubic interpolation) to create an evenly spaced and continuous time series for further analysis.

Fast Fourier transformations were used to calculate the spectral power for HP. Each epoch was detrended and divided into 4 overlapping segments with 75% overlap. A Hamming window was used to reduce spectral leakage and the halving of measured power caused by windowing was corrected for. Power spectra were calculated for HRV within two frequency

bands: low frequency (LF) (0.04-0.15 Hz) reflecting slow oscillations attributed to the baroreflex which occur maximally at a frequency of approximately 0.1 Hz and high frequency (HF) which is calculated for each infant based on respiratory frequency and is defined by the 10^{th} and 90^{th} centiles of the respiratory rate. Total power (TP) and the LF/HF ratio (LF/HF) were also calculated. The power values represent the square of the amplitude of an oscillatory signal in the identified frequency range.[29,30]

Statistical Analysis

Statistical analysis was performed using Sigmaplot 12.0 (Systat Software Inc, IL, USA). Data that failed normality were transformed using the logarithm function. The effects of GA were tested with linear regression. The effect of sleep state and position was determined using two way analysis of variance (ANOVA). The effect of gestational age at birth (very preterm, preterm or term) and post-term CA was determined using two way ANOVA within each sleep state and position. Where a significant difference was detected on ANOVA ($p<0.05$), Student-Newman-Keuls post-hoc analysis was used to determine where the difference occurred. Values are presented as mean ± standard error of the mean (SEM).

Results

By design, very preterm and preterm infants had younger GA at birth and lower birth weight compared to term infants (very preterm < preterm < term; $p<0.05$ for all). Very preterm infants had lower 1 minute Apgar scores compared to preterm and term infants ($p<0.05$) and lower 5 minute Apgar scores compared to term infants ($p<0.05$). There were no differences in age or weight between the three groups at the time of each study (Table 1).

Effect of Gestational Age

The effect of gestational age at birth on HRV in QS is shown in Figure 1. There was no significant effect of gestational age on LF HRV in either the supine or prone position. At 2-3 months CA, HF HRV was lower in very preterm compared to term infants ($p<0.01$) in the supine position and in both the very preterm and preterm groups compared to the term group in the prone position ($p<0.05$ for both). The LF/HF averaged higher in very preterm compared to both the preterm and term groups at 2-3 months CA, reaching statistical significance in the supine position ($p<0.05$ for both). TP HRV was not different between groups in either the supine or prone position.

The effect of gestational age at birth on HRV in AS is shown in Figure 2. The LF/HF ratio was significantly higher in preterm compared to term infants at 2-4 weeks CA ($p<0.05$). There were no other differences in HRV parameters between groups in either sleep position.

Maturation of HRV parameters

The effects of increasing post-term age on HRV indices during QS are presented in Figure 3. LF HRV increased in the supine position in preterm infants between 2-4 weeks and 2-3 months ($p<0.05$) and between 2-4 weeks and 5-6 months ($p<0.001$). In the prone position there was no effect of post-term age. HF HRV increased from 2-4 weeks to 2-3 months CA in all infant groups in both the supine ($p<0.01$ for all) and prone positions ($p<0.05$ for all). However, in very preterm infants this developmental increase was delayed, with the increase in HF HRV starting at a later age of 2-3 months CA. The LF/HF did not change with age in the preterm or term groups in the supine position. In contrast, there was a peak in the LF/HF at 2-3 months CA in very preterm infants, resulting in a sharp decrease between 2-3 months and 5-6 months CA. In the prone position, there was no effect of post-term age on LF/HF in any group. TP HRV increased with age in all infant groups, with a greater increase seen in

the preterm and term groups in the supine position (2-4 weeks versus 5-6 months: very preterm $p<0.05$; preterm $p<0.001$ and term $p<0.01$) and in the term group in the prone position (2-4 weeks versus 5-6 months: very preterm $p<0.01$; preterm $p<0.01$; term $p<0.001$).

Figure 4 shows the effect of post-term age on HRV parameters in AS in the supine and prone positions. LF HRV was not altered by post-term age in either sleep position. HF HRV increased from 2-4 weeks to 5-6 months CA in both very preterm ($p<0.05$) and preterm infants ($p<0.05$) in the supine position and in very preterm infants ($p<0.05$) in the prone position. LF/HF decreased from 2-4 weeks to 5-6 months CA in very preterm ($p<0.05$) and preterm infants ($p<0.05$) in both sleep positions. In term infants, post-term age had no effect on LF/HF in the supine position but LF/HF decreased from 2-4 weeks to 5-6 months in the prone position ($p<0.05$). There was no significant effect of post-term age on TP HRV in any group in either sleep position.

Effect of Sleeping Position

The effect of sleep position on HRV parameters is shown in Table 2. There was no significant effect of sleeping position on LF, HF or TP HRV or LF/HF in either the very preterm or preterm infants in either AS or QS at any age. In contrast, in term infants, LF/HF was higher in the prone position in AS at 2-4 weeks ($p<0.05$). There was no significant effect of sleep position on LF, HF or TP HRV, however LF HRV tended to be lower in the prone position in QS at 2-3 months ($p=0.09$).

Effect of Sleep State

The effect of sleep state on HRV parameters is also shown in Table 2. In very preterm infants LF HRV, LF/HF and TP HRV were higher in AS compared to QS in the prone

position at 2-4 weeks CA ($p<0.05$ for all). There was no effect of sleep state on HRV at 2-3 months or 5-6 months CA in either position.

In preterm infants LF HRV and TP HRV were higher in AS compared to QS in both sleep positions ($p<0.01$) and LF/HF was higher in AS compared to QS in the supine position ($p<0.05$) at 2-4 weeks CA. At 2-3 months, there was an overall effect of sleep state on LF HRV ($p<0.05$), however post-hoc analysis was unable to identify where the difference occurred. At 5-6 months there was no effect of sleep state on HRV.

In term infants LF HRV was higher in AS compared to QS at 2-4 weeks and 2-3 months in both the supine and prone positions ($p<0.05$ for all). LF/HF was higher in AS compared to QS in the prone position at 2-4 weeks ($p<0.01$) and 2-3 months ($p<0.05$) and in the supine position at 5-6 months ($p<0.05$). TP HRV was higher in AS compared to QS in both sleep positions at 2-4 weeks and in the prone position at 2-3 months ($p<0.05$ for all). There was no effect of sleep state on HF HRV at any age or on LF or TP HRV at 5-6 months.

Discussion

This study provides novel data on the effect of gestational age at birth and sleeping position on HRV parameters in preterm infants across the first six months following term-equivalent age. We have shown that HF HRV is lower and LF/HF is higher at 2-3 months post-term in very preterm compared to preterm and term infants. This suggests that autonomic heart rate control is altered in very preterm infants during the developmental period in which the risk of SIDS is maximal. However, contrary to our hypothesis we did not find an effect of prone sleeping on HRV parameters in this cohort of preterm infants even in those infants born at younger gestational ages.

Effect of Gestational Age at Birth

We have demonstrated that preterm birth has long lasting effects on autonomic control of HR, particularly in those infants born very preterm. At 2-3 months CA, HF HRV, reflecting parasympathetic activity, was significantly reduced in very preterm compared to both preterm and term infants. As a result, the LF/HF ratio was elevated in very preterm infants most prominently at 2-3 months CA suggesting altered sympathovagal balance with a predominance of sympathetic activity.

Our findings of significantly reduced HF HRV and elevated LF/HF ratio at 2-3 months CA have significant implications for SIDS. Studies of infants who later succumbed to SIDS have found similar alterations in autonomic control of HR with reduced respiratory sinus arrhythmia,[31] reflecting parasympathetic activity, and elevated LF/HF ratio.[32] Furthermore, our data suggest that the delay in maturation of HF HRV and subsequent alteration in sympathovagal balance in infants born very preterm only becomes significant at 2-3 months CA, coinciding with the period of peak risk for SIDS. This supports Filiano and colleague's Triple Risk Model which suggests that SIDS deaths occur when three elements of risk interact, thus an underlying vulnerability may lay dormant until a critical developmental period is reached and an external stressor is also present.[33] We acknowledge that the period of peak SIDS risk in preterm infants occurs between 7-9 weeks post-term depending on GA at birth,[2] slightly earlier than the peak seen in term infants. Therefore, it is possible that our study underestimates the effect of preterm birth on HRV and deficits in HF HRV in very preterm infants may be greater at a slightly earlier post-term age.

When we looked at the maturational trajectories of HRV across the first 6 months post-term we identified delayed maturation of parasympathetic activity in very preterm infants seems to be most prominent prior to 2-3 months CA. Between 2-3 months and 5-6 months CA HF

HRV follows a similar trajectory to that seen in preterm and term infants, however, although HF HRV activity increases to 5-6 months it remains low in very preterm infants in comparison to the other groups. This may be an indicator of early cardiovascular dysfunction which could predispose infants born preterm to cardiovascular disease in adult life.[34] In adults, reduced HRV has been reported in hypertensive patients[18] and is associated with a significantly increased risk of experiencing a cardiac event.[35]

A number of previous studies in preterm infants carried out prior to term age have also found that maturation of parasympathetic activity is predominantly affected by preterm birth, while sympathetic maturation is relatively maintained.[13,15,17] Our data build on these data and suggests that greater impairment in parasympathetic maturation occurs in infants born very preterm (prior to 32 weeks of gestation). This is likely to be due to differences in the fetal maturation of the sympathetic and parasympathetic branches of the autonomic nervous system. While sympathetic activity is predominant throughout gestation, parasympathetic activity undergoes a period of rapid maturation between 25 and 32 weeks of gestation.[21,36,37] Therefore, very preterm birth, which occurs during this period, and the accompanying stresses of ex-utero life may significantly impact on normal parasympathetic maturation. We have demonstrated that this results in significantly reduced parasympathetic activity and altered sympathovagal balance in healthy infants born very preterm, that persists until at least 2-3 months post-term age.

Effect of Sleep Position and Sleep State

In this study we found no significant effect of prone sleeping on HRV assessed in the frequency-domain in either preterm or very preterm infants studied between 2-4 weeks and 5-6 months post-term CA. In term infants, LF/HF ratio was higher in the prone compared to the supine position at 2-4 weeks in AS. Prone sleeping is well established as a major risk

factor for SIDS[4] and in term infants prone sleeping has been associated with reduced blood pressure[38] and alterations in cardiovascular control.[7,39] However, studies assessing the effect of sleep position on HRV in term infants have produced conflicting results. Gabai et al., found reduced short and long-term HRV in the prone compared to the supine position in term infants assessed within 3 days of birth.[40] Similarly, HRV parameters were found to be reduced in the prone compared to the supine position in term infants studied at up to 4 months of age.[41,42] In contrast, Broadfield et al. found no significant effect of sleep position on HRV in term infants studied at 2-3 months of age.[43] In preterm infants assessed prior to term-equivalent age, prone sleeping was associated with diminished HRV compared to that in the supine position in QS.[44] Another study found prone sleeping particularly affected TP and LF HRV, suggesting diminished sympathetic activity.[8] When assessed at 1 and 3 months CA, only time-domain HRV parameters have been found to be lower in the prone position in QS with no effect of position on frequency-domain HRV parameters.[9] In our study, we also found no effect of prone sleeping on HRV assessed in the frequency-domain in either preterm group, thus any effect of prone sleeping on HRV parameters in preterm infants appears to be maximal prior to term age and improves with age. Similarly, in term infants the effect of prone sleeping was only present at 2-4 weeks and diminished with increasing age.

Sleep state had a significant effect on HRV with elevated LF, LF/HF and TP HRV in AS compared to QS at 2-4 weeks CA, with similar effects seen in both very preterm and preterm infants. This reflects the predominance of sympathetic activity in AS and may also be influenced by greater respiratory variability and more frequent body movements associated with AS.[23,45] Consistent with previous studies in term[23,42] and preterm infants,[9] we found that the effect of sleep state on HRV was maximal at 2-4 weeks CA becoming less marked with increasing age. It is thought that this is due to increasing parasympathetic activity during this

period resulting in a relative reduction in the influence of sympathetic activity on HR during sleep.[45]

Conclusions

We have shown that preterm birth results in impaired maturation of parasympathetic autonomic control of HR, most prominently in those infants born prior to 32 weeks of gestation. This delayed maturation results in significantly altered sympathovagal balance with a predominance of sympathetic activity in very preterm infants at 2-3 months post-term age. Altered autonomic cardiovascular control during the period of peak risk for SIDS may contribute to the increased risk of SIDS seen in infants born at earlier gestational ages; however this does not appear to be exacerbated by prone sleeping.

Acknowledgements

We would like to thank the parents and infants involved in this study and the staff at the Melbourne Children's Sleep Centre.

References

1. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller A-B, Narwal R, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. *The Lancet*. 2012;379(9832):2162-2172.
2. Malloy MH. Prematurity and sudden infant death syndrome: United States 2005-2007. *J Perinatol*. 2013;33(6):470-475.
3. Trachtenberg FL, Haas EA, Kinney HC, Stanley C, Krous HF. Risk Factor Changes for Sudden Infant Death Syndrome After Initiation of Back-to-Sleep Campaign. *Pediatrics*. 2012;129(4):630-638.
4. Task Force on Sudden Infant Death Syndrome. SIDS and Other Sleep-Related Infant Deaths: Expansion of Recommendations for a Safe Infant Sleeping Environment. *Pediatrics*. 2011;128(5):1030-1039.
5. Harper RM. Sudden infant death syndrome: a failure of compensatory cerebellar mechanisms? *Pediatr Res*. 2000;48(2):140-142.
6. Franco P, Groswasser J, Sottiaux M, Broadfield E, Kahn A. Decreased cardiac responses to auditory stimulation during prone sleep. *Pediatrics*. 1996;97(2):174-178.
7. Yiallourou SR, Sands SA, Walker AM, Horne RS. Baroreflex sensitivity during sleep in infants: impact of sleeping position and sleep state. *Sleep*. 2011;34(6):725-732.
8. Jean-Louis M, Anwar M, Rosen H, Craelius W, Hiatt M, Hegyi T. Power spectral analysis of heart rate in relation to sleep position. *Biol Neonate*. 2004;86(2):81-84.
9. Ariagno RL, Mirmiran M, Adams MM, Saporito AG, Dubin AM, Baldwin RB. Effect of position on sleep, heart rate variability, and QT interval in preterm infants at 1 and 3 months' corrected age. *Pediatrics*. 2003;111(3):622-625.
10. Electrophysiology Task Force of the European Society of Cardiology. Heart Rate Variability. *Circulation*. 1996;93(5):1043-1065.
11. Pagani M, Lombardi F, Guzzetti S, Rimoldi O, Furlan R, Pizzinelli P, et al. Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. *Circ Res*. 1986;59(2):178-193.
12. Eiselt M, Curzi-Dascalova L, Clairambault J, Kauffmann F, Medigue C, Peirano P. Heart-rate variability in low-risk prematurely born infants reaching normal term: A comparison with full-term newborns. *Early Hum Dev*. 1993;32(2-3):183-195.
13. Longin E, Gerstner T, Schaible T, Lenz T, Konig S. Maturation of the autonomic nervous system: differences in heart rate variability in premature vs. term infants. *J Perinat Med*. 2006;34(4):303-308.
14. De Rogalski Landrot I, Roche F, Pichot V, Teyssier G, Gaspoz J-M, Barthelemy J-C, et al. Autonomic nervous system activity in premature and full-term infants from theoretical term to 7 years. *Auton Neurosci*. 2007;136(1-2):105-109.
15. Patural H, Barthelemy JC, Pichot V, Mazzocchi C, Teyssier G, Damon G, et al. Birth prematurity determines prolonged autonomic nervous system immaturity. *Clin Auton Res*. 2004;14(6):391-395.
16. Patural H, Pichot V, Jaziri F, Teyssier G, Gaspoz J-M, Roche Fdr, et al. Autonomic cardiac control of very preterm newborns: A prolonged dysfunction. *Early Hum Dev*. 2008;84(10):681-687.
17. Clairambault J, Curzi-Dascalova L, Kauffmann F, Medigue C, Leffler C. Heart rate variability in normal sleeping full-term and preterm neonates. *Early Hum Dev*. 1992;28(2):169-183.

18. Singh JP, Larson MG, Tsuji H, Evans JC, O'Donnell CJ, Levy D. Reduced heart rate variability and new-onset hypertension: insights into pathogenesis of hypertension: the Framingham Heart Study. *Hypertension*. 1998;32(2):293-297.
19. Karin J, Hirsch M, Akselrod S. An estimate of fetal autonomic state by spectral analysis of fetal heart rate fluctuations. *Pediatr Res*. 1993;34(2):134-138.
20. Kimura Y, Okamura K, Yajima A. Spectral Analysis of Beat-to-Beat Intervals of the Fetal Heart Obtained by Doppler Ultrasound. *Gynecol Obstet Invest*. 1996;41(1):5-9.
21. Tsukasa O, Kunihiro O, Yoshitaka K, Toshiaki S, Takanori W, Tomoharu Y, et al. Alteration in the Low-Frequency Domain in Power Spectral Analysisof Feta l Heart Beat Fluctuations. *Fetal Diagn Ther*. 1999;14(2):92-97.
22. Katona PG, Frasz A, Egbert J. Maturation of cardiac control in full-term and preterm infants during sleep. *Early Hum Dev*. 1980;4(2):145-159.
23. Yiallourou SR, Witcombe NB, Sands SA, Walker AM, Horne RS. The development of autonomic cardiovascular control is altered by preterm birth. *Early Hum Dev*. 2013;89(3):145-152.
24. Yiallourou SR, Walker AM, Horne RS. Validation of a new noninvasive method to measure blood pressure and assess baroreflex sensitivity in preterm infants during sleep. *Sleep*. 2006;29(8):1083-1088.
25. Fyfe KL, Yiallourou SR, Wong FY, Odoi A, Walker AM, Horne RS (in press). Cerebral oxygenation in preterm infants. *Pediatrics*. 2014.
26. Witcombe NB, Yiallourou SR, Sands SA, Walker AM, Horne RS. Preterm birth alters the maturation of baroreflex sensitivity in sleeping infants. *Pediatrics*. 2012;129(1):e89-96.
27. Yiallourou SR, Sands SA, Walker AM, Horne RS. Postnatal development of baroreflex sensitivity in infancy. *J Physiol*. 2010;588(Pt 12):2193-2203.
28. Yiallourou SR, Sands SA, Walker AM, Horne RSC. Postnatal development of baroreflex sensitivity in infancy. *The Journal of Physiology*. 2010;588(12):2193-2203.
29. Yiallourou SR, Sands SA, Walker AM, Horne RS. Maturation of heart rate and blood pressure variability during sleep in term-born infants. *Sleep*. 2012;35(2):177-186.
30. Andriessen P, Koolen AM, Berendsen RC, Wijn PF, ten Broeke ED, Oei SG, et al. Cardiovascular fluctuations and transfer function analysis in stable preterm infants. *Pediatr Res*. 2003;53(1):89-97.
31. Kluge KA, Harper RM, Schechtman VL, Wilson AJ, Hoffman HJ, Southall DP. Spectral analysis assessment of respiratory sinus arrhythmia in normal infants and infants who subsequently died of sudden infant death syndrome. *Pediatr Res*. 1988;24(6):677-682.
32. Franco P, Verheulpen D, Valente F, Kelmanson I, de Broca A, Scaillet S, et al. Autonomic responses to sighs in healthy infants and in victims of sudden infant death. *Sleep Med*. 2003;4(6):569-577.
33. Filiano JJ, Kinney HC. A perspective on neuropathologic findings in victims of the sudden infant death syndrome: the triple-risk model. *Biol Neonate*. 1994;65(3-4):194-197.
34. De Boo HA, Harding JE. The developmental origins of adult disease (Barker) hypothesis. *Aust N Z J Obstet Gynaecol*. 2006;46(1):4-14.
35. Tsuji H, Larson MG, Venditti FJ, Manders ES, Evans JC, Feldman CL, et al. Impact of Reduced Heart Rate Variability on Risk for Cardiac Events: The Framingham Heart Study. *Circulation*. 1996;94(11):2850-2855.
36. Schneider U, Schleussner E, Fiedler A, Jaekel S, Liehr M, Haueisen J, et al. Fetal heart rate variability reveals differential dynamics in the intrauterine development of the sympathetic and parasympathetic branches of the autonomic nervous system. *Physiol Meas*. 2009;30(2):215-226.

37. David M, Hirsch M, Karin J, Toledo E, Akselrod S. An estimate of fetal autonomic state by time-frequency analysis of fetal heart rate variability. *J Appl Physiol*. 2007;102(3):1057-1064.
38. Yiallourou SR, Walker AM, Horne RS. Effects of sleeping position on development of infant cardiovascular control. *Arch Dis Child*. 2008;93(10):868-872.
39. Yiallourou SR, Walker AM, Horne RS. Prone sleeping impairs circulatory control during sleep in healthy term infants: implications for SIDS. *Sleep*. 2008;31(8):1139-1146.
40. Gabai N, Cohen A, Mahagney A, Bader D, Tirosh E. Arterial blood flow and autonomic function in full-term infants. *Clin Physiol Funct Imaging*. 2006;26(2):127-131.
41. Galland BC, Reeves G, Taylor BJ, Bolton DP. Sleep position, autonomic function, and arousal. *Archives of Disease in Childhood Fetal & Neonatal Edition*. 1998;78(3):F189-194.
42. Galland BC, Taylor BJ, Bolton DPG, Sayers RM. *Heart rate variability and cardiac reflexes in small for gestational age infants*2006.
43. Broadfield E, Franco P, Groswasser J, Kahn A, Sottiaux M. Decreased cardiac responses to auditory stimulation during prone sleep. *Pediatrics*. 1996;97(2):174+.
44. Adams MM, Ariagno RL, Baldwin RB, Boeddiker MA, Goto K, Longford RV, et al. More Awakenings and Heart Rate Variability During Supine Sleep in Preterm Infants. Pediatrics 1999 1999/03//:603.
45. Harper RM, Hoppenbrouwers T, Sterman MB, McGinty DJ, Hodgman J. Polygraphic studies of normal infants during the first six months of life. I. Heart rate and variability as a function of state. *Pediatr Res*. 1976;10(11):945-948.

Table 1: Characteristics of very preterm, preterm and term infants. Values are mean (SEM) with the exception of Apgar scores which are median (range). Age at study is corrected age for preterm infants.

		Very Preterm N=19	Preterm N=14	Term N=17
Gestation (wk)		29.4 (0.3)*#	33.5 (0.3)^	40.1 (0.3)
Birth Weight (g)		1366 (62)*#	2221 (109)^	3666 (105)
Apgar Score	1min	6 (2-9) *#	8.5 (3-9)	9 (7-9)
	5min	8 (4-9)#	9 (5-9)	9 (9-10)
2-4 Weeks	Age (wk)	3.1 (0.2)	3.2 (0.1)	3.4 (0.1)
	Weight (kg)	3.6 (0.1)	3.9 (0.2)	4.0 (0.1)
2-3 Months	Age (wk)	10.6 (0.1)	10.6 (0.4)	10.6 (0.2)
	Weight (kg)	5.0 (0.2)	5.8 (0.3)	5.2 (0.2)
5-6 Months	Age (wk)	23.0 (0.3)	22.4 (0.4)	22.3 (0.3)
	Weight (kg)	6.9 (0.2)	7.6 (0.4)	7.0 (0.2)

*$p<0.05$ very preterm versus preterm; #$p<0.05$ very preterm versus term; ^$p<0.05$ preterm versus term

Table 2: Effect of sleep state and sleep position on heart rate variability parameters in very preterm, preterm and term infants. Values are mean (SEM).

		LF HRV		HF HRV		LF/HF		Total Power HRV	
		Supine	Prone	Supine	Prone	Supine	Prone	Supine	Prone
Very Preterm									
2-4 wk	QS	227 (53)	147 (31)**	27 (7)	30 (14)	15 (4)	16 (5)*	347 (71)	253 (61)*
	AS	664 (227)	586 (167)	29 (6)	43 (17)	22 (5)	36 (11)	852 (281)	753 (214)
2-3 mo	QS	355 (89)	261 (63)	33 (9)	45 (15)	27 (8)	16 (5)	481 (108)	392 (87)
	AS	411 (95)	386 (103)	30 (11)	37 (14)	19 (4)	22 (7)	566 (148)	548 (157)
5-6 mo	QS	339 (56)	336 (83)	113 (27)	141 (59)	9 (2)	7 (2)	641 (101)	657 (139)
	AS	436 (149)	341 (47)	168 (59)	104 (29)	6 (2)	6 (2)	793 (236)	638 (99)
Preterm									
2-4 wk	QS	121 (34)**	137 (53)**	20 (8)	29 (16)	20 (7)*	12 (3)	190 (50)**	231 (80)**
	AS	554 (166)	591 (194)	25 (14)	23 (6)	39 (10)	38 (11)	680 (193)	761 (233)
2-3 mo	QS	284 (51)	273 (82)	75 (20)	86 (21)	9 (2)	7 (2)	501 (66)	523 (110)
	AS	581 (128)	553 (178)	109 (35)	56 (14)	15 (5)	13 (3)	1021 (211)	786 (237)
5-6 mo	QS	381 (78)	239 (63)	203 (59)	152 (59)	5 (1)	4 (1)	840 (163)	577 (147)
	AS	355 (63)	340 (131)	128 (38)	127 (61)	10 (3)	7 (2)	652 (109)	713 (291)
Term									
2-4 wk	QS	172 (59)*	112 (27)**	70 (30)	41 (18)	8 (2)	10 (3)**	363 (126)*	217 (59)*
	AS	390 (110)	306 (55)	121 (56)	52 (33)	11 (4)†	23 (4)	866 (288)	510 (133)
2-3 mo	QS	292 (51)*	208 (58)***	120 (34)	83 (24)	10 (4)	6 (1)*	595 (131)	407 (105)*
	AS	448 (51)	437 (63)	82 (25)	92 (24)	18 (8)	16 (5)	764 (127)	746 (133)
5-6 mo	QS	414 (87)	307 (60)	70 (71)	214 (55)	4 (1)*	6 (2)	965 (194)	852 (217)
	AS	469 (131)	315 (51)	120 (52)	109 (31)	11 (3)	11 (3)	808 (235)	581 (89)

AS – active sleep; HF – high frequency; HRV – heart rate variability; LF – low frequency; QS – quiet sleep

*p<0.05; **p<0.01 QS versus AS; †<0.05 supine versus prone

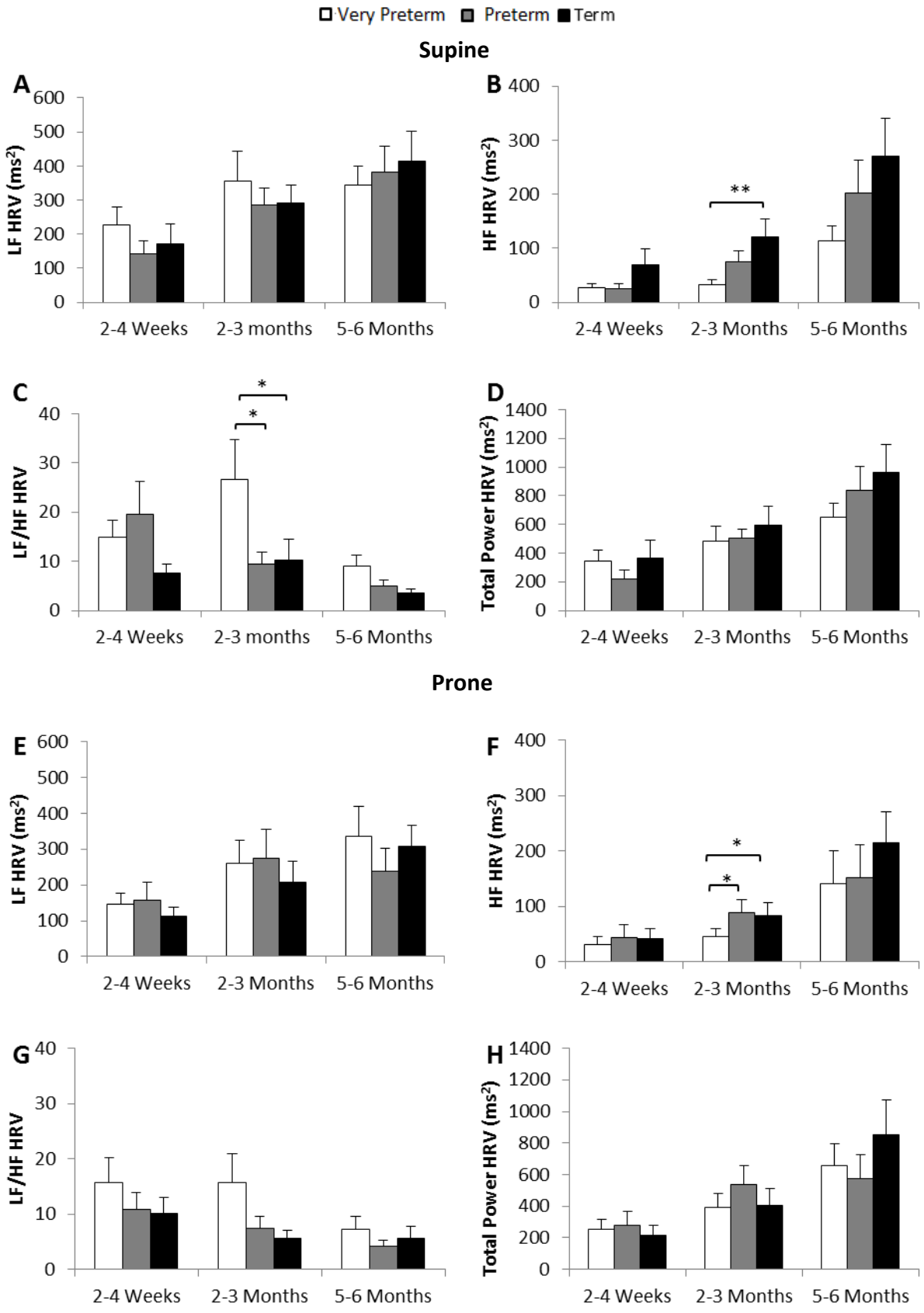


Figure 1: Effect of gestational age on HRV parameters in **quiet sleep** in the supine (A-D) and prone (E-H) positions. Values are mean ± SEM. *p<0.05, **p<0.01, ***p<0.001

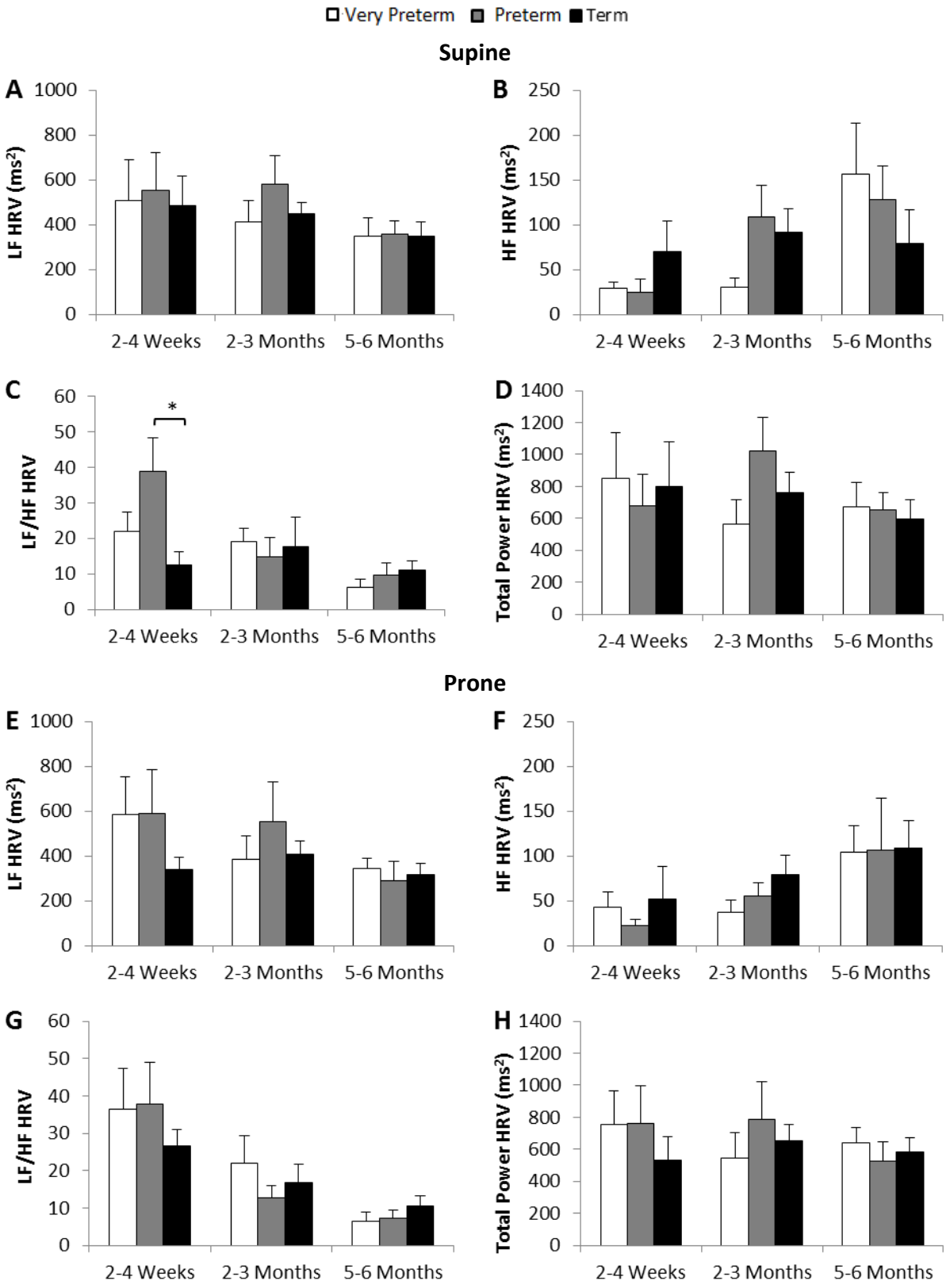


Figure 2: Effect of gestational age on HRV parameters in **active sleep** in the supine (A-D) and prone (E-H) positions. Values are mean ± SEM. *p<0.05

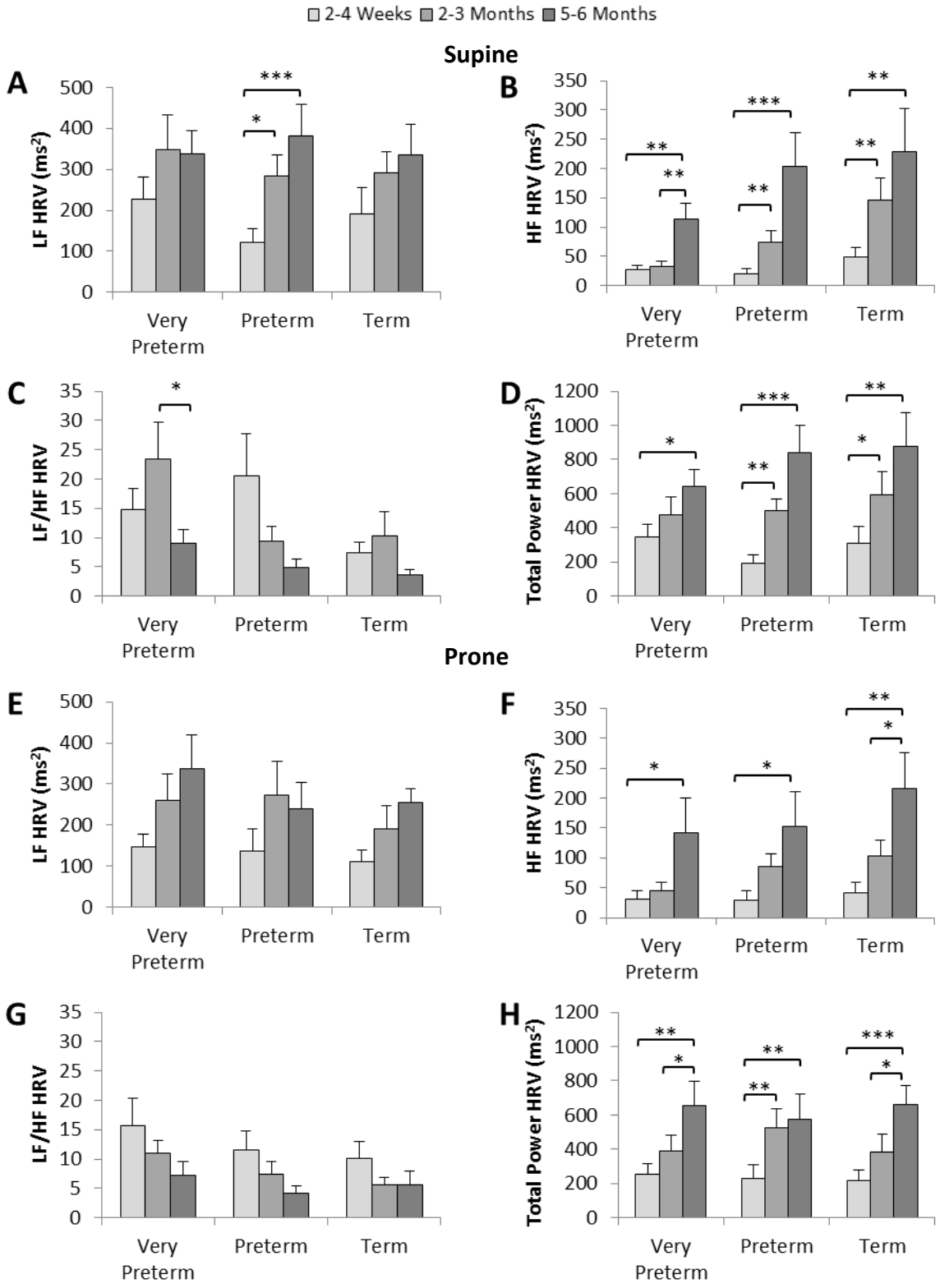


Figure 3: Effect of post-term age on HRV parameters in **quiet sleep** in the supine (A-D) and prone (E-H) positions in infants born very preterm, preterm and term. Values are mean ± SEM. *p<0.05, **p<0.01, ***p<0.001

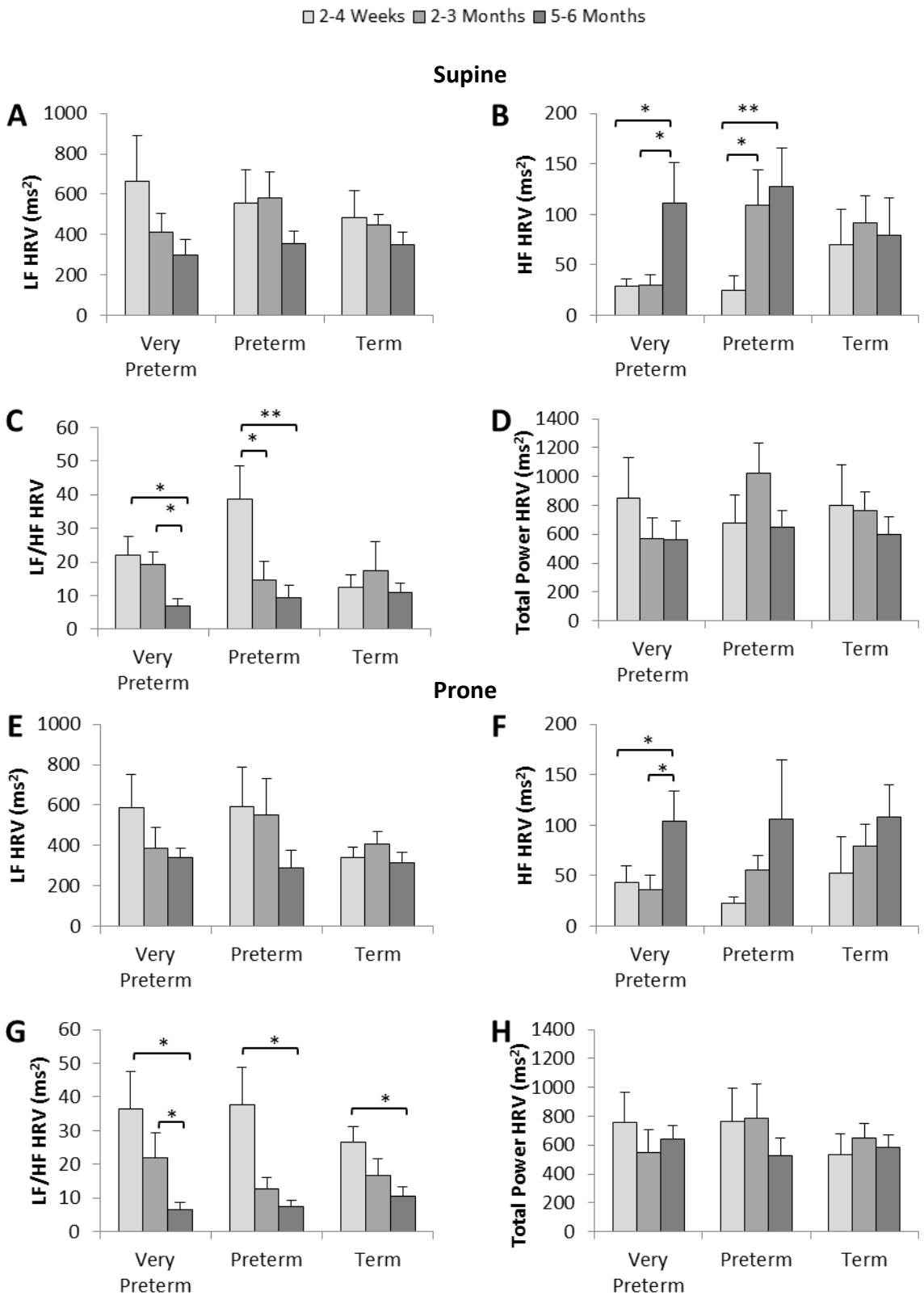


Figure 4: Effect of post-term age on HRV parameters in **active sleep** in the supine (A-D) and prone (E-H) positions in infants born very preterm, preterm and term. Values are mean ± SEM. *p<0.05, **p<0.01

Chapter 7

General Discussion

7 General Discussion

Longitudinal data on the incidence of preterm birth from a range of countries suggests that the rate of preterm birth is increasing (Blencowe et al., 2012) with infants now surviving in greater numbers and at earlier gestational ages (Blencowe et al., 2013). Prematurity is associated with a range of both short and long-term consequences (Saigal and Doyle, 2008) including an increased risk of the Sudden Infant Death Syndrome (SIDS) (Blair et al., 2006a, Malloy, 2013).

It is currently thought that SIDS occurs due to the combination of an uncompensated cardiorespiratory event during sleep and a failure of the life-saving arousal response (Harper, 2000). In support of this, studies have found both impaired arousal (Kato et al., 2003) and altered cardiovascular control (Schechtman et al., 1989) in infants who went on to die from SIDS. SIDS occurs almost exclusively in the first six months of life with a peak in incidence between 2-3 months of age in term infants (Task Force on Sudden Infant Death Syndrome, 2011). In preterm infants, SIDS occurs at a later post-natal age but a similar post-term age of approximately 7-9 weeks, depending on gestational age at birth (Malloy, 2013). This suggests that 2-3 months post-term is a critical developmental period during which infants are more vulnerable to SIDS. Previous studies have provided evidence suggesting cardiovascular control (Yiallourou et al., 2008b, Yiallourou et al., 2008a, Yiallourou et al., 2011) and arousal (Horne et al., 2001) are impaired during this period in term infants .

Through extensive epidemiological studies, it has been identified that prone sleeping is a major risk factor for SIDS (Irgens et al., 1995, Mitchell et al., 1991, Engelberts et al., 1991), particularly amongst infants born preterm (Oyen et al., 1997, Trachtenberg et al., 2012). In healthy term infants, prone sleeping is associated with reduced blood pressure (BP) (Yiallourou et al., 2008a, Chong et al., 2000) and altered cardiovascular control (Yiallourou et al., 2008b, Yiallourou et al., 2011) during the period of peak risk for SIDS. In addition to these cardiovascular effects, prone sleeping has been associated with impaired arousal (Horne et al., 2001), reduced cerebral oxygenation (Wong et al., 2011) and altered cerebrovascular control (Wong et al., 2013) in healthy term born infants. Our group

has previously suggested that impaired cerebral oxygenation may contribute to impaired arousal which plays a causal role in the final pathway of SIDS (Wong et al., 2011).

Despite the increased incidence of SIDS in preterm infants, to date the effects of prone sleeping on cardiovascular and cerebrovascular regulation have not been studied across the first 6 months after term-equivalent age when infants are most vulnerable to SIDS. To address these deficits in the literature, this thesis aimed to elucidate the effects of prone sleeping and preterm birth on cerebral oxygenation during sleep across the first six months post-term (Chapter 3). We also aimed to investigate cerebrovascular control (Chapter 4) as well as cardiovascular control assessed by baroreflex sensitivity (BRS) (Chapter 5) and heart rate variability (HRV) (Chapter 6) during sleep in the prone position in preterm infants. By recruiting infants across a wide range of gestational ages we also aimed to examine the effects of gestational age at birth on these variables during sleep across the first 6 months post-term, when the majority of infants die from SIDS.

7.1 Effects of Prone Sleeping on Cerebral Oxygenation, Cerebrovascular Control and Cardiovascular Control in Preterm Infants

Chapter 3 of this thesis established that cerebral oxygenation is reduced in the prone compared to the supine sleeping position until at least 5-6 months post-term corrected age (CA) in preterm infants. These findings are supported by previous observations in term infants studied at similar post-conceptional ages (Wong et al., 2011) and in preterm infants studied prior to term age (Bembich et al., 2012), which have also found significant perturbations in cerebral oxygenation in the prone sleeping position. It has been suggested that reduced cerebral oxygenation in the prone position occurs as a result of impaired cerebral blood flow due to positional occlusion of the vessels supplying the brain and in particular, the brain stem (Wong et al., 2011). In support of this idea, post-mortem studies in infants who died from SIDS (Pamphlett et al., 1999, Saternus and Adam, 1985) and Doppler flow studies in preterm infants (Eichler et al., 2001) have found that extension and rotation of the neck, as seen in the prone position, is associated with vertebral artery compression and impaired blood flow due to anatomical characteristics of the immature infant which appear to be maximal at 1 month post-term age in preterm infants (Eichler et al., 2001).

Given that cerebral oxygenation is reduced in the prone position in preterm infants after term-equivalent age we hypothesised that cerebrovascular control would also be altered in the prone position. Preterm infants have been reported to have immature cerebrovascular control prior to term age (Brew et al., 2014), with evidence to suggest that both cerebral autoregulation (Wong et al., 2008, Boylan et al., 2000, Soul et al., 2007, Tsuji et al., 2000) and cerebral blood flow-metabolism coupling (Wong et al., 2009a, Arichi et al., 2012) are immature following preterm birth. This study has shown that cerebral oxygenation is well controlled in the supine position, remaining unchanged despite a surge in BP. In contrast, in the prone position in quiet sleep at 5-6 months and in active sleep at all three ages, cerebral oxygenation increased following a head-up positional change, with the observed increase in cerebral oxygenation actually preceding any increase in BP. Due to this temporal relationship, we suggest that changes in cerebral oxygenation in the prone position occur due to a vestibular-mediated increase in cerebral blood flow. This may be a mechanism to protect against critically reduced cerebral oxygenation in the prone position where cerebral oxygenation is already low, a finding which has also been shown in term infants (Wong et al., 2011, Wong et al., 2013). Thus failure of the expected increase in cerebral oxygenation in the prone position at 2-4 weeks and 2-3 months CA in quiet sleep suggests that preterm infants are at risk of impaired cerebral oxygenation during this period.

We found that impairment in baseline cerebral oxygenation in the prone position is maximal at 2-3 months CA, particularly in quiet sleep, coinciding with altered arousal responses in preterm infants sleeping prone during this period, particularly in quiet sleep (Richardson and Horne, 2013). We suggest that impaired cerebral blood flow is exacerbated by an altered systemic cardiovascular response to prone sleeping at 2-3 months CA. In preterm infants at 2-4 weeks and 5-6 months CA we reported an increase in HR in the prone position, which maintained BP despite increased skin temperature which suggests peripheral vasodilation. In contrast, at 2-3 months CA HR did not increase in the prone sleep position coinciding with a tendency for BP to be reduced, suggesting that cardiovascular control is altered at this age. In Chapter 5 of this thesis we assessed cardiovascular control via the baroreflex, however, we found no effect of prone sleeping on BRS at 2-3 months CA

suggesting impaired BRS does not underlie the cardiovascular differences seen in the prone position at 2-3 months CA. Furthermore, in Chapter 6 we identified that prone sleeping had no significant effect on HRV parameters at 2-3 months CA again failing to explain our observations. Alternatively, reduced HR and BP could be indicative of reduced cardiac output in the prone position, which has previously been shown in both children (Brown et al., 2013) and adults (Yokoyama et al., 1991), possibly due to increased intra-thoracic pressure leading to reducing atrial filling and reduced stroke volume (Brown et al., 2013). Our study did not permit assessment of cardiac output, nor has the influence of prone sleeping on cardiac output in preterm infants been previously studied, this idea warrants further investigation in the future.

7.2 Effects of Preterm Birth on Cerebral Oxygenation, Cerebrovascular Control and Cardiovascular Control

This study has identified that cerebral oxygenation is diminished in preterm compared to term infants across the first six months post-term which could be due to a mismatch between cerebral oxygen delivery and consumption. At term-equivalent age, healthy preterm infant brains have reduced white matter volumes (Mewes et al., 2006) with immature neural networks (Bassi et al., 2008, Smyser et al., 2010) compared to term-newborn brains suggesting that preterm birth results in delayed brain maturation prior to term age (Inder et al., 2005). Whilst there has been little examination of cerebral growth and changes in cerebral oxygen consumption beyond term-equivalent age in preterm infants, it could be that the preterm infant brain undergoes significant catch-up growth during the early post-term period resulting in an increased cerebral demand for oxygen.

The normal mechanism by which increased cerebral metabolic demand for oxygen is met is cerebral blood flow (CBF)-metabolism coupling. In preterm infants prior to term age, CBF-metabolism coupling appears to be immature with the haemodynamic response being both inadequate (Wong et al., 2009a), failing to meet the metabolic demands of active neural tissue, and delayed due to immaturity of the cerebral vasculature (Roche-Labarbe et al., 2014, Arichi et al., 2012). As a result, the increased demand for oxygen is met via increased oxygen extraction and thus an overall reduction in cerebral oxygenation. Although there has been little investigation of CBF-metabolism coupling in preterm

infants beyond term-equivalent age it could be that immaturity of CBF-metabolism coupling persists beyond term-equivalent age, contributing to reduced cerebral oxygenation in preterm compared to term infants. Furthermore, anaemia during infancy is more severe in preterm compared to term infants (Strauss, 2010) and the associated reduction in blood oxygen carrying capacity could result in decreased cerebral oxygenation due to increased cerebral oxygen extraction (van Hoften et al., 2010). However, both of these theories require further investigation in preterm infants beyond term-equivalent age.

Whilst overall deficits in cerebral oxygenation in preterm compared to term infants improved with age, the greatest deficit (~ 10 percentage points) was seen at 2-3 months CA in the prone sleep position. Notably, this coincides with a reduction in both BP and HR in preterm compared to term infants in the prone sleep position at 2-3 months post-term age suggesting that deficits in cerebral oxygen delivery in preterm infants may be exacerbated by reduced BP. Cerebral autoregulation is known to be impaired in preterm infants prior to term age, particularly in infants born at earlier gestation (Wong et al., 2008, Soul et al., 2007, Tsuji et al., 2000, Boylan et al., 2000). Beyond term-equivalent age, our data suggest that cerebral autoregulation functions similarly between preterm and term infants. However, greater variability in the response of cerebral oxygenation to a positional change in infants born preterm may represent persistent immaturity and could contribute to reduced cerebral oxygenation in preterm compared to term infants.

The deficit in HR and BP seen in preterm compared to term infants in the prone sleep position at 2-3 months CA is intriguing, as we found no difference in BRS between very preterm, preterm or term infants in either the supine or prone sleep positions during this period. This suggests that the observed alterations in HR and BP between term and preterm infants are unlikely to be due to deficits in autonomic control of BP. However, consistent with previous findings in the supine position (Yiallourou et al., 2013), we found reduced HF HRV and elevated LF/HF ratio in preterm compared to term infants at 2-3 months CA, most prominently in those infants born very preterm. In the prone position, there was no significant peak in the LF/HF ratio at 2-3 months post-term age in very preterm infants. It may be that the predominance of sympathetic activity in the supine position in very

preterm infants at 2-3 months CA is maintaining HR and BP at similar levels to term infants, thus in the prone position where sympathetic activity is less dominant, HR and BP are reduced in preterm compared to term infants. However, this theory is incomplete as the differences observed in HRV are predominantly in infants born very preterm, suggesting greater impairment in infants born at earlier gestational ages. In contrast, BP was reduced regardless of gestational age at birth. Therefore, whilst alterations in autonomic control of HR may play a role in the observed differences in BP and HR between term and preterm infants, other factors are likely to also contribute. These may include factors affecting cardiac output such as cardiac contractility or ventricular diastolic filling; however, these are beyond the scope of this thesis.

7.3 Effects of Gestational Age at Birth on Cerebral Oxygenation, Cerebrovascular Control and Cardiovascular Control

Reduced gestational age at birth is associated with a greater risk of complications following preterm birth (Saigal and Doyle, 2008) and also a greater risk of SIDS (Malloy, 2013). However, in this study we did not demonstrate an effect of gestational age at birth on cerebral oxygenation or cerebrovascular control. MRI studies assessing brain maturation following preterm birth have found strong associations between cerebral injury such as intraventricular haemorrhage and altered brain maturation at term-equivalent age (Inder et al., 2005). However, studies in healthy preterm infants have reported no correlation between gestational age at birth and total maturation score at term-equivalent age suggesting that in the absence of cerebral pathology brain maturation is relatively preserved in infants born at earlier gestation (Natalucci et al., 2013).

In contrast, gestational age at birth did have significant effects on maturation of cardiovascular control, with delayed maturation seen particularly in infants born very preterm. Of note, HF HRV was reduced in very preterm (<32 weeks) compared to term infants at 2-3 months CA in both sleep positions and this resulted in altered sympathovagal balance most markedly at 2-3 months CA. This is consistent with previous findings (Patural et al., 2008) and likely to be due to interruption of the normal vagal maturation that occurs between 25 and 32 weeks gestation (Schneider et al., 2009). We also found that gestational age at birth influences the post-term maturation of BRS. In very preterm

infants BRS failed to increase between 2-4 weeks and 5-6 months CA in comparison to preterm and term infants in whom BRS increased during this period. Altered post-term maturation of BRS may also occur due to delayed parasympathetic maturation in very preterm infants.

7.4 Implications

This thesis has identified a significant effect of both preterm birth and prone sleeping on cerebral oxygenation and cerebrovascular control, which may play an important role in the pathophysiology of SIDS. It could be that reduced baseline cerebral oxygenation in preterm compared to term infants, coupled with a further reduction in the prone position represents a reduced functional reserve for cerebral oxygenation in these infants. This may place preterm infants at risk of critically impaired cerebral oxygenation during a cardiorespiratory event during sleep (Figure 28). Furthermore, reduced cerebral oxygenation may contribute to blunted arousal responses that have been reported in preterm infants sleeping prone at 2-3 months CA (Richardson and Horne, 2013) and that ultimately result in a SIDS death (Kato et al., 2003). Our results are also suggestive of altered cardiovascular control in preterm infants, particularly those born at earlier gestational ages which may increase the risk of an uncompensated cardiovascular event occurring during sleep.

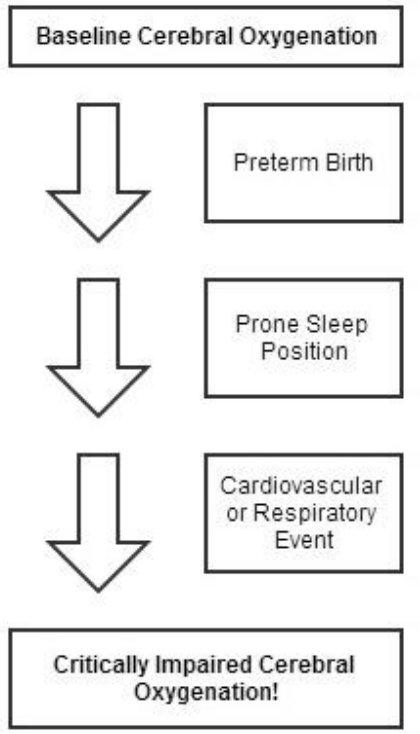


Figure 28: Implications for SIDS. Reduced baseline cerebral oxygenation in preterm compared to term infants and a further reduction in the prone position represents a reduced functional reserve for cerebral oxygenation in preterm infants. Preterm infants may be at risk of critically impaired cerebral oxygenation during a cardiovascular event during sleep.

It remains unknown in which of the two infant sleep states SIDS deaths occur. This thesis has identified greater deficits in cerebral oxygenation and cerebrovascular control in quiet sleep compared to active sleep in the prone position. Furthermore, delayed maturation of BRS and HRV is seen predominantly in quiet sleep. In combination with the knowledge that quiet sleep is associated with fewer spontaneous arousals, higher arousal thresholds (Horne et al., 2002) and incomplete arousal processes at 2-3 months CA in preterm infants (Richardson and Horne, 2013), it could be inferred that it may be quiet sleep in the prone position that poses the greatest risk to sleeping preterm infants.

Furthermore, the alterations reported in this thesis in maturation of autonomic cardiovascular control in infants born very preterm may have significant implications for their long-term cardiovascular function. Reduced parasympathetic activity and baroreflex function have been implicated in a range of cardiovascular diseases, particularly hypertension (Singh et al., 1998) for which preterm birth is a significant risk factor (Parkinson et al., 2013, Bonamy et al., 2012, Dalziel et al., 2007). It may be

that alterations in sympathovagal balance and autonomic control of BP present in infancy contribute to the development of cardiovascular disease later in life.

7.5 Methodological Considerations

To our knowledge, this is the first study to continuously measure cerebral oxygenation using near-infrared spectroscopy during sleep in preterm infants beyond term-equivalent age. Furthermore, concurrent measurement of blood pressuring using a photoplethysmographic cuff enabled investigation of the interaction between systemic and cerebral haemodynamics. Collection of data in both the supine and prone sleep positions and in both sleep states has enabled the presentation of an in depth description of the influences on cerebral and cardiovascular control during sleep in preterm infants. The longitudinal study design has permitted examination of the effects of preterm birth and of gestational age at birth on maturation of cerebral and cardiovascular control. Furthermore, studying infants from a range of gestational ages and excluding any infants with additional medical conditions that could have altered physiology enabled examination of the effects of earlier gestational age at birth, un-confounded by significant differences in medical history. Similarly, exclusion of infants with additional risk factors for SIDS enabled isolation of the effect of preterm birth on physiology in the context of SIDS risk.

7.6 Limitations

The original design for this study was to include three groups of 20 preterm infants according to gestational age at birth; 24-28 weeks gestation, 28-32 weeks gestation and 32-36 weeks gestation. This sample size was generated by the performance of a power calculation. However, it soon became clear that recruiting healthy infants born prior to 28 weeks of gestation was challenging. Many of these infants were excluded due to significant brain or lung injury or a protracted hospital stay extending beyond term-equivalent age. As a result, we reconsidered our three group design and instead recruited infants across a range of gestational ages. The final sample size generated, whilst adequate, was limited by time constraints associated with completion of the project within the timeframe allocated by the MBBS/PhD program. Infants were later divided into very preterm (<32

weeks gestation) or preterm (32-36weeks gestation) only if an effect of gestational age was seen on linear regression.

7.7 Future Directions

In order to elucidate the pathways involve in SIDS a number of areas require future research. These include the association between cerebral oxygenation and arousal. We have suggested that reduced cerebral oxygenation underpins reduced arousal seen in the prone sleeping position and believed to be involved in the final pathway of SIDS. The relationship between cerebral oxygenation and arousal has not been studied previously and this knowledge would greatly benefit our understanding of the pathophysiology of SIDS. As would measurement of haemoglobin concentrations, performance of echocardiography to assess cardiac output and function as well as functional neuroimaging to assess cerebral blood flow-metabolism coupling in preterm and term infants beyond term-equivalent age. Furthermore, there is still a paucity of data investigating the mechanisms by which protective factors, including breastfeeding and the use of a dummy or pacifier, infer a reduced risk of SIDS, particularly amongst infants born preterm. Further research investigating the effects of breast feeding and pacifier use on cerebral oxygenation and cardiovascular control in preterm infants would be of benefit, potentially providing further evidence to promote these as safe sleeping practices. In our study we actively excluded any infant with intrauterine growth restriction as these infants are known to be at greater risk for SIDS and of developing cardiovascular disease later in life. It would be of interest to see if greater deficits in cerebral oxygenation, cerebrovascular and cardiovascular control are seen in infants with a history of intrauterine growth restriction.

Whilst conducting the studies for this PhD thesis, we also identified that a number of our preterm infants exhibited periodic breathing, occasionally accompanied by significant fluctuations in oxygen saturation and cardiovascular parameters. This has prompted further investigation, with plans to study the effects of periodic breathing on cerebral oxygenation and BP in preterm infants both before and after discharge from the neonatal intensive care unit.

7.8 Overall Summary

In summary in this thesis, we have shown that in preterm infants, prone sleeping is associated with significantly reduced cerebral oxygenation which persists until at least 5-6 months CA and is maximal at 2-3 months CA. Whilst the primary reason for this reduction in cerebral oxygenation is likely to be anatomical immaturity leading to compression of the vessels supplying the brain in the prone sleeping position, this does not explain why the difference is maximal at 2-3 months CA. Instead, alterations in systemic cardiovascular control resulting in reduced BP and HR may exacerbate impaired cerebral blood flow. However, when the effect of prone sleeping on autonomic measures of cardiovascular control was assessed we found no effect of prone sleeping on autonomic control of either BP or HR. It is possible that reduced HR and BP may be due to reduced cardiac output during this period, although this requires further investigation.

This thesis has also shown that preterm birth is associated with significantly reduced cerebral oxygenation compared to term infants which it is suggested is due to a mismatch between cerebral oxygen delivery and consumption in preterm infants. Overall, cerebrovascular control is similar between term and preterm infants however greater variability in preterm infants suggests immaturity of cerebrovascular control persists beyond term-equivalent age in preterm infants. Greatest deficits in cerebral oxygenation between term and preterm infants were seen at 2-3 months post-term age in the prone position, possibly due to a concurrent reduction in BP and HR. While altered sympathovagal balance in preterm infants in the prone position may contribute to this difference in cardiovascular parameters, the exact mechanisms remain unclear and require further investigation.

Finally, gestational age at birth does not appear to influence cerebral oxygenation or cerebrovascular control when infants were studied after term-equivalent age, suggesting that in the absence of intracranial pathology earlier gestational age does not increase the deleterious effects of preterm birth on cerebral oxygenation. In contrast, impaired maturation of cardiovascular control following preterm birth primarily affects those infants born before 32 weeks of gestation, possibly due to interruption of parasympathetic maturation which normally undergoes a period of rapid development between 25 and 32 weeks of gestation (Schneider et al., 2009).

7.9 Conclusions

Prematurity is increasing in incidence with increasing survival rates, particularly amongst infants born very preterm (Blencowe et al., 2012, Horbar et al., 2012). Infants born preterm are at risk of a wide range of short and long-term complications including an increased risk of SIDS (Trachtenberg et al., 2012, Malloy, 2013) in infancy and of cardiovascular disease, particularly hypertension (Parkinson et al., 2013), later in life. Both morbidities may be due to impaired control of both the cerebral (Wong et al., 2009a, Wong et al., 2008, Soul et al., 2007, Tsuji et al., 2000, Boylan et al., 2000) and systemic (Patural et al., 2004, Patural et al., 2008, Clairambault et al., 1992) vascular beds which has been shown in infants born preterm. In this thesis the influence of prone sleeping and preterm birth was assessed on cerebral oxygenation, cerebrovascular control and systemic cardiovascular control between 2-4 weeks and 5-6 months post-term age. Reduced cerebral oxygenation and altered cerebrovascular control in the prone position and in preterm compared to term infants may contribute to the increased risk of SIDS seen in infants born preterm. Furthermore, altered maturation of cardiovascular control in infants born very preterm may underlie the increased risk of cardiovascular disease in adulthood seen in survivors of preterm birth.

8 References

AN, H. & LIN, W. 2002. Cerebral venous and arterial blood volumes can be estimated separately in humans using magnetic resonance imaging. *Magnetic Resonance in Medicine,* 48**,** 583-588.

ANANTH, C. V., VINTZILEOS, A. M., ANANTH, C. V. & VINTZILEOS, A. M. 2006. Epidemiology of preterm birth and its clinical subtypes. *Journal of Maternal-Fetal & Neonatal Medicine,* 19**,** 773-82.

ANDRIESSEN, P., KOOLEN, A. M., BERENDSEN, R. C., WIJN, P. F., TEN BROEKE, E. D., OEI, S. G. & BLANCO, C. E. 2003. Cardiovascular fluctuations and transfer function analysis in stable preterm infants. *Pediatric Research,* 53**,** 89-97.

ANDRIESSEN, P., OETOMO, S. B., PETERS, C., VERMEULEN, B., WIJN, P. F. F. & BLANCO, C. E. 2005. Baroreceptor reflex sensitivity in human neonates: the effect of postmenstrual age. *The Journal of Physiology,* 568**,** 333-341.

ANDRIESSEN, P., SCHOFFELEN, R. L., BERENDSEN, R. C., DE BEER, N. A., OEI, S. G., WIJN, P. F. & BLANCO, C. E. 2004. Noninvasive assessment of blood pressure variability in preterm infants. *Pediatric Research,* 55**,** 220-3.

ARDURA, J., ANDRÉS, J., ALDANA, J. & REVILLA, M. A. 1995. Development of sleep–wakefulness rhythm in premature babies. *Acta Pædiatrica,* 84**,** 484-489.

ARIAGNO, R. L., VAN LIEMPT, S. & MIRMIRAN, M. 2006. Fewer spontaneous arousals during prone sleep in preterm infants at 1 and 3 months corrected age. *Journal of Perinatology,* 26**,** 306-312.

ARICHI, T., FAGIOLO, G., VARELA, M., MELENDEZ-CALDERON, A., ALLIEVI, A., MERCHANT, N., TUSOR, N., COUNSELL, S. J., BURDET, E., BECKMANN, C. F. & EDWARDS, A. D. 2012. Development of BOLD signal hemodynamic responses in the human brain. *Neuroimage,* 63**,** 663-73.

BACK, S. A., GAN, X., LI, Y., ROSENBERG, P. A. & VOLPE, J. J. 1998. Maturation-dependent vulnerability of oligodendrocytes to oxidative stress-induced death caused by glutathione depletion. *Journal of Neuroscience,* 18**,** 6241-53.

BALAIN, M. & ODDIE, S. 2014. Management of apnoea and bradycardia in the newborn. *Paediatrics and Child Health (United Kingdom),* 24**,** 17-22.

BASSI, L., RICCI, D., VOLZONE, A., ALLSOP, J. M., SRINIVASAN, L., PAI, A., RIBES, C., RAMENGHI, L. A., MERCURI, E., MOSCA, F., EDWARDS, A. D., COWAN, F. M., RUTHERFORD, M. A. & COUNSELL, S. J. 2008. Probabilistic diffusion tractography of the optic radiations and visual function in preterm infants at term equivalent age. *Brain,* 131**,** 573-82.

BECK, S., WOJDYLA, D., SAY, L., BETRAN, A. P., MERIALDI, M., REQUEJO, J. H., RUBENS, C., MENON, R. & LOOK, P. F. V. 2010. The worlwide incidence of preterm birth: a systematic review of maternal mortality and morbidity. *Bulletin of the World Health Organization,* 88**,** 31-38.

BEMBICH, S., ORETTI, C., TRAVAN, L., CLARICI, A., MASSACCESI, S. & DEMARINI, S. 2012. Effects of Prone and Supine Position on Cerebral Blood Flow in Preterm Infants. *The Journal of Pediatrics,* 160**,** 162-164.

BERGER, R., GARNIER, Y., JENSEN, A., BERGER, R., GARNIER, Y. & JENSEN, A. 2002. Perinatal brain damage: underlying mechanisms and neuroprotective strategies. *Journal of the Society for Gynecologic Investigation,* 9**,** 319-28.

BERTINIERI, G., DI RIENZO, M., CAVALLAZZI, A., FERRARI, A. U., PEDOTTI, A. & MANCIA, G. 1988. Evaluation of baroreceptor reflex by blood pressure monitoring in unanesthetized cats.[Erratum appears in Am J Physiol 1988 Sep;255(3 Pt 2):following H405]. *American Journal of Physiology,* 254**,** H377-83.

BHAT, R. Y., HANNAM, S., PRESSLER, R., RAFFERTY, G. F., PEACOCK, J. L., GREENOUGH, A., BHAT, R. Y., HANNAM, S., PRESSLER, R., RAFFERTY, G. F., PEACOCK, J. L. & GREENOUGH, A. 2006. Effect of prone and supine position on sleep, apneas, and arousal in preterm infants. *Pediatrics,* 118**,** 101-7.

BIONDO, B., LAVEZZI, A., TOSI, D., TURCONI, P., MATTURRI, L., BIONDO, B., LAVEZZI, A., TOSI, D., TURCONI, P. & MATTURRI, L. 2003. Delayed neuronal maturation of the medullary arcuate nucleus in sudden infant death syndrome. *Acta Neuropathologica,* 106**,** 545-51.

BLAIR, P. S., FLEMING, P. J., SMITH, I. J., PLATT, M. W., YOUNG, J., NADIN, P., BERRY, P. J. & GOLDING, J. 1999. Babies sleeping with parents: case-control study of factors influencing the risk of the sudden infant death syndrome. CESDI SUDI research group. *BMJ,* 319**,** 1457-61.

BLAIR, P. S., PLATT, M. W., SMITH, I. J., FLEMING, P. J., GROUP, C. S. R. & PLATT, M. W. 2006a. Sudden infant death syndrome and sleeping position in pre-term and low birth weight infants: an opportunity for targeted intervention. *Archives of Disease in Childhood,* 91**,** 101-6.

BLAIR, P. S., WARD PLATT, M., SMITH, I. J. & FLEMING, P. J. 2006b. Sudden infant death syndrome and sleeping position in pre-term and low birth weight infants: an opportunity for targeted intervention. *Archives of Disease in Childhood,* 91**,** 101-106.

BLENCOWE, H., COUSENS, S., OESTERGAARD, M. Z., CHOU, D., MOLLER, A.-B., NARWAL, R., ADLER, A., VERA GARCIA, C., ROHDE, S., SAY, L. & LAWN, J. E. 2012. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. *The Lancet,* 379**,** 2162-2172.

BLENCOWE, H., LEE, A. C., COUSENS, S., BAHALIM, A., NARWAL, R., ZHONG, N., CHOU, D., SAY, L., MODI, N., KATZ, J., VOS, T., MARLOW, N. & LAWN, J. E. 2013. Preterm birth-associated neurodevelopmental impairment estimates at regional and global levels for 2010. *Pediatr Res,* 74 Suppl 1**,** 17-34.

BLONDEL, B., MACFARLANE, A., GISSLER, M., BREART, G., ZEITLIN, J. & GROUP, P. S. 2006. Preterm birth and multiple pregnancy in European countries participating in the PERISTAT project. *BJOG: An International Journal of Obstetrics & Gynaecology,* 113**,** 528-35.

BOLTON, D. P., TAYLOR, B. J., CAMPBELL, A. J., GALLAND, B. C. & CRESSWELL, C. 1993. Rebreathing expired gases from bedding: a cause of cot death? *Archives of Disease in Childhood,* 69**,** 187-90.

BONAMY, A. K., KALLEN, K., NORMAN, M., BONAMY, A.-K. E., KALLEN, K. & NORMAN, M. 2012. High blood pressure in 2.5-year-old children born extremely preterm. *Pediatrics,* 129**,** e1199-204.

BORST, C., WIELING, W., VAN BREDERODE, J. F., HOND, A., DE RIJK, L. G. & DUNNING, A. J. 1982. Mechanisms of initial heart rate response to postural change. *American Journal of Physiology,* 243**,** H676-81.

BOWEN, P. & MAXWELL, N. C. 2014. Management of bronchopulmonary dysplasia. *Paediatrics and Child Health (United Kingdom),* 24**,** 27-35.

BOYLAN, G. B., PANERAI, R. B., RENNIE, J. M., EVANS, D. H., RABE-HESKETH, S. & BINNIE, C. D. 1999. Cerebral blood flow velocity during neonatal seizures. *Archives of Disease in Childhood - Fetal and Neonatal Edition,* 80**,** F105-F110.

BOYLAN, G. B., YOUNG, K., PANERAI, R. B., RENNIE, J. M. & EVANS, D. H. 2000. Dynamic cerebral autoregulation in sick newborn infants. *Pediatric Research,* 48**,** 12-7.

BREW, N., WALKER, D. & WONG, F. Y. 2014. Cerebral Vascular Regulation and Brain Injury in Preterm Infants. *Am J Physiol Regul Integr Comp Physiol*.

BROWN, Z. E., GÖRGES, M., COOKE, E., MALHERBE, S., DUMONT, G. A. & ANSERMINO, J. M. 2013. Changes in cardiac index and blood pressure on positioning children prone for scoliosis surgery. *Anaesthesia,* 68**,** 742-746.

BRUCKLACHER, R. M., HEITJAN, D. F., TOWFIGHI, J. & VANNUCCI, R. C. 1995. Carbon dioxide protects the perinatal brain from hypoxic-ischemic damage: an experimental study in the immature rat.

CAICEDO, A., DE SMET, D., VANDERHAEGEN, J., NAULAERS, G., WOLF, M., LEMMERS, P., VAN BEL, F., AMEYE, L., VAN HUFFEL, S., CAICEDO, A., DE SMET, D., VANDERHAEGEN, J., NAULAERS, G., WOLF, M., LEMMERS, P., VAN BEL, F., AMEYE, L. & VAN HUFFEL, S. 2011. Impaired cerebral

autoregulation using near-infrared spectroscopy and its relation to clinical outcomes in premature infants. *Advances in Experimental Medicine & Biology,* 701**,** 233-9.
CARPENTER, R. G., IRGENS, L. M., BLAIR, P. S., ENGLAND, P. D., FLEMING, P., HUBER, J., JORCH, G. & SCHREUDER, P. 2004. Sudden unexplained infant death in 20 regions in Europe: case control study. *The Lancet,* 363**,** 185-191.
CARTER, J. R. & RAY, C. A. 2008. Sympathetic responses to vestibular activation in humans. *Am J Physiol Regul Integr Comp Physiol,* 294**,** R681-8.
CHAE, K. Y. 2007. Physiology of sleep. *Korean Journal of Pediatrics,* 50**,** 711-717.
CHONG, A., MURPHY, N. & MATTHEWS, T. 2000. Effect of prone sleeping on circulatory control in infants. *Archives of Disease in Childhood,* 82**,** 253-256.
CITERIO, G. & ANDREWS, P. J. D. 2009. Intracranial pressure. Part Two: Clinical applications and technology. *In:* PINSKY, M., BROCHARD, L., MANCEBO, O. & HEDENSTIERNA, G. (eds.) *Applied Physiology in Intesnive Care Medicine.* Second ed. New York: Springer.
CLAIRAMBAULT, J., CURZI-DASCALOVA, L., KAUFFMANN, F., MEDIGUE, C. & LEFFLER, C. 1992. Heart rate variability in normal sleeping full-term and preterm neonates. *Early Human Development,* 28**,** 169-183.
CLARKE, D. D. & SOKOLOFF, L. 1999. Regulation of Cerebral Metabolic Rate. *In:* SIEGEL, G., AGRANOFF, B., ALBERS, R., FISHER, S. & UHLER, M. (eds.) *Basic neurochemistry: Molecular, Cellular and Medical Aspects.* 6th ed. Philadelphia: Lippincott-Raven.
COHEN, G., VELLA, S., JEFFERY, H. & LAGERCRANTZ, H. 2008. Cardiovascular stress hyperreactivity in babies of smokers and in babies born preterm. *Circulation,* 118**,** 1848-53.
COMMITTEE ON FETUS NEWBORN AMERICAN ACADEMY OF PEDIATRICS 2003. Apnea, sudden infant death syndrome, and home monitoring. *Pediatrics,* 111**,** 914-7.
COONS, S. & GUILLEMINAULT, C. 1985. Motility and arousal in near miss sudden infant death syndrome. *The Journal of Pediatrics,* 107**,** 728-732.
COSTELOE, K. L., HENNESSY, E. M., HAIDER, S., STACEY, F., MARLOW, N. & DRAPER, E. S. 2012. Short term outcomes after extreme preterm birth in England: comparison of two birth cohorts in 1995 and 2006 (the EPICure studies). *BMJ,* 345.
COSTELOE, K. L., HENNESSY, E. M., HAIDER, S., STACEY, F., MARLOW, N. & DRAPER, E. S. 2013. Short term outcomes after extreme preterm birth in England: comparison of two birth cohorts in 1995 and 2006 (the EPICure studies). *BMJ,* 345.
COWAN, F., ERIKSEN, M. & THORESEN, M. 1983. An evaluation of the plethysmographic method of measuring cranial blood flow in the new-born infant. *The Journal of Physiology,* 335**,** 41-50.
DALZIEL, S. R., PARAG, V., RODGERS, A. & HARDING, J. E. 2007. Cardiovascular risk factors at age 30 following pre-term birth. *International Journal of Epidemiology,* 36**,** 907-15.
DAVID, M., HIRSCH, M., KARIN, J., TOLEDO, E. & AKSELROD, S. 2007. An estimate of fetal autonomic state by time-frequency analysis of fetal heart rate variability. *Journal of Applied Physiology,* 102**,** 1057-64.
DE BEER, N. A., ANDRIESSEN, P., BERENDSEN, R. C., OEI, S. G., WIJN, P. F., OETOMO, S. B., DE BEER, N. A. M., BERENDSEN, R. C. M., WIJN, P. F. F. & OETOMO, S. B. 2004. Customized spectral band analysis compared with conventional Fourier analysis of heart rate variability in neonates. *Physiological Measurement,* 25**,** 1385-95.
DE BOO, H. A. & HARDING, J. E. 2006. The developmental origins of adult disease (Barker) hypothesis. *Australian and New Zealand Journal of Obstetrics and Gynaecology,* 46**,** 4-14.
DE ROGALSKI LANDROT, I., ROCHE, F., PICHOT, V., TEYSSIER, G., GASPOZ, J.-M., BARTHELEMY, J.-C. & PATURAL, H. 2007. Autonomic nervous system activity in premature and full-term infants from theoretical term to 7 years. *Autonomic Neuroscience,* 136**,** 105-109.
DIMITRIOU, G., FOUZAS, S., GEORGAKIS, V., VERVENIOTI, A., PAPADOPOULOS, V. G., DECAVALAS, G. & MANTAGOS, S. 2010. Determinants of morbidity in late preterm infants. *Early Human Development,* 86**,** 587-591.

DOYLE, L. W. & VICTORIAN INFANT COLLABORATIVE STUDY, G. 2001. Outcome at 5 years of age of children 23 to 27 weeks' gestation: refining the prognosis. *Pediatrics,* 108**,** 134-41.

DROUIN, E., GOURNAY, V., CALAMEL, J., MOUZARD, A. & ROZE, J.-C. 1997. Assessment of spontaneous baroreflex sensitivity in neonates. *Archives of Disease in Childhood - Fetal and Neonatal Edition,* 76**,** F108-F112.

DUNCAN, J. R., PATERSON, D. S., HOFFMAN, J. M., MOKLER, D. J., BORENSTEIN, N. S., BELLIVEAU, R. A., KROUS, H. F., HAAS, E. A., STANLEY, C., NATTIE, E. E., TRACHTENBERG, F. L. & KINNEY, H. C. 2010. Brainstem Serotonergic Deficiency in Sudden Infant Death Syndrome. *JAMA: The Journal of the American Medical Association,* 303**,** 430-437.

EDNER, A., ERICSON, M., MILERAD, J. & KATZ-SALAMON, M. 2002. Abnormal heart rate response to hypercapnia in boys with an apparent life-threatening event. *Acta Pædiatrica,* 91**,** 1318-1323.

EDWARDS, A. D., RICHARDSON, C., COPE, M., WYATT, J. S., DELPY, D. T. & REYNOLDS, E. O. R. 1988. Cotside measurement of cerebral blood flow in ill newborn infants by near infrared spectroscopy *The Lancet,* 332**,** 770-771.

EICHLER, F., IPSIROGLU, O., ARIF, T., POPOW, C., HEINZL, H., URSCHITZ, M. & POLLAK, A. 2001. Position dependent changes of cerebral blood flow velocities in premature infants. *European Journal of Pediatrics,* 160**,** 633-9.

EISELT, M., CURZI-DASCALOVA, L., CLAIRAMBAULT, J., KAUFFMANN, F., MEDIGUE, C. & PEIRANO, P. 1993. Heart-rate variability in low-risk prematurely born infants reaching normal term: A comparison with full-term newborns. *Early Human Development,* 32**,** 183-195.

ELECTROPHYSIOLOGY TASK FORCE OF THE EUROPEAN SOCIETY OF CARDIOLOGY 1996. Heart Rate Variability. *Circulation,* 93**,** 1043-1065.

ENGELBERTS, A. C., DE JONGE, G. A. & KOSTENSE, P. J. 1991. An analysis of trends in the incidence of sudden infant death in The Netherlands 1969-89. *Journal of Paediatrics & Child Health,* 27**,** 329-33.

FILIANO, J. J. & KINNEY, H. C. 1992. Arcuate nucleus hypoplasia in the sudden infant death syndrome. *Journal of Neuropathology & Experimental Neurology,* 51**,** 394-403.

FILIANO, J. J. & KINNEY, H. C. 1994. A perspective on neuropathologic findings in victims of the sudden infant death syndrome: the triple-risk model. *Biology of the Neonate,* 65**,** 194-7.

FINLEY, J. P., HAMILTON, R. & MACKENZIE, M. G. 1984. Heart rate response to tilting in newborns in quiet and active sleep. *Biology of the Neonate,* 45**,** 1-10.

FRANCO, P., CHABANSKI, S., SZLIWOWSKI, H., DRAMAIX, M. & KAHN, A. 2000a. Influence of maternal smoking on autonomic nervous system in healthy infants. *Pediatric Research,* 47**,** 215-20.

FRANCO, P., KATO, I., RICHARDSON, H. L., YANG, J. S. C., MONTEMITRO, E. & HORNE, R. S. C. 2010. Arousal from sleep mechanisms in infants. *Sleep Medicine,* 11**,** 603-614.

FRANCO, P., SZLIWOWSKI, H., DRAMAIX, M. & KAHN, A. 2000b. Influence of ambient temperature on sleep characteristics and autonomic nervous control in healthy infants. *Sleep,* 23**,** 401-7.

FRANCO, P., VERHEULPEN, D., VALENTE, F., KELMANSON, I., DE BROCA, A., SCAILLET, S., GROSWASSER, J. & KAHN, A. 2003. Autonomic responses to sighs in healthy infants and in victims of sudden infant death. *Sleep Medicine,* 4**,** 569-577.

FRANKS, C. I., WATSON, J. B., BROWN, B. H. & FOSTER, E. F. 1980. Respiratory patterns and risk of sudden unexpected death in infancy. *Archives of Disease in Childhood,* 55**,** 595-9.

FRIEDMAN, W. F. 1972. The intrinsic physiologic properties of the developing heart. *Progress in Cardiovascular Diseases,* 15**,** 87-111.

GALLAND, B. C., REEVES, G., TAYLOR, B. J. & BOLTON, D. P. G. 1998. Sleep position, autonomic function, and arousal. *Archives of Disease in Childhood - Fetal and Neonatal Edition,* 78**,** F189-F194.

GEORGIEFF, M. K., MILLS, M. M., GOMEZ-MARIN, O. & SINAIKO, A. R. 1996. Rate of change of blood pressure in premature and full term infants from birth to 4 months. *Pediatric Nephrology,* 10**,** 152-5.

GILMORE, M. M., STONE, B. S., SHEPARD, J. A., CZOSNYKA, M., EASLEY, R. B. & BRADY, K. M. 2011. Relationship between cerebrovascular dysautoregulation and arterial blood pressure in the premature infant. *Journal of Perinatology,* 31**,** 722-729.

GOFF, D. A., BUCKLEY, E. M., DURDURAN, T., WANG, J., LICHT, D. J., GOFF, D. A., BUCKLEY, E. M., DURDURAN, T., WANG, J. & LICHT, D. J. 2010. Noninvasive cerebral perfusion imaging in high-risk neonates. *Seminars in Perinatology,* 34**,** 46-56.

GOURNAY, V., DROUIN, E. & ROZE, J. C. 2002. Development of baroreflex control of heart rate in preterm and full term infants. *Archives of Disease in Childhood Fetal & Neonatal Edition,* 86**,** F151-4.

GRAZEL, R., PHALEN, A. G., POLOMANO, R. C., GRAZEL, R., PHALEN, A. G. & POLOMANO, R. C. 2010. Implementation of the American Academy of Pediatrics recommendations to reduce sudden infant death syndrome risk in neonatal intensive care units: An evaluation of nursing knowledge and practice. *Advances in Neonatal Care,* 10**,** 332-42.

GRAZIANI, L. J., SPITZER, A. R., MITCHELL, D. G., MERTON, D. A., STANLEY, C., ROBINSON, N. & MCKEE, L. 1992. Mechanical ventilation in preterm infants: neurosonographic and developmental studies. *Pediatrics,* 90**,** 515-22.

GREENOUGH, A. & EMERY, E. F. 1993. Blood pressure levels of preterm infants in the first year of life. *Acta Pædiatrica,* 82**,** 528-529.

GREISEN, G. 2005. Autoregulation of cerebral blood flow in newborn babies. *Early Human Development,* 81**,** 423-428.

GREISEN, G., HELLSTROM-VESTAS, L., LOU, H., ROSEN, I. & SVENNINGSEN, N. 1985. Sleep-waking shifts and cerebral blood flow in stable preterm infants. *Pediatric Research,* 19**,** 1156-9.

GREISEN, G. & TROJABORG, W. 1987. Cerebral blood flow, PaCO2 changes, and visual evoked potentials in mechanically ventilated, preterm infants. *Acta Paediatrica Scandinavica,* 76**,** 394-400.

GUPTA, A. K., MENON, D. K., CZOSNYKA, M., SMIELEWSKI, P. & JONES, J. G. 1997. Thresholds for hypoxic cerebral vasodilation in volunteers. *Anesthesia & Analgesia,* 85**,** 817-20.

HAHN, G. H., MAROUN, L. L., LARSEN, N., HOUGAARD, D. M., SORENSEN, L. C., LOU, H. C., GREISEN, G., HAHN, G. H., MAROUN, L. L., LARSEN, N., HOUGAARD, D. M., SORENSEN, L. C., LOU, H. C. & GREISEN, G. 2012. Cerebral autoregulation in the first day after preterm birth: no evidence of association with systemic inflammation. *Pediatric Research,* 71**,** 253-60.

HALASZ, P., TERZANO, M., PARRINO, L. & BODIZS, R. 2004. The nature of arousal in sleep. *Journal of Sleep Research,* 13**,** 1-23.

HALLORAN, D. R. & ALEXANDER, G. R. 2006. Preterm delivery and age of SIDS death. *Annals of Epidemiology,* 16**,** 600-6.

HANZER, M., KERBL, R., URLESBERGER, B., MUELLER, W., PICHLER, G., ZOTTER, H., HANZER, M., KERBL, R., URLESBERGER, B., MUELLER, W., PICHLER, G. & ZOTTER, H. 2007. Comparison of heart rate responses during cortical and subcortical arousals in term and preterm infants. *Early Human Development,* 83**,** 511-5.

HARPER, A. 1990. Physiological control of the cerebral circulation. *In:* HARPER, A. & JENNET, S. (eds.) *Cerebral Blood Flow and Metabolism.* Manchester: Manchester University Press.

HARPER, R. M. 2000. Sudden infant death syndrome: a failure of compensatory cerebellar mechanisms? *Pediatric Research,* 48**,** 140-2.

HARPER, R. M. 2001. Autonomic control during sleep and risk for sudden death in infancy. *Archives Italiennes de Biologie,* 139**,** 185-94.

HARPER, R. M., HOPPENBROUWERS, T., STERMAN, M. B., MCGINTY, D. J. & HODGMAN, J. 1976. Polygraphic studies of normal infants during the first six months of life. I. Heart rate and variability as a function of state. *Pediatric Research,* 10**,** 945-8.

HARRINGTON, C., KIRJAVAINEN, T., TENG, A. & SULLIVAN, C. E. 2001. Cardiovascular responses to three simple, provocative tests of autonomic activity in sleeping infants. *Journal of Applied Physiology,* 91**,** 561-8.

HAUCK, F. R., HERMAN, S. M., DONOVAN, M., IYASU, S., MERRICK MOORE, C., DONOGHUE, E., KIRSCHNER, R. H. & WILLINGER, M. 2003. Sleep Environment and the Risk of Sudden Infant Death Syndrome in an Urban Population: The Chicago Infant Mortality Study. *Pediatrics,* 111**,** 1207-1214.

HAUCK, F. R., OMOJOKUN, O. O. & SIADATY, M. S. 2005. Do pacifiers reduce the risk of sudden infant death syndrome? A meta-analysis. *Pediatrics,* 116**,** e716-23.

HAUCK, F. R. & TANABE, K. O. 2008. International Trends in Sudden Infant Death Syndrome: Stabilization of Rates Requires Further Action. *Pediatrics,* 122**,** 660-666.

HAUCK, F. R., THOMPSON, J. M., TANABE, K. O., MOON, R. Y. & VENNEMANN, M. M. 2011. Breastfeeding and reduced risk of sudden infant death syndrome: a meta-analysis. *Pediatrics,* 128**,** 103-10.

HENSLEE, J. A., SCHECHTMAN, V. L., LEE, M. Y. & HARPER, R. M. 1997. Developmental patterns of heart rate and variability in prematurely-born infants with apnea of prematurity. *Early Human Development,* 47**,** 35-50.

HOLDEN, K., MORGAN, J. S., KRAUSS, A. N. & AULD, P. A. 1985. Incomplete baroreceptor responses in newborn infants. *American Journal of Perinatology,* 2**,** 31-4.

HOPPENBROUWERS, T., HODGMAN, J. E., RAMANATHAN, A. & DOREY, F. 2008. Extreme and Conventional Cardiorespiratory Events and Epidemiologic Risk Factors for SIDS. *The Journal of Pediatrics,* 152**,** 636-641.

HORBAR, J. D., CARPENTER, J. H., BADGER, G. J., KENNY, M. J., SOLL, R. F., MORROW, K. A. & BUZAS, J. S. 2012. Mortality and neonatal morbidity among infants 501 to 1500 grams from 2000 to 2009. *Pediatrics,* 129**,** 1019-26.

HORNE, R. S., BANDOPADHAYAY, P., VITKOVIC, J., CRANAGE, S. M. & ADAMSON, T. M. 2002. Effects of age and sleeping position on arousal from sleep in preterm infants. *Sleep,* 25**,** 746-50.

HORNE, R. S., FERENS, D., WATTS, A. M., VITKOVIC, J., LACEY, B., ANDREW, S., CRANAGE, S. M., CHAU, B. & ADAMSON, T. M. 2001. The prone sleeping position impairs arousability in term infants. *Journal of Pediatrics,* 138**,** 811-6.

HORNE, R. S. C., PARSLOW, P. M. & HARDING, R. 2004. Respiratory control and arousal in sleeping infants. *Paediatric Respiratory Reviews,* 5**,** 190-198.

HORNER, R. L. 1996. Autonomic consequences of arousal from sleep: mechanisms and implications. *Sleep,* 19**,** S193-5.

HUNT, C. E. 1992. The cardiorespiratory control hypothesis for sudden infant death syndrome. *Clinics in Perinatology,* 19**,** 757-71.

HUNT, C. E. 2001. Sudden infant death syndrome and other causes of infant mortality: diagnosis, mechanisms, and risk for recurrence in siblings. *American Journal of Respiratory & Critical Care Medicine,* 164**,** 346-57.

HUNT, C. E. & HAUCK, F. R. 2006. Sudden infant death syndrome. *CMAJ Canadian Medical Association Journal,* 174**,** 1861-9.

IKONEN, R. S., JANAS, M. O., KOIVIKKO, M. J., LAIPPALA, P. & KUUSINEN, E. J. 1992. Hyperbilirubinemia, hypocarbia and periventricular leukomalacia in preterm infants: relationship to cerebral palsy. *Acta Paediatrica,* 81**,** 802-7.

INDER, T. E., WARFIELD, S. K., WANG, H., HUPPI, P. S. & VOLPE, J. J. 2005. Abnormal cerebral structure is present at term in premature infants. *Pediatrics,* 115**,** 286-94.

INTERNATIONAL PAEDIATRIC WORK GROUP ON AROUSALS 2005. The scoring of arousals in healthy term infants (between the ages of 1 and 6 months). *Journal of Sleep Research,* 14**,** 37-41.

IRGENS, L. M., MARKESTAD, T., BASTE, V., SCHREUDER, P., SKJAERVEN, R. & OYEN, N. 1995. Sleeping position and sudden infant death syndrome in Norway 1967-91. *Archives of Disease in Childhood,* 72**,** 478-82.

JAYASINGHE, D., GILL, A. B., LEVENE, M. I., JAYASINGHE, D., GILL, A. B. & LEVENE, M. I. 2003. CBF reactivity in hypotensive and normotensive preterm infants. *Pediatric Research,* 54**,** 848-53.

JOBSIS, F. F. 1977. Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. *Science,* 198**,** 1264-7.

JOHANSSON, S., ILIADOU, A., BERGVALL, N., TUVEMO, T., NORMAN, M. & CNATTINGIUS, S. 2005. Risk of high blood pressure among young men increases with the degree of immaturity at birth. *Circulation,* 112**,** 3430-6.

JONES, M. D., JR., TRAYSTMAN, R. J., SIMMONS, M. A. & MOLTENI, R. A. 1981. Effects of changes in arterial O2 content on cerebral blood flow in the lamb. *American Journal of Physiology,* 240**,** H209-15.

KAHN, A., GROSWASSER, J., REBUFFAT, E., SOTTIAUX, M., BLUM, D., FOERSTER, M., FRANCO, P., BOCHNER, A., ALEXANDER, M., BACHY, A. & ET AL. 1992. Sleep and cardiorespiratory characteristics of infant victims of sudden death: a prospective case-control study. *Sleep,* 15**,** 287-92.

KAHN, A., GROSWASSER, J., SOTTIAUX, M., REBUFFAT, E., FRANCO, P. & DRAMAIX, M. 1993. Prone or supine body position and sleep characteristics in infants. *Pediatrics,* 91**,** 1112-5.

KAISER, J. R. 2008. Neurological sequelae following mechanical ventilation. *In:* BERGER, I. & SCHIMMEL, M. S. (eds.) *Hot Topics in Neonatal Neurology.* New York: Nova Science Publishers.

KAISER, J. R., GAUSS, C. H., WILLIAMS, D. K., KAISER, J. R., GAUSS, C. H. & WILLIAMS, D. K. 2005. The effects of hypercapnia on cerebral autoregulation in ventilated very low birth weight infants. *Pediatric Research,* 58**,** 931-5.

KATO, I., FRANCO, P., GROSWASSER, J., SCAILLET, S., KELMANSON, I., TOGARI, H. & KAHN, A. 2003. Incomplete Arousal Processes in Infants Who Were Victims of Sudden Death. *American Journal of Respiratory and Critical Care Medicine,* 168**,** 1298-1303.

KATO, I., SCAILLET, S., GROSWASSER, J., MONTEMITRO, E., TOGARI, H., LIN, J. S., KAHN, A., FRANCO, P., KATO, I., SCAILLET, S., GROSWASSER, J., MONTEMITRO, E., TOGARI, H., LIN, J.-S., KAHN, A. & FRANCO, P. 2006. Spontaneous arousability in prone and supine position in healthy infants. *Sleep,* 29**,** 785-90.

KATONA, P. G., FRASZ, A. & EGBERT, J. 1980. Maturation of cardiac control in full-term and preterm infants during sleep. *Early Human Development,* 4**,** 145-159.

KELLY, D. H., GOLUB, H., CARLEY, D. & SHANNON, D. C. 1986. Pneumograms in infants who subsequently died of sudden infant death syndrome. *The Journal of Pediatrics,* 109**,** 249-254.

KELLY, D. H., PATHAK, A. & MENY, R. 1991. Sudden severe bradycardia in infancy. *Pediatric Pulmonology,* 10**,** 199-204.

KEMP, J. S. & THACH, B. T. 1991. Sudden death in infants sleeping on polystyrene-filled cushions. *New England Journal of Medicine,* 324**,** 1858-64.

KENT, B. B., DRANE, J. W., BLUMENSTEIN, B. B. & MANNING, J. W. 1972. A Mathematical Model to Assess Changes in the Baroreceptor Reflex. *Cardiology,* 57**,** 295-310.

KINNEY, H. C. 2009. Brainstem mechanisms underlying the sudden infant death syndrome: Evidence from human pathologic studies. *Developmental Psychobiology,* 51**,** 223-233.

KINNEY, H. C., BURGER, P. C., HARRELL, F. E., JR. & HUDSON, R. P., JR. 1983. 'Reactive gliosis' in the medulla oblongata of victims of the sudden infant death syndrome. *Pediatrics,* 72**,** 181-7.

KINNEY, H. C., FILIANO, J. J. & WHITE, W. F. 2001. Medullary serotonergic network deficiency in the sudden infant death syndrome: review of a 15-year study of a single dataset. *Journal of Neuropathology & Experimental Neurology,* 60**,** 228-47.

KINNEY, H. C., MCHUGH, T., MILLER, K., BELLIVEAU, R. A. & ASSMANN, S. F. 2002. Subtle developmental abnormalities in the inferior olive: an indicator of prenatal brainstem injury in the sudden infant death syndrome. *Journal of Neuropathology & Experimental Neurology,* 61**,** 427-41.

KINNEY, H. C., RANDALL, L. L., SLEEPER, L. A., WILLINGER, M., BELLIVEAU, R. A., ZEC, N., RAVA, L. A., DOMINICI, L., IYASU, S., RANDALL, B., HABBE, D., WILSON, H., MANDELL, F., MCCLAIN, M., WELTY, T. K., KINNEY, H. C., RANDALL, L. L., SLEEPER, L. A., WILLINGER, M., BELLIVEAU, R. A.,

ZEC, N., RAVA, L. A., DOMINICI, L., IYASU, S., RANDALL, B., HABBE, D., WILSON, H., MANDELL, F., MCCLAIN, M. & WELTY, T. K. 2003. Serotonergic brainstem abnormalities in Northern Plains Indians with the sudden infant death syndrome. *Journal of Neuropathology & Experimental Neurology,* 62**,** 1178-91.

KINNEY, H. C. & THACH, B. T. 2009. The Sudden Infant Death Syndrome. *New England Journal of Medicine,* 361**,** 795-805.

KISSACK, C. M., GARR, R., WARDLE, S. P. & WEINDLING, A. M. 2005. Cerebral fractional oxygen extraction is inversely correlated with oxygen delivery in the sick, newborn, preterm infant. *J Cereb Blood Flow Metab,* 25**,** 545-553.

KISTNER, A., CELSI, G., VANPÉE, M. & JACOBSON, S. H. 2005. Increased systolic daily ambulatory blood pressure in adult women born preterm. *Pediatric Nephrology,* 20**,** 232-3.

KITSANTAS, P. & GAFFNEY, K. F. 2010. Racial/ethnic disparities in infant mortality. *Journal of Perinatal Medicine,* 38**,** 87-94.

KLEM, G. H., LUDERS, H. O., JASPER, H. H. & ELGER, C. 1999. The ten-twenty electrode system of the International Federation. The International Federation of Clinical Neurophysiology. *Electroencephalography & Clinical Neurophysiology - Supplement,* 52**,** 3-6.

KLUGE, K. A., HARPER, R. M., SCHECHTMAN, V. L., WILSON, A. J., HOFFMAN, H. J. & SOUTHALL, D. P. 1988. Spectral analysis assessment of respiratory sinus arrhythmia in normal infants and infants who subsequently died of sudden infant death syndrome. *Pediatric Research,* 24**,** 677-82.

KORINTHENBERG, R. 1993. Morphological and Functional Maturation of the Brain: Possible Relations to Different EEG Generators *In:* ZSCHOCKE, S. & SPECKMANN, E. (eds.) *Basic Mechanisms of the EEG.* Boston: Birkhauser.

KROUS, H. F., BECKWITH, J. B., BYARD, R. W., ROGNUM, T. O., BAJANOWSKI, T., COREY, T., CUTZ, E., HANZLICK, R., KEENS, T. G. & MITCHELL, E. A. 2004. Sudden infant death syndrome and unclassified sudden infant deaths: a definitional and diagnostic approach. *Pediatrics,* 114**,** 234-8.

KRYGER, M. H., ROTH, T. & DEMENT, W. C. 2010. *Principles and Practice of Sleep Medicine,* Missouri, USA, Elsevier Saunders.

LA ROVERE, M. T., PINNA, G. D. & RACZAK, G. 2008. Baroreflex Sensitivity: Measurement and Clinical Implications. *Annals of Noninvasive Electrocardiology,* 13**,** 191-207.

LACOVIDOU, N., VARSAMI, M. & SYGGELLOU, A. 2010 Neonatal outcome of preterm delivery. *Annals of the New York Academy of Sciences,* 1205**,** 130-134.

LAGERCRANTZ, H., EDWARDS, D., HENDERSON-SMART, D., HERTZBERG, T. & JEFFERY, H. 1990. Autonomic reflexes in preterm infants. *Acta Paediatrica Scandinavica,* 79**,** 721-8.

LARSEN, W. J., SHERMAN, L. S., POTTER, S. S. & SCOTT, W. J. 2001. *Human embryology*, Churchill Livingstone.

LAWS, P. & SULLIVAN, E. 2010. Australia's Mothers and Babies 2008. *Perinatal Statistics Series* [Online], 24.

LEAHY, F. A., CATES, D., MACCALLUM, M. & RIGATTO, H. 1980. Effect of CO2 and 100% O2 on cerebral blood flow in preterm infants. *Journal of Applied Physiology,* 48**,** 468-472.

LEMONS, J. A., BAUER, C. R., OH, W., KORONES, S. B., PAPILE, L.-A., STOLL, B. J., VERTER, J., TEMPROSA, M., WRIGHT, L. L., EHRENKRANZ, R. A., FANAROFF, A. A., STARK, A., CARLO, W., TYSON, J. E., DONOVAN, E. F., SHANKARAN, S., STEVENSON, D. K. & NETWORK, F. T. N. N. R. 2001. Very Low Birth Weight Outcomes of the National Institute of Child Health and Human Development Neonatal Research Network, January 1995 Through December 1996. *Pediatrics,* 107**,** e1.

LEOR-LIBRACH, R. J., BOBROVSKY, B. Z., ELIASH, S., KAPLINSKY, E., LEOR-LIBRACH, R. J., BOBROVSKY, B.-Z., ELIASH, S. & KAPLINSKY, E. 2002. A common origin of the very low frequency heart rate and blood pressure variability--a new insight into an old debate. *Autonomic Neuroscience-Basic & Clinical,* 96**,** 140-8.

LI, T., LIN, Y., SHANG, Y., HE, L., HUANG, C., SZABUNIO, M. & YU, G. 2013. Simultaneous measurement of deep tissue blood flow and oxygenation using noncontact diffuse correlation spectroscopy flow-oximeter. *Scientific Reports,* 3.

LI, Z., ZEKI, R., HILDER, L. & SULLIVAN, E. 2012. Australia's mothers and babies 2010. *Perinatal Statistics Series.* Canberra: Australian Institute of Health and Welfare.

LINACRE, S. 2007. Australia's Babies. *Australian Social Trends 2007.* Canberra: Australian Bureau of Statistics.

LISTER, G., RYBIN, D. V., COLTON, T., HEEREN, T. C., HUNT, C. E., COLSON, E. R., WILLINGER, M., CORWIN, M. J. & COLLABORATIVE HOME INFANT MONITORING EVALUATION STUDY, G. 2012. Relationship between sleep position and risk of extreme cardiorespiratory events. *Journal of Pediatrics,* 161**,** 22-5.e1.

LONGIN, E., GERSTNER, T., SCHAIBLE, T., LENZ, T. & KONIG, S. 2006. Maturation of the autonomic nervous system: differences in heart rate variability in premature vs. term infants. *Journal of Perinatal Medicine,* 34**,** 303-8.

LOUIS, J., CANNARD, C., BASTUJI, H. & CHALLAMEL, M. J. 1997. Sleep ontogenesis revisited: a longitudinal 24-hour home polygraphic study on 15 normal infants during the first two years of life. *Sleep,* 20**,** 323-33.

LUNDSTRØM, K. E., PRYDS, O. & GREISEN, G. 1995. Oxygen at birth and prolonged cerebral vasoconstriction in preterm infants. *Archives of Disease in Childhood - Fetal and Neonatal Edition,* 73**,** F81-F86.

MACHAALANI, R. & WATERS, K. A. 2008. Neuronal cell death in the Sudden Infant Death Syndrome brainstem and associations with risk factors. *Brain,* 131**,** 218-228.

MALIK, M. 1996. Heart rate variability. *Annals of Noninvasive Electrocardiology,* 1**,** 151-181.

MALLIANI, A., PAGANI, M., LOMBARDI, F. & CERUTTI, S. 1991. Cardiovascular neural regulation explored in the frequency domain. *Circulation,* 84**,** 482-92.

MALLOY, M. H. 2013. Prematurity and sudden infant death syndrome: United States 2005-2007. *Journal of Perinatology,* 33**,** 470-5.

MALLOY, M. H. & HOFFMAN, H. J. 1995. Prematurity, sudden infant death syndrome, and age of death. *Pediatrics,* 96**,** 464-71.

MALLY, P. V., BAILEY, S. & HENDRICKS-MUÑOZ, K. D. 2010. Clinical Issues in the Management of Late Preterm Infants. *Current Problems in Pediatric and Adolescent Health Care,* 40**,** 218-233.

MARTIN, R. J., WANG, K., KOROGLU, O., DI FIORE, J. & KC, P. 2011. Intermittent hypoxic episodes in preterm infants: do they matter? *Neonatology,* 100**,** 303-10.

MASSIN, M. M., MAEYNS, K., LOMBET, J., RIGO, J., GERARD, P., MASSIN, M. M., MAEYNS, K., LOMBET, J., RIGO, J. & GERARD, P. 2002. Heart rate response profiles to tilting in healthy and unhealthy neonates. *Medical Science Monitor,* 8**,** CR321-5.

MATHEWS, T. J. & MACDORMAN, M. F. 2010. Infant mortality statistics from the 2006 period linked birth/infant death data set. *National Vital Statistics Reports,* 58**,** 1-31.

MAZURSKY, J. E., BIRKETT, C. L., BEDELL, K. A., BEN-HAIM, S. A. & SEGAR, J. L. 1998. Development of baroreflex influences on heart rate variability in preterm infants. *Early Human Development,* 53**,** 37-52.

MCLAURIN, K. K., HALL, C. B., JACKSON, E. A., OWENS, O. V. & MAHADEVIA, P. J. 2009. Persistence of Morbidity and Cost Differences Between Late-Preterm and Term Infants During the First Year of Life. *Pediatrics,* 123**,** 653-659.

MEEK, J. H., ELWELL, C. E., KHAN, M. J., ROMAYA, J., WYATT, J. S., DELPY, D. T. & ZEKI, S. 1995. Regional changes in cerebral haemodynamics as a result of a visual stimulus measured by near infrared spectroscopy. *Proceedings of the Royal Society of London. Series B: Biological Sciences,* 261**,** 351-356.

MEEK, J. H., FIRBANK, M., ELWELL, C. E., ATKINSON, J., BRADDICK, O. & WYATT, J. S. 1998a. Regional hemodynamic responses to visual stimulation in awake infants. *Pediatric Research,* 43**,** 840-3.

MEEK, J. H., TYSZCZUK, L., ELWELL, C. E. & WYATT, J. S. 1998b. Cerebral blood flow increases over the first three days of life in extremely preterm neonates. *Archives of Disease in Childhood Fetal & Neonatal Edition,* 78**,** F33-7.

MENON, D. K. 2000. The cerebral circulation. *In:* MATTA, B. F., MENON, D. K. & TURNER, J. M. (eds.) *Textbook of Neuroanaesthesia and Critical Care.* London: Greenwich Medical Media Ltd.

MEWES, A. U., HUPPI, P. S., ALS, H., RYBICKI, F. J., INDER, T. E., MCANULTY, G. B., MULKERN, R. V., ROBERTSON, R. L., RIVKIN, M. J. & WARFIELD, S. K. 2006. Regional brain development in serial magnetic resonance imaging of low-risk preterm infants. *Pediatrics,* 118**,** 23-33.

MILLIGAN, D. W. A. 1980. Failure of autoregulation and intraventricular haemorrhage in preterm infants. *The Lancet,* 315**,** 896-898.

MINDELL, J. A. & OWENS, J. A. 2010. *A Clinical Guide to Pediatric Sleep: Diagnosis and Management of Sleep Problems,* Philadelphia, USA, Wolters Kluwer Health.

MIRMIRAN, M., MAAS, Y. G. H. & ARIAGNO, R. L. 2003. Development of fetal and neonatal sleep and circadian rhythms. *Sleep Medicine Reviews,* 7**,** 321-334.

MITCHELL, E. A., SCRAGG, R., STEWART, A. W., BECROFT, D. M., TAYLOR, B. J., FORD, R. P., HASSALL, I. B., BARRY, D. M., ALLEN, E. M. & ROBERTS, A. P. 1991. Results from the first year of the New Zealand cot death study. *New Zealand Medical Journal,* 104**,** 71-6.

MONTANO, N., RUSCONE, T. G., PORTA, A., LOMBARDI, F., PAGANI, M. & MALLIANI, A. 1994. Power spectrum analysis of heart rate variability to assess the changes in sympathovagal balance during graded orthostatic tilt. *Circulation,* 90**,** 1826-31.

MONTI, A., MEDIGUE, C., NEDELCOUX, H. & ESCOURROU, P. 2002. Autonomic control of the cardiovascular system during sleep in normal subjects. *European Journal of Applied Physiology,* 87**,** 174-81.

MOON, R. Y., HORNE, R. S. C. & HAUCK, F. R. 2007. Sudden infant death syndrome. *The Lancet,* 370**,** 1578-1587.

MOSCA, F., BRAY, M., COLNAGHI, M. R., FUMAGALLI, M. & COMPAGNONI, G. 1999. Cerebral vasoreactivity to arterial carbon dioxide tension in preterm infants: The effect of ibuprofen. *The Journal of Pediatrics,* 135**,** 644-646.

MULLER, A. M., MORALES, C., BRINER, J., BAENZIGER, O., DUC, G. & BUCHER, H. U. 1997. Loss of CO2 reactivity of cerebral blood flow is associated with severe brain damage in mechanically ventilated very low birth weight infants. *European Journal of Paediatric Neurology,* 1**,** 157-63.

MUNGER, D. M., BUCHER, H. U. & DUC, G. 1998. Sleep state changes associated with cerebral blood volume changes in healthy term newborn infants. *Early Human Development,* 52**,** 27-42.

MURKIN, J. M. & ARANGO, M. 2009. Near-infrared spectroscopy as an index of brain and tissue oxygenation. *British Journal of Anaesthesia,* 103**,** i3-i13.

NAEYE, R. L. 1976. Brain-stem and adrenal abnormalities in the sudden-infant-death syndrome. *American Journal of Clinical Pathology,* 66**,** 526-30.

NATALUCCI, G., LEUCHTER, R. H., BUCHER, H. U., LATAL, B., KOLLER, B., HUPPI, P. S. & HAGMANN, C. 2013. Functional brain maturation assessed during early life correlates with anatomical brain maturation at term-equivalent age in preterm infants. *Pediatric Research,* 74**,** 68-74.

NAVELET, Y., PAYAN, C., GUILHAUME, A. & BENOIT, O. 1984. Nocturnal sleep organization in infants "at risk" for sudden infant death syndrome. *Pediatric Research,* 18**,** 654-7.

NICKLIN, S. E., HASSAN, I. A., WICKRAMASINGHE, Y. A., SPENCER, S. A. & HASSAN, I. A. A. 2003. The light still shines, but not that brightly? The current status of perinatal near infrared spectroscopy. *Archives of Disease in Childhood Fetal & Neonatal Edition,* 88**,** F263-8.

NONNIS MARZANO, F., MALDINI, M., FILONZI, L., LAVEZZI, A. M., PARMIGIANI, S., MAGNANI, C., BEVILACQUA, G. & MATTURRI, L. 2008. Genes regulating the serotonin metabolic pathway in the brain stem and their role in the etiopathogenesis of the sudden infant death syndrome. *Genomics,* 91**,** 485-491.

NORMAN, M. 2008. Low birth weight and the developing vascular tree: a systematic review. *Acta Pædiatrica,* 97**,** 1165-1172.

O'LEARY, H., GREGAS, M. C., LIMPEROPOULOS, C., ZARETSKAYA, I., BASSAN, H., SOUL, J. S., DI SALVO, D. N., DU PLESSIS, A. J., O'LEARY, H., GREGAS, M. C., LIMPEROPOULOS, C., ZARETSKAYA, I., BASSAN, H., SOUL, J. S., DI SALVO, D. N. & DU PLESSIS, A. J. 2009. Elevated cerebral pressure passivity is associated with prematurity-related intracranial hemorrhage. *Pediatrics,* 124**,** 302-9.

ORIOT, D., BERTHIER, M., SAULNIER, J. P., BLAY, D., FOHR, J. P., VUILLERME, V. & SAULNIER, J. B. 1998. Prone position may increase temperature around the head of the infant. *Acta Paediatrica,* 87**,** 1005-7.

OYEN, N., MARKESTAD, T., SKAERVEN, R., IRGENS, L. M., HELWEG-LARSEN, K., ALM, B., NORVENIUS, G. & WENNERGREN, G. 1997. Combined effects of sleeping position and prenatal risk factors in sudden infant death syndrome: the Nordic Epidemiological SIDS Study. *Pediatrics,* 100**,** 613-21.

PADHYE, N. S., VERKLAN, M. T., BRAZDEIKIS, A., WILLIAMS, A. L., KHATTAK, A. Z. & LASKY, R. E. A comparison of fetal and neonatal heart rate variability at similar post-menstrual ages. Engineering in Medicine and Biology Society, 2008. EMBS 2008. 30th Annual International Conference of the IEEE, 20-25 Aug. 2008 2008. 2801-2804.

PAGANI, M., LOMBARDI, F., GUZZETTI, S., RIMOLDI, O., FURLAN, R., PIZZINELLI, P., SANDRONE, G., MALFATTO, G., DELL'ORTO, S., PICCALUGA, E. & ET AL. 1986. Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. *Circulation Research,* 59**,** 178-93.

PAMPHLETT, R., RAISANEN, J. & KUM-JEW, S. 1999. Vertebral artery compression resulting from head movement: a possible cause of the sudden infant death syndrome. *Pediatrics,* 103**,** 460-8.

PARKINSON, J. R., HYDE, M. J., GALE, C., SANTHAKUMARAN, S. & MODI, N. 2013. Preterm birth and the metabolic syndrome in adult life: a systematic review and meta-analysis. *Pediatrics,* 131**,** e1240-63.

PATEL, J., MARKS, K., ROBERTS, I., AZZOPARDI, D. & EDWARDS, A. D. 1998. Measurement of cerebral blood flow in newborn infants using near infrared spectroscopy with indocyanine green. *Pediatric Research,* 43**,** 34-9.

PATERSON, D. S., TRACHTENBERG, F. L., THOMPSON, E. G., BELLIVEAU, R. A., BEGGS, A. H., DARNALL, R., CHADWICK, A. E., KROUS, H. F. & KINNEY, H. C. 2006. Multiple serotonergic brainstem abnormalities in sudden infant death syndrome. *JAMA,* 296**,** 2124-32.

PATURAL, H., BARTHELEMY, J. C., PICHOT, V., MAZZOCCHI, C., TEYSSIER, G., DAMON, G. & ROCHE, F. 2004. Birth prematurity determines prolonged autonomic nervous system immaturity. *Clinical Autonomic Research,* 14**,** 391-5.

PATURAL, H., PICHOT, V., JAZIRI, F., TEYSSIER, G., GASPOZ, J.-M., ROCHE, F. D. R. & BARTHELEMY, J.-C. 2008. Autonomic cardiac control of very preterm newborns: A prolonged dysfunction. *Early Human Development,* 84**,** 681-687.

PEETERS, L. L., SHELDON, R. E., JONES, M. D., JR., MAKOWSKI, E. L. & MESCHIA, G. 1979. Blood flow to fetal organs as a function of arterial oxygen content. *American Journal of Obstetrics & Gynecology,* 135**,** 637-46.

PERLMAN, J. M., RISSER, R. & BROYLES, R. S. 1996. Bilateral cystic periventricular leukomalacia in the premature infant: associated risk factors. *Pediatrics,* 97**,** 822-7.

PERLMAN, J. M. & VOLPE, J. J. 1983. Seizures in the preterm infant: effects on cerebral blood flow velocity, intracranial pressure, and arterial blood pressure. *Journal of Pediatrics,* 102**,** 288-93.

POLIN, R. A., FOX, W. W. & ABMAN, S. H. 2011. *Fetal and neonatal physiology: Expert consult*, Elsevier Limited, Oxford.

POLLAK, C., THORPY, M. J. & YAGER, J. 2010. *The Encyclopedia of Sleep and Sleep Disorders,* New York, Hermitage Publishing Services

PRYDS, O., ANDERSEN, G. E. & FRIIS-HANSEN, B. 1990a. Cerebral blood flow reactivity in spontaneously breathing, preterm infants shortly after birth. *Acta Paediatrica Scandinavica,* 79**,** 391-6.

PRYDS, O., GREISEN, G. & FRIIS-HANSEN, B. 1988. Compensatory increase of CBF in preterm infants during hypoglycaemia. *Acta Paediatrica Scandinavica,* 77**,** 632-7.

PRYDS, O., GREISEN, G., LOU, H. & FRIIS-HANSEN, B. 1990b. Vasoparalysis associated with brain damage in asphyxiated term infants. *The Journal of Pediatrics,* 117**,** 119-125.

PRYDS, O., GREISEN, G., LOU, H. & FRILS-HANSEN, B. 1989. Heterogeneity of cerebral vasoreactivity in preterm infants supported by mechanical ventilation. *The Journal of Pediatrics,* 115**,** 638-645.

RAMANATHAN, R., CORWIN, M. J., HUNT, C. E. & ET AL. 2001. Cardiorespiratory events recorded on home monitors: Comparison of healthy infants with those at increased risk for sids. *JAMA,* 285**,** 2199-2207.

RAVEN, P. B., FADEL, P. J. & OGOH, S. 2006. Arterial baroreflex resetting during exercise: a current perspective. *Experimental Physiology,* 91**,** 37-49.

RICHARDSON, H. L. & HORNE, R. S. C. 2013. Arousal from sleep pathways are affected by the prone sleeping position and preterm birth: Preterm birth, prone sleeping and arousal from sleep. *Early Human Development,* 89**,** 705-711.

RICHARDSON, H. L., WALKER, A. M. & HORNE, R. S. 2009. Maternal smoking impairs arousal patterns in sleeping infants. *Sleep,* 32**,** 515-21.

ROCHE-LABARBE, N., FENOGLIO, A., AGGARWAL, A., DEHAES, M., CARP, S. A., FRANCESCHINI, M. A., GRANT, P. E., ROCHE-LABARBE, N., FENOGLIO, A., AGGARWAL, A., DEHAES, M., CARP, S. A., FRANCESCHINI, M. A. & GRANT, P. E. 2012. Near-infrared spectroscopy assessment of cerebral oxygen metabolism in the developing premature brain. *Journal of Cerebral Blood Flow & Metabolism,* 32**,** 481-8.

ROCHE-LABARBE, N., FENOGLIO, A., RADHAKRISHNAN, H., KOCIENSKI-FILIP, M., CARP, S. A., DUBB, J., BOAS, D. A., GRANT, P. E. & FRANCESCHINI, M. A. 2014. Somatosensory evoked changes in cerebral oxygen consumption measured non-invasively in premature neonates. *Neuroimage,* 85 Pt 1**,** 279-86.

SAIGAL, S. & DOYLE, L. W. 2008. An overview of mortality and sequelae of preterm birth from infancy to adulthood. *The Lancet,* 371**,** 261-269.

SALADIN, K. 2011. *Anatomy & physiology: The unity of form and function*, McGraw-Hill Companies,Incorporated.

SATERNUS, K. S. & ADAM, G. 1985. Sudden infant death. Postmortem flow measurements in the large vessels of the neck for the demonstration of posture-dependent cerebral hypoxemia. *Deutsche Medizinische Wochenschrift,* 110**,** 297-303.

SCHECHTMAN, V. L., HARPER, R. M., KLUGE, K. A., WILSON, A. J., HOFFMAN, H. J. & SOUTHALL, D. P. 1988. Cardiac and respiratory patterns in normal infants and victims of the sudden infant death syndrome. *Sleep,* 11**,** 413-24.

SCHECHTMAN, V. L., HARPER, R. M., KLUGE, K. A., WILSON, A. J., HOFFMAN, H. J. & SOUTHALL, D. P. 1989. Heart rate variation in normal infants and victims of the sudden infant death syndrome. *Early Human Development,* 19**,** 167-181.

SCHECHTMAN, V. L., HARPER, R. M., KLUGE, K. A., WILSON, A. J. & SOUTHALL, D. P. 1990. Correlations between cardiorespiratory measures in normal infants and victims of sudden infant death syndrome. *Sleep,* 13**,** 304-17.

SCHECHTMAN, V. L., HARPER, R. M., WILSON, A. J. & SOUTHALL, D. P. 1992. Sleep state organization in normal infants and victims of the sudden infant death syndrome. *Pediatrics,* 89**,** 865-70.

SCHNEIDER, U., SCHLEUSSNER, E., FIEDLER, A., JAEKEL, S., LIEHR, M., HAUEISEN, J. & HOYER, D. 2009. Fetal heart rate variability reveals differential dynamics in the intrauterine development of the sympathetic and parasympathetic branches of the autonomic nervous system. *Physiological Measurement,* 30**,** 215-26.

SEGAR, J. L. 2011. Fetal and neonatal cardiovascular physiology. *In:* RICHARD A POLIN, W. W. F., STEVEN H ABMAN (ed.) *Fetal and Neonatal Physiology.* Philadelphia: Elsevier Saunders.

SHERRY L MURPHEY, JIAQUAN XU & KOCHANEK, K. D. 2013. Deaths: Final Data for 2010. *In:* SUDOL, J. (ed.) *National Vital Statistics Reports.* Hyattsville, MD: National Centre for Health Statistics.

SHNEERSON, J. M. 2005. *Sleep Medicine: A guide to sleep and its disorders* Massachusetts Wiley-Blackwell

SIEGEL, J. M. 2005. Clues to the functions of mammalian sleep. *Nature,* 437**,** 1264-71.

SILAS, R., SEHGAL, A., WALKER, A. M. & WONG, F. Y. 2012. Cerebral oxygenation during subclinical seizures in neonatal hypoxic-ischaemic encephalopathy. *European Journal of Paediatric Neurology,* 16**,** 304-307.

SILBER, M. H., ANCOLI-ISRAEL, S., BONNET, M. H., CHOKROVERTY, S., GRIGG-DAMBERGER, M. M., HIRSHKOWITZ, M., KAPEN, S., KEENAN, S. A., KRYGER, M. H., PENZEL, T., PRESSMAN, M. R. & IBER, C. 2007. The visual scoring of sleep in adults. *Journal of Clinical Sleep Medicine,* 3**,** 121-31.

SINGH, J. P., LARSON, M. G., TSUJI, H., EVANS, J. C., O'DONNELL, C. J. & LEVY, D. 1998. Reduced heart rate variability and new-onset hypertension: insights into pathogenesis of hypertension: the Framingham Heart Study. *Hypertension,* 32**,** 293-7.

SMYSER, C. D., INDER, T. E., SHIMONY, J. S., HILL, J. E., DEGNAN, A. J., SNYDER, A. Z. & NEIL, J. J. 2010. Longitudinal Analysis of Neural Network Development in Preterm Infants. *Cerebral Cortex,* 20**,** 2852-2862.

SOUL, J. S. & DU PLESSIS, A. J. 1999. Near-infrared spectroscopy. *Seminars in Pediatric Neurology,* 6**,** 101-110.

SOUL, J. S., HAMMER, P. E., TSUJI, M., SAUL, J. P., BASSAN, H., LIMPEROPOULOS, C., DISALVO, D. N., MOORE, M., AKINS, P., RINGER, S., VOLPE, J. J., TRACHTENBERG, F., DU PLESSIS, A. J., SOUL, J. S., HAMMER, P. E., TSUJI, M., SAUL, J. P., BASSAN, H., LIMPEROPOULOS, C., DISALVO, D. N., MOORE, M., AKINS, P., RINGER, S., VOLPE, J. J., TRACHTENBERG, F. & DU PLESSIS, A. J. 2007. Fluctuating pressure-passivity is common in the cerebral circulation of sick premature infants. *Pediatric Research,* 61**,** 467-73.

SOUTHALL, D. P., RICHARDS, J. M., RHODEN, K. J., ALEXANDER, J. R., SHINEBOURNE, E. A., ARROWSMITH, W. A., CREE, J. E., FLEMING, P. J., GONCALVES, A. & ORME, R. L. 1982. Prolonged apnea and cardiac arrhythmias in infants discharged from neonatal intensive care units: failure to predict an increased risk for sudden infant death syndrome. *Pediatrics,* 70**,** 844-51.

SPEER, C. P., SWEET, D. G. & HALLIDAY, H. L. 2013. Surfactant therapy: past, present and future. *Early Human Development,* 89 Suppl 1**,** S22-4.

STEINSCHNEIDER, A. 1972. Prolonged apnea and the sudden infant death syndrome: clinical and laboratory observations. *Pediatrics,* 50**,** 646-54.

STERN, E., PARMELEE, A. H., AKIYAMA, Y., SCHULTZ, M. A. & WENNER, W. H. 1969. Sleep cycle characteristics in infants. *Pediatrics,* 43**,** 65-70.

STRAUSS, R. G. 2010. Anaemia of prematurity: Pathophysiology and treatment. *Blood Reviews,* 24**,** 221-225.

SUZUKI, S., TAKASAKI, S., OZAKI, T. & KOBAYASHI, Y. 1999. Tissue oxygenation monitor using NIR spatially resolved spectroscopy. 582-592.

TAKASHIMA, S., ARMSTRONG, D., BECKER, L. & BRYAN, C. 1978. Cerebral hypoperfusion in the sudden infant death syndrome? Brainstem gliosis and vasculature. *Annals of Neurology,* 4**,** 257-62.

TAKASHIMA, S. & BECKER, L. E. 1991. Delayed dendritic development of catecholaminergic neurons in the ventrolateral medulla of children who died of sudden infant death syndrome. *Neuropediatrics,* 22**,** 97-9.

TASK FORCE ON SUDDEN INFANT DEATH SYNDROME 2011. SIDS and Other Sleep-Related Infant Deaths: Expansion of Recommendations for a Safe Infant Sleeping Environment. *Pediatrics,* 128**,** 1030-1039.

THILO, E. H. & ROSENBERG, A. A. 2010. The Late Preterm Infant *In:* HAY, W., LEVIN, M., SONDHEIMER, J. & DETERDING, R. (eds.) *Current Diagnosis and Treatment: Pediatrics.* 20 ed. Aurora, Colorado McGraw-Hill

THORESEN, M., COWAN, F. & WALLOE, L. 1991. Cardiovascular responses to tilting in healthy newborn babies. *Early Human Development,* 26**,** 213-22.

TOLCOS, M., HARDING, R., LOELIGER, M., BREEN, S., COCK, M., DUNCAN, J. & REES, S. 2003. The fetal brainstem is relatively spared from injury following intrauterine hypoxemia. *Brain Research. Developmental Brain Research,* 143**,** 73-81.

TRACHTENBERG, F. L., HAAS, E. A., KINNEY, H. C., STANLEY, C. & KROUS, H. F. 2012. Risk Factor Changes for Sudden Infant Death Syndrome After Initiation of Back-to-Sleep Campaign. *Pediatrics,* 129**,** 630-638.

TSUJI, M., SAUL, J. P., DU PLESSIS, A., EICHENWALD, E., SOBH, J., CROCKER, R. & VOLPE, J. J. 2000. Cerebral intravascular oxygenation correlates with mean arterial pressure in critically ill premature infants. *Pediatrics,* 106**,** 625-32.

TUCKER, J. & MCGUIRE, W. 2004. Epidemiology of preterm birth. *British Medical Journal,* 329**,** 675-678.

TUFFNELL, C. S., PETERSEN, S. A. & WAILOO, M. P. 1995. Prone sleeping infants have a reduced ability to lose heat. *Early Human Development,* 43**,** 109-116.

TULADHAR, R., HARDING, R., CRANAGE, S. M., ADAMSON, T. M. & HORNE, R. S. C. 2003. Effects of sleep position, sleep state and age on heart rate responses following provoked arousal in term infants. *Early Human Development,* 71**,** 157-169.

TULADHAR, R., HARDING, R., MICHAEL ADAMSON, T. & HORNE, R. S. C. 2005. Comparison of postnatal development of heart rate responses to trigeminal stimulation in sleeping preterm and term infants. *Journal of Sleep Research,* 14**,** 29-36.

TYSZCZUK, L., MEEK, J., ELWELL, C. & WYATT, J. S. 1998. Cerebral blood flow is independent of mean arterial blood pressure in preterm infants undergoing intensive care. *Pediatrics,* 102**,** 337-41.

VAN BEL, F., LEMMERS, P. & NAULAERS, G. 2008. Monitoring neonatal regional cerebral oxygen saturation in clinical practice: Value and pitfalls. *Neonatology,* 94**,** 237-244.

VAN HOFTEN, J. C., VERHAGEN, E. A., KEATING, P., TER HORST, H. J. & BOS, A. F. 2010. Cerebral tissue oxygen saturation and extraction in preterm infants before and after blood transfusion. *Archives of Disease in Childhood Fetal & Neonatal Edition,* 95**,** F352-8.

VECCHIERINI-BLINEAU, M. F., NOGUES, B., LOUVET, S. & DESFONTAINES, O. 1994. Maturation of generalized motility, spontaneous during sleep, from birth at term to the age of 6 months. *Neurophysiologie Clinique,* 24**,** 141-54.

VERBEEK, M. M., RICHARDSON, H. L., PARSLOW, P. M., WALKER, A. M., HARDING, R., HORNE, R. S., VERBEEK, M. M. A., RICHARDSON, H. L., PARSLOW, P. M., WALKER, A. M., HARDING, R. & HORNE, R. S. C. 2008. Arousal and ventilatory responses to mild hypoxia in sleeping preterm infants. *Journal of Sleep Research,* 17**,** 344-53.

VERHAGEN, E. A., HUMMEL, L. A., BOS, A. F. & KOOI, E. M. W. 2014. Near-infrared spectroscopy to detect absence of cerebrovascular autoregulation in preterm infants. *Clinical Neurophysiology,* 125**,** 47-52.

VISKARI, S., ANDERSSON, S., HYTINANTTI, T., KIRJAVAINEN, T., VISKARI, S., ANDERSSON, S., HYTINANTTI, T. & KIRJAVAINEN, T. 2007. Altered cardiovascular control in preterm infants with bronchopulmonary dysplasia. *Pediatric Research,* 61**,** 594-9.

VOLPE, J. J. 2008. *Neurology of the Newborn,* Philadelphia, PA, Saunders Elsevier.

VOLTOLINI, C., TORRICELLI, M., CONTI, N., VELLUCCI, F. L., SEVERI, F. M. & PETRAGLIA, F. 2013. Understanding Spontaneous Preterm Birth: From Underlying Mechanisms to Predictive and Preventive Interventions. *Reproductive Sciences,* 20**,** 1274-1292.

WAKAI, R. T. 2004. Assessment of fetal neurodevelopment via fetal magnetocardiography. *Experimental Neurology,* 190, Supplement 1**,** 65-71.

WALDMAN, S., KRAUSS, A. N. & AULD, P. A. M. 1979. Baroreceptors in preterm infants: Their telationship to maturity and disease. *Developmental Medicine & Child Neurology,* 21**,** 714-722.

WILLINGER, M., HOFFMAN, H. J. & HARTFORD, R. B. 1994. Infant sleep position and risk for sudden infant death syndrome: report of meeting held January 13 and 14, 1994, National Institutes of Health, Bethesda, MD. *Pediatrics,* 93**,** 814-9.

WILSON, A. J., STEVENS, V., FRANKS, C. I., ALEXANDER, J. & SOUTHALL, D. P. 1985. Respiratory and heart rate patterns in infants destined to be victims of sudden infant death syndrome: average rates and their variability measured over 24 hours. *British Medical Journal Clinical Research Ed,* 290**,** 497-501.

WISWELL, T. E., GRAZIANI, L. J., KORNHAUSER, M. S., STANLEY, C., MERTON, D. A., MCKEE, L. & SPITZER, A. R. 1996. Effects of hypocarbia on the development of cystic periventricular leukomalacia in premature infants treated with high-frequency jet ventilation. *Pediatrics,* 98**,** 918-24.

WITCOMBE, N. B., YIALLOUROU, S. R., SANDS, S. A., WALKER, A. M. & HORNE, R. S. 2012. Preterm birth alters the maturation of baroreflex sensitivity in sleeping infants. *Pediatrics,* 129**,** e89-96.

WITCOMBE, N. B., YIALLOUROU, S. R., WALKER, A. M. & HORNE, R. S. C. 2008. Blood pressure and heart rate patterns during sleep are altered in preterm-born infants: implications for sudden infant death syndrome. *Pediatrics,* 122**,** e1242-e1248.

WITCOMBE, N. B., YIALLOUROU, S. R., WALKER, A. M. & HORNE, R. S. C. 2009. Delayed blood pressure recovery after head-up tilting during sleep in preterm infants. *Journal of Sleep Research,* 19**,** 93-102.

WOLF, M. & GREISEN, G. 2009. Advances in near-infrared spectroscopy to study the brain of the preterm and term neonate. *Clinics in Perinatology,* 36**,** 807-34.

WONG, F., YIALLOUROU, S. R., ODOI, A., BROWNE, P., WALKER, A. M. & HORNE, R. S. C. 2013. Cerebrovascular control is altered in healthy term infants when they sleep prone. *Sleep,* 36**,** 1911-1918.

WONG, F. Y., ALEXIOU, T., SAMARASINGHE, T., BRODECKY, V. & WALKER, A. M. 2010. Cerebral arterial and venous contributions to tissue oxygenation index measured using spatially resolved spectroscopy in newborn lambs. *Anesthesiology,* 113**,** 1385-91.

WONG, F. Y., BARFIELD, C. P., HORNE, R. S., WALKER, A. M., WONG, F. Y., BARFIELD, C. P., HORNE, R. S. C. & WALKER, A. M. 2009a. Dopamine therapy promotes cerebral flow-metabolism coupling in preterm infants. *Intensive Care Medicine,* 35**,** 1777-82.

WONG, F. Y., LEUNG, T. S., AUSTIN, T., WILKINSON, M., MEEK, J. H., WYATT, J. S., WALKER, A. M., WONG, F. Y., LEUNG, T. S., AUSTIN, T., WILKINSON, M., MEEK, J. H., WYATT, J. S. & WALKER, A. M. 2008. Impaired autoregulation in preterm infants identified by using spatially resolved spectroscopy. *Pediatrics,* 121**,** e604-11.

WONG, F. Y., NAKAMURA, M., ALEXIOU, T., BRODECKY, V. & WALKER, A. M. 2009b. Tissue oxygenation index measured using spatially resolved spectroscopy correlates with changes in cerebral blood flow in newborn lambs. *Intensive Care Medicine,* 35**,** 1464-70.

WONG, F. Y., WITCOMBE, N. B., YIALLOUROU, S. R., YORKSTON, S., DYMOWSKI, A. R., KRISHNAN, L., WALKER, A. M. & HORNE, R. S. C. 2011. Cerebral oxygenation is depressed during sleep in healthy term infants when they sleep prone. *Pediatrics,* 127**,** e558-e565.

YATES, B. J. 1996. Vestibular influences on the autonomic nervous system. *Annals of the New York Academy of Sciences,* 781**,** 458-73.

YATES, B. J. & MILLER, A. D. 1994. Properties of sympathetic reflexes elicited by natural vestibular stimulation: implications for cardiovascular control. *Journal of Neurophysiology,* 71**,** 2087-92.

YIALLOUROU, S. R., SANDS, S. A., WALKER, A. M. & HORNE, R. S. 2010. Postnatal development of baroreflex sensitivity in infancy. *Journal of Physiology,* 588**,** 2193-203.
YIALLOUROU, S. R., SANDS, S. A., WALKER, A. M. & HORNE, R. S. 2011. Baroreflex sensitivity during sleep in infants: impact of sleeping position and sleep state. *Sleep,* 34**,** 725-32.
YIALLOUROU, S. R., SANDS, S. A., WALKER, A. M. & HORNE, R. S. 2012. Maturation of heart rate and blood pressure variability during sleep in term-born infants. *Sleep,* 35**,** 177-86.
YIALLOUROU, S. R., WALKER, A. M. & HORNE, R. S. 2006. Validation of a new noninvasive method to measure blood pressure and assess baroreflex sensitivity in preterm infants during sleep. *Sleep,* 29**,** 1083-8.
YIALLOUROU, S. R., WALKER, A. M. & HORNE, R. S. 2008a. Effects of sleeping position on development of infant cardiovascular control. *Archives of Disease in Childhood,* 93**,** 868-72.
YIALLOUROU, S. R., WALKER, A. M. & HORNE, R. S. 2008b. Prone sleeping impairs circulatory control during sleep in healthy term infants: implications for SIDS. *Sleep,* 31**,** 1139-46.
YIALLOUROU, S. R., WITCOMBE, N. B., SANDS, S. A., WALKER, A. M. & HORNE, R. S. 2013. The development of autonomic cardiovascular control is altered by preterm birth. *Early Human Development,* 89**,** 145-52.
YOKOYAMA, M., UEDA, W., HIRAKAWA, M. & YAMAMOTO, H. 1991. Hemodynamic effect of the prone position during anesthesia. *Acta Anaesthesiologica Scandinavica,* 35**,** 741-4.
YOSHITANI, K., KAWAGUCHI, M., MIURA, N., OKUNO, T., KANODA, T., OHNISHI, Y., KURO, M., YOSHITANI, K., KAWAGUCHI, M., MIURA, N., OKUNO, T., KANODA, T., OHNISHI, Y. & KURO, M. 2007. Effects of hemoglobin concentration, skull thickness, and the area of the cerebrospinal fluid layer on near-infrared spectroscopy measurements. *Anesthesiology,* 106**,** 458-62.
ZOCCOLI, G., ANDREOLI, E., BOJIC, T., CIANCI, T., FRANZINI, C., PREDIERI, S. & LENZI, P. 2001. Central and baroreflex control of heart rate during the wake-sleep cycle in rat. *Sleep,* 24**,** 753-8.
ZOTTER, H., GROSSAUER, K., REITERER, F., PICHLER, G., MUELLER, W., URLESBERGER, B., ZOTTER, H., GROSSAUER, K., REITERER, F., PICHLER, G., MUELLER, W. & URLESBERGER, B. 2008. Is bladder voiding in sleeping preterm infants accompanied by arousals? *Sleep Medicine,* 9**,** 137-41.
ZOTTER, H., KERBL, R., REITERER, F., PICHLER, G., HANZER, M., MUELLER, W., ZOTTER, H., KERBL, R., REITERER, F., PICHLER, G., HANZER, M. & MUELLER, W. 2009. Unchanged heart rate-respiratory frequency ratio in preterm infants during spontaneous arousals. *Acta Paediatrica,* 98**,** 47-51.

Appendices

Appendix A

ARTICLE IN PRESS

Sleep Medicine Reviews xxx (2013) 1–12

Contents lists available at SciVerse ScienceDirect

Sleep Medicine Reviews

journal homepage: www.elsevier.com/locate/smrv

CLINICAL REVIEW

The development of cardiovascular and cerebral vascular control in preterm infants

Karinna L. Fyfe [a], Stephanie R. Yiallourou [a], Flora Y. Wong [a,b,c], Rosemary S.C. Horne [a,*]

[a] The Ritchie Centre, Monash Institute of Medical Research, Monash University, Melbourne, Australia
[b] Monash Newborn, Monash Medical Centre, Melbourne, Australia
[c] Department of Paediatrics, Monash University, Melbourne, Australia

ARTICLE INFO

Article history:
Received 21 December 2012
Received in revised form
20 June 2013
Accepted 25 June 2013
Available online xxx

Keywords:
Premature infant
Cardiovascular control
Heart rate
Blood pressure
Cerebral vascular control
Cerebral pressure autoregulation
Cerebral blood flow–metabolism coupling
Cerebral vasoreactivity

SUMMARY

Over the past three decades there has been a steady increase in the incidence of preterm birth. The worldwide rate of preterm birth is estimated to be 9.6% of all births, a total of almost 13 million births annually. Preterm birth is associated with a range of adverse cardiovascular and central nervous system outcomes, which may be attributed to altered development of these systems following preterm birth. Preterm birth has a considerable impact on cardiovascular parameters with preterm infants displaying higher heart rates and reduced blood pressure when compared to term born infants at matched ages. Furthermore, premature infants have altered autonomic control of cardiovascular parameters which manifests as abnormalities in heart rate variability and baroreflex mediated control of heart rate and blood pressure. As a result, systemic cardiovascular parameters can be unstable following preterm birth which may place stress on the neonatal brain. The brain of a preterm infant is particularly vulnerable to these fluctuations due to immature cerebral haemodynamics. Preterm infants, particularly those who are very preterm or unwell, display fluctuating pressure-passivity between systemic blood pressure and cerebral blood flow representing a considerably increased risk of cerebral haemorrhage or hypoxia. This is further compounded by immaturity of cerebral blood flow–metabolism coupling, which means increased metabolic demand cannot adequately be met by increased cerebral blood flow. It has been suggested that adverse long-term outcomes following preterm birth may occur as a result of exposure to physiological stress either in-utero or early in infancy.

Introduction

Preterm birth, defined as birth prior to 37 wk of gestation, has been steadily increasing in recent years and now accounts for 9.6% of births worldwide, a total of approximately 13 million births annually [1]. The rate of preterm birth is rising due in part to advances in assisted reproduction technology leading to an increase in the number of multiple births and an increase in the number of medically indicated preterm births [2].

Increasing rates of preterm birth are being accompanied by increasing survival rates in infants born prematurely, particularly those born very prematurely. Prior to the introduction of assisted ventilation, antenatal corticosteroids and artificial surfactant, survival rates of infants born prior to 28 wk gestational age (GA) were low. Currently, survival rates for infants born at 22 wk vary from 0 to 12%, increasing to 53–88% at 26 wk GA [3].

However, despite improved survival, prematurity is associated with a range of both short and long-term poor outcomes. At the time of birth, preterm infants are more likely to be growth restricted, exposed to intrauterine inflammation in the form of chorioamnionitis or to have experienced foetal distress, as these are common reasons for preterm labour or early delivery [2]. In the immediate neonatal period, preterm infants are at an increased risk of short-term complications including respiratory distress syndrome, necrotising enterocolitis and intracranial haemorrhage. As a consequence, poor long-term outcomes including neurodevelopmental delay and chronic lung disease are also common in preterm infants [3]. The risk of major medical disability as a result of preterm birth increases significantly with decreasing GA, with one in nine infants born at 23–27 wk GA receiving a disability pension at 19–35 y compared with one in 42 for those born at 34–36 wk GA [4].

* Corresponding author. The Ritchie Centre, Level 5, Monash Medical Centre, 246 Clayton Road, PO Box 5418, Clayton, Victoria 3168, Australia. Tel.: +61 3 9594 5100; fax: +61 3 9594 6811.
E-mail address: [redacted] (R.S.C. Horne).

1087-0792/$ – see front matter Crown Copyright © 2013 Published by Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.smrv.2013.06.002

Please cite this article in press as: Fyfe KL, et al., The development of cardiovascular and cerebral vascular control in preterm infants, Sleep Medicine Reviews (2013), http://dx.doi.org/10.1016/j.smrv.2013.06.002

Abbreviations

ANS	autonomic nervous system
AS	active sleep
BP	blood pressure
BRS	baroreflex sensitivity
CA	corrected age
CBF	cerebral blood flow
CBV	cerebral blood volume
$CMRO_2$	cerebral metabolic rate of oxygen consumption
CNS	central nervous system
CO_2	carbon dioxide
CRIB	clinical risk index for babies
GA	gestational age
Hb	haemoglobin
HbD	haemoglobin difference
HF	high frequency
Hb	haemoglobin
HbT	total haemoglobin
HR	heart rate
HRV	heart rate variability
IVH	intraventricular haemorrhage
LF	low frequency
MAP	mean arterial pressure
NIRS	near-infrared spectroscopy
O_2	oxygen
O_2Hb	oxygenated haemoglobin
$PaCO_2$	partial pressure of carbon dioxide
PaO_2	partial pressure of oxygen
PDA	patent ductus arteriosus
PVL	periventricular leukomalacia
$rScO_2$	regional cerebral oxygen saturation
QS	quiet sleep
$S_{CT}O_2$	percentage of saturated oxygen in the cortical tissue
TOI	tissue oxygenation index

Although the major morbidities associated with preterm birth are well documented, the more subtle effects of premature birth on development are largely unexplored. It has been suggested that cardiovascular and central nervous system (CNS) disease may develop later in life as a result of disrupted development following preterm birth [5]. The exact mechanisms resulting in disrupted development remain unclear but are likely to be complex and multifactorial; we suggest impaired vascular control may play a role. As such, this review aims to investigate the influence of premature birth on the development of cardiovascular and cerebral vascular control early in infancy.

Development and control of the cardiovascular system

At term the cardiovascular system is not yet fully mature and maturation continues for several weeks after birth. Mitotic divisions of the myocardium have been found to continue for several weeks after birth and the mechanical performance of the myocardium shows improvement with increasing postnatal age [6]. An additional challenge during this period of rapid cardiovascular development is the transition from intrauterine to extrauterine life which occurs at birth and requires significant circulatory changes. In order to switch from a placental oxygen source to a pulmonary source, critical structural changes must occur, including the closing of circulatory shunts such as the ductus arterious, ductus venosus and foramen ovale [7]. In infants born prematurely, these shunts often do not close immediately after birth, contributing to cardiovascular instability during this period and placing infants at risk of circulatory complications [7].

The cardiovascular system is largely controlled by the autonomic nervous system (ANS). The ANS can be separated into two divisions: the sympathetic nervous system, responsible for increasing heart rate (HR) and blood pressure (BP), and the parasympathetic nervous systems, responsible for reducing HR and BP [8]. Autonomic control of the cardiovascular system undergoes considerable development during foetal life, however the parasympathetic and sympathetic branches develop differently. The sympathetic branch appears to develop most rapidly during the first trimester, developing more slowly thereafter, whilst parasympathetic or vagal control becomes dominant later in foetal development at 25–30 wk GA [9]. ANS control of cardiovascular parameters involves a complex interaction between the two branches and the degree of input of each branch, known as the sympathovagal balance [10].

Heart rate variability (HRV), the fluctuation in the length of time between consecutive heart beats, is a commonly used tool to assess autonomic cardiovascular control. In adults, altered HRV has been associated with adverse cardiovascular mortality [11]. HRV can be divided into short-term or high frequency (HF) variability and long-term or low frequency (LF) variability [11]. HF variability reflects parasympathetic vagal tone and is affected by respiratory frequency while LF variability is influenced by a combination of both parasympathetic and sympathetic inputs and baroreflex mediated HR changes [12,13]. Although spectral divisions have been clearly defined in adults, these cannot be applied to infants as immaturity of autonomic control results in altered parasympathetic influence and rapid fluctuations in HR and BP. Recently, taking into account these differences and based on previous studies, neonatal spectral divisions have been proposed; these are 0.04–0.15 Hz for LF and 0.4–1.5 Hz for HF [14]. ANS control of the cardiovascular system and the sympathovagal balance are influenced by a range of factors including sleep state and age.

Infant sleep

Sleep is a physiologically important state during which repair, restoration and growth of the body occurs. Sleep is particularly important during infancy, when growth and development are most rapid, and this is reflected in the amount of time infants spend sleeping. Term born infants spend up to 70% of each day asleep, while in preterm infants this can increase up to 90%, meaning over 20 h each day are spent asleep [15]. Infant sleep is immature when compared to adult sleep with infants exhibiting two distinct sleep states; quiet sleep (QS), which is the immature equivalent to non-rapid eye movement sleep in adults and active sleep (AS) which is the precursor to adult rapid-eye movement sleep. Sleep state has a significant influence on the cardiovascular system; in term born infants, AS is associated with sympathetic dominance resulting in elevated HR and BP and increased LF power in HR and BP variability compared to QS [16]. Thus, it is important to take sleep state into consideration when assessing cardiovascular parameters during sleep in infants.

Postnatal age

Postnatal age also has a considerable influence on ANS cardiovascular control with a significant reduction in HR seen during the

Please cite this article in press as: Fyfe KL, et al., The development of cardiovascular and cerebral vascular control in preterm infants, Sleep Medicine Reviews (2013), http://dx.doi.org/10.1016/j.smrv.2013.06.002

first few months of life due to increased parasympathetic input [10]. At term age, autonomic control is not yet fully mature and alterations in sympathovagal balance continue throughout infancy until at least six months of age [16]. Consequently, following preterm birth infants display a significant immaturity of the ANS and its control of cardiovascular parameters [17]. As such, it is pertinent to consider both GA at birth and postnatal age at the time of assessment when considering cardiovascular parameters in term and preterm infants.

Cardiovascular control in preterm infants

Cardiovascular parameters following preterm birth

Heart rate

Preterm birth has a considerable effect on cardiovascular parameters including HR and BP. Preterm infants at term-equivalent age have higher resting HRs than infants born at term and this persists up until seven months of age [18,19]. It has been suggested that while HR is primarily dependent on post-conceptional age, fluctuations in HR are also influenced by postnatal age, with HR in both preterm and term infants peaking between 4 and 10 wk postnatal age [18]. Similar studies have also found HR to be significantly higher in preterm infants assessed at term-equivalent age than term born control infants [19]; with one study finding preterm infants to have a HR of 155 beats per minute versus 117 beats per minute in term infants [20]. However, some conflicting studies have found no difference in HR between preterm and term infants when studied at 2–3 wk and 2–3 mo post-term corrected age (CA) [21]. Similarly, in preterm infants born between 28 and 32 wk GA, no difference in HR between preterm and term infants was seen when followed up to six months post-term corrected age [22]. These studies also found that the increase in HR from QS to AS due to the increased sympathetic activity in AS, seen in term infants was absent in preterm infants until 5–6 mo post-term age, suggesting that impaired autonomic function persists past term-equivalent age in preterm infants, despite finding no baseline difference in HR between preterm and term infants [21,22].

Blood pressure

Only a limited number of studies have assessed how BP changes with increasing postnatal age in preterm infants. Early studies assessing BP in preterm infants found that at approximately 12 wk post-term age there was no difference in BP between preterm and term infants [23]. A supporting study assessing BP in very low birth weight and low birth weight preterm infants and normal birth weight term infants at four months post-conceptional age found no significant difference in BP between groups [24]. More recently, a study assessing BP continuously during sleep in preterm infants has reported BP to be lower in preterm compared to term infants at matched ages up until 5–6 mo post-term age [22]. This study found no difference in HR between the preterm and term infants and the authors concluded that altered vascular regulation, as opposed to impaired cardiac function, was responsible for the discrepancy in BP between groups. This study found BP to be significantly higher in AS compared to QS in preterm infants studied at 2–4 wk, 2–3 mo and 5–6 mo CA [22]. These studies suggest that baseline HR and BP may be altered as a result of preterm birth which implies that preterm birth may have a considerable effect on cardiovascular control.

Cardiovascular control following preterm birth

Heart rate variability

HR variability is commonly used to determine the integrity of ANS control of HR and can provide information about sympathetic and parasympathetic activity. A number of studies have investigated the normal maturation of autonomic HR control. Clairambault et al., compared the HR and HRV parameters of eight preterm infants (31–36 wk gestation), eight intermediate infants (37–38 wk gestation) and eight full term infants (38–41 wk gestation) in order to assess maturation of the ANS [25]. This study found that all HRV parameters increased from preterm to intermediate to term infants reflecting autonomic maturation. The authors also reported that HF variability underwent a steep increase from preterm age to intermediate age infants, plateauing thereafter, while LF variability increased steadily from 31 to 41 wk [25], thus parasympathetic activity undergoes a period of rapid development in late gestation. Similar results have been reported more recently in a study which compared 39 premature neonates born at 29–35 wk GA and studied within one week of birth with normative data for term infants. Consistent with previous studies, this study revealed preterm infants to have reduced HRV parameters compared to term infants, particularly in the HF variability domain [26]. Furthermore, when the premature infants were divided into those born prior to 32 wk and those born after 32 wk those born at a later gestation had higher HRV parameters, particularly in the HF domain [26]. In summary, shortly after birth preterm infants display immature ANS cardiovascular control, particularly the parasympathetic branch, as a direct result of a reduced gestational period. However, these studies did not follow infants longitudinally to term age and thus did not investigate maturation of cardiovascular control following preterm birth.

Studies assessing the effect of preterm birth on the postnatal maturation of autonomic HR control suggest that preterm birth impairs normal maturation, as preterm infants reaching theoretical term have reduced HRV compared to term infants [19,27]. One study comparing 12 prematurely born infants studied between 37 and 41 wk post-conceptional age with 16 term born infants studied at <10 d postnatal age, found the preterm cohort to have reduced HRV and an altered sympathovagal balance with diminished parasympathetic activity [19]. This study also demonstrated that while in the term infants HR and LF variability were higher in AS compared to QS, in preterm infants there was no apparent effect of sleep state. Similar results were found in a study which compared 23 preterm infants born between 25 and 37 wk GA and studied at term-equivalent age with eight full term infants studied within the first week of life. HF HRV was found to be significantly lower in the preterm compared to the term born infants, suggesting delayed parasympathetic maturation, with greater prematurity being associated with lower parasympathetic activity at term age [27]. A recent, study which compared HRV parameters between foetuses at 25–36 wk GA and premature infants born between 24 and 36 wk GA, found lower HF variability in the premature infants, thus supporting previous studies suggesting preterm birth results in delayed maturation of cardiovascular control [28].

In summary, a number of studies have suggested that preterm delivery is associated with altered autonomic activity, particularly suppression of the parasympathetic branch, representing an impaired ability to control HR in healthy, low risk preterm infants. It has been suggested that prematurity impairs parasympathetic maturation, possibly due to prioritisation of processes necessary for life, such as breathing and digestion, over the growth and development of less essential systems, such as the nervous system [19,28]. Altered cardiovascular control may place these infants at risk of cardiovascular instability, particularly during sleep, in the first year of life.

Baroreflex mediated cardiovascular control

The arterial baroreceptors, located in the aortic arch and the carotid sinuses, play an important role in short-term regulation of

Please cite this article in press as: Fyfe KL, et al., The development of cardiovascular and cerebral vascular control in preterm infants, Sleep Medicine Reviews (2013), http://dx.doi.org/10.1016/j.smrv.2013.06.002

BP. Alterations in BP, detected as changes in vascular stretch, modify the rate of firing of the afferent baroreceptor fibres and this signal is carried via afferent fibres in the vagus and glossopharyngeal nerve primarily to the nucleus tractus solitarius located in the lower brainstem. From here, modulation of efferent sympathetic and parasympathetic activity results in alterations in HR, cardiac contractility and peripheral vascular resistance [29]. Increased BP results in decreases in HR, heart contractility and vascular tone, whilst decreased BP stimulates the opposite in order to return BP to normal levels. Thus the baroreflex is the most important autonomic mechanism for short-term regulation of BP. Sensitivity of the baroreflex is commonly tested using head-up or head-down tilts. In adults, head-up tilting results in a small, transient decrease in arterial BP resulting in a baroreflex mediated increase in HR and peripheral vascular tone [30]. There is also an increase in the LF component and a decrease in the HF component of HR variability, the magnitude of which corresponds to the degree of the tilt [31]. In term infants in the supine position, head-up tilting results in a biphasic response with a transient increase and then decrease in HR and BP followed by a return to baseline [32–34]. In the prone position, BP tends to drop initially following the tilt, while HR displays the biphasic response seen in the supine position [32].

Early studies investigating baroreflex function in preterm infants focused primarily on HR and produced conflicting results. One early study found no significant tachycardia when non-distressed preterm infants aged between 26 and 38 wk were head-up tilted to an angle of 45° [35]. Following on from this study, the same group later reported a significant increase in HR in the first 5 s following the tilt, but stated that individual responses varied greatly and concluded that the HR component of the baroreflex was immature in the neonatal period [36]. Neither of these studies took into account sleep state which significantly affects HR. Similar results were produced from a later study which failed to illicit a significant increase in HR following a 45° head-up tilt in preterm infants born between 27 and 36 wk [37]. In contrast, further studies investigating the effect of tilting on HR in term [38,39] and preterm infants [38,40] have found significant increases in HR following a head-up tilt in both QS and AS. These differences may be attributed to the varying gestational ages of the infants studied, a suggestion supported by Mazursky et al., who studied infants born at 28–32 wk gestational age longitudinally across the first five postnatal weeks. This study revealed an increased HR response to 45° head-up tilting with increasing postnatal age, suggesting that in preterm infants baroreflex control of HR matures with age [41].

Only a limited number of studies have assessed baroreflex control of BP, due to a paucity of appropriate methods for non-invasively inducing changes in BP and techniques for measuring BP continuously and non-invasively. Drouin et al., validated a method of analysing spontaneous fluctuations in BP and the corresponding changes in HR to assess baroreflex sensitivity (BRS) [42], and found that preterm infants studied prior to term age had lower BRS than term born infants. Using similar methods, postnatal maturation of BRS following preterm birth was assessed in a cohort of preterm infants (mean gestation of 30.6 wk), studied longitudinally once a week until discharge from hospital. This study revealed significant maturation of BRS with increasing postnatal age, however preterm infants reaching term still had significantly lower BRS than infants born at term [43]. Similar results were reported by Andreissen et al., who investigated BRS in two groups of preterm infants born at 28–32 and 32–37 wk GA and a cohort of term infants, using spontaneous fluctuations in HR and BP. Consistent with previous studies, they found that BRS increased with increasing postnatal age and this was attributed to parasympathetic maturation because vagally mediated HF variability also increased with age [44]. Furthermore, a recent study following preterm infants up to 5–6 mo CA found preterm infants had significantly reduced BRS at 5–6 mo CA compared to term infants [45]. This was despite having higher BRS at 2–4 wk CA, suggesting that while term infants undergo considerable maturation during the first six months of life, this maturation is significantly altered in preterm infants [45]. Thus, reduced BRS may leave preterm infants vulnerable to both hypotensive and hypertensive episodes, as short-term regulation of BP is impaired.

BP control in preterm infants has also been assessed using head-up tilts. Witcombe et al., studied preterm infants born between 28 and 32 wk GA at 2–4 wk, 2–3 mo and 5–6 mo CA using 15° head-up tilts during QS and AS. They found that although HR responses were comparable between preterm and term infants, the BP response was significantly altered at 2–4 wk and 2–3 mo, with BP in the preterm cohort taking significantly more heart beats to return to baseline following the tilt [46]. Similarly, Cohen et al., found that appropriately grown preterm infants exhibited an exaggerated BP response to a 60° head-up tilt compared to term born control infants, with the exaggeration being much greater in small for gestational age preterm infants and infants born to smoking mothers [34]. Altered BP responses were also found in preterm infants with bronchopulmonary dysplasia compared with term control infants who underwent sideways-motion and 45° head-up tilts at 12 wk CA [47]. These responses have been attributed to sympathetic hyperactivity and may represent early physiological programming in response to adverse circumstances experienced early in development. It has been suggested that this may represent the early manifestations of impaired cardiovascular function which can lead to cardiovascular disease later in life.

In summary, studies investigating both HR and BP control have found autonomic cardiovascular control, predominantly parasympathetic activity, to be immature in preterm infants up to and beyond term-equivalent age. This may be because premature birth stunts the development of parasympathetic activity or alternatively, altered ANS activity may have contributed to the premature birth. A number of theories have been suggested to explain ANS immaturity in preterm infants, including cardiac and vessel innervation, neurotransmitter production and receptor efficiency, however, it is possible that ANS immaturity reflects global central nervous system (CNS) immaturity related directly to a reduced gestational period [27]. Following preterm birth, normal development may be impaired as vital functions previously undertaken by the placenta take precedence over planned maturation [27]. In this case, global CNS immaturity may imply immaturity of other functions, and in the case of very preterm birth, this may even include functions of the vital organs such as control of the cerebral vascular circulation.

Cerebrovascular control

The brain is a highly metabolically active organ, requiring 3.5 ml of oxygen per 100 g of brain tissue per minute which accounts for approximately 15% of the total resting cardiac output. Approximately 60% of the total energy usage of the brain is for generation of continuous electrical activity by neurons. The remaining 40% of energy usage is responsible for homeostatic cellular functions undertaken largely by the supporting cells within the brain. The neuronal component of cerebral energy usage is more variable, responding to changes in functional state and arousal, thus the major contributor to changes in cerebral metabolic activity is neuronal activity [48].

Consciousness is lost within 10 s of complete occlusion of cerebral blood flow with corresponding irreversible damage to tissues. Due to this high metabolic activity, impaired cerebral blood flow (CBF) resulting in hypoxia and ischaemia or haemorrhage can

Please cite this article in press as: Fyfe KL, et al., The development of cardiovascular and cerebral vascular control in preterm infants, Sleep Medicine Reviews (2013), http://dx.doi.org/10.1016/j.smrv.2013.06.002

have catastrophic effects on cerebral tissue. Furthermore, the immature brain is particularly susceptible to oxidative stress, thus hyper-perfusion and hyper-oxygenation are major concerns in the context of preterm brain injury [49,50]. Thus, it is important to maintain relatively constant CBF in the presence of changing systemic variables. In the healthy, adult brain, CBF is influenced by myogenic mechanisms principally cerebral pressure autoregulation; metabolic mechanisms including cerebral blood flow–metabolism coupling; chemical influences, particularly oxygen (O_2) and carbon dioxide (CO_2) and to a lesser degree neural mechanisms, including efferent vasomotor effects, mechanoreceptors and chemoreceptors. As such, clinicians and scientists alike have been interested in investigation of cerebral haemodynamics for clinical and research purposes.

Methods of investigating cerebral haemodynamics

When clinicians and scientists initially became interested in the investigation of CBF in preterm neonates the common measurement techniques had a number of limitations. Xenon-133 and positron emission tomography, which involves measurement of xenon-133 clearance to determine CBF, is limited by its use of ionising radiation and the associated risks. Another commonly used technique, Doppler ultrasound velocimetry has limited use due to operator-dependence and the technical difficulty in maintaining angle of insonation for optimal measurement. Furthermore, jugular occlusion plethysmography, which involves complete occlusion of the jugular vein by direct pressure, is both inaccurate and risky in small, unstable preterm infants [51].

Thus, the need existed for a simple, non-invasive and safe method of measuring CBF which became available with the introduction of near-infrared spectroscopy (NIRS). NIRS utilises near-infrared light which is capable of penetrating biological tissue and is absorbed in an oxygen-dependent manner by haemoglobin [52]. Near-infrared light passes particularly easily through the thin and soft bone of the neonatal skull, thus enabling NIRS to provide non-invasive measurement of cerebral haemodynamics in neonates [53].

Although a significant improvement on previous techniques, NIRS is not without its own limitations. These include a relatively high signal-to-noise ratio, susceptibility to movement artefact and intra-patient and inter-patient variation [54]. Another concern is the non-specific, regional measurement of tissue oxygenation which includes measurement of all tissues between the light source and the detector including skin, bone, cerebrospinal fluid, and brain matter to an unknown depth [55]. Furthermore, NIRS provides a weighted average of the saturations within the venous and arterial compartments; this weighting is difficult to determine precisely and may differ over time [55]. However, it is currently one of the most widely used techniques for assessment of cerebral haemodynamics in infants [54].

The most common prototype of NIRS used in clinical research is the continuous wave NIRS. Continuous wave NIRS provides continuous changes in oxygenated Hb (ΔO_2Hb) and deoxygenated Hb (ΔHHb). As oxygenated Hb can fall as a result of reduced oxygen saturation and reduced Hb concentration, the haemoglobin difference signal (HbD), calculated by subtracting ΔHHb from ΔO_2Hb, is used to assess changes due to oxygen saturation alone. Furthermore, total Hb (HbT), calculated by adding ΔO_2Hb and ΔHHb, is an important indicator of cerebral blood volume (CBV) [48]. Continuous wave NIRS can be used to obtain absolute intermittent quantification of CBF and CBV, by employing spontaneous or induced (by haemodynamic or biochemical manipulation) parameter changes in tissue. Most commonly, measurement of CBF by NIRS utilises a modification of the Fick principle and a purely intravascular and non-diffusable tracer. The tracer can be either endogenous, such as the oxygen bolus technique [56] or exogenous, such as the near-infrared dye, indocyanine green, administered intravenously [57].

The clinical drive for absolute values of cerebral haemodynamics without the need for biochemical or haemodynamic manipulation has led to the development of "cerebral oximetry" using NIRS techniques. Using multi-distanced sensors and different algorithms [58–60] absolute values of cerebral oxygenation can be calculated from the changes in oxygenated and deoxygenated Hb. This is often expressed as tissue oxygenation index (TOI) or regional cerebral oxygen saturation ($rScO_2$), depending on the NIRS prototype and algorithms used [55].

HbD, TOI and $rScO_2$ have been used as surrogates of CBF with a few assumptions which include stability of arterial oxygen saturation and cerebral metabolic rate [55]. Additional parameters discussed in this review include cerebral metabolic rate of oxygen consumption ($CRMO_2$) which refers to the rate at which oxygen is used within the cerebral tissue and thus is a marker of cerebral metabolic activity. Cerebral fractional tissue oxygen extraction refers to the percentage of oxygen being extracted from the arterial blood by the cerebral tissue and can be used to determine the balance between oxygen delivery and consumption. Cerebral oxygen delivery refers to the combination of CBF and cerebral arterial oxygen content. Cerebral arterial oxygen content can be calculated using the standard formula: arterial oxygen saturation $\times$ Hb $\times$ 1.39 (stoichiometric oxygen capacity of Hb) + dissolved oxygen [50].

New technologies for non-invasive assessment of cerebral haemodynamics are under investigation and include techniques such as arterial spin-labelled perfusion magnetic resonance spectroscopy, however this requires the patient to be transported to a magnetic resonance imaging facility and provides only a cross-sectional snapshot of data, and diffuse optical correlation spectroscopy for which portable devices are currently being developed [61,62].

Cerebral autoregulation

In adults, CBF is tightly controlled in order to ensure that the brain's metabolic requirements are constantly met. CBF is determined by the cerebral perfusion pressure and cerebrovascular resistance. Cerebral perfusion pressure is the pressure gradient which drives blood flow to the brain, and is influenced by systemic arterial pressure and intracranial pressure [63]. Due to the rigid nature of the skull, intracranial pressure is determined by the contents of the skull, and in the absence of oedema, postural changes or occlusion of the neck vessels, should remain relatively stable. Systemic arterial pressure, however, can undergo large fluctuations and thus the cerebral vasculature must be capable of protecting the brain against these fluctuations in order to maintain a constant perfusion pressure. This is referred to as cerebral pressure autoregulation and involves changes in cerebrovascular resistance by constriction and dilation of cerebral vessels in the presence of increasing or decreasing arterial pressure in order to ensure CBF remains steady [63]. In adults, cerebral pressure autoregulation operates within a range of BPs (mean arterial pressure (MAP) between 60 and 150 mmHg) above and below which CBF becomes pressure-passive, changing in direct correlation with changes in BP [8]. Cerebral autoregulation can be divided into 'static' and 'dynamic' with static autoregulation referring to the steady-state relationship between MAP and CBF while dynamic autoregulation describes the short-term response of CBF to sudden changes in MAP [64]. In infants, especially those born preterm and requiring intensive care, cerebral pressure autoregulation may be immature, may operate within a narrower range of arterial pressures, or be impaired to the extent of having a pressure-passive cerebral circulation [65].

Please cite this article in press as: Fyfe KL, et al., The development of cardiovascular and cerebral vascular control in preterm infants, Sleep Medicine Reviews (2013), http://dx.doi.org/10.1016/j.smrv.2013.06.002

Cerebral blood flow–metabolism coupling

In addition to BP, CBF is also influenced by cerebral metabolic demand. CBF–metabolism coupling ensures that regions with increased cerebral metabolism due to increased neuronal activity receive increased CBF. This mechanism is believed to be more linearly related to increased glucose requirements than to increased oxygen demand [66]. A number of different substances have been suggested to mediate increased blood flow in the presence of increased neuronal activity including potassium, adenosine and nitric oxide; however the precise interactions between these substances and CBF remain unclear [66]. In the healthy adult brain, increased blood flow actually overshoots the oxygen requirements of working neurones, resulting in an increase in cerebral oxygenation [67]. In infants, CBF–metabolism coupling is likely to be immature and so increasing neuronal activity requirements are met by increased oxygen extraction which results in a reduction in cerebral oxygenation [68]. This is evidenced by a decrease in cerebral oxyhaemoglobin concentration following the transition from QS, a state of brain quiescence and low metabolic activity, to AS, a state of increased brain metabolic activity similar to wakefulness [69]. In studies of brain activation following visual stimulation, NIRS detected an increase in cerebral blood volume as well as an increase in deoxygenated haemoglobin suggesting that in term infants, increases in oxygen consumption due to neuronal activity outstrip the haemodynamic response of increased blood flow [70]. Evidence of maturation of CBF–metabolism coupling after term birth was shown in one study which longitudinally investigated cerebral tissue oxygenation index across the first six months of life in term infants during both QS and AS. At 2–4 wk of age cerebral oxygenation was higher in QS than in AS, which suggests immature cerebral blood flow–metabolism coupling as the increased metabolic demand of AS is not being met by increased CBF resulting in increased oxygen extraction and a reduction in cerebral oxygenation to meet the brains oxygen requirement. At 2–3 mo there was no difference between the sleep states while at 5–6 mo cerebral oxygenation was higher in AS than in QS, as would be expected with effective CBF–metabolism coupling, as CBF is increased, exceeding the metabolic requirements of the brain during AS. This suggests that maturation of CBF–metabolism coupling occurs during this period [68].

Influence of oxygen and carbon dioxide on cerebral haemodynamics

CBF is largely influenced by the partial pressure of carbon dioxide ($PaCO_2$) and oxygen (PaO_2) in the arterial circulation and in ventilated patients these variables are easily influenced by altering ventilation parameters. CO_2 is known to be a potent cerebrovasodilator while increasing arterial O_2 content results in vasoconstriction [71,72]. These mechanisms aim to protect the brain from hypoxia which will result in neuronal death and hyperoxia which may lead to oxidative stress. In adults, $PaCO_2$ has a linear relationship with CBF resulting in a 2–6% increase in CBF with each torr increase in $PaCO_2$. This change in CBF in response to changes in $PaCO_2$ is known as cerebral carbon dioxide vasoreactivity. In healthy term newborns, carbon dioxide reactivity is present at birth with a mean CBF-CO_2 reactivity of 25.4%/kPa, thus CBF increased 25.4% per kPa (7.5 mmHg) increase in $PaCO_2$ [73]. However, in severely asphyxiated term neonates CO_2 reactivity was abolished with a mean CBF-CO_2 reactivity of −8.7%, suggesting that brain injury disrupts normal cerebral vascular control in term infants [73]. Conversely, an inverse relationship exists between PaO_2 and CBF, with increasing arterial oxygen gas tension resulting in reduced CBF [74]. This relationship has been illustrated in healthy adults, with hypoxia resulting in increased blood flow velocity and decreased vascular resistance in cerebral vessels [75]. The influence of CO_2 and O_2, as well as MAP and cerebral metabolism, on cerebrovascular control is particularly important amongst preterm infants who are at increased risk of brain injury.

Cerebrovascular control in preterm infants

Cerebral autoregulation in preterm infants

With the preterm brain being particularly susceptible to haemorrhage and ischaemia, which may be due to fluctuations in CBF, there has been much interest in the ability of preterm infants to regulate their cerebral haemodynamics (Table 1). A number of studies have found that cerebral autoregulation is impaired in preterm infants [76–78]. Tsuji et al., found that in 32 infants with gestational ages ranging from 23 to 31 wk, 17 exhibited a high correlation between MAP and HbD, a measure of cerebral intravascular oxygenation calculated using NIRS used as a surrogate for CBF [78]. These results were supported by Soul et al., in 2007 who found that pressure-passivity in the cerebral circulation, again calculated from the coherence between MAP and HbD, existed in 87 out of 90 preterm infants with birth weight <1500 g [77]. Furthermore, this study found that pressure-passivity fluctuates over time, suggesting that cerebral autoregulation is not simply intact or impaired but changes over time [77].

Impaired autoregulation is more common in high-risk preterm infants. Infants born at earlier gestational ages and with lower birth weights are more likely to experience pressure-passivity [77]. Similarly, very sick preterm infants with higher clinical risk index for babies (CRIB) scores are associated with impaired autoregulation as shown by greater coherence between MAP and cerebral oxygenation [76]. Impaired cerebral autoregulation has not been associated with antenatal or postnatal inflammation [79], despite chorioamnionitis being associated with an increased risk of periventricular leukomalacia (PVL) [80]. However, cerebrovascular pressure-passivity is more likely to occur during episodes of hypotension than during hypertensive episodes, suggesting that baseline MAP may rest closer to the lower limit of the cerebral autoregulation plateau in preterm infants [81]. This may explain the increased risk of PVL in infants exposed to chorioamnionitis, as infection and inflammation are often associated with hypotension. Hypotension may lead to low CBF due to BP falling below the limit of the autoregulatory threshold or due to impaired autoregulation secondary to prematurity or adverse clinical conditions.

Impaired cerebral autoregulation has been linked to an increased risk of preterm brain pathology. An early study by Milligan in 1980 found that four out of five preterm infants who received a blood transfusion which resulted in a significant rise in MAP and CBF measured using jugular vein occlusion plethysmography, developed fatal intraventricular haemorrhages (IVH) [82]. Despite the limitations of the technique used for assessment of CBF used in this study, it does suggest that a sudden increase in CBF may have played a causal role in the development of IVH [82]. In support of this, another study found cerebrovascular pressure-passivity due to perinatal stress and the presence of vasoactive substances was present prior to the development of severe intracranial haemorrhage [83]. A more recent study found that in a cohort of 32 preterm infants, 8 out of the 10 infants who developed severe brain pathology (germinal matrix haemorrhage, IVH or PVL) had a high correlation between MAP and cerebral oxygenation, consistent with impaired cerebral autoregulation [78]. Furthermore, it has been shown that there is a significant correlation between high-magnitude cerebral pressure-passivity and the development of haemorrhage [84].

Most of the studies investigating cerebral autoregulation in the preterm population have been conducted in sick or high-risk

Please cite this article in press as: Fyfe KL, et al., The development of cardiovascular and cerebral vascular control in preterm infants, Sleep Medicine Reviews (2013), http://dx.doi.org/10.1016/j.smrv.2013.06.002

Table 1
Summary of studies assessing cerebral autoregulation and cerebral blood flow–metabolism coupling in preterm infants.

Reference	N, Gestational age	Main finding *(Method of CBF Assessment)*	Conclusion
Cerebral autoregulation			
Milligan et al., 1980 [82]	5, 25–31 wk	Four out of five infants who received a blood transfusion causing significant increase in CBF developed fatal IVH *(jugular vein occlusion plethysmography)*	A sudden increase in CBF may play a causal role in brain haemorrhage
Pryds et al. 1989 [83]	57, mean gestation 30.4 wk	Cerebral pressure-passivity is present prior to the development of severe IVH *(Xe-133 clearance)*	Pressure-passivity may contribute to brain haemorrhage
Tyszczuk et al. 1998 [86]	30, 24–34 wk	No correlation between MAP and CBF within the range of 23–39 mmHg *(NIRS)*	Cerebral autoregulation is functional even in very preterm infants
Boylan et al. 2000 [85]	25, 25–42 wk	Cerebral autoregulation is absent in high-risk preterm and term infants and low risk preterm infants *(Transcranial Doppler ultrasound)*	Cerebral autoregulation may be impaired in stable, preterm infants
Tsuji et al. 2000 [78]	32, 23–31 wk	High correlation between MAP and cerebral oxygenation in 17 infants; eight of which developed severe IVH *(NIRS and HbD signal)*	Impaired cerebral autoregulation is common in preterm infants and is associated with risk of severe intracranial haemorrhage
Soul et al. 2007 [77]	90, <1500 g	High correlation between MAP and HbD in 87 infants; fluctuating pressure/passivity over time *(NIRS and HbD signal)*	Cerebral pressure-passivity occurs frequently in preterm infants in the first few days of life
Wong et al. 2008 [76]	24, mean gestation 26 wk	Infants with higher CRIB scores, lower GA, lower birth weight and lower MAP display greater coherence between MAP and TOI *(NIRS and TOI)*	Cerebral autoregulation is impaired in clinically sick preterm infants and is associated with subsequent mortality
O'Leary et al. 2009 [84]	88, mean gestation 26 wk	A greater degree of correlation between MAP and HbD is significantly correlated with early intracranial haemorrhage *(NIRS and HbD signal)*	High-magnitude pressure-passivity is associated with development of IVH in preterm infants
Caicedo et al. 2011 [87]	33, mean gestation 28.9 wk	Infants with abnormal outcomes at one year had more time with abnormal autoregulation in the first three days of life *(NIRS and TOI and HbD signal)*	Impaired autoregulation may predict abnormal outcomes
Gilmore et al. 2011 [81]	23, mean gestation 26.7 wk	Lower BP was associated with impaired autoregulation and a greater percentage of time with dysautoregulation *(NIRS)*	Pressure-passivity is associated with low arterial blood pressure
Chock et al. 2012 [103]	28 very low birth weight and 12 low birth weight infants	Infants with PDA had higher pressure-passivity index than control infants, infants undergoing surgical ligation had higher pressure-passivity for 2 h following surgery *(NIRS and $rScO_2$)*	Haemodynamically significant PDA and surgical ligation of PDA increase the risk of pressure-passive CBF
Hahn et al. 2012 [79]	60, mean gestation 27 wk	Inflammatory markers did not affect cerebral autoregulation; autoregulation impairment increased with decreasing MAP *(NIRS and TOI)*	Impaired cerebral autoregulation is not associated with antenatal or postnatal inflammation
Cerebral blood flow-metabolism coupling			
Greisen et al. 1985 [88]	15, 29–34 wk	CBF increased in AS compared to QS *(Xe-133 clearance)*	Cerebral blood flow–metabolism coupling is present in the preterm infant brain
Wong et al. 2009 [50]	26, mean gestation 26 wk	No correlation between CBF and $CMRO_2$ in control preterm infants *(NIRS and TOI)*	CBF–metabolism coupling in very preterm infants is significantly different from that seen in the mature brain

Abbreviations: AS, active sleep; BP, blood pressure; CBF, cerebral blood flow; CRIB, critical risk index for babies; GA, gestational age; HbD, haemoglobin difference; IVH, intraventricular haemorrhage; LF, low frequency; MAP, mean arterial pressure; NIRS, near-infrared spectroscopy; PDA, patent ductus areteriosus; QS, quiet sleep; $rScO_2$, regional cerebral oxygen saturation; TOI, tissue oxygenation index; Xe, xenon.

preterm infants within the first few days after birth, however there is some evidence to suggest that cerebral autoregulation is impaired even in clinically well preterm infants. Boylan et al., found that cerebral autoregulation was absent in high-risk preterm and term infants as well as absent in low risk preterm infants, but was present in low risk term infants [85]. This suggests that autoregulation may mature with age in an otherwise healthy preterm infant however, there is a distinct paucity of research investigating the maturation of cerebral autoregulation in otherwise healthy preterm infants up to term age and beyond.

Despite extensive data suggesting that cerebral autoregulation is absent or impaired in preterm infants, some studies have found cerebral autoregulation to be functional even in very preterm infants. Tyszczuk et al., found no relationship between MAP within the range of 23–39 mmHg and CBF in preterm infants with gestational ages ranging from 24 to 34 wk [86]. However, this study investigated only steady-state static autoregulation with a single measurement of MAP and CBF per infant, and did not assess dynamic autoregulation. Furthermore, the infants included in the study were of a wide range of gestational and postnatal ages and weights, and importantly, had a wide range of CO_2 levels which would significantly influence CBF. Further evidence in support of intact cerebral autoregulation, Caicedo et al. found that preterm infants (mean gestation 28 wk) with normal outcomes, determined by Bayley's assessment at 12 and 24 mo, displayed minimal pressure-passivity in the first three days after birth. Conversely, those with poor outcomes and higher CRIB scores were more likely to have spent longer periods with pressure-passive CBF in the first days after birth [87].

In summary, cerebral autoregulation is likely to be immature in preterm infants with greater impairment displayed by infants who are clinically unwell or of an earlier gestational age. Although the exact arterial pressures within which cerebral autoregulation functions in preterm infants are unclear, it would appear that the autoregulatory curve is narrower and MAP sits closer to the lower end of the autoregulatory plateau in preterm infants. Furthermore, impaired autoregulation is associated with an increased risk of neuropathology including IVH and PVL, leading to poor neurodevelopmental outcomes.

Cerebral blood flow–metabolism coupling in preterm infants

A number of studies have assessed CBF–metabolism coupling in preterm infants (Table 1). Despite findings suggestive of immature CBF–metabolism coupling in term infants, there is some evidence

Please cite this article in press as: Fyfe KL, et al., The development of cardiovascular and cerebral vascular control in preterm infants, Sleep Medicine Reviews (2013), http://dx.doi.org/10.1016/j.smrv.2013.06.002

that flow–metabolism coupling is intact in preterm infants. Greisen et al., found that CBF, assessed using Xenon-133 clearance, increased in response to a change from AS to QS concluding that coupling between blood flow and metabolism was present in the preterm infant brain as early as 32 wk GA [88].

In contrast, a more recent study conducted by Wong et al. found flow–metabolism coupling to be absent in preterm infants. CBF was determined using NIRS and the oxygen bolus technique and cerebral metabolic rate for oxygen ($CMRO_2$) was determined using NIRS and jugular venous occlusion in preterm infants with a median gestation of 26 wk. A lack of correlation between CBF and $CMRO_2$ was found. Instead changes in cerebral fractional oxygen extraction, not CBF, occurred to meet changes in $CMRO_2$ [50]. This study also found that administration of dopamine clinically indicated to treat hypotension in preterm infants resulted in flow–metabolism coupling more similar to that seen in the mature brain, possibly due to improved microvascular tone [50].

In summary, the evidence describing cerebral blood flow–metabolism coupling in preterm infants is limited and largely conflicting. Early studies have suggested that flow–metabolism coupling is intact in preterm infants, even in very preterm infants. However, more recent studies have suggested that flow–metabolism coupling remains immature in preterm infants, particularly those born very preterm. These discrepancies may be due to differences in the techniques used to assess metabolism–flow coupling and further research is needed to elucidate the relationship between cerebral metabolism and cerebral blood flow in preterm infants. However, it is likely that flow–metabolism coupling does function in the preterm infant brain but is immature and thus inadequately meets the cerebral metabolic requirements.

Cerebral vasoreactivity in preterm infants

Intact cerebral carbon dioxide vasoreactivity in preterm infants has been documented and is associated with improved neurological outcomes. The cerebral vasodilation to CO_2 is thought to be protective of the perinatal brain, especially when there is ventilatory failure with hypoxia and hypercapnia [89,90]. On the other hand, cerebral vasoreactivity might also lead to cerebral hypoperfusion and ischaemia in the presence of hypocapnia. In support of this, hypocapnia in preterm infants has repeatedly been associated with increased risk of a range of neurological pathologies including IVH, PVL and cerebral palsy [91–93]. A summary of studies assessing cerebral vasoreactivity is provided in Table 2.

A number of studies have assessed cerebral CO_2 vasoreactivity in preterm infants. One of the earliest studies to describe cerebral CO_2 vasoreactivity in preterm infants was conducted by Leahy et al. in 1980 [94]. This study assessed CBF in 24 stable preterm infants with a mean gestation of 34 wk. Infants were divided into two groups with one group inhaling 2–3% CO_2 and the other inhaling 100% O_2. Inhalation of CO_2 produced a mean increase in

Table 2
Summary of studies assessing cerebral vasoreactivity in preterm infants.

Reference	*N*, Gestational age	Main finding *(Method of CBF Assessment)*	Conclusion
Leahy et al. 1980 [94]	24, mean gestation 34.1 wk	CBF increase 7.8% per torr increase in alveolar carbon dioxide pressure and decreased 15% when infants inhaled 100% O_2 *(Venous occlusion plethysmography)*	CO_2 is an important regulator of CBF in preterm infants and CO_2 sensitivity may be greater in preterm infants than in adults
Greisen et al. 1987 [95]	16, <33 wk	CBF-CO_2 reactivity was significantly greater than the reactivity estimated from inter-individual changes in flow and $PaCO_2$ *(Xe-133 clearance)*	CBF-CO_2 reactivity appears to be normal in clinically well, mechanically ventilated preterm infants
Pryds et al. 1989 [83]	57, mean gestation 30.1 wk	In infants with normal cranial ultrasounds CBF-CO_2 was significantly lower in the first day of life compared with the second. Infants who later developed severe intracranial haemorrhage had absent CBF-CO_2 reactivity in the first days of life *(Xe-133 clearance)*	Functional impairment of cerebral blood flow regulation may be present in preterm infants and vasoparalysis may be involved in the pathogenesis of cerebral pathology in newborns.
Pryds et al. 1990 [96]	18, mean gestation 30.3 wk	Changes in CBF were significantly related to changes in $PaCO_2$ and the calculated CBF-CO_2 reactivity was comparable to that seen in older infants and healthy adults *(Xe-133 clearance)*	In healthy, preterm infants cerebral blood flow is well regulated within physiological ranges of $PaCO_2$ and MAP
Graziani et al. 1992 [92]	251, <34 wk	$PaCO_2$ values of <17 mmHg in the first three days of life were associated with a significantly increased risk of brain pathology including severe intracranial haemorrhage *(Serial cranial ultrasounds*)*	Hypocapnia is associated with poor neurodevelopmental outcomes in preterm infants
Ikonen et al. 1992 [91]	103, <33 wk	Duration of $PaCO_2$ ≤30 mmHg in the first three days of life was significantly associated with PVL *(Cranial ultrasound*)*	Hypocapnia is associated with the development of brain pathology in preterm infants
Wiswell et al. 1996 [93]	67, mean gestation 27.2 wk	Infants who developed cystic PVL were more likely to have cumulative hypocapnia below 25 mmHg in the first day of life *(Serial cranial ultrasounds*)*	Hypocapnia is associated with later development of cystic PVL
Muller et al. 1997 [99]	18, 26–32 wk	Infants with normal development at 18 mo or normal cerebral autopsy had mean CBF-CO_2 reactivity of 24.4%/kPa CO_2 while infants with abnormal development or hypoxic-ischaemic encephalopathy on cerebral autopsy had mean CBF-CO_2 reactivity of 3.4%/kPa CO_2 *(Xe-133 clearance)*	Loss of cerebral CO_2 reactivity may play a role in the pathogenesis of severe brain injury in preterm infants
Mosca et al. 1999 [89]	14, 25–31 wk	Total Hb increased linearly with increased $PaCO_2$ *(NIRS and Total Hb)*	Cerebral vascular reactivity to CO_2 is present in very preterm infants on the first day of life
Jayasinghe et al. 2003 [97]	16, 24–32 wk	Both normotensive and hypotensive preterm infants had significantly lower CBF-CO_2 reactivity than shown in previous studies *(Xe-133 clearance)*	Normotensive infants display attenuated CBF-CO_2 reactivity while hypotensive infants display absent CBF-CO_2 reactivity
Kaiser et al. 2005 [98]	43, mean gestation 26.9 wk	As $PaCO_2$ increased from 30 to 60 mmHg, the autoregulatory curve also increased *(Transcranial Doppler ultrasound)*	There is a progressive loss of autoregulatory function with increasing hypercapnia

Abbreviations: CBF, cerebral blood flow; CO_2, carbon dioxide; Hb, haemoglobin; MAP, mean arterial pressure; NIRS, near-infrared spectroscopy; $PaCO_2$, partial pressure of carbon dioxide; PVL, periventricular leukomalacia; Xe, xenon.
* Not used to assess CBF.

Please cite this article in press as: Fyfe KL, et al., The development of cardiovascular and cerebral vascular control in preterm infants, Sleep Medicine Reviews (2013), http://dx.doi.org/10.1016/j.smrv.2013.06.002

CBF of 7.8% per torr alveolar CO_2 pressure, a value approximately twice that seen in adults, suggesting that CO_2 is an important regulator of CBF in preterm infants. Conversely, inhalation of 100% O_2 produced a 15% decrease in CBF [94]. Following on from this work, a study by Greisen et al. investigated cerebral CO_2 vasoreactivity following both ventilator adjustment induced and spontaneous fluctuations in CO_2 in 16 infants of less than 33 wk gestation undergoing mechanical ventilation and determined that CBF-CO_2 reactivity appeared normal in this cohort of stable preterm infants [95]. A similar study, by Pryds et al., investigated the effects of spontaneous fluctuations in $PaCO_2$ on CBF in 18 healthy, preterm infants with a mean gestation of 30 wk. They found a mean CO_2 reactivity of 28.9%/kPa CO_2, a value comparable to that found in term infants and adults, concluding that within the physiological ranges of $PaCO_2$ and MAP, CBF is well controlled in preterm infants [96].

However, cerebral CO_2 reactivity may be immature or impaired in the very early period after preterm birth undergoing subsequent improvement with increasing postnatal age. Pryds et al., assessed cerebral CO_2 reactivity using xenon-133 clearance at 2–12, 12–24 and 24–48 h of life in 57 preterm infants and found that cerebral CO_2 reactivity was significantly attenuated at 2–12 h (11.2%/kPa CO_2) and 12–24 h (11.8%/kPa CO_2) of life despite normal cranial ultrasounds, while at 24–48 h (32.6%/kPa CO_2) cerebral vasoreactivity had reached the hypothesised level of 30%/kPa CO_2 [83]. In further support of impaired cerebral vasoreactivity following preterm birth, Jayasinghe et al., studied cerebral autoregulation and CO_2 reactivity, also using the Xenon-133 clearance technique, in 15 very low birth weight preterm infants within four days of life [97]. They divided the cohort into normotensive and hypotensive infants and found that the normotensive preterm infants exhibited intact cerebral autoregulation but impaired cerebral CO_2 reactivity in comparison with previous studies conducted in preterm infants of two days postnatal age which had reported higher mean CBF-CO_2 reactivity values using the same methodology (11.1%/kPa CO_2 compared with 32.6%/kPa CO_2) [83]. They also found that hypotensive preterm infants had impaired cerebral autoregulation as well as absent cerebral CO_2 vasoreactivity [97]. This may be due to the effect of $PaCO_2$ on cerebral autoregulation, as it has been shown in very low birth weight infants that increasing $PaCO_2$ can lead to progressive impairment of cerebral autoregulation [98]. This suggests that CO_2 induced vasodilation overrides cerebral autoregulatory mechanisms in the presence of increasing BP, while in the presence of hypotension, maximally dilated vessels have limited capacity for further dilation in order to increase CBF.

Furthermore, impaired cerebral CO_2 vasoreactivity has been associated with adverse neurodevelopmental outcomes. Muller et al., assessed cerebral CO_2 reactivity using xenon-133 clearance in 18 sick, very low birth weight preterm infants (mean GA 26 wk) within 36 h of birth and assessed cerebral pathology on autopsy in eight infants and neurodevelopmental outcome in 10 infants at 18 mo of age [99]. They found that the infants with normal development and normal cerebral autopsy had a mean CO_2 reactivity of 24.4%/kPa CO_2 while those infants with poor developmental outcome and cerebral pathology on autopsy had a mean CO_2 reactivity of 3.4%/kPa CO_2. They concluded that reduced cerebral CO_2 reactivity may play a role in the pathology of hypoxic-ischaemic encephalopathy and thus be predictive of severe neonatal brain injury [99].

In summary, cerebral vasoreactivity to O_2 and CO_2 appears to function in healthy, preterm infants. However, some impairment may be present and those infants with the greatest impairment appear to be at increased risk for cerebral pathology and poor long-term neurodevelopmental outcomes.

Effect of patent ductus arteriosus on cerebral haemodynamics

Another important consideration in preterm infants is the effect of a haemodynamically significant patent ductus arteriosus (PDA) on CBF and autoregulation. It has been shown that infants with PDA have impaired CBF assessed using Doppler ultrasound [100,101], lower cerebral oxygenation, assessed with NIRS [102], and a tendency towards greater pressure-passivity [103] than control infants.

Treatment of PDA can be conservative, medical or surgical and closure of the duct usually results in increased cerebral oxygenation. However, evidence suggests that surgical ligation presents a particular risk for unstable CBF. A number of studies have found a decrease in cerebral oxygenation during surgical ligation [104] with one study finding a fall in both $rScO_2$ and amplitude integrated electroencephalogram amplitude in 13 out of 20 infants [105]. Furthermore, it has been shown that surgical closure results in significantly increased pressure-passivity for up to 6 h post-surgery when compared to medical or conservative management options [103]. Thus surgical ligation may present a risk for critically reduced cerebral oxygenation in a population of infants known to have impaired cerebral haemodynamics. Medical management of PDA with cyclooxygenase inhibitors, particularly ibuprofen, appears to improve cerebral oxygenation while avoiding the haemodynamic instability associated with surgery [102,106]. With evidence suggesting that surgical management of PDA may also be associated with long-term neurodevelopmental impairment [107], this is an area which requires further investigation.

Implications

Long-term cardiovascular outcomes

It is becoming increasingly apparent that infants born preterm are at increased risk of developing cardiovascular disease in adulthood. The theory "foetal origins of adult disease" was first described more the 20 years ago by Barker et al., who found an increased risk of death from ischaemic heart disease amongst adult men who had been born with a low birth weight [108]. They suggested that an adverse intrauterine environment results in increased cardiovascular risk in adulthood due to the effects of two physiological phenomena; developmental plasticity and compensatory growth [5]. More recently studies have assessed the effect of preterm birth alone, regardless of foetal growth, on cardiovascular outcomes. Studies have found that low GA at birth is associated with elevated systolic BP and insulin resistance during adulthood [109] concluding that preterm birth plays a predominant role in these associations. Further compounding the increased cardiovascular risk, it has recently been shown that preterm infants are at increased risk of developing obstructive sleep apnoea in childhood, which places additional strain on the cardiovascular system [110]. Thus impairments in autonomic cardiovascular control following preterm birth may be early manifestations of an increased risk for cardiovascular disease in adult life. With increasing survival rates amongst infants born at earlier GA and increases in the burden of cardiovascular disease on society this association merits further research particularly into early interventions to reduce cardiovascular morbidity.

Long-term neurodevelopmental outcomes

There is a growing body of research regarding the long-term neurodevelopmental outcomes of infants born preterm. Cerebral palsy occurs at a higher rate amongst survivors of preterm birth

Please cite this article in press as: Fyfe KL, et al., The development of cardiovascular and cerebral vascular control in preterm infants, Sleep Medicine Reviews (2013), http://dx.doi.org/10.1016/j.smrv.2013.06.002

than term birth, with rates increasing with decreasing GA at birth [111]. Sensory deficits including bilateral blindness and deafness occur more commonly amongst preterm survivors than term born infants, with bilateral blindness occurring at a rate of approximately 2–3% amongst extremely preterm infants [3]. In addition, evidence suggests that infants surviving preterm birth without major neurodevelopmental morbidity may still exhibit subtle impairments in a range of areas. Preterm infants tend to have global executive dysfunction, display learning and behavioural impairments and have deficiencies in both fine and gross motor skills [3]. Furthermore, preterm infants are at increased risk of developing psychological disorders including hyperactivity, anxiety or depressive disorders in childhood [111]. Although the exact mechanisms underlying these associations remain unclear, it is likely to be related to altered cerebral development possibly due to immature cerebral haemodynamics placing the brain under stress early in development.

Conclusions

The rate of preterm birth across the world is increasing and due to significant improvements in neonatal intensive care, the survival rates for infants born preterm have increased dramatically. However, despite improved mortality, preterm infants still experience considerable morbidity and are at increased risk for a range of adverse outcomes later in life. Preterm birth is associated with impaired cardiovascular control largely due to immaturity of the ANS which manifests as higher HRs, reduced HRV and impairments in short-term regulation of HR and BP. Furthermore, at birth preterm infants have immature cerebrovascular control displaying pressure-passivity between CBF and MAP, immature CBF–metabolism coupling and altered cerebral CO_2 vasoreactivity. Although evidence suggests these mechanisms improve with increasing postnatal age, there has been little investigation of cerebral haemodynamics up to term-equivalent age and beyond. It is becoming increasingly evident that premature birth places an individual at increased risk of cardiovascular, neurodevelopmental and psychological disease in childhood, adolescence and adulthood. It is possible that deficiencies in cardiovascular and cerebral vascular control seen early in infancy may be early manifestation of long-term impairment. Therefore, improved understanding of the effects of preterm birth on cardiovascular and cerebral vascular development may enable identification of those infants who are at greatest risk, thus enabling early intervention to improve cardiovascular and cerebral outcomes in preterm infants reaching adulthood.

Practice points

As result of a shortened gestational period and possible exposure to an adverse intrauterine environment and physiological stressors early in life, preterm infants:

1) have higher HRs, reduced HRV and impaired ANS control of HR and BP.
2) impaired cerebral autoregulation and immature CBF–metabolism coupling.
3) increased risk of developing cardiovascular disease later in life including hypertension and insulin resistance.
4) increased risk of developing CNS disease later in life including learning and neuropsychiatric disorders.

Research agenda

Further research is required to:

1) develop improved methods to assess cerebral haemodynamics accurately and non-invasively.
2) determine if and when preterm infants 'catch-up' to term born infants in regards to cardiovascular and cerebral vascular control.
3) determine the limits beyond which changes in CBF becomes injurious to the developing preterm brain and any additional mechanisms of injury.
4) identify potential early interventions to improve cardiovascular and CNS outcomes in preterm infants.

Acknowledgements

The authors have no conflicts of interest to declare. Karinna Fyfe is supported by an Australian Postgraduate Award. Stephanie Yiallourou is supported by a project grant from the National Health and Medical Research Council of Australia. Flora Wong is a National Health and Medical Research Council of Australia Health Professional Research Fellow. Rosemary Horne is a National Health and Medical Research Council of Australia Senior Research Fellow. All of the research was supported by the Victorian Government's Operational Infrastructure Support Support Program.

References

[1] Beck S, Wojdyla D, Say L, Betran AP, Merialdi M, Requejo JH, et al. Worldwide incidence of preterm birth: a systematic review of maternal mortality and morbidity. Bull WHO 2010;88:31–8.
[2] Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. Lancet 2008;371:75–84.
[3] Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. Lancet 2008;371:261–9.
[4] Moster D, Lie RT, Markestad T. Long-term medical and social consequences of preterm birth. N Engl J Med 2008;359:262–73. [Research Support, Non-U.S. Gov't].
[5] Barker DJ, Eriksson JG, Forsen T, Osmond C, Barker DJP. Fetal origins of adult disease: strength of effects and biological basis. Int J Epidemiol 2002;31:1235–9.
[6] Friedman WF. The intrinsic physiologic properties of the developing heart. Prog Cardiovasc Dis 1972;15:87–111.
[7] Polin RA, Fox WW, Abman SH. Fetal and neonatal physiology: expert consult. Oxford: Elsevier Limited; 2011.
[8] Saladin K. Anatomy & physiology: the unity of form and function. 6th ed. McGraw-Hill Companies, Incorporated; 2011.
[9] Wakai RT. Assessment of fetal neurodevelopment via fetal magnetocardiography. Exp Neurol 2004;190(Suppl. 1):65–71.
[10] Harper RM, Hoppenbrouwers T, Sterman MB, McGinty DJ, Hodgman J. Polygraphic studies of normal infants during the first six months of life. I. Heart rate and variability as a function of state. Pediatr Res 1976;10:945–8.
[11] Malik M. Heart rate variability. Ann Noninvasive Electrocardiol 1996;1:151–81.
[12] Malliani A, Pagani M, Lombardi F, Cerutti S. Cardiovascular neural regulation explored in the frequency domain. Circulation 1991;84:482–92.
[13] Pagani M, Lombardi F, Guzzetti S, Rimoldi O, Furlan R, Pizzinelli P, et al. Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. Circ Res 1986;59:178–93.
[14] de Beer NA, Andriessen P, Berendsen RC, Oei SG, Wijn PF, Oetomo SB, et al. Customized spectral band analysis compared with conventional Fourier analysis of heart rate variability in neonates. Physiol Meas 2004;25:1385–95.
[15] Ardura J, Andres J, Aldana J, Revilla MA. Development of sleep-wakefulness rhythm in premature babies. Acta Paediatr 1995;84:484–9.
[16] Yiallourou SR, Sands SA, Walker AM, Horne RS, Yiallourou SR, Sands SA, et al. Maturation of heart rate and blood pressure variability during sleep in term-born infants. Sleep 2012;35:177–86.

* The most important references are denoted by an asterisk.

Please cite this article in press as: Fyfe KL, et al., The development of cardiovascular and cerebral vascular control in preterm infants, Sleep Medicine Reviews (2013), http://dx.doi.org/10.1016/j.smrv.2013.06.002

[17] De Rogalski Landrot I, Roche F, Pichot V, Teyssier G, Gaspoz J-M, Barthelemy J-C, et al. Autonomic nervous system activity in premature and full-term infants from theoretical term to 7 years. Auton Neurosci 2007;136:105–9.
[18] Katona PG, Frasz A, Egbert J. Maturation of cardiac control in full-term and preterm infants during sleep. Early Hum Dev 1980;4:145–59.
[19] Eiselt M, Curzi-Dascalova L, Clairambault J, Kauffmann F, Médigue C, Peirano P. Heart-rate variability in low-risk prematurely born infants reaching normal term: a comparison with full-term newborns. Early Hum Dev 1993;32:183–95.
[20] Patural H, Pichot V, Jaziri F, Teyssier G, Gaspoz J-M, Roche F, et al. Autonomic cardiac control of very preterm newborns: a prolonged dysfunction. Early Hum Dev 2008;84:681–7.
[21] Tuladhar R, Harding R, Michael Adamson T, Horne RSC. Comparison of postnatal development of heart rate responses to trigeminal stimulation in sleeping preterm and term infants. J Sleep Res 2005;14:29–36.
*[22] Witcombe NB, Yiallourou SR, Walker AM, Horne RSC. Blood pressure and heart rate patterns during sleep are altered in preterm-born infants: implications for sudden infant death syndrome. Pediatrics 2008;122:e1242–8.
[23] Greenough A, Emery EF. Blood pressure levels of preterm infants in the first year of life. Acta Paediatr 1993;82:528–9.
[24] Georgieff MK, Mills MM, Gomez-Marin O, Sinaiko AR. Rate of change of blood pressure in premature and full term infants from birth to 4 months. Pediatr Nephrol 1996;10:152–5.
[25] Clairambault J, Curzi-Dascalova L, Kauffmann F, Medigue C, Leffler C. Heart rate variability in normal sleeping full-term and preterm neonates. Early Hum Dev 1992;28:169–83.
[26] Longin E, Gerstner T, Schaible T, Lenz T, Konig S, Longin E, et al. Maturation of the autonomic nervous system: differences in heart rate variability in premature vs. term infants. J Perinat Med 2006;34:303–8.
[27] Patural H, Barthelemy JC, Pichot V, Mazzocchi C, Teyssier G, Damon G, et al. Birth prematurity determines prolonged autonomic nervous system immaturity. Clin Auton Res 2004;14:391–5.
[28] Padhye NS, Verklan MT, Brazdeikis A, Williams AL, Khattak AZ, Lasky RE, editors. A comparison of fetal and neonatal heart rate variability at similar post-menstrual ages. 30th Annual Int Conference IEEE; 2008 20–25 Aug. Engineering in Medicine and Biology Society, 2008. EMBS 2008; 2008.
[29] Segar JL. Fetal and neonatal cardiovascular physiology. In: Polin RA, Fox WW, Abman SH, editors. Fetal and neonatal physiology. Philadelphia: Elsevier Saunders; 2011. p. 789–93.
[30] Borst C, Wieling W, van Brederode JF, Hond A, de Rijk LG, Dunning AJ. Mechanisms of initial heart rate response to postural change. Am J Physiol 1982;243:H676–81.
[31] Montano N, Ruscone TG, Porta A, Lombardi F, Pagani M, Malliani A. Power spectrum analysis of heart rate variability to assess the changes in sympathovagal balance during graded orthostatic tilt. Circulation 1994;90:1826–31.
[32] Yiallourou SR, Walker AM, Horne RS, Yiallourou SR, Walker AM, Horne RSC. Prone sleeping impairs circulatory control during sleep in healthy term infants: implications for SIDS. Sleep 2008;31:1139–46.
[33] Harrington C, Kirjavainen T, Teng A, Sullivan CE. Cardiovascular responses to three simple, provocative tests of autonomic activity in sleeping infants. J Appl Physiol 2001;91:561–8.
[34] Cohen G, Vella S, Jeffery H, Lagercrantz H, Katz-Salamon M, Cohen G, et al. Cardiovascular stress hyperreactivity in babies of smokers and in babies born preterm. Circulation 2008;118:1848–53.
[35] Waldman S, Krauss AN, Auld PAM. Baroreceptors in preterm infants: their relationship to maturity and disease. Dev Med Child Neurol 1979;21:714–22.
[36] Holden K, Morgan JS, Krauss AN, Auld PA. Incomplete baroreceptor responses in newborn infants. Am J Perinatol 1985;2:31–4.
[37] Lagercrantz H, Edwards D, Henderson-Smart D, Hertzberg T, Jeffery H. Autonomic reflexes in preterm infants. Acta Paediatr Scand 1990;79:721–8.
[38] Finley JP, Hamilton R, MacKenzie MG. Heart rate response to tilting in newborns in quiet and active sleep. Biol Neonate 1984;45:1–10.
[39] Thoresen M, Cowan F, Walloe L. Cardiovascular responses to tilting in healthy newborn babies. Early Hum Dev 1991;26:213–22.
[40] Massin MM, Maeyns K, Lombet J, Rigo J, Gerard P, Massin MM, et al. Heart rate response profiles to tilting in healthy and unhealthy neonates. Med Sci Monit 2002;8:CR321–5.
[41] Mazursky JE, Birkett CL, Bedell KA, Ben-Haim SA, Segar JL. Development of baroreflex influences on heart rate variability in preterm infants. Early Hum Dev 1998;53:37–52.
[42] Drouin E, Gournay V, Calamel J, Mouzard A, Roze J-C. Assessment of spontaneous baroreflex sensitivity in neonates. Arch Dis Child Fetal Neonatal Ed 1997;76:F108–12.
*[43] Gournay V, Drouin E, Roze JC. Development of baroreflex control of heart rate in preterm and full term infants. Arch Dis Child Fetal Neonatal Ed 2002;86:F151–4.
[44] Andriessen P, Oetomo SB, Peters C, Vermeulen B, Wijn PFF, Blanco CE. Baroreceptor reflex sensitivity in human neonates: the effect of post-menstrual age. J Physiol 2005;568:333–41.
[45] Witcombe NB, Yiallourou SR, Sands SA, Walker AM, Horne RS, Witcombe NB, et al. Preterm birth alters the maturation of baroreflex sensitivity in sleeping infants. Pediatrics 2012;129:e89–96.
*[46] Witcombe NB, Yiallourou SR, Walker AM, Horne RSC. Delayed blood pressure recovery after head-up tilting during sleep in preterm infants. J Sleep Res 2009;19:93–102.
[47] Viskari S, Andersson S, Hytinantti T, Kirjavainen T, Viskari S, Andersson S, et al. Altered cardiovascular control in preterm infants with bronchopulmonary dysplasia. Pediatr Res 2007;61:594–9.
[48] Volpe JJ. Neurology of the newborn. 5th ed. Philadelphia, PA: Saunders Elsevier; 2008.
[49] Back SA, Gan X, Li Y, Rosenberg PA, Volpe JJ. Maturation-dependent vulnerability of oligodendrocytes to oxidative stress-induced death caused by glutathione depletion. J Neurosci 1998;18:6241–53.
*[50] Wong FY, Barfield CP, Horne RS, Walker AM, Wong FY, Barfield CP, et al. Dopamine therapy promotes cerebral flow-metabolism coupling in preterm infants. Intensive Care Med 2009;35:1777–82.
[51] Cowan F, Eriksen M, Thoresen M. An evaluation of the plethysmographic method of measuring cranial blood flow in the new-born infant. J Physiol 1983;335:41–50.
[52] Jobsis FF. Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. Science 1977;198:1264–7.
[53] Soul JS, du Plessis AJ. Near-infrared spectroscopy. Sem Pediatr Neurol 1999;6:101–10.
[54] van Bel F, Lemmers P, Naulaers G. Monitoring neonatal regional cerebral oxygen saturation in clinical practice: value and pitfalls. Neonatology 2008;94:237–44.
[55] Wolf M, Greisen G, Wolf M, Greisen G. Advances in near-infrared spectroscopy to study the brain of the preterm and term neonate. Clin Perinatol 2009;36:807–34.
[56] Edwards AD, Richardson C, Cope M, Wyatt JS, Delpy DT, Reynolds EOR. Cotside measurement of cerebral blood flow in ill newborn infants by near infrared spectroscopy. Lancet 1988;332:770–1.
[57] Patel J, Marks K, Roberts I, Azzopardi D, Edwards AD. Measurement of cerebral blood flow in newborn infants using near infrared spectroscopy with indocyanine green. Pediatr Res 1998;43:34–9.
[58] Suzuki S, Takasaki S, Ozaki T, Kobayashi Y. Tissue oxygenation monitor using NIR spatially resolved spectroscopy. Proc SPIE 1999;3597:582–92.
[59] Yoshitani K, Kawaguchi M, Miura N, Okuno T, Kanoda T, Ohnishi Y, et al. Effects of hemoglobin concentration, skull thickness, and the area of the cerebrospinal fluid layer on near-infrared spectroscopy measurements. Anesthesiology 2007;106:458–62.
[60] Nicklin SE, Hassan IA, Wickramasinghe YA, Spencer SA, Hassan IAA. The light still shines, but not that brightly? The current status of perinatal near infrared spectroscopy. Arch Dis Child Fetal Neonatal Ed 2003;88:F263–8.
[61] Li T, Lin Y, Shang Y, He L, Huang C, Szabunio M, et al. Simultaneous measurement of deep tissue blood flow and oxygenation using noncontact diffuse correlation spectroscopy flow-oximeter. Sci Rep 2013;3.
[62] Goff DA, Buckley EM, Durduran T, Wang J, Licht DJ, Goff DA, et al. Noninvasive cerebral perfusion imaging in high-risk neonates. Semin Perinatol 2010;34:46–56.
[63] Kaiser JR. Neurological sequelae following mechanical ventilation. In: Berger I, SchimmelMS, editors. Hot topics in neonatal neurology. New York: Nova Science Publishers; 2008.
[64] Greisen G. Autoregulation of cerebral blood flow in newborn babies. Early Hum Dev 2005;81:423–8.
[65] Berger R, Garnier Y, Jensen A, Berger R, Garnier Y, Jensen A. Perinatal brain damage: underlying mechanisms and neuroprotective strategies. J Soc Gynecol Investig 2002;9:319–28.
[66] Menon DK. The cerebral circulation. In: Matta BF, Menon DK, Turner JM, editors. Textbook of neuroanaesthesia and critical care. London: Greenwich Medical Media Ltd; 2000.
[67] Meek JH, Elwell CE, Khan MJ, Romaya J, Wyatt JS, Delpy DT, et al. Regional changes in cerebral haemodynamics as a result of a visual stimulus measured by near infrared spectroscopy. Proc Biol Sci 1995;261:351–6.
*[68] Wong FY, Witcombe NB, Yiallourou SR, Yorkston S, Dymowski AR, Krishnan L, et al. Cerebral oxygenation is depressed during sleep in healthy term infants when they sleep prone. Pediatrics 2011;127:e558–65.
[69] Munger DM, Bucher HU, Duc G. Sleep state changes associated with cerebral blood volume changes in healthy term newborn infants. Early Hum Dev 1998;52:27–42.
[70] Meek JH, Firbank M, Elwell CE, Atkinson J, Braddick O, Wyatt JS. Regional hemodynamic responses to visual stimulation in awake infants. Pediatr Res 1998;43:840–3.
[71] Wong FY, Alexiou T, Samarasinghe T, Brodecky V, Walker AM. Cerebral arterial and venous contributions to tissue oxygenation index measured using spatially resolved spectroscopy in newborn lambs. Anesthesiology 2010;113:1385–91.
[72] Jones Jr MD, Traystman RJ, Simmons MA, Molteni RA. Effects of changes in arterial O_2 content on cerebral blood flow in the lamb. Am J Physiol 1981;240:H209–15.
*[73] Pryds O, Greisen G, Lou H, Friis-Hansen B. Vasoparalysis associated with brain damage in asphyxiated term infants. J Pediatr 1990;117:119–25.
[74] Citerio G, Andrews PJD. Intracranial pressure. Part two: clinical applications and technology. In: Pinsky M, Brochard L, Mancebo O, Hedenstierna G, editors. Applied physiology in intensive care medicine. 2nd ed. New York: Springer; 2009.
[75] Gupta AK, Menon DK, Czosnyka M, Smielewski P, Jones JG. Thresholds for hypoxic cerebral vasodilation in volunteers. Anesth Analg 1997;85:817–20.

Please cite this article in press as: Fyfe KL, et al., The development of cardiovascular and cerebral vascular control in preterm infants, Sleep Medicine Reviews (2013), http://dx.doi.org/10.1016/j.smrv.2013.06.002

*[76] Wong FY, Leung TS, Austin T, Wilkinson M, Meek JH, Wyatt JS, et al. Impaired autoregulation in preterm infants identified by using spatially resolved spectroscopy. Pediatrics 2008;121:e604–11.
[77] Soul JS, Hammer PE, Tsuji M, Saul JP, Bassan H, Limperopoulos C, et al. Fluctuating pressure-passivity is common in the cerebral circulation of sick premature infants. Pediatr Res 2007;61:467–73.
[78] Tsuji M, Saul JP, du Plessis A, Eichenwald E, Sobh J, Crocker R, et al. Cerebral intravascular oxygenation correlates with mean arterial pressure in critically ill premature infants. Pediatrics 2000;106:625–32.
[79] Hahn GH, Maroun LL, Larsen N, Hougaard DM, Sorensen LC, Lou HC, et al. Cerebral autoregulation in the first day after preterm birth: no evidence of association with systemic inflammation. Pediatr Res 2012;71:253–60.
[80] Perlman JM, Risser R, Broyles RS. Bilateral cystic periventricular leukomalacia in the premature infant: associated risk factors. Pediatrics 1996;97:822–7.
[81] Gilmore MM, Stone BS, Shepard JA, Czosnyka M, Easley RB, Brady KM. Relationship between cerebrovascular dysautoregulation and arterial blood pressure in the premature infant. J Perinatol 2011;31:722–9.
[82] Milligan DWA. Failure of autoregulation and intraventricular haemorrhage in preterm infants. Lancet 1980;315:896–8.
*[83] Pryds O, Greisen G, Lou H, Frils-Hansen B. Heterogeneity of cerebral vasoreactivity in preterm infants supported by mechanical ventilation. J Pediatr 1989;115:638–45.
[84] O'Leary H, Gregas MC, Limperopoulos C, Zaretskaya I, Bassan H, Soul JS, et al. Elevated cerebral pressure passivity is associated with prematurity-related intracranial hemorrhage. Pediatrics 2009;124:302–9.
[85] Boylan GB, Young K, Panerai RB, Rennie JM, Evans DH. Dynamic cerebral autoregulation in sick newborn infants. Pediatr Res 2000;48:12–7.
[86] Tyszczuk L, Meek J, Elwell C, Wyatt JS. Cerebral blood flow is independent of mean arterial blood pressure in preterm infants undergoing intensive care. Pediatrics 1998;102:337–41.
[87] Caicedo A, De Smet D, Vanderhaegen J, Naulaers G, Wolf M, Lemmers P, et al. Impaired cerebral autoregulation using near-infrared spectroscopy and its relation to clinical outcomes in premature infants. Adv Exp Med Biol 2011;701:233–9.
[88] Greisen G, Hellstrom-Vestas L, Lou H, Rosen I, Svenningsen N. Sleep-waking shifts and cerebral blood flow in stable preterm infants. Pediatr Res 1985;19:1156–9.
[89] Mosca F, Bray M, Colnaghi MR, Fumagalli M, Compagnoni G. Cerebral vasoreactivity to arterial carbon dioxide tension in preterm infants: the effect of ibuprofen. J Pediatr 1999;135:644–6.
[90] Vannucci RC, Heitjan DF, Towfighi J, Brucklacher RM. Carbon dioxide protects the perinatal brain from hypoxic-ischemic damage: an experimental study in the immature rat. Pediatrics 1995:868–74.
[91] Ikonen RS, Janas MO, Koivikko MJ, Laippala P, Kuusinen EJ. Hyperbilirubinemia, hypocarbia and periventricular leukomalacia in preterm infants: relationship to cerebral palsy. Acta Paediatr 1992;81:802–7.
[92] Graziani LJ, Spitzer AR, Mitchell DG, Merton DA, Stanley C, Robinson N, et al. Mechanical ventilation in preterm infants: neurosonographic and developmental studies. Pediatrics 1992;90:515–22.
*[93] Wiswell TE, Graziani LJ, Kornhauser MS, Stanley C, Merton DA, McKee L, et al. Effects of hypocarbia on the development of cystic periventricular leukomalacia in premature infants treated with high-frequency jet ventilation. Pediatrics 1996;98:918–24.
[94] Leahy FA, Cates D, MacCallum M, Rigatto H. Effect of CO_2 and 100% O_2 on cerebral blood flow in preterm infants. J Appl Physiol 1980;48:468–72.
[95] Greisen G, Trojaborg W. Cerebral blood flow, $PaCO_2$ changes, and visual evoked potentials in mechanically ventilated, preterm infants. Acta Paediatr Scand 1987;76:394–400.
[96] Pryds O, Andersen GE, Friis-Hansen B. Cerebral blood flow reactivity in spontaneously breathing, preterm infants shortly after birth. Acta Paediatr Scand 1990;79:391–6.
*[97] Jayasinghe D, Gill AB, Levene MI, Jayasinghe D, Gill AB, Levene MI. CBF reactivity in hypotensive and normotensive preterm infants. Pediatr Res 2003;54:848–53.
[98] Kaiser JR, Gauss CH, Williams DK, Kaiser JR, Gauss CH, Williams DK. The effects of hypercapnia on cerebral autoregulation in ventilated very low birth weight infants. Pediatr Res 2005;58:931–5.
[99] Muller AM, Morales C, Briner J, Baenziger O, Duc G, Bucher HU. Loss of CO_2 reactivity of cerebral blood flow is associated with severe brain damage in mechanically ventilated very low birth weight infants. Europ J Paediatr Neurol 1997;1:157–63.
[100] Lipman B, Serwer GA, Brazy JE. Abnormal cerebral hemodynamics in preterm infants with patent ductus arteriosus. Pediatrics 1982;69:778–81.
[101] Martin CG, Snider AR, Katz SM, Peabody JL, Brady JP. Abnormal cerebral blood flow patterns in preterm infants with a large patent ductus arteriosus. J Pediatr 1982;101:587–93.
[102] Lemmers PM, Toet MC, van Bel F, Lemmers PMA, Toet MC, van Bel F. Impact of patent ductus arteriosus and subsequent therapy with indomethacin on cerebral oxygenation in preterm infants. Pediatrics 2008;121:142–7.
[103] Chock VY, Ramamoorthy C, Van Meurs KP. Cerebral autoregulation in neonates with a hemodynamically significant patent ductus arteriosus. J Pediatr 2012;160:936–42.
[104] Zaramella P, Freato F, Quaresima V, Ferrari M, Bartocci M, Rubino M, et al. Surgical closure of patent ductus arteriosus reduces the cerebral tissue oxygenation index in preterm infants: a near-infrared spectroscopy and Doppler study. Pediatr Int 2006;48:305–12.
[105] Lemmers PM, Molenschot MC, Evens J, Toet MC, van Bel F. Is cerebral oxygen supply compromised in preterm infants undergoing surgical closure for patent ductus arteriosus? Arch Dis Child Fetal Neonatal Ed 2010;95:F429–34.
[106] Patel J, Roberts I, Azzopardi D, Hamilton P, Edwards AD. Randomized double-blind controlled trial comparing the effects of ibuprofen with indomethacin on cerebral hemodynamics in preterm infants with patent ductus arteriosus. Pediatr Res 2000;47:36–42.
[107] Madan JC, Kendrick D, Hagadorn JI, Frantz 3rd ID., National Institute of Child Health and Human Development Neonatal Research Network., et al. Patent ductus arteriosus therapy: impact on neonatal and 18-month outcome. Pediatrics 2009;123:674–81.
[108] Barker DJ, Winter PD, Osmond C, Margetts B, Simmonds SJ. Weight in infancy and death from ischaemic heart disease. Lancet 1989;2:577–80.
[109] Dalziel SR, Parag V, Rodgers A, Harding JE, Dalziel SR, Parag V, et al. Cardiovascular risk factors at age 30 following pre-term birth. Int J Epidemiol 2007;36:907–15.
[110] Raynes-Greenow C, Hadfield R, Cistulli P, Bowen J, Allen H, Roberts C. Sleep apnea in early childhood associated with preterm birth but not small for gestational age: a population-based record linkage study. Sleep 2012;35:1475–80.
[111] Doyle LW, Anderson PJ, Doyle LW, Anderson PJ. Pulmonary and neurological follow-up of extremely preterm infants. Neonatology 2010;97:388–94.

Please cite this article in press as: Fyfe KL, et al., The development of cardiovascular and cerebral vascular control in preterm infants, Sleep Medicine Reviews (2013), http://dx.doi.org/10.1016/j.smrv.2013.06.002

Appendix B

15

Cardiovascular Consequences of Preterm Birth in the First Year of Life

Karinna Fyfe, Stephanie R. Yiallourou and Rosemary S.C. Horne
The Ritchie Centre, Monash Institute for Medical Research, Monash University, Melbourne, Australia

1. Introduction

The definition of a premature infant includes any infant born less than 37 completed weeks of gestation (Beck et al., 2009). This can be further divided into extremely, early and late preterm birth with those infants being born before 26 weeks of gestation being regarded as extremely preterm, between 26 and 34 weeks of gestation regarded as early preterm and those born between 34 and 37 weeks regarded as late preterm (Thilo and Rosenberg, 2010). Due to their reduced gestation, preterm infants are often born with a low birth weight (LBW) defined as a birth weight of less than 2500g, preterm infants are frequently also categorised as very low birth weight (VLBW), defined as less than 1500g and extremely low birth weight (ELBW), defined as less than 1000g (WHO, 2007). The worldwide rate of preterm birth is estimated to be 9.6% of all births, a total of almost 13 million births annually (Beck et al., 2009). Rates of premature birth vary between countries, but are around 10.6% in the USA, 6.2% in Europe and 6.4% in Australia (Beck et al., 2009). Despite a slight decrease in the last 4 years, the number of preterm births has been steadily increasing with a rise of greater than 30% over the past 30 years (Thilo and Rosenberg, 2010). This is due to a combination of factors including changing obstetric practices with a shift towards earlier delivery via either induction of labour or caesarean section and an increase in the number of multiple births (Thilo and Rosenberg, 2010). With improvements in neonatal intensive care techniques, the percentage of infants surviving premature birth has increased dramatically over the last two decades however, premature birth still has a significant impact on infant health and is associated with numerous neonatal problems both in the short and long term (Saigal et al., 2008). This review will focus on the problems associated with the cardiovascular system and its control during the first year of life.

1.1 Preterm birth and sleep

During infancy, the risks of cardiovascular instabilities are most marked during sleep, which has a marked influence on cardio-respiratory control (Gaultier, 1995). Sleep-related instability is of particular importance in infancy, as term infants spend up to 70% of each 24 hours asleep, while preterm infants devote almost 90% of their day to sleeping (Curzi-Dascalova and Challamel, 2000). In infants, two sleep states are defined, active sleep, the precursor to adult rapid eye movement sleep, and quiet sleep, the precursor to adult non

rapid eye movement sleep. Postnatal maturation of sleep is one of the most important physiological changes occurring during the first six months after birth, and infants spend the majority of the time in active sleep, a state where cardio-respiratory control is most unstable (Gaultier, 1995). Significant differences in sleep patterns and the structure of sleep exist between term and preterm infants with preterm infants spending a much larger amount of time in active sleep. Thus studies of cardio-respiratory development and control in preterm infants have predominantly been carried out during sleep. As sleep state has a marked effect on the cardio-respiratory system it is also critical that the sleep state of the infant be taken into account when the results are interpreted.

2. Development of cardiovascular control

The formation of the cardiovascular system begins in early embryological development when the heart and blood vessels first appear (Guyton, 1991, Larson, 2001), and continues to develop and mature throughout fetal life. The cardiovascular system remains immature and continues to develop for several weeks after term birth (Larson, 2001). DNA synthesis and mitotic divisions of the myocardium have been found to continue for several weeks after birth and the mechanical performance of the myocardium improves with postnatal age (Davis et al., 1975, Friedman, 1972). Furthermore, the sympathetic nerve supply to the myocardium is thought to be immature at term (Tynan et al., 1977). In addition to the rapid maturation of the cardiovascular system after birth, the newborn circulation undergoes critical structural changes whereby circulatory shunts, including the ductus arteriosus, ductus venosus and foramen ovale close and transform the system from having a placental oxygen source to a pulmonary source (Guyton, 1991). In infants born preterm, circulatory shunts do not always close immediately after birth (Rhoades and Pflanzer, 1996), adding to the immaturity of the cardiovascular system and placing these infants at a significant risk of circulatory complications.

The autonomic nervous system (ANS) is responsible for control of the involuntary organs of the body and has a huge variety of functions. It is particularly important in the control of cardiovascular parameters such as heart rate, heart rate variability (HRV) and blood pressure. It consists of two opposing arms, the sympathetic which is responsible for 'fight or flight' responses and parasympathetic which plays the 'rest and digest' role. Autonomic function has been demonstrated to increase with gestational age in the fetus during pregnancy (Gagnon et al., 1987, Karin et al., 1993). The sympathetic arm is believed to develop at a consistent rate throughout gestation, while the parasympathetic arm undergoes a period of accelerated development at around 37 to 38 weeks conceptional age (Clairambault et al., 1992). Autonomic function has been demonstrated to be immature in preterm infants compared with term infants at term corrected age, and this is inversely related to gestational age at birth (Gournay et al., 2002, Lagercrantz et al., 1990). To perform effective cardio-respiratory and thermoregulatory functions the autonomic nervous system (ANS) needs to be mature and it has been suggested that this is why preterm infants are at a greater risk of cardiovascular instability.

2.1 Heart rate and blood pressure after preterm birth

It has recently been shown that immediately after birth, heart rate is lower amongst preterm infants than those infants born at term (Dawson et al., 2010). Heart rate also rises more slowly, taking a median time of 1.9 minutes to reach a heart rate of 100 beats per minute,

which is considered normal (Dawson et al., 2010). This is important as heart rate is a commonly used indicator of the health of a newborn infant and reflects the infant's ability to transition from intra to extra-uterine life. Although heart rate may be lower initially amongst preterm infants, once haemodynamic stability is achieved preterm infants display a higher heart rate as a result of ANS immaturity.

Early studies which examined heart rate over gestation found heart rate differences between healthy preterm (born at 29-36 wks gestational age (GA)) and term infants at matched corrected ages (CA) HR was elevated in preterm infants compared with term infants in both active sleep and quiet sleep and these differences in quiet sleep persisted until a chronological age of 7 months (Katona et al., 1980). More recent studies, which followed infants born at 28 weeks PMA and studied longitudinally at weekly intervals until term equivalent age, have also shown that heart rate is elevated in preterm infants compared to term born infants (Patural et al., 2008). In support of these findings, studies comparing preterm and term infants at term have also shown that preterm infants had elevated heart rate in both sleep states compared with term infants (Eiselt et al., 1993). In contrast, other studies have demonstrated no heart rate differences between term and preterm infants (born at 26-32 wks GA) when compared at 2-3 weeks and 2-3 months CA (Tuladhar et al., 2005b) or when followed up to 6 months CA in infants born 28-32 wks GA (Witcombe et al., 2008). The differences between studies may have been due to the neonatal history of the infants. However, the marked sleep state difference in heart rate observed in term infants where heart rate is significantly elevated in active sleep compared with quiet sleep was not present in the preterm infants (Tuladhar et al., 2005b) and did not appear until 5-6 months of age (Witcombe et al., 2008) indicating that there may be a delay in the maturation of sleep state related autonomic control of heart rate.

Blood pressure measured longitudinally with an oscillometric device has also been shown to increase with gestational age and postnatal age in preterm infants over the first month of life (Pejovic et al., 2007). Blood pressure increased more rapidly in the preterm infants than in term infants and was higher in the groups with higher birth weight (Pejovic et al., 2007). There have been limited studies on blood pressure in preterm infants past term equivalent age. This has been primarily because of the difficulty of measuring blood pressure continuously and non-invasively in infants. Recent studies have validated the use of a photoplethysmographic cuff designed for an adult finger for use around the infant wrist (Andriessen et al., 2004b, Drouin et al., 1997, Yiallourou et al., 2006). This technique has been shown to provide an accurate beat-to-beat measure of blood pressure when compared to an arterial catheter (Yiallourou et al., 2006). Studies have shown that blood pressure is lower in preterm infants born at 28-32 weeks GA and studied longitudinally across the first six months after term CA compared to age matched term infants in both active sleep and quiet sleep (Witcombe et al., 2008). In contrast when awake a recent study has reported that systolic blood pressure in VLBW infants was elevated at one year of age compared to published reference values when adjusted for age, gender and height (Duncan et al., 2011). These findings suggest that the elevated blood pressure reported in adolescence and adulthood born preterm appears as early as the first year of life. Furthermore, there was no age related rise in blood pressure between one and three years of age (Duncan et al., 2011).

In summary, it appears that heart rate and blood pressure are altered after preterm birth and these differences persist across the first year after term CA. These differences may underpin the increased risk for cardiovascular problems later in life.

2.2 Heart rate and blood pressure control after preterm birth

Autonomic function can be assessed by examining fluctuations in heart rate termed heart rate variability (HRV). Traditionally, HRV has been analysed using two methods: time domain analyses and frequency domain analyses. Time domain analysis usually calculates the standard deviation of the variability between successive heart beats. The standard deviation of the change in R-R interval from one beat to the next (SDR-R) which relates to the variance of the R-R histogram data projected on the x-axis and the standard deviation of the difference between R-R intervals (SDΔR-R) which relates the variance of the R-R interval histogram data points parallel to the line of identity can be calculated (Galland et al., 1998).

HRV reflect changes in efferent excitatory and inhibitory autonomic activity. Computerised spectral analysis of HRV shows that these rhythmical oscillations are concentrated in two main frequency ranges (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). The long term or low frequency (LF) component (in adults 0.04-0.15 Hz) depends on both sympathetic and parasympathetic branches of the ANS and reflects baroreflex mediated changes in heart rate (Malliani et al., 1991, Pagani et al., 1986, Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). The short term or high frequency (HF) peak occurring above 0.15-0.4 Hz (in adults) is related to parasympathetic vagal activity and corresponds to the respiratory frequency (Malliani et al., 1991, Pagani et al., 1986, Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). These adult values are not appropriate for infants because of their higher respiratory rates which may range between 30 and 90 breaths per minute, similar to 0.5 and 1.5 Hz respectively and heart rates which may range between 100 and 200 beats per minute (similar to 1.7 and 3.3 Hz respectively) (De Beer et al., 2004). In the past, neonatal studies have used different spectral divisions for defining LF and HF components to account for these heart and respiratory rate differences from adults and this different band width used may explain some of the differences in findings of these studies. Recently it has been proposed that based on previous studies and taking into account the ranges of neonatal heart and respiratory rates that the spectral divisions for neonates be 0.04-0.15Hz for LF and 0.4-1.5 Hz for HF (De Beer et al., 2004). In adults, the ratio of low to high spectral power (LF/HF) has been used to reflect sympathovagal balance(Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996) and this has also been used in neonates (Franco et al., 2003, Kluge et al., 1988).

2.2.1 Heart rate variability in healthy preterm infants

There have been a number of studies examining the development of cardiovascular control by assessing HRV in low risk healthy preterm infants, however the majority of studies have studied infants cross-sectionally, usually placing infants in gestational age groups. The effects of preterm birth on autonomic control prior to term has been studied in healthy preterm infants (born at 26 – 37 wks GA with birth weights of 795 – 1600g) and studied at 31 – 38 wks CA. The study demonstrated a decrease in heart rate in quiet sleep with increasing chronological age. In addition, in both quiet sleep and active sleep there was an increase in both time and frequency domain measures of HRV, indicating that there was a maturation of autonomic cardiovascular control during this period before term (Patural et al., 2004).

In a comparative study of healthy low risk preterm infants at term CA and term infants, Eiselt et al (Eiselt et al., 1993) demonstrated that in both active sleep and quiet sleep heart rate was elevated and HRV as measured by spectral analysis, was lower in the preterm group. In addition, in contrast to the term group where heart rate was lower in quiet sleep with higher HF power and lower LF power compared with active sleep, there were no sleep state differences in heart rate or HRV in the preterm group. In a later study by the same group in which 3 groups of infants were compared, a preterm group 31-36 wks conceptional age (ConA), an intermediate group 37-38 wks ConA and a term group 39-41 wks ConA the HF power, mid frequency (MF) power, LF power and mean RR interval all increased with age and the differences were more marked in active sleep compared with quiet sleep. In addition, HF power showed the greatest increase from the preterm to term group, while LF power showed equal differences from preterm to intermediate and intermediate to term indicating that there is a steep increase in vagal tone at 37-38 wks ConA which plateaux to term and a steady increase in sympathetic tone from 31-41 wks (Clairambault et al., 1992). In a similar study of preterm infants divided into groups of 25-27, 28-31, and 32-37 weeks GA and studied at term CA compared with full term infants, it was found that all three groups of preterm infants had significantly lower HF power values in quiet sleep compared to the term infants (Patural et al., 2004). Furthermore, preterm infants had lower parasympathetic activity at term CA. The authors suggested that preterm birth may prevent the maturation of parasympathetic activity, or alternatively low ANS activity may be involved in premature delivery (Patural et al., 2004). In a study of healthy preterm infants born at 29-35 weeks GA there was no affect of behavioural state (quiet sleep or active sleep) or gender in the group. The authors also did not identify any correlation between HRV parameters and birth-weight or length (Longin et al., 2006). When the group was divided into those infants born <32 weeks and those >32 weeks GA there was an increase in all HRV parameters in the older group. When compared to a group of healthy term infants studied at 1-7 days of age (Longin et al., 2005) the preterm infants had higher heart rates and lower HRV in all parameters measured (Longin et al., 2006). In a study of preterm infants born at 26-32 weeks GA and studied within 36h of birth spectral analysis was performed before and after administration of atropine sulphate a parasympathetic blocker. Atropine increased heart rate without altering systolic blood pressure, decreased HRV, and the decrease in LF power was larger than the decrease in HF power. These findings suggest that although the higher heart rate of preterm infants indicate relatively low vagal tone, the response to provides evidence that that a significant amount of vagal tone is present shortly after birth (Andriessen et al., 2004a). A recent study which followed 31 low risk preterm infants born at 28 weeks PMA to 34 weeks PMA at weekly intervals found no significant changes in the total, HF or ratio of LF/HF HRV components in the group overall. However, female infants had increased HF power compared to male infants from 31 weeks PMA onwards suggesting a more mature ANS (Krueger et al., 2010).

In a novel study where HRV was compared between fetuses who were 26-35 weeks PMA and prematurely born infants of 24-36 weeks PMA Padhye et al., reported that HF HRV was elevated and multiscale entropy (a measure of heart rate irregularity) were higher in the fetuses, suggesting that autonomic balance was poorer in the premature neonates than in the fetuses of identical PMA (Padhye et al., 2008). In a longitudinal study of preterm infants born 25-37 weeks GA and studied at term equivalent age both HF and LF power were significantly lower in the preterm groups compared to age matched term born infants,

however the LF/HF ratio was not different (De Rogalski Landrot et al., 2007). When the subjects were re-studied at 2-3 years of age there was no difference between the groups for any of the variables measured suggesting that maturation of the ANS was faster in the preterm group and that by this age was fully mature (De Rogalski Landrot et al., 2007).
In summary these studies provide evidence of a reduced ability to control heart rate in healthy low risk preterm infants and suggest that there is a delayed maturation of the ANS and control of the cardiovascular system in this group of infants which may place them at risk for increased cardiovascular instability particularly during sleep in the early period after term equivalent age. Recent studies however suggest that control is equivalent to that of infants born at term by 2-3 years of age.

2.2.2 Heart rate variability in high risk preterm infants

There are somewhat fewer studies examining the development of cardiovascular control in high risk preterm infants. A study of 38 high risk VLBW infants from 23-38 weeks PMA where HRV was assessed weekly or biweekly found that there was an increase in LF power with PMA and that ventilated infants had lower HRV (Khattak et al., 2007). In the same group of infants, heart rate responses to blood sampling were also assessed (Padhye et al., 2009). A reduction in HRV was observed in both HF and LF bands during the heel lance procedure together with an increase in heart rate. As found in the previous study those infants who were mechanically ventilated showed substantially reduced heart rate responses to pain. Similar findings were reported by Patural et al., (Patural et al., 2008) in a similarly designed study which also compared preterm infants to those born at term. Compared to term born infants preterm infants had lower values of all HRV indices at term equivalent age (Patural et al., 2008).
In summary, these limited studies also suggest that cardiovascular control is impaired in high risk preterm infants, however further studies are required to elucidate if these deficits persist past term equivalent age and into infancy and childhood and if high risk preterm infants have increased impairment compared to age matched "healthy" preterm infants.

2.2.3 Effects of apnoea of prematurity on heart rate variability

Apnoea of prematurity is the most common disorder affecting infants born prematurely and the incidence and severity of apnoea are also inversely related to gestational age (Henderson-Smart, 1981). Apnoea is associated with bradycardia and hence these infants exhibit increased cardiovascular instability. In a comparative study of preterm infants born at 24 – 35 wks ConA with a neonatal history of persistent apnoea of prematurity and term infants it was found that heart rate was higher and HRV reduced at term age in the preterm group (Henslee et al., 1997). Furthermore, in infants born prior to 30 wks ConA these differences persisted over the next 6 months as did the differences in HRV in infants born at 30 - 35 wks ConA who had experienced respiratory distress syndrome (RDS). In a later study by the same group, infants with apnoea of prematurity (born at 31 - 35 wks ConA) were compared with both healthy term infants and term infants with persistent apnoea (Schechtman et al., 1998). It was found that the preterm infants showed similar alterations in cardiovascular control to the term group with apnoea in that heart rate was lower and HRV increased. These studies suggest that the mechanisms associated with apnoea have long lasting alterations on autonomic control.

2.2.4 Reflex heart rate responses

Stimulation of the trigeminal area of the face can induce arousal in sleeping infants and the tachycardia following arousal has been used as an index of autonomic function in term (Tuladhar et al., 2003) and preterm infants (Tuladhar et al., 2005b). When trigeminal stimulation does not evoke arousal, a reflex bradycardia is elicited (Ramet et al., 1990) which, together with apnoea and peripheral vasoconstriction, is a feature of the diving reflex. Non-arousing trigeminal cutaneous stimulation has been used to assess autonomic function in both preterm (Lagercrantz et al., 1990, Ramet et al., 1990, Tuladhar et al., 2005b) and term infants (Goksor et al., 2002, Harrington et al., 2001, Tuladhar et al., 2005b).

In studies comparing heart rate responses at arousal following trigeminal stimulation in term and preterm infants (born at 26 - 32 wks GA) with a neonatal history of apnoea of prematurity it was found that although there was no difference in the maximum value of heart rate, the normalized heart rate response (ΔHR%) was significantly greater in the term infants compared to the preterm infants at 2-3 weeks of CA in quiet sleep (Tuladhar et al., 2005b). This finding suggests a reduction of autonomic function in preterm infants at 2-3 weeks of age and supports the hypothesis that the postnatal maturation of autonomic function is delayed in preterm infants. The study also demonstrated that in the preterm infants the relative tachycardia following arousing stimuli (ΔHR%) was significantly greater at 2-3 months of CA compared to 36 weeks GA in active sleep, suggesting a maturation of autonomic control with increasing chronological age. In contrast, there was no evidence of maturation in the term infants (Tuladhar et al., 2005b). In addition, there was no difference between sleep states in maximum heart rate at either 36 weeks GA or 2-3 weeks CA in the preterm infants, however term infants had significantly greater maximum heart rate responses in active sleep at 2-3 weeks, indicated the effects of sleep state on heart rate control appear to be delayed in preterm infants.

In studies examining heart rate responses following trigeminal stimulation in which there was no arousal there is a fall in heart rate or bradycardia. Studies by Ramet et al., (Ramet et al., 1990) in preterm and term infants aged 26.5 - 40.5 wks GA in active sleep showed a significant maturation of the bradycardic response with post conceptual age, suggesting a dominance of vagal influences on autonomic regulation of the heart in preterm infants. Studies comparing this bradycardic response between term and preterm infants found no differences at either 2-3 weeks or 2-3 months CA (Tuladhar et al., 2005a). In active sleep no maturation in heart rate responses was observed in either preterm or term infants, however in quiet sleep the magnitude of the heart rate response increased with chronological age in both preterm and term infants (Tuladhar et al., 2005b). These findings are in contrast to other studies which have reported that the bradycardic reflex decreases with age after birth in both preterm and term infants in responses to trigeminal air-stream stimulation to the face, ocular compression and esophageal dilation and during active sleep and that by term responses were minimal (Ramet et al., 1995, Ramet et al., 1988, Ramet et al., 1990). The authors suggested that this bradycardic reflex may be inappropriate and increase the risk of the Sudden Infant Death Syndrome (SIDS) in preterm infants. The studies were however, not carried out longitudinally in the same infant and the tests performed only in active sleep up to term CA. The findings of Tuladhar et al.,(Tuladhar et al., 2005a) that a bradycardic reflex occurred until 2-3 months post term age are supported by a recent study of awake term infants between 4 and 12 months of age which found that the reflex bradycardia in response to submersion, although decreasing with chronological age, was still present at 12

months of age (Goksor et al., 2002). Despite these conflicting findings as to the age at which the bradycardic reflex response to trigeminal stimulation disappears, it appears that the response is increased in preterm infants which may contribute to their vulnerability to cardiovascular instability.

Heart rate responses after spontaneous cortical and sub-cortical arousal from sleep have also been compared between term and preterm infants (Hanzer et al., 2007). In term infants heart rate increased after arousal and this was greater after cortical arousal compared with sub-cortical. In contrast heart rate significantly decreased in the preterm infants and there was no difference in responses between cortical and sub-cortical arousal. However, the infants were not studied at matched ages with the preterm infants being studied at around 35 weeks PCA and the term infants at 45±12 days after birth, thus the findings could simply be that the preterm group was less mature when studied (Hanzer et al., 2007).

In summary, it appears that preterm infants have immature or impaired heart rate responses to both trigeminal stimulation and after arousal from sleep further suggesting that they are at increased risk of cardiovascular instability.

2.2.5 Baroreflex control of heart rate and blood pressure

The arterial baroreflex is the most important autonomic regulatory mechanism for short term control of arterial pressure, heart rate and cardiac contractility. This reflex corrects fluctuations in arterial pressure principally by altering both heart rate and arterial vascular tone. Thus, when there is an increase in arterial pressure this is countered by a decrease in both heart rate and arterial vascular tone. The responses of heart rate and vascular tone are mediated by the efferent parasympathetic and sympathetic limb of the baroreflex respectively. As both systems are involved, studies of the baroreflex provide information on the sympathovagal balance of control of the autonomic nervous system. Head-up and head-down tilting has also been used as a simple non-invasive method of assessing baroreflex control. In adults, it has been shown that head-up tilting results in a small transient decrease in arterial blood pressure, which in turn evokes a peripheral vasoconstriction and heart rate acceleration (Borst et al., 1984, Borst et al., 1982). Tilting also results in an increase in the LF component of HRV and a decrease in the HF component, the size of the changes being correlated to the degree of the tilt (Montano et al., 1994).

Early studies in preterm infants demonstrated that head up tilting (45°) did not produce significant tachycardia in infants between 28 - 40 wks GA (Holden et al., 1985, Waldman et al., 1979) or in infants 25 - 36 wks GA studied between 1-11 wks chronological age (Lagercrantz et al., 1990), however these studies combined a number of ages of preterm infants with differing clinical histories which may have effected results. In the latter study, blood pressure was also unchanged on tilting however peripheral vascular resistance increased significantly, and there was no correlation between cardiovascular parameters and gestational or chronological age (Lagercrantz et al., 1990). In contrast, Finley et al., (Finley et al., 1984) showed that both term infants studied in the first week after birth and preterm infants (born at 33 -37 week GA) studied at 2 -29 d had significant increases in heart rate on head-up tilting (30°) and significant decreases on head-down tilting, results were however very variable between infants. In addition, there was no difference in responses between sleep states, and they concluded that control of heart rate was well developed at term. In healthy preterm infants (born at 28-32 wks GA) heart rate responses to tilting (45°) in quiet sleep were studied serially at 1-5 weeks chronological age. The study found that at

the first age there was no significant change in heart rate following the tilts and that the change in heart rate increased with increasing chronological age (Mazursky et al., 1998). In addition the LF/HF ratio progressively decreased with increasing chronological age indicating maturation of sympathovagal balance (Mazursky et al., 1998). In a study where heart rate responses to head up tilting (45°) and baseline heart rate values in active sleep were compared between healthy preterm infants (30-34 wks ConA) and term infants at term corrected age no differences were found, however responses in both groups were immature with half of the infants not exhibiting the tachycardia observed in older infants (Massin et al., 2002). Overall, these studies suggest that that there is maturation of baroreflex control of heart rate prior to term however control is still immature in preterm infants at term CA when compared with term infants.

There have been a limited number of studies of baroreflex control of blood pressure in the newborn infant, mainly due to the limited means of inducing and recording blood pressure changes in neonates. With advances in non-invasive and continuous recording of blood pressure in preterm infants (Andriessen et al., 2004b, Gournay et al., 2002, Yiallourou et al., 2006) using beat-beat analyses of spontaneously occurring changes in heart rate and systolic blood pressure (Gournay et al., 2002) have demonstrated that baroreflex sensitivity in preterm infants (born at 24-36 wks GA) increased with both gestational and chronological age. However, it was still lower in preterm infants at term corrected age compared to infants born at term, suggesting an immaturity of baroreflex control in the preterm infants (Gournay et al., 2002). In a cross-sectional study of preterm and term infants born at 28-32 wks postmenstrual age (PMA), 32-37 wks PMA and 37-42 wks PMA Andriesson et al., (Andriessen et al., 2005) also found that baroreflex sensitivity increased with PMA and suggested that this was an effect of a progressive increase in parasympathetic activity. They suggested that the very low BRS in the very preterm infants may be of importance in the clinical management of blood pressure in these infants.

There have been limited studies assessing baroreflex control of blood pressure after term equivalent age. Studies using a 15° head up tilt demonstrated that preterm infants born at 28-32 weeks GA and studied longitudinally at 2-4 weeks, 2-3 months and 5-6 months CA had similar heart rate and blood pressure responses to age matched term infants, i.e. initial increase in both heart rate and blood pressure followed by a bradycardia and subsequent return of blood pressure and heart rate to baseline values. However, return of blood pressure to baseline following the tilt was considerably delayed in the preterm group ~37 beats post-tilt compared to the term infants ~23 beats post-tilt at both 2-3 weeks and 2-3 months CA (Witcombe et al., 2010). These findings suggest that control of blood pressure is immature or maturationally delayed until 5-6 months post term corrected age in preterm infants. These studies support earlier reports of abnormal responses to circulatory stress induced by hypercapnia (4% CO_2 administered during quiet sleep) of healthy preterm infants born at 27-34 weeks GA and preterm infants diagnosed with bronchopulmonary dysplasia born at 23-33 weeks GA and studied at 36 weeks and 40 weeks PMA (Cohen et al., 2007). In a later study, the same group also performed 60° head up tilts in addition to hypercapnia exposure and also found that responses of preterm infants studied at term equivalent age to be markedly different to term infants, with a 3-4 fold greater rise in blood pressure following the tilt and a reduced heart rate response to hypercapnia (Cohen et al., 2008). Preterm infants with bronchopulmonary dysplasia have also been demonstrated to display abnormal cardiovascular responses to side motion and head up tilt (45°) tests when studied at 2-4 months CA (Viskari et al., 2007).

3. Preterm infants and the Sudden Infant Death Syndrome (SIDS)

In recent years, the incidence of SIDS has been more than halved by world-wide public health campaigns introduced in the early 1990's which published the known major risk factors of prone sleeping, maternal smoking and overheating (Moon et al., 2007). However, despite this dramatic decline in incidence, SIDS still remains the major cause of unexpected death in infants in western countries contributing to 47% of all post-neonatal deaths (Byard and Krous, 2003, Carpenter et al., 2004). SIDS was the third leading cause of infant death in the United States in 2007 (Xu et al., 2010) and was the fourth leading cause of infant death in Australia in 2005 (Australian Bureau of Statistics, 2009, Linacre, 2007).

Preterm infants have been shown to be at increased risk for SIDS, with approximately 20% of all SIDS cases occurring in the preterm population (Blair et al., 2006, Thompson and Mitchell, 2006). The most recent study showed that this risk was 4 times greater than for an infant born at term (Blair et al., 2006). The risk for SIDS in preterm infants has also been shown to be inversely related to gestational age (Grether and Schulman, 1989, Hoffman et al., 1988, Hoffman and Hillman, 1992, Malloy and Freeman, 2000, Malloy and Hoffman, 1995, Peterson, 1966, Standfast et al., 1979), with one study demonstrating that the incidence of SIDS in infants born at 24-28 weeks, 29-32 weeks, 33-36 weeks and more than 37 weeks was 3.52, 3.01, 2.27 and 1.06 deaths / 1000 live births respectively (Malloy and Hoffman, 1995). Recent studies of data collected following the introduction of public awareness campaigns of the risks for SIDS have shown that risk factors for preterm infants are similar to those of term infants (Blair et al., 2006, Thompson and Mitchell, 2006).

Although the exact causal mechanisms remain an enigma, it is commonly believed that the final event of SIDS involves a failed or impaired arousal response from sleep to a life-threatening cardio-respiratory challenge (Harper, 1996, Kahn et al., 2002, Phillipson and Sullivan, 1978). In further support of this hypothesis, studies have identified disturbances in the cholinergic and serotonergic systems of SIDS victims (Kinney et al., 1995, Paterson et al., 2006), as well as structural abnormalities in medullary nuclei intimately involved in the central control of cardio-respiratory defensive responses and sleep/wake states (Lavezzi et al., 2004, Machaalani and Waters, 2008). Over 20 years ago it has been suggested that autonomic dysfunction may be a possible cause of SIDS (Kahn et al., 1983). More recently, studies have demonstrated that infants at increased risk for SIDS such as those sleeping prone (Franco et al., 1996, Galland et al., 1998), exposed to maternal smoking (Franco et al., 2000a) or to high ambient temperatures (Franco et al., 2000b) had reduced parasympathetic activity as measured from HRV. Additionally, infants who had been studied previously and who subsequently died from SIDS had higher baseline heart rates (Kelly et al., 1986), lower HRV (Schechtman, 1998), prolonged QT indexes (Schwartz et al., 1998) low parasympathetic tone and/or high sympathovagal balance (Franco et al., 2003, Kluge et al., 1988).

3.1 SIDS risk factors and preterm birth

Prone sleeping is the major risk factor for SIDS with some studies suggesting a causal relation between prone sleep and SIDS (Moon et al., 2007). LBW preterm infants (born at 26-34 wks GA) and studied at 30-38 wks had higher heart rate and respiratory rate together with lower HRV and respiratory variability when they slept prone compared to supine in both active sleep and quiet sleep (Sahni et al., 1999a). Healthy preterm infants born at 27 - 36 wks CA were studied at around 36 wks CA prior to discharge from hospital whilst sleeping both prone and supine (Goto et al., 1999). Heart rate was found to be higher in the supine

position compared with the prone position in active sleep. In addition maximum heart rate was higher in both sleep states and HRV was increased in quiet sleep in the supine position. In a later study by the same group healthy preterm infants born at 28 - 36 wks CA were studied at 1 and 3 months CA age at home whist sleeping prone and supine (Ariagno et al., 2003). In active sleep, heart rate and HRV were not different between sleeping positions at either 1 or 3 months of age. In contrast, in quiet sleep heart rate was higher at 3 months and time domain estimates of HRV were increased at both 1 and 3 months in the supine position. Frequency domain analysis showed that HF power was elevated at 1 month in quiet sleep in the supine position. In addition, both JTc and QTc were shorter at 1 month in quiet sleep in the supine position. A study of low birth weight preterm infants (born at 26 - 37 wks GA and weighing 795-1600g) found that when placed to sleep prone these infants had higher heart rate with lower time and frequency domain measures of HRV than when sleeping supine in both active sleep and quiet sleep (Sahni et al., 1999b). There were also fewer sustained accelerations or decelerations of heart rate in the prone position. In addition, the positional differences in heart rate increased in quiet sleep with increasing postnatal age and the differences in HRV increased in both sleep states (Sahni et al., 2000).

Maternal smoking during pregnancy is associated with preterm birth and is also an independent risk factor for SIDS. When HRV in preterm infants whose mothers had smoked during pregnancy was compared with that in age matched preterm infants whose mother had not smoked, at 33-34 weeks PCA the infants in the smoking group had lower LF power. In addition, in contrast to the non-smoking group, there was no correlation between heart rate and total power with gestational age at birth in the smoking group (Thiriez et al., 2009).

Current theories for the final mechanism of SIDS propose that an infant fails to arouse from sleep after a prolonged cardio-respiratory event (Moon et al., 2007). Arousal from sleep is a vital protective response to a life-threatening challenge as simply by arousing from sleep heart rate, blood pressure and respiration are increased and most importantly a behavioural response can be initiated (Phillipson and Sullivan, 1978). Studies from our laboratory have shown that preterm infants have abnormal or impaired arousal responses compared to term born infants. Compared to healthy term infants (37-42 weeks gestation), preterm infants born at 31-35 weeks gestation have a delay in the maturation of sleep-state-related difference in arousability between active sleep and quiet sleep; this difference only appeared at 2-3 months of age as compared to 2-3 weeks for term infants (Horne et al., 2002). Moreover, preterm infants (26-32 weeks of gestation) with a history of apnoea and bradycardia of prematurity showed decreased responses in both active sleep and quiet sleep at term, and in quiet sleep at 2-3 months post-term (Horne et al., 2001). After a mild hypoxia challenge (15% oxygen), preterm infants had a longer arousal latency in active sleep at 2-3 weeks of age and reached significantly lower SpO_2 levels at 2-5 weeks in both active sleep and quiet sleep and at 2-3 months in quiet sleep (Verbeek et al., 2008). The greater desaturation during the hypoxic challenge combined with the longer arousal latency suggested that in preterm infants there was an impairment or inadequate response to hypoxia during sleep, which may explain the enhanced risk for SIDS in this group. Recently in studies by our group we have investigated the link between impaired cardiovascular control in the prone sleeping position and the decreased arousability which is also associated with this position. Using Near Infrared Spectroscopy techniques in conjunction with continuous blood pressure measurements we showed that in health term infants the prone position was associated with

lower cerebral oxygenation in both quiet sleep and active sleep at 2-3 months of age and in quiet sleep at 2-3 months of age (Wong et al., 2011). We suggest that this reduction may underpin the reduced arousability from sleep exhibited by normal infants when sleeping prone, and provides new insight into potential risks of prone sleeping and mechanisms of SIDS. Further studies are currently underway to determine if preterm infants show similar or greater reductions in cerebral oxygenation when they sleep prone and if this is related to gestational age at birth.

It has been suggested that monitoring of infants at increased risk for SIDS may be useful in identifying infants with abnormal cardiorespiratory control so that these infants could be targeted for interventions to prevent their deaths. In the 1980's Andre Kahn initiated a unique study which brought over 45,000 infants into 10 sleep laboratories across Belgian for an overnight sleep study. Of these, 40 infants subsequently died from SIDS some days or weeks after their study. Results from various sub-groups of this study have been published. In the first report which examined the sleep studies of 30 of the infants who died and compared their sleep and respiratory characteristics to 60 controls matched for age, postnatal age, gestational age and weight at birth the only two polysomnographic characteristics which identified the infants who subsequently died were that they moved less during sleep and had more obstructive breathing events (Kahn et al., 1992). Subsequently it was shown in a subset of 16 of these infants that they had fewer cortical arousals during both active sleep and quiet sleep and that the duration and frequency of sub cortical activation was significantly greater, findings suggestive of an incomplete arousal response (Kato et al., 2003). The differences in the sleep and arousal characteristics of the infants who subsequently died were subtle and as such a large number of studies resulted in such a few infant deaths the cost of studying infants with overnight polysomnography is probably not warranted to try to identify infants who might subsequently die. To test the effectiveness of monitoring infants who were perceived at increased risk for SIDS the Collaborative Home Infant Monitoring Evaluation (CHIME) study was funded by the National Institutes of Health in the USA. Between May 1994 to February 1998 over 1000 infants were monitored with a device which recorded both heart rate and breathing in the home. Preterm infants, siblings of infants who had died from SIDS and infants who had suffered an apparent life threatening event (ALTE) were studied and results compared to healthy term controls. It was hypothesised that those infants in the "at risk groups" would have more frequent cardiorespiratory events and that these would be related to PCA. 1079 infants were studied with over 700,000 hours of recordings. Events were divided into "conventional" which were defined as apnoeas lasting <20s duration, bradycardias <60 bpm for 5s in infants < 44 weeks PMA or <80 bpm for 15s in infants <44 weeks PMA or bradycardias <50bpm for 5s or <60 bpm for at least 15s in infants ≤ 44 weeks PMA. "Extreme events" were defined as apnoeas persisting <30s duration or bradycardia <60 bpm for at least 10s in infants ≤ 44 weeks PMA. Either of these events could be accompanied by oxygen desaturation. The initial report found that conventional events were quite common even in term control infants. Extreme events were only common in the preterm group but their timing which peaked before 43 weeks PCA did not coincide with the peak risk period for SIDS and it was concluded that these events were not likely to be precursors of SIDS (Ramanathan et al., 2001). Subsequent analyses of the data set have concluded that the extreme events are associated with immaturity of autonomic control of the cardiorespiratory system rather than risk factors for SIDS and do not seem to be causally related to SIDS (Hoppenbrouwers et al., 2008, Hunt et al., 2008). Thus it would appear that home

cardiorespiratory monitoring is unlikely to identify abnormal events before the SIDS event and is also unlikely to prevent a SIDS death. At risk infants are frequently monitored at home but apart from providing reassurance to the parents there seems to be little evidence to support this practice as preventative for SIDS. However to date no home monitoring studies have examined autonomic control using such methods as heart rate variability analysis which could perhaps be a marker of infants at increased risk.

In summary, preterm infants are at significantly increased risk for SIDS and the factors which increase the risk in healthy term infants also increase the risk in preterm infants. Immature cardiovascular control may underpin this increased risk which may be further exacerbated by prone sleep or maternal smoking. The importance of alerting parents and health professionals to this increased risk must be stressed as preterm infants are often nursed prone in the intensive care setting to enhance respiratory mechanics. It has been demonstrated that very prematurely born infants studied before neonatal unit discharge slept longer, had fewer arousals from sleep, and more central apnoeas when sleeping prone (Bhat et al., 2006). However, other studies have shown no differences in the incidence of clinically significant apnoea, bradycardia or desaturations in preterm infants (Keene et al., 2000). A recent study has also shown no effect of sleep position on oxygen saturation levels in preterm infants and after 36 weeks GA there was no additional requirement for oxygen (Elder et al., 2011). Thus it is critical that premature infants be placed supine as soon as is medically safe, and well before hospital discharge, to ensure that the infant and parents are accustomed to supine placement. However, further studies are required to define the exact age at which this can be done and whether or not high risk infants are able to be placed supine safely at the same age as healthy preterm infants.

4. Conclusions

Preterm birth is associated with immaturity of autonomic nervous system control of the cardiovascular system. This is manifest with higher heart rates, reduced heart rate variability, decreased baroreflex sensitivity, lower parasympathetic activity, decreased reflex heart rate responses to trigeminal stimulation and at arousal from sleep and lower blood pressure. There also appears to be a significant relationship between gestational age at birth and reduced autonomic control, with infants born at younger gestation ages having more immature responses at equivalent PCA. The most rapid maturation of autonomic control appears to be in the last 8-10 weeks of gestation. This reduced autonomic control compared to age matched term infants appears to last for several months post term, however there are few longitudinal studies to confirm the exact age at which preterm infants "catch-up" with term infants. When preterm birth is associated with apnoea of prematurity this immaturity appears to be more severe and prolonged, however there are also limited longitudinal studies in these infants. It is well known that infants born preterm go on to have cardiovascular complications later in life including elevated blood pressure and increased arterial stiffness (Bonamy et al., 2005, Irving et al., 2000). It appears that abnormalities in cardiovascular control can be identified very early in postnatal life in preterm infants but further studies are needed to identify the role these play in the development of cardiovascular complications later in life.

The major risk factors for SIDS namely prone sleeping and maternal smoking have been shown to exert a major influence on autonomic function during sleep in term infants and this is also the case in preterm infants, although there are fewer studies. The immaturity of

the autonomic nervous system in preterm infants may explain the increased risk of SIDS in this group and assessment of autonomic control could also provide insights into the underlying mechanisms of preterm problems such as the propensity for apnoea-bradycardia and provide new methods of assessment of risk for sudden and unexplained death.

5. References

Andriessen, P., Janssen, B. J., Berendsen, R. C., Oetomo, S. B., Wijn, P. F. and Blanco, C. E. (2004a). Cardiovascular autonomic regulation in preterm infants: the effect of atropine. *Pediatric Research*, Vol.56, No. 6, pp. 939-946.

Andriessen, P., Oetomo, S. B., Peters, C., Vermeulen, B., Wijn, P. F. and Blanco, C. E. (2005). Baroreceptor reflex sensitivity in human neonates: the effect of postmenstrual age. *The Journal of Physiology*, Vol.568, No. Pt 1, pp. 333-341.

Andriessen, P., Schoffelen, R. L., Berendsen, R. C., De Beer, N. A., Oei, S. G., Wijn, P. F. and Blanco, C. E. (2004b). Noninvasive assessment of blood pressure variability in preterm infants. *Pediatric Research*, Vol.55, No. 2, pp. 220-223.

Ariagno, R. L., Mirmiran, M., Adams, M. M., Saporito, A. G., Dubin, A. M. and Baldwin, R. B. (2003). Effect of position on sleep, heart rate variability, and QT interval in preterm infants at 1 and 3 months' corrected age. *Pediatrics*, Vol.111, No. 3, pp. 622-625.

Australian Bureau of Statistics Causes of Death, Australia, 2007. In. Australian Bureau of Statistics, Canberra, 2009.

Beck, S., Wojdyla, D., Say, L., Betran, A. P., Merialdi, M., Requejo, J. H., Rubens, C., Menon, R. and Van Look, P. F. (2009). The worldwide incidence of preterm birth: a systematic review of maternal mortality and morbidity. *Bull World Health Organ*, Vol.88, No. 1, pp. 31-38.

Bhat, R. Y., Hannam, S., Pressler, R., Rafferty, G. F., Peacock, J. L. and Greenough, A. (2006). Effect of prone and supine position on sleep, apneas, and arousal in preterm infants. *Pediatrics*, Vol.118, No. 1, pp. 101-107.

Blair, P. S., Platt, M. W., Smith, I. J. and Fleming, P. J. (2006). Sudden infant death syndrome and sleeping position in pre-term and low birth weight infants: an opportunity for targeted intervention. *Archives of Diseases in Childhood*, Vol.91, No. 2, pp. 101-106.

Bonamy, A. K., Bendito, A., Martin, H., Andolf, E., Sedin, G. and Norman, M. (2005). Preterm birth contributes to increased vascular resistance and higher blood pressure in adolescent girls. *Pediatr Res*, Vol.58, No. 5, pp. 845-849.

Borst, C., Van Brederode, J. F., Wieling, W., Van Montfrans, G. A. and Dunning, A. J. (1984). Mechanisms of initial blood pressure response to postural change. *Clinical Science (London)*, Vol.67, No. 3, pp. 321-327.

Borst, C., Wieling, W., Van Brederode, J. F., Hond, A., De Rijk, L. G. and Dunning, A. J. (1982). Mechanisms of initial heart rate response to postural change. *American Journal of Physiology*, Vol.243, No. 5, pp. H676-681.

Byard, R. W. and Krous, H. F. (2003). Sudden infant death syndrome: overview and update. *Pediatric and Development Pathology*, Vol.6, No. 2, pp. 112-127.

Carpenter, R. G., Irgens, L. M., Blair, P. S., England, P. D., Fleming, P., Huber, J., Jorch, G. and Schreuder, P. (2004). Sudden unexplained infant death in 20 regions in Europe: case control study. *The Lancet*, Vol.363, No. 9404, pp. 185-191.

Clairambault, J., Curzi-Dascalova, L., Kauffmann, F., Medigue, C. and Leffler, C. (1992). Heart rate variability in normal sleeping full-term and preterm neonates. *Early Human Development*, Vol.28, No., pp. 169-183.

Cohen, G., Lagercrantz, H. and Katz-Salamon, M. (2007). Abnormal circulatory stress responses of preterm graduates. *Pediatric Research*, Vol.61, No. 3, pp. 329-334.

Cohen, G., Vella, S., Jeffery, H., Lagercrantz, H. and Katz-Salamon, M. (2008). Cardiovascular stress hyperreactivity in babies of smokers and in babies born preterm. *Circulation*, Vol.118, No. 18, pp. 1848-1853.

Curzi-Dascalova, L. and Challamel, M. (2000). *Sleep and Breathing in Children* Marcel Dekker, New York

Davis, P., Dewar, J., Tynan, M. and Ward, R. (1975). Post-natal developmental changes in the length-tension relationship of cat papillary muscles. *J Physiol*, Vol.253, No., pp. 95-102.

Dawson, J. A., Kamlin, C. O., Wong, C., Te Pas, A. B., Vento, M., Cole, T. J., Donath, S. M., Hooper, S. B., Davis, P. G., Morley, C. J. and Kamlin, C. O. F. (2010). Changes in heart rate in the first minutes after birth. *Archives of Disease in Childhood Fetal & Neonatal Edition*, Vol.95, No. 3, pp. F177-181.

De Beer, N. A., Andriessen, P., Berendsen, R. C., Oei, S. G., Wijn, P. F. and Oetomo, S. B. (2004). Customized spectral band analysis compared with conventional Fourier analysis of heart rate variability in neonates. *Physiological Measurement*, Vol.25, No. 6, pp. 1385-1395.

De Rogalski Landrot, I., Roche, F., Pichot, V., Teyssier, G., Gaspoz, J. M., Barthelemy, J. C. and Patural, H. (2007). Autonomic nervous system activity in premature and full-term infants from theoretical term to 7 years. *Autonomic Neuroscience*, Vol.136, No. 1-2, pp. 105-109.

Drouin, E., Gournay, V., Calamel, J., Mouzard, A. and Roze, J. C. (1997). Feasibility of using finger arterial pressure in neonates. *Archives of Disease in Childhood: Fetal and Neonatal Edition*, Vol.77, No. 2, pp. F139-140.

Duncan, A. F., Heyne, R. J., Morgan, J. S., Ahmad, N. and Rosenfeld, C. R. (2011). Elevated systolic blood pressure in preterm very-low-birth-weight infants </=3 years of life. *Pediatric Nephrology*, Vol.26, No. 7, pp. 1115-1121.

Eiselt, M., Curzi-Dascalova, L., Clairambault, J., Kauffmann, F., Medigue, C. and Peirano, P. (1993). Heart-rate variability in low-risk prematurely born infants reaching normal term: a comparison with full-term newborns. *Early Human Development*, Vol.32, No. 2-3, pp. 183-195.

Elder, D. E., Campbell, A. J. and Galletly, D. (2011). Effect of position on oxygen saturation and requirement in convalescent preterm infants. *Acta Paediatrica*, Vol.100, No. 5, pp. 661-665.

Finley, J. P., Hamilton, R. and Mackenzie, M. G. (1984). Heart rate response to tilting in newborns in quiet and active sleep. *Biology of the Neonate*, Vol.45, No. 1, pp. 1-10.

Franco, P., Chabanski, S., Szliwowski, H., Dramaix, M. and Kahn, A. (2000a). Influence of maternal smoking on autonomic nervous system in healthy infants. *Pediatric Research*, Vol.47, No. 2, pp. 215-220.

Franco, P., Grosswasser, J., Sottiaux, M., Broadfield, E. and Kahn, A. (1996). Decreased cardiac responses to auditory stimulation during prone sleep. *Pediatrics*, Vol.97, No., pp. 174-178.

Franco, P., Szliwowski, H., Dramaix, M. and Kahn, A. (2000b). Influence of ambient temperature on sleep characteristics and autonomic nervous control in healthy infants. *Sleep*, Vol.23, No. 3, pp. 401-407.

Franco, P., Verheulpen, D., Valente, F., Kelmanson, I., De Broca, A., Scaillet, S., Groswasser, J. and Kahn, A. (2003). Autonomic responses to sighs in healthy infants and in victims of sudden infant death. *Sleep Medicine*, Vol.4, No. 6, pp. 569-577.

Friedman, W. F. (1972). The intrinsic physiologic properties of the developing heart. *Progress in Cardiovascular Diseases*, Vol.XV, No. 1, pp. 87-111.

Gagnon, R., Campbell, K., Hunse, C. and Patrick, J. (1987). Patterns of human fetal heart rate accelerations from 26 weeks to term. *American Journal of Obstetrics and Gynecololgy*, Vol.157, No., pp. 743-748.

Galland, B., Reeves, G., Taylor, B. J. and Bolton, D. P. G. (1998). Sleep position, autonomic function and arousal. *Archives of Disease in Childhood Fetal & Neonatal Edition*, Vol.78, No. 3, pp. F189-F194.

Gaultier, C. (1995). Cardiorespiratory Adaptation During Sleep in Infants and Children. *Pediatric Pulmonology*, Vol.19, No., pp. 105-117.

Goksor, E., Rosengren, L. and Wennergren, G. (2002). Bradycardic response during submersion in infant swimming. *Acta Paediatrica*, Vol.91, No. 3, pp. 307-312.

Goto, K., Mirmiran, M., Adams, M. M., Longford, R. V., Baldwin, R. B., Boeddiker, M. A. and Ariagno, R. L. (1999). More awakenings and heart rate variability during supine sleep in preterm infants. *Pediatrics*, Vol.103, No., pp. 603-609.

Gournay, V., Drouin, E. and Roze, J. C. (2002). Development of baroreflex control of heart rate in preterm and full term infants. *Archives of Disease in Childhood Fetal & Neonatal Edition*, Vol.86, No. 3, pp. F151-154.

Grether, J. K. and Schulman, J. (1989). Sudden infant death syndrome and birth weight. *Journal of Paediatrics*, Vol.114, No., pp. 561-567.

Guyton, A. C. (1991). *Textbook of Medical Physiology* (8th), W.B Saunders Company, Philadelphia

Hanzer, M., Reinhold, K., Urlesberger, B., Mueller, W., Pichler, G. and Zotter, H. (2007). Comparison of heart rate responses during cortical and subcortical arousals in term and preterm infants. *Early Human Development*, Vol.83, No., pp. 511-515.

Harper, R. M. (1996). The Cerebral regulation of Cardiovascular and respiratory function. *Seminars in Pediatric Neurology*, Vol.3, No. 1, pp. 13-22.

Harrington, C., Kirjavainen, T., Teng, A. and Sullivan, C. E. (2001). Cardiovascular responses to three simple, provocative tests of autonomic activity in sleeping infants. *Journal of Applied Physiology*, Vol.91, No. 2, pp. 561-568.

Henderson-Smart, D. J. (1981). The effect of gestational age on the incidence and duration of recurrent apnoea in newborn babies. *Australian Paediatric Journal*, Vol.17, No. 4, pp. 273-276.

Henslee, J. A., Schechtman, V. L., Lee, M. Y. and Harper, R. M. (1997). Developmental patterns of heart rate and variability in prematurely-born infants with apnea of prematurity. *Early Human Development*, Vol.47, No., pp. 35-50.

Hoffman, H. J., Damus, K., Hillman, L. and Krongrad, E. (1988). Risk factors for SIDS: Results of the National Institute of Child Health and Human Development SIDS cooperative epidemiology study. *Annals of the New York Academy of Sciences*, Vol.533, No., pp. 13-30.

Hoffman, H. J. and Hillman, L. S. (1992). Epidemiology of the sudden infant death syndrome: maternal , neonatal, and postneonatal risk factors. *Clinics in Perinatology*, Vol.19, No. 4, pp. 717-737.

Holden, K., Morgan, J. S., Krauss, A. N. and Auld, P. A. (1985). Incomplete baroreceptor responses in newborn infants. *American Journal of Perinatology*, Vol.2, No. 1, pp. 31-34.

Hoppenbrouwers, T., Hodgman, J. E., Ramanathan, A. and Dorey, F. (2008). Extreme and conventional cardiorespiratory events and epidemiologic risk factors for SIDS. *J Pediatr*, Vol.152, No. 5, pp. 636-641.

Horne, R. S., Andrew, S., Mitchell, K., Sly, D. J., Cranage, S. M., Chau, B. and Adamson, T. M. (2001). Apnoea of prematurity and arousal from sleep. *Early Human Development*, Vol.61, No. 2, pp. 119-133.

Horne, R. S., Bandopadhayay, P., Vitkovic, J., Cranage, S. M. and Adamson, T. M. (2002). Effects of age and sleeping position on arousal from sleep in preterm infants. *Sleep*, Vol.25, No. 7, pp. 746-750.

Hunt, C. E., Corwin, M. J., Lister, G., Weese-Mayer, D. E., Ward, S. L., Tinsley, L. R., Neuman, M. R., Willinger, M., Ramanathan, R. and Rybin, D. (2008). Precursors of cardiorespiratory events in infants detected by home memory monitor. *Pediatr Pulmonol*, Vol.43, No. 1, pp. 87-98.

Irving, R. J., Belton, N. R., Elton, R. A. and Walker, B. R. (2000). Adult cardiovascular risk factors in premature babies. *Lancet*, Vol.355, No. 9221, pp. 2135-2136.

Kahn, A., Groswasser, J., Rebuffat, E., Sottiaux, M., Blum, D., Foerster, M., Franco, P., Bochner, A., Alexander, M., Bachy, A., Richard, P., Verghote, M., Polain, D. L. and Wayenberg, J. L. (1992). Sleep and Cardiorespiratory Characteristics of Infant Victims of Sudden Death: A Prospective Case-Control Study. *Sleep*, Vol.15, No. 4, pp. 287-292.

Kahn, A., Riazi, J. and Blum, D. (1983). Oculocardiac reflex in near miss for sudden infant death syndrome infants. *Pediatrics*, Vol.71, No. 1, pp. 49-52.

Kahn, A., Sawaguchi, T., Sawaguchi, A., Groswasser, J., Franco, P., Scaillet, S., Kelmanson, I. and Dan, B. (2002). Sudden infant deaths: from epidemiology to physiology. *Forensic Science International*, Vol.130 Suppl, No., pp. S8-20.

Karin, J., Hirsch, M. and Akselrod, S. (1993). An estimate of fetal autonomic state by spectral analysis of fetal heart rate fluctuations. *Pediatric Research*, Vol.34, No., pp. 134-138.

Kato, I., Franco, P., Groswasser, J., Scaillet, S., Kelmanson, I., Togari, H. and Kahn, A. (2003). Incomplete arousal processes in infants who were victims of sudden death. *Am J Respir Crit Care Med*, Vol.168, No. 11, pp. 1298-1303.

Katona, P. G., Frasz, A. and Egbert, J. (1980). Maturation of cardiac control in full-term and preterm infants during sleep. *Early Human Development*, Vol.4, No. 2, pp. 145-159.

Keene, D. J., Wimmer, J. E., Jr. and Mathew, O. P. (2000). Does supine positioning increase apnea, bradycardia, and desaturation in preterm infants? *J Perinatol*, Vol.20, No. 1, pp. 17-20.

Kelly, D. H., Golub, H., Carley, D. and Shannon, D. C. (1986). Pneumograms in infants who subsequently died of sudden infant death syndrome. *Journal of Pediatrics*, Vol.109, No. 2, pp. 249-254.

Khattak, A. Z., Padhye, N. S., Williams, A. L., Lasky, R. E., Moya, F. R. and Verklan, M. T. (2007). Longitudinal assessment of heart rate variability in very low birth weight infants during their NICU stay. *Early Human Development*, Vol.83, No. 6, pp. 361-366.

Kinney, H., Filiano, J., Sleeper, L., Mandell, F., Valdes-Dapena, M. and White, W. (1995). Decreased muscarinic receptor binding in the arcuate nucleus in sudden infant death syndrome. *Science*, Vol.269, No. 5229, pp. 1146-1150.

Kluge, K. A., Harper, R. M., Schechtman, V. L., Wilson, A. J., Hoffman, H. J. and Southall, D. P. (1988). Spectral analysis assessment of respiratory sinus arrhythmia in normal infants and infants who subsequently died of sudden infant death syndrome. *Pediatric Research*, Vol.24, No. 6, pp. 677-682.

Krueger, C., Van Oostrom, J. H. and Shuster, J. (2010). A longitudinal description of heart rate variability in 28--34-week-old preterm infants. *Biological Research for Nursing*, Vol.11, No. 3, pp. 261-268.

Lagercrantz, H., Henderson-Smart, D. and Jeffrey, H. (1990). Autonomic Reflexes in Preterm Infants. *Acta Paediatrica Scandinavica*, Vol.79, No., pp. 721-728.

Larson, W. J. (2001). *Human Embryology* (3rd ed), Churchill Livingstone, Philadelphia

Lavezzi, A. M., Ottaviani, G., Mauri, M. and Matturri, L. (2004). Hypoplasia of the arcuate nucleus and maternal smoking during pregnancy in sudden unexplained perinatal and infant death. *Neuropathology*, Vol.24, No. 4, pp. 284-289.

Linacre, S. (2007). Australia's Babies. *ABS: Australian Social Trends*, Vol.4102.0, No., pp.

Longin, E., Gerstner, T., Schaible, T., Lenz, T. and Konig, S. (2006). Maturation of the autonomic nervous system: differences in heart rate variability in premature vs. term infants. *Journal of Perinatal Medicine*, Vol.34, No. 4, pp. 303-308.

Longin, E., Schaible, T., Lenz, T. and Konig, S. (2005). Short term heart rate variability in healthy neonates: normative data and physiological observations. *Early Human Development*, Vol.81, No. 8, pp. 663-671.

Machaalani, R. and Waters, K. A. (2008). Neuronal cell death in the Sudden Infant Death Syndrome brainstem and associations with risk factors. *Brain*, Vol.131, No., pp. 218-228.

Malliani, A., Pagani, M., Lombardi, F. and Cerutti, S. (1991). Cardiovascular neural regulation explored in the frequency domain. *Circulation*, Vol.84, No. 2, pp. 482-492.

Malloy, M. H. and Freeman, D. H., Jr. (2000). Birth weight- and gestational age-specific sudden infant death syndrome mortality: United States, 1991 versus 1995. *Pediatrics*, Vol.105, No. 6, pp. 1227-1231.

Malloy, M. H. and Hoffman, M. A. (1995). Prematurity, sudden infant death syndrome and age of death. *Pediatrics*, Vol.96, No. 3, pp. 464-471.

Massin, M. M., Maeyns, K., Lombet, J., Rigo, J. and Gerard, P. (2002). Heart rate response profiles to tilting in healthy and unhealthy neonates. *Medical Science Monitor*, Vol.8, No. 5, pp. CR321-325.

Mazursky, J. E., Birkett, C. L., Bedell, K. A., Ben-Haim, S. A. and Segar, J. L. (1998). Development of baroreflex influences on heart rate variability in preterm infants. *Early Human Development*, Vol.53, No., pp. 37- 52.

Montano, N., Ruscone, T. G., Porta, A., Lombardi, F., Pagani, M. and Malliani, A. (1994). Power spectrum analysis of heart rate variability to assess the changes in sympathovagal balance during graded orthostatic tilt. *Circulation*, Vol.90, No. 4, pp. 1826-1831.

Moon, R. Y., Horne, R. S. and Hauck, F. R. (2007). Sudden infant death syndrome. *The Lancet*, Vol.370, No. 9598, pp. 1578-1587.

Padhye, N. S., Verklan, M., Brazdeikis, A., Williams, A. L., Khattak, A. Z. and Lasky, R. E. (2008). A comparison of fetal and neonatal heart rate variability at similar post-menstrual ages. *Conference Proceedings IEEE Engineering in Medicine and Biology Society*, Vol.2008, No., pp. 2801-2804.

Padhye, N. S., Williams, A. L., Khattak, A. Z. and Lasky, R. E. (2009). Heart rate variability in response to pain stimulus in VLBW infants followed longitudinally during NICU stay. *Developmental Psychobiology*, Vol.51, No. 8, pp. 638-649.

Pagani, M., Lombardi, F., Guzzetti, S., Rimoldi, O., Furlan, R., Pizzinelli, P., Sandrone, G., Malfatto, G., Dell'orto, S., Piccaluga, E. and Et Al. (1986). Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. *Circulation Research*, Vol.59, No. 2, pp. 178-193.

Paterson, D. S., Trachtenberg, F. L., Thompson, E. G., Belliveau, R. A., Beggs, A. H., Darnall, R., Chadwick, A. E., Krous, H. F. and Kinney, H. C. (2006). Multiple serotonergic brainstem abnormalities in sudden infant death syndrome. *Journal of the American Medical Association*, Vol.296, No. 17, pp. 2124-2132.

Patural, H., Barthelemy, J. C., Pichot, V., Mazzocchi, C., Teyssier, G., Damon, G. and Roche, F. (2004). Birth prematurity determines prolonged autonomic nervous system immaturity. *Clinical Autonomic Research*, Vol.14, No. 6, pp. 391-395.

Patural, H., Pichot, V., Jaziri, F., Teyssier, G., Gaspoz, J. M., Roche, F. and Barthelemy, J. C. (2008). Autonomic cardiac control of very preterm newborns: a prolonged dysfunction. *Early Human Development*, Vol.84, No. 10, pp. 681-687.

Pejovic, B., Peco-Antic, A. and Marinkovic-Eric, J. (2007). Blood pressure in non-critically ill preterm and full-term neonates. *Pediatric Nephrology*, Vol.22, No. 2, pp. 249-257.

Peterson, D. R. (1966). Sudden, unexpected death in infants. An epidemiologic study. *American Journal of Epidemiology*, Vol.84, No. 3, pp. 478-482.

Phillipson, E. A. and Sullivan, C. E. (1978). Arousal: The Forgotten Response to Respiratory Stimuli. *American Review of Respiratory Disease*, Vol.118, No., pp. 807-809.

Ramanathan, R., Corwin, M. J., Hunt, C. E., Lister, G., Tinsley, L. R., Baird, T., Silvestri, J. M., Crowell, D. H., Hufford, D., Martin, R. J., Neuman, M. R., Weese-Mayer, D. E., Cupples, L. A., Peucker, M., Willinger, M. and Keens, T. G. (2001). Cardiorespiratory events recorded on home monitors: Comparison of healthy infants with those at increased risk for SIDS. *Jama*, Vol.285, No. 17, pp. 2199-2207.

Ramet, J., Hauser, B., Dehan, M., Curzi-Dascalova, L. and Gaultier, C. (1995). Effect of State of Alertness on the Heart Rate Response to Ocular Compression in Human Infants. *Biology of the Neonate*, Vol.68, No., pp. 270-275.

Ramet, J., Praud, J., D'allest, A., Carofilis, A., Dehan, M. and Guilleminault, C. (1988). Effect of Maturation on Heart Rate Response to Ocular Compression Test during Rapid Eye Movement Sleep in Human Infants. *Pediatric Research*, Vol.24, No. 4, pp. 477-480.

Ramet, J., Praud, J. P., D'allest, A. M., Dehan, M. and Gaultier, C. (1990). Trigeminal airstream stimulation. Maturation-related cardiac and respiratory responses during REM sleep in human infants. *Chest*, Vol.98, No. 1, pp. 92-96.

Rhoades, R. and Pflanzer, R. (1996). *Human Physiology* Saunders College Publishing, USA

Sahni, R., Schulze, K. F., Kashyap, S., Ohira-Kist, K., Fifer, W. P. and Myers, M. M. (1999a). Postural differences in cardiac dynamics during quiet and active sleep in low birthweight infants. *Acta Paediatr*, Vol.88, No. 12, pp. 1396-1401.

Sahni, R., Schulze, K. F., Kashyap, S., Ohira-Kist, K., Fifer, W. P. and Myers, M. M. (2000). Maturational changes in heart rate and heart rate variability in low birth weight infants. *Developmental Psychobiology*, Vol.37, No. 2, pp. 73-81.

Sahni, R., Schulze, K. F., Kashyap, S., Ohira-Kist, K., Myers, M. M. and Fifer, W. P. (1999b). Body position, sleep states, and cardiorespiratory activity in developing low birth weight infants. *Early Human Development*, Vol.54, No. 3, pp. 197-206.

Saigal, S., Doyle, L. W., Saigal, S. and Doyle, L. W. (2008). An overview of mortality and sequelae of preterm birth from infancy to adulthood. *Lancet*, Vol.371, No. 9608, pp. 261-269.

Schechtman, V. L., Henslee, J. A. and Harper, R. M. (1998). Developmental patterns of heart rate and variability in infants with persistant apnea of infancy. *Early Human Development*, Vol.50, No., pp. 251- 262.

Schechtman, V. L., Henslee, J.A., Harper, R.M. (1998). Developmental patterns of heart rate and variability in infants with persistant apnea of infancy. *Early Human Development*, Vol.50, No., pp. 251- 262.

Schwartz, P. J., Stramba-Badiale, M., Segantini, A., Austoni, P., Bosi, G., Giorgetti, R., Grancini, F., Marni, E. D., Perticone, F., Rosti, D. and Salice, P. (1998). Prolongation of the QT interval and the sudden infant death syndrome. *The New England Journal of Medicine*, Vol.338, No. 24, pp. 1709- 1714.

Standfast, S. J., Jereb, S. and Janerich, D. T. (1979). The epidemiology of sudden infant death in upstate New York. *Journal of the American Medical Association*, Vol.241, No. 11, pp. 1121-1124.

Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (1996). Heart rate variability: Standards of measurement, physiological interpretation, and clinical use. *Circulation*, Vol.93, No. 5, pp. 1043-1065.

Thilo, E. H. and Rosenberg, A. A. (2010) The Late Preterm Infant In: *Current Diagnosis and Treatment: Pediatrics* W. HAY, M. LEVIN, J. SONDHEIMER and R. DETERDING (Eds), *Current Diagnosis and Treatment: Pediatrics*. McGraw-Hill Aurora, Colorado

Thiriez, G., Bouhaddi, M., Mourot, L., Nobili, F., Fortrat, J. O., Menget, A., Franco, P. and Regnard, J. (2009). Heart rate variability in preterm infants and maternal smoking during pregnancy. *Clinical Autonomic Research*, Vol.19, No. 3, pp. 149-156.

Thompson, J. M. and Mitchell, E. A. (2006). Are the risk factors for SIDS different for preterm and term infants? *Archives of Diseases in Childhood*, Vol.91, No. 2, pp. 107-111.

Tuladhar, R., Harding, R., Adamson, T. M. and Horne, R. S. (2005a). Heart rate responses to non-arousing trigeminal stimulation in infants: effects of sleep position, sleep state and postnatal age. *Early Human Development*, Vol.81, No. 8, pp. 673-681.

Tuladhar, R., Harding, R., Cranage, S. M., Adamson, T. M. and Horne, R. S. (2003). Effects of sleep position, sleep state and age on heart rate responses following provoked arousal in term infants. *Early Human Development*, Vol.71, No. 2, pp. 157-169.

Tuladhar, R., Harding, R., Michael Adamson, T. and Horne, R. S. (2005b). Comparison of postnatal development of heart rate responses to trigeminal stimulation in sleeping preterm and term infants. *Journal of Sleep Research*, Vol.14, No. 1, pp. 29-36.

Tynan, M., Davis, P. and Sheridan, D. (1977). Postnatal maturation of noradrenaline uptake and release in cat papillary muscles. *Cardiovascular Research*, Vol.11, No., pp. 206-209.

Verbeek, M. M., Richardson, H. L., Parslow, P. M., Walker, A. M., Harding, R. and Horne, R. S. (2008). Arousal and ventilatory responses to mild hypoxia in sleeping preterm infants. *Journal of Sleep Research*, Vol.17, No. 3, pp. 344-353.

Viskari, S., Andersson, S., Hytinantti, T. and Kirjavainen, T. (2007). Altered cardiovascular control in preterm infants with bronchopulmonary dysplasia. *Pediatric Research*, Vol.61, No. 5 Pt 1, pp. 594-599.

Waldman, S., Krauss, A. N. and Auld, P. A. (1979). Baroreceptors in preterm infants: their relationship to maturity and disease. *Developmental Medicine and Child Neurology*, Vol.21, No. 6, pp. 714-722.

WHO (2007) Certain conditions originating in the perinatal period, In: *International Statistical Classification of Diseases and Related Health Problems*), *International Statistical Classification of Diseases and Related Health Problems*. World Health Organization Geneva

Witcombe, N. B., Yiallourou, S. R., Walker, A. M. and Horne, R. S. (2008). Blood pressure and heart rate patterns during sleep are altered in preterm-born infants: implications for sudden infant death syndrome. *Pediatrics*, Vol.122, No. 6, pp. e1242-1248.

Witcombe, N. B., Yiallourou, S. R., Walker, A. M. and Horne, R. S. C. (2010). Delayed blood pressure recovery after head-up tilting during sleep in preterm infants. *Journal of Sleep Research*, Vol.19, No., pp. 93-102.

Wong, F. Y., Witcombe, N. B., Yiallourou, S. R., Yorkston, S., Dymowski, A. R., Krishnan, L., Walker, A. M. and Horne, R. S. (2011). Cerebral oxygenation is depressed during sleep in healthy term infants when they sleep prone. *Pediatrics*, Vol.127, No. 3, pp. e558-565.

Xu, J., Kochanek, K. D., Murphy, S. L. and Tejada-Vera, B. (2010). Deaths: Final Data for 2007. *National Vital Statistics Reports*, Vol.58, No. 19, pp.

Yiallourou, S. R., Walker, A. M. and Horne, R. S. (2006). Validation of a new noninvasive method to measure blood pressure and assess baroreflex sensitivity in preterm infants during sleep. *Sleep*, Vol.29, No. 8, pp. 1083-1088.

Appendix C

BABY	BIRTH WEIGHT (g)	BIRTH LENGTH (cm)	APGAR 1min	APGAR 5min	GENDER	GA (wk)
1	3800	51	9	10	F	40
2	3605	52	9	9	M	41
3	4195	50.5	9	9	F	40
4	4165	52	9	9	M	41
6	3605	52	9	9	M	40.2
7	3590	49.5	8	9	F	41.4
8	3260	49	9	9	M	38
10	3540	52	9	9	F	40
11	3690	49	9	10	M	40
12	2900	47	9	9	M	38.5
13	3278	51	9	9	M	40
14	4615	51.5	8	9	F	42
15	3530	49	9	9	F	40.5
16	4300	52	7	10	F	39
17	3480	54	9	9	M	41
18	3276	50.5	9	9	F	39.4
19	3495	49	9	10	M	40.1

BABY	STUDY 1			STUDY 2			STUDY 3		
	AGE (wk)	WEIGHT (g)	LENGTH (cm)	AGE (wk)	WEIGHT (g)	LENGTH (cm)	AGE (wk)	WEIGHT (g)	LENGTH (cm)
1	4	4900	54.5	11.6	6020	61	22.6	6600	67
2	4	4085	52	12	6000	60	22	6500	63
3	2.2	4195	52	9.1	5430	57.8	22.2	6630	62.8
4	4.4	4800	53.5	11.4	6000	59	22.3	7505	66
6	3.2	3595	52	10.2	4800	55.5	24.1	8000	65
7	3	3560	62	10	5500		22.6	8150	66
8	3.3	3418	52.5	10.3	3856	55	22.3	8340	65.5
10	3.1	3295	51.8	11.1	4460	56	22.1	5765	61.7
11	3.4	3898	53	10.2	5398	59	22.2	7300	65
12	3.6	3280	52	11	5040	57.5	22.1	6660	63.5
13	3	3420	51.5	12	5265	58	23	6440	63.5
14	4.3	5340	55	11	6065	57	24.3	7450	61.5
15	3	3928	52	12	5300	58	20.5	5900	61
16	3.3	4360	54	10.3	6025	60.5	23.3	7000	68
17	2.2	3595	54.1	10.1	3960	56.8	20.5	5900	63
18	4.3	3444	53	9	4194	56	20.1		
19	3.4	4130	51.5	10.1	5330	57.3	23.4	7280	66

Appendix D

PARENT INFORMATION and consent form

Version 4 Dated March 2012
Southern Health

Full Project Title: DEVELOPMENT OF CARDIOVASCULAR CONTROL DURING SLEEP IN HUMAN INFANTS AFTER PRETERM BIRTH

Principal Researcher: Professor Rosemary Horne

Associate Researchers: Dr Flora Wong

This Parent Information and Consent Form is **6** pages long. Please make sure you have all the pages.

1. Your Consent

You and your infant are invited to take part in this research project.

This Parent Information contains detailed information about the research project. Its purpose is to explain to you as openly and clearly as possible all the procedures involved in this project before you decide whether or not you wish your infant to take part in it.

Please read this Parent Information carefully. Feel free to ask questions about any information in the document. You may also wish to discuss the project with a relative or friend or your local health worker. Feel free to do this.

Once you understand what the project is about and if you agree to take part in it, you will be asked to sign the Consent Form. By signing the Consent Form, you indicate that you understand the information and that you give your consent to participate in the research project.

You will be given a copy of the Parent Information and Consent Form to keep as a record.

2. Purpose and Background

The purpose of this project is to investigate the effects of sleeping position on blood pressure and brain oxygen levels in preterm and term infants.

A total of ***80*** infants will participate in this project.

Sleeping in the prone position (on the tummy) is a major risk factor for Sudden Infant Death Syndrome (SIDS). Currently it is believed that babies who die from SIDS are unable to control their heart rate and blood pressure and that this impairment in control is exacerbated by sleeping in the prone position. In this study we want to examine the development of heart rate and blood pressure control during sleep in term and preterm infants over the first 6 months of life so that we can identify any if there are any maturational changes which could explain the increased risk of SIDS at 2-3 months of age.

You and your infant are invited to participate in this research project.

3. Procedures

We are asking you to let us monitor your baby's sleep in the Melbourne Children's Sleep Unit at Monash Medical Centre on three occasions at 2-3 weeks after term birth (or 42-43 weeks corrected age in preterm infants), 2-3 months and 5-6 months corrected age. There will be facilities for you to observe the study throughout. From monitor leads applied to your sleeping baby, we will record heart activity, brain activity, breathing and breathing movements, blood oxygen levels, body temperature, and muscle activity. None of these measurements hurt or disturb your baby, and are all used routinely for monitoring babies. In addition we will also apply 2 stick on leads from the NIRO monitor to your baby's head to record brain oxygenation levels and a small cuff around your baby's wrist to measure blood pressure.

On the morning of arrival at the laboratory, some of the monitor leads will be attached to your baby while feeding. At the end of the feed, your baby will be placed in a bassinet and the rest of the leads applied. When your baby falls asleep, the sleep recordings will continue until your baby awakes for the next feed. During the study you baby will be slept both on his/her tummy and on his/her back and will be tilted to 15 degrees to induce a small change in blood pressure and heart rate in each position. The study will take 3-4 hours and will end by 3.00pm. During the study you will be able to pick up and feed or change you baby as required.

4. Possible Benefits

During the study experienced investigators will explain the recordings being made and can describe normal infant sleep patterns to you and discuss any problems you are having with your infant's sleep. There is an opportunity to have a rest in an adjacent room whilst the researchers look after your infant.

5. Possible Risks

Based on our experience of safely studying over 150 babies in similar studies over the past 10 years, we do not believe that there are any risks involved in this study. All the measurements are obtained through standard techniques, which have been designed to safeguard your baby's comfort. None of the lead attachments pierce the skin or hurt your baby in any way. Tape and glue used for attaching leads are wiped off at the end of the study. You will certainly have the opportunity, in the presence of experienced investigators, to observe your baby throughout the study.

6. Alternatives to Participation

Participation is entirely voluntary.

7. Privacy, Confidentiality and Disclosure of Information

All recordings are down loaded to computer disk for analysis. By consenting to your participation in this study, you also consent to the release of your infant's medical records to the researchers conducting the study. You and your baby's names are given a code for confidentiality; neither you nor your baby shall be identified in any publications arising from this study. Records are stored securely for 7 years in accordance with NH&MRC regulations. If any abnormality in your baby's recordings should be detected it will be referred to the appropriate medical specialist. In any publication, information will be provided in such a way that you cannot be identified.

8. New Information Arising During the Project

During the research project, new information about the risks and benefits of the project may become known to the researchers. If this occurs, you will be told about this new information. This new information may mean that you can no longer participate in this research. If this occurs, the person(s) supervising the research will stop your participation. In all cases, you will be offered all available care to suit your needs.

9. Results of Project

There is usually an informal presentation to all the participating families at the end of the project and an informative annual report is sent each year. We will be glad to discuss your baby's studies if you have any questions. Results will be published in scientific journals on completion of the project, however the identity of you and your baby will remain confidential.

10. Further Information or Any Problems

If you require further information, or if you have any problems concerning this project (for example, any side effects), you can contact the principal researcher responsible for this project Associate Rosemary Horne 9594 5100 (W) 9387 5900(H).

11. Other Issues

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about your rights as a research participant, then you may contact

Name: Ms Malar Thiagarajan

Position: Manager, Research Directorate

Telephone: (03) 9594 4611

You will need to tell Malar the name of one of the researchers given in section 10 above.

12. Participation is Voluntary

Participation in any research project is voluntary. If you do not wish your baby to take part you are not obliged to. If you decide to take part and later change your mind, you are free to withdraw your baby from the project at any stage.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with Monash Medical Centre.

Before you make your decision, a member of the research team will be available to answer any questions you have about the research project. You can ask for any information you want. Sign the Consent Form only after you have had a chance to ask your questions and have received satisfactory answers.

If you decide to withdraw from this project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to inform you if there are any health risks or special requirements linked to withdrawing.

13. Ethical Guidelines

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research* (2007) produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.

The ethical aspects of this research project have been approved by the Human Research Ethics Committees of Southern Health and Monash University.

14. Reimbursement for your costs

You will not be paid for your participation in this project.

However, you will be reimbursed for any parking costs that you incur as a result of participating in this study.

Third Party Consent Form
Version 4 Dated March 2012

Southern Health

Full Project Title: DEVELOPMENT OF CARDIOVASCULAR CONTROL DURING SLEEP IN HUMAN INFANTS AFTER PRETERM BIRTH

I have read, and I understand the Parent Information version 3 dated May 2009.

I give my permission for my baby to participate in this project according to the conditions in the Participant Information.

I will be given a copy of Parent Information and Consent Form to keep.

The researcher has agreed not to reveal my baby's identity and personal details if information about this project is published or presented in any public form.

Participant's Name (printed) ……

Name of Person giving Consent (printed) ……

Relationship to Participant: ……

Signature Date

Name of Witness to Parent/Guardian Signature (printed) ……

Signature Date

Researcher's Name (printed) ……

Signature Date

Note: All parties signing the Consent Form must date their own signature.

Revocation of Consent Form

Full Project Title: DEVELOPMENT OF CARDIOVASCULAR CONTROL DURING SLEEP IN HUMAN INFANTS AFTER PRETERM BIRTH

I hereby wish to WITHDRAW my consent to participate in the research proposal described above and understand that such withdrawal WILL NOT jeopardise any treatment or my relationship with Monash Medical Centre.

Participant's Name (printed) …….

Signature Date

Appendix E

BABY	Sex	GA AT BIRTH	BIRTH WEIHT	BIRTH LENGTH	APGAR 1	APGAR 2	EVER USED A DUMMY	MATERNAL SMOKING
			(g)	(cm)				
BPNIRO5	F	29.3	1155	38.5	4	5	Y	Nil
BPNIRO9	F	36.2	3060	49	8	8	N	Nil
1	M	26.3	860	37	5	8	N	Nil
3	F	32.6	2140	46	8	8	N	Nil
4	M	30.2	1575	35.5	7	9	Y	Nil
5	F	34.2	2040	42.5	5	9	Y	Nil
6	M	29.1	1600	39	4	8	Y	Nil
8	M	30.6	1546	44	2	6	Y	Nil
10	F	30.6	1676	42.5	2	7	Y	Nil
11	M	32.3	1840	43.5	9	9	Y	Nil
13	M	29.2	1566	43.5	7	9	N	Nil
14	M	33.3	2310	48	8	9	Y	Nil
15	M	34.4	2745	49	6	9	Y	Nil
16	F	31.3	1489	38.5	9	9	Y	Nil
17	M	29.5	1004	38.5	5	6	Y	Nil
18	M	27.3	1087	38.5	6	8	Y	Nil
19	M	29.6	1325	39	4	7	Y	Nil
20	M	30.3	1145	40	5	9	Y	Nil
21	F	33.6	1545	46.5	5	8	N	Nil
22	M	32.2	1850	43	3	5	Y	Smoked prior to pregnancy
23	M	35.5	2485	48	9	9	N	Nil
24	M	27.6	1104	37.5	4	6	Y	Nil
25	M	33.2	2285	42	9	9	Y	Nil
26	F	27.5	925	38	2	8	N	Nil
27	M	31.2	1755	39	7	9	Y	Nil
28	F	28.3	1220	39.5	6	9	Y	Nil
29	F	34.1	2446	48	9	9	Y	Nil
30	F	34.6	1845	42	9	9	Y	Nil
31	M	34.4	2518	48	9	9	N	Nil
32	M	31.5	1660	42	8	9	Y	Nil
33	M	33.2	1985	46	9	9	N	Nil
34	F	29.1	1244	39	6	8	Y	Nil
35	M	30.2	1400	41	6	9	Y	Nil
36	F	29.1	1320	39	7	8	Y	Nil
37	F	30.5	1635	40	2	4	Y	Nil

BABY	SLEEP Position	TWIN	APNOEA OF PREMATURITY	RDS/HMD	ANAEMIA OF PREMATURITY	PDA
BPNIRO5*	Supine	N	N	Y	N	N
BPNIRO9*	Supine	N	N	N	N	N
1	supine	Y	N	Y	Y	Y - resolved by final echo
3	supine	Y	N	N	N	N
4	supine	N	N	Y	Y	N
5	supine	Y	N	N	N	N
6	supine	N	Y	Y	Y	N
8	supine	Y	N	Y	N	N
10	supine	N	N	Y	N	N
11	supine	N	Y	N	N	N
13	supine	N	N	Y	N	Y - clinically well
14	supine	N	Y	N	N	N
15	supine	N	N	N	N	N
16	supine	N	N	N	N	N
17	supine	N	N	Y	Y	N
18	supine	N	N	Y	Y	N
19	supine	N	N	Y	Y	N
20	Supine	Y	Y	Y	Y	N
21	Supine	N	N	N	N	N
22	Supine	N	N	Y	N	N
23	Supine	N	N	N	N	N
24	Supine	N	Y	Y	Y	Y - clinically well
25	supine	Y	N	N	N	N
26	supine	N	Y	N	Y	N
27	supine	N	N	Y	N	N
28	supine	N	Y	Y	Y	N
29	supine	N	N	N	N	N
30	supine	N	N	N	unknown	N
31	supine	N	N	Y	N	N
32	supine	Y	Y	Y	Y	Y - clinically well
33	supine	Y	N	N	N	N
34	supine	Y	Y	Y	Y	Y - clinically well
35	supine	N	Y	N	Y	N
36	supine	N	Y	Y	Y	N
37	Supine	Y	Y	Y	N	N

* BPNIRO5 and BPNIRO9 are the infant identifier codes for two preterm infants studied with the term infant cohort.

BABY	Days in NICU	Days in SCN	Days Ventilated			Final Cranial Ultrasound	Caffeine
			Intubated	CPAP	Oxygen; low flow (LF); high flow (HF)		
BPNIRO5	12	35	1	9	0	Normal	theophylline/ aminophylline
BPNIRO9	0	7	0	0	0	N/A	N
1	111	15	22	43	16 HF	Normal	Y
3	7	23	0	1	0	N/A	N
4	25	5	0	7	8 HF	Normal	Y
5	0	7	0	0	0	N/A	N
6	57	18	12hrs	45	12 HF	Normal	Y
8	3	23	0	0	1 HF	Normal	Y
10	8	3	0	2	0	Normal	N
11	0	6	0	0	0	Normal	Y
13	4	10	0	3	0	Normal	Y
14	0	7	0	0	0	N/A	Y
15	0	8	0	0	0	N/A	N
16	0	13	0	0	0	Normal	N
17	58	34	9	9	10 LF	Minor old IVH	Y
18	65	12	1	41	8 HF	Normal	Y
19	21	7	2	16	0	Normal	Y
20	3	53	0	2	0	Normal	Y
21	0	7	0	0	0	N/A	N
22	10	0	2hrs	4	2 HF	Normal	N
23	0	10	0	0	0	N/A	N
24	52	14	15	30	18 HF	Normal	Y
25	0	9	0	0	0	Normal	N
26	22	13	1	3	11 HF	Normal	Y
27	10	0	0	5	0	Normal	Y
28	50	12	1	13	40 HF	Normal	Y
29	0	4	0	0	0	N/A	N
30	0	21	0	0	0	N/A	N
31	4	8	0	0	0	N/A	N
32	4	47	0	3	3 HF	Normal	N
33	0	10	0	0	0	N/A	N
34	24	48	13	2	14 HF	Normal	Y
35	5	45	0	1	0	Small cyst, clinically insignificant	Y
36	61	0	2	19	14 HF; 9 LF	Normal	Y
37	30	6	1	7	21 HF	Normal	Y

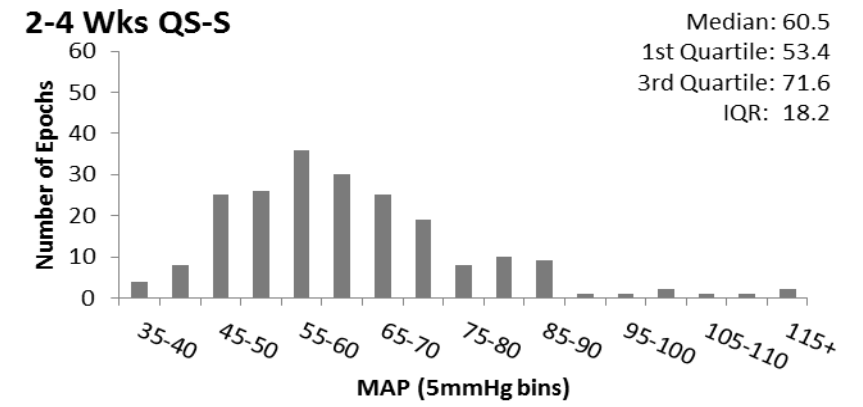
Appendix F

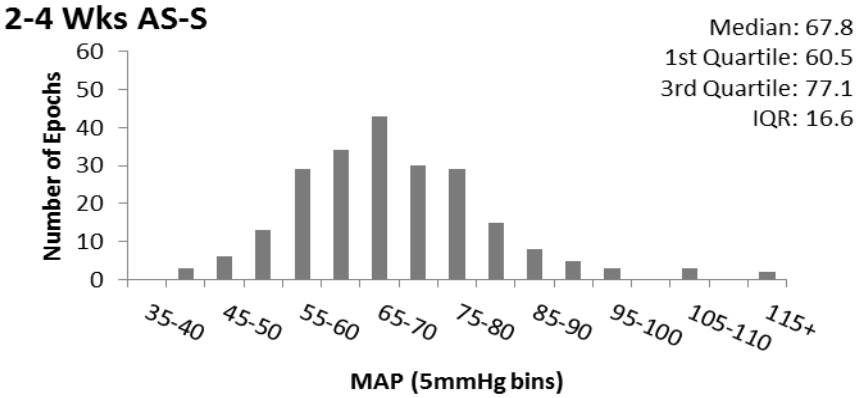
STUDY 1	GA	CA	WEIGHT	LENGTH	DUMMY	FEEDING
BABY	weeks	weeks	kg	cm		
BPNIRO5	43	3	2.96	47.5	Y	Formula
BPNIRO9	43.2	3.2	4.07	53.3	N	Breast
1	43.1	3.1	3.7		N	Breast and bottle
3	43.3	3.3	4	52	N	Breast
4	-	-	-	-	-	-
5	43.6	3.6	3.5	50	Y	Breast
6	43.3	3.3	3.5	51.5	N	Breast
8	44.6	4.6	4.4	48	Y	Breast
10	43.4	3.4	3.845	52	Y	Formula
11	-	-	-	-	-	-
13	43.4	3.4	4.1	53	N	Breast
14	43.6	3.6	4.13	52.5	Y	Formula
15	43.4	3.4	4	55	Y	Breast
16	44	4	2.6	52	Y	Breast and formula
17	42.6	2.6	2.85	48	Y	EBM
18	44.3	4.3	4	55	Y	EBM and formula
19	45.2	5.2	4.1	53	Y	Breast
20	44.3	4.3	3.2	49	Y	Breast
21	43.5	3.5	2.75	50	N	Breast and EBM
22	42.5	2.5	5	55	Y	Breast
23	-	-	-	-	-	-
24	42.1	2.1	3.1	52	N	Formula
25	43	3			N	Formula and breast
26	42.6	2.6	3.63	47	N	Formula and EBM (both thickened)
27	43	3	4	49	Y	Breast and EBM
28	-	-	-	-	-	-
29	43.4	3.4	3.777	51.3	N	Breast
30	43.2	3.2	3.8	52	Y	Breast
31	43.2	3.2	4.75	54	N	Breast
32	43.3	3.3	4	55	Y	Formula
33	43.4	3.4	3.9	56	N	Formula
34	42.2	2.2	3.1	52	Y	Breast
35	42.2	2.2	4	55	Y	EBM
36	42.3	2.3	3.4	54	Y	Breast
37	42.3	2.3	4.1	52	Y	Breast and EBM

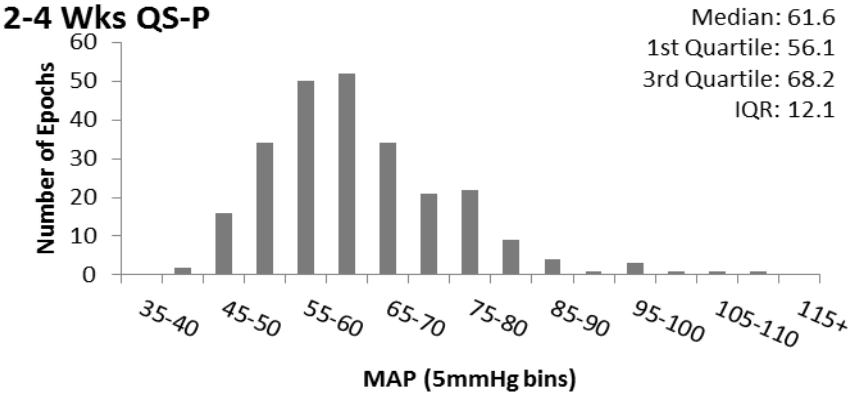
STUDY 2	GA	CA	WEIGHT	LENGTH	DUMMY	FEEDING
BABY	wk	wk	kg	cm		
BPNIRO5	51	11	3.9	51	Y	Formula
BPNIRO9	52	12	5.835	59.5	N	Breast
1	-	-	-	-	-	-
3	-	-	-	-	-	-
4	50.4	10.4	4.8	47	Y	Breast
5	50.4	10.4	4.9	56	Y	Breast
6	51.1	11.1	5.3	58.5	N	Breast
8	50.4	10.4	5.2	56	Y	Breast
10	-	-	-	-	-	-
11	49.3	9.3	5.46	55.5	Y	Formula
13	50.6	10.6	5.5	55	N	Breast
14	52.2	12.2	6	60	Y	Formula
15	49.6	9.6	4.3	65	Y	Breast
16	52	12	5.5	55	Y	Formula
17	-	-	-	-	-	-
18	50.5	10.5	5.5	58	Y	EBM and formula
19	-	-	-	-	-	-
20	50.3	10.3	4.16	53	Y	EBM
21	52	12	5.5	62	N	Breast and very occasional formula
22	50.2	10.2	6	58	Y	Breast
23	48.5	8.5	6.5	62	N	EBM
24	50.1	10.1	5.1	55	Y	Formula
25	50.3	10.3	8	59	Y	Formula
26	50.1	10.1	5.5	55	N	Formula
27	51.5	11.5	5.81	57.5	Y	Breast and EBM
28	50.3	10.3	4.02	54	Y	EBM and breast
29	50.3	10.3	5	55	Y	Breast and EBM
30	52.5	12.5	5.885	59.5	Y	Breast
31	-	-	-	-	-	-
32	50.1	10.1	5.1	56	Y	Formula and EBM
33	-	-	-	-	-	-
34	51.3	11.3	4.2	56	Y	Breast and formula
35	50.2	10.2	6.5	60	Y	Formula
36	50.4	10.4	4.6	59	Y	Breast
37	50.5	10.5	5	55	Y	Breast and EBM

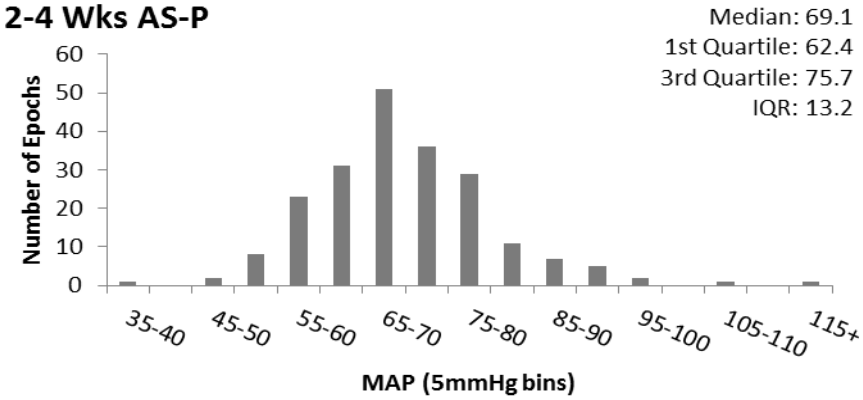
STUDY 3	GA	CA	WEIGHT	LENGTH	DUMMY	FEEDING
BABY	wk	wk	kg	cm		
BPNIRO5	65	25	5.35	60.25	Y	Formula and solids
BPNIRO9	64	24	8.26	64.7	N	Breast and solids
1	-	-	-	-	-	-
3	-	-	-	-	-	-
4	63.5	23.5	6.2	60.5	Y	Solids and formula
5	63.2	23.2	6	60	Y	Breast
6	63.2	23.2	7.6	62	Y	Breast
8	62.3	22.3	7.5	61	N	Breast
10	-	-	-	-	-	-
11	62.2	22.2	7	65	N	Formula and solids
13	65	25	7.7	67.7	N	Breast and solids
14	65.6	25.6	8.6	65	Y	Formula and solids
15	61.2	21.2	8	65	Y	Breast and solids
16	63.6	23.6	7	63	Y	Formula and solids
17	-	-	-	-	-	-
18	62.6	22.6	7.8	67	Y	Formula and solids
19	-	-	-	-	-	-
20	61.3	21.3	5.2	58	Y	EBM
21	62.6	22.6	7	66	N	Breast and solids
22	61.4	21.4	8.05	67	Y	Breast
23	61.5	21.5	7	65	N	Formula
24	63.3	23.3	7.5	65	Y	Formula
25	61.1	21.1	10.4	65	N	Formula
26	62.4	22.4	7.2	65	N	Formula
27	65.1	25.1	7.08	63.2	Y	Breast and solids
28	64	24	6	62	Y	EBM and solids
29	61.1	21.1	6.2	61	Y	Formula
30	62.1	22.1	7.2	65	Y	Breast and solids
31	-	-	-	-	-	-
32	63.1	23.1	8.2	67	Y	Formula and solids
33	-	-	-	-	-	-
34	61	21	5.86	62	N	Formula and solids
35	62.2	22.2	7.5	70	Y	Formula
36	61.3	21.3	5.9	61	Y	Breast
37	61.5	21.5	7.7	60	Y	Breast and solids

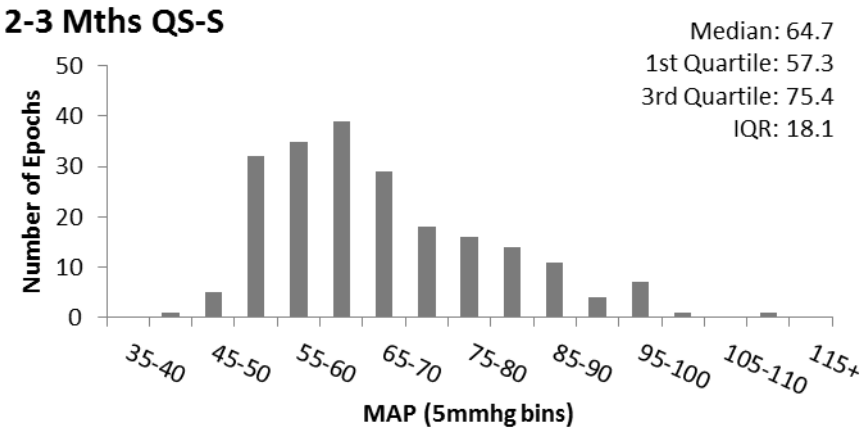
Appendix G

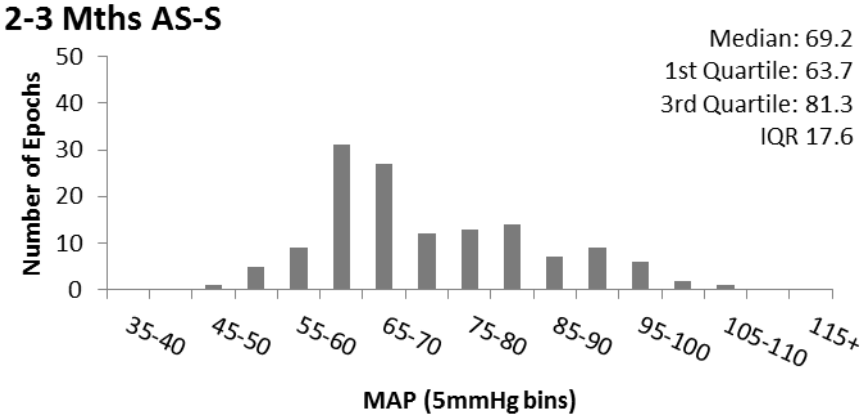

2-4 Wks QS-S
Median: 60.5
1st Quartile: 53.4
3rd Quartile: 71.6
IQR: 18.2
Number of Epochs
0
10
20
30
40
50
60
35-40
45-50
55-60
65-70
75-80
85-90
95-100
105-110
115+
MAP (5mmHg bins)

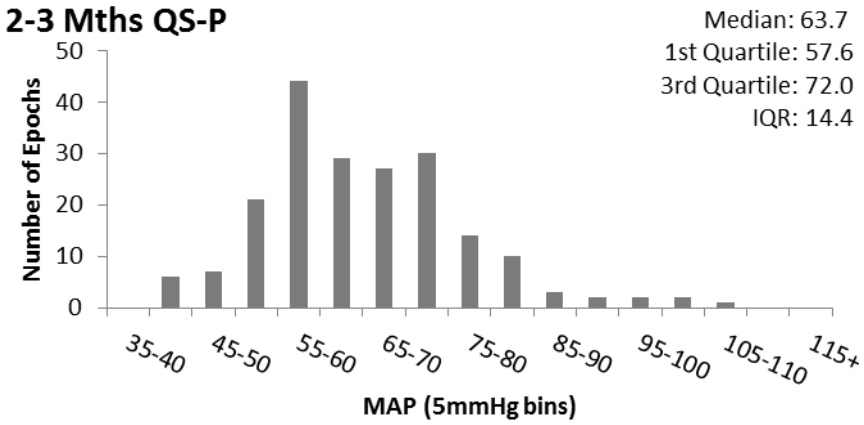

2-4 Wks AS-S
Median: 67.8
1st Quartile: 60.5
3rd Quartile: 77.1
IQR: 16.6
Number of Epochs
0
10
20
30
40
50
60
35-40
45-50
55-60
65-70
75-80
85-90
95-100
105-110
115+
MAP (5mmHg bins)

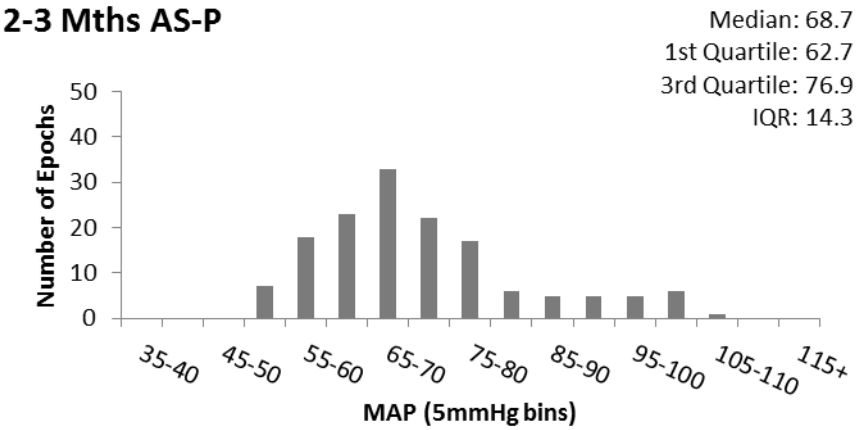

2-4 Wks QS-P
Median: 61.6
1st Quartile: 56.1
3rd Quartile: 68.2
IQR: 12.1
Number of Epochs
0
10
20
30
40
50
60
35-40
45-50
55-60
65-70
75-80
85-90
95-100
105-110
115+
MAP (5mmHg bins)


2-4 Wks AS-P
Median: 69.1
1st Quartile: 62.4
3rd Quartile: 75.7
IQR: 13.2
Number of Epochs
0
10
20
30
40
50
60
35-40
45-50
55-60
65-70
75-80
85-90
95-100
105-110
115+
MAP (5mmHg bins)


2-3 Mths QS-S
Median: 64.7
1st Quartile: 57.3
3rd Quartile: 75.4
IQR: 18.1
Number of Epochs
0
10
20
30
40
50
35-40
45-50
55-60
65-70
75-80
85-90
95-100
105-110
115+
MAP (5mmhg bins)

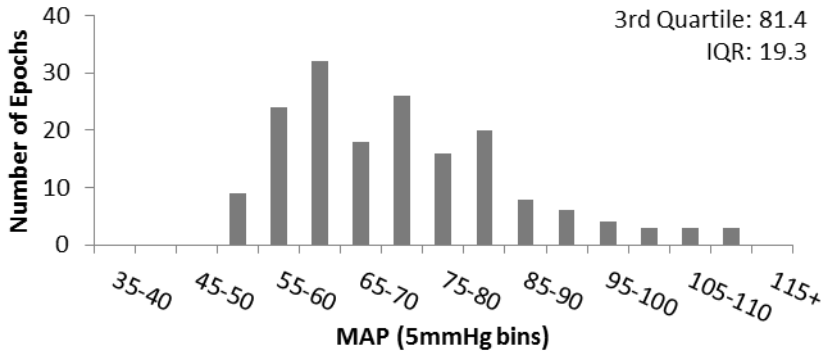

2-3 Mths AS-S
Median: 69.2
1st Quartile: 63.7
3rd Quartile: 81.3
IQR 17.6
Number of Epochs
0
10
20
30
40
50
35-40
45-50
55-60
65-70
75-80
85-90
95-100
105-110
115+
MAP (5mmHg bins)


2-3 Mths QS-P
Median: 63.7
1st Quartile: 57.6
3rd Quartile: 72.0
IQR: 14.4
Number of Epochs
0
10
20
30
40
50
35-40
45-50
55-60
65-70
75-80
85-90
95-100
105-110
115+
MAP (5mmHg bins)


2-3 Mths AS-P
Median: 68.7
1st Quartile: 62.7
3rd Quartile: 76.9
IQR: 14.3
Number of Epochs
0
10
20
30
40
50
35-40
45-50
55-60
65-70
75-80
85-90
95-100
105-110
115+
MAP (5mmHg bins)

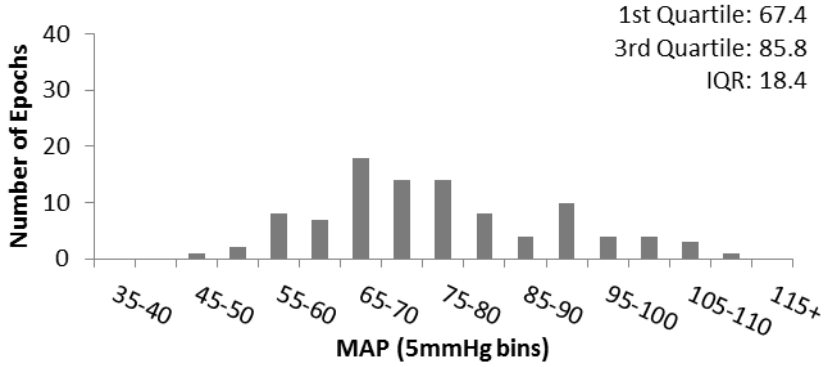
5-6 Mths QS-S

Median: 70.5
1st Quartile: 62.1
3rd Quartile: 81.4
IQR: 19.3



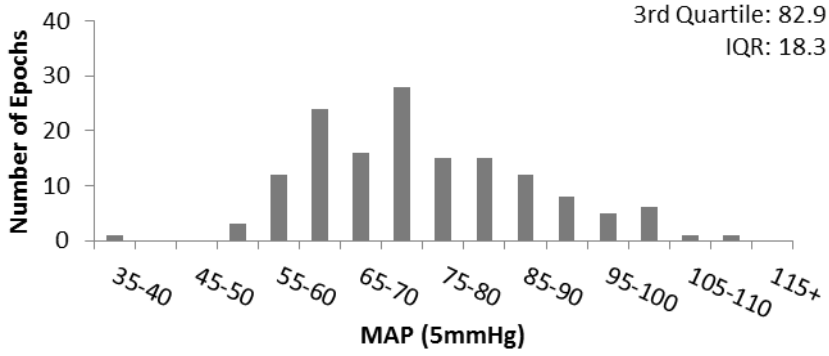
5-6 Mths AS-S

Median: 74.8
1st Quartile: 67.4
3rd Quartile: 85.8
IQR: 18.4



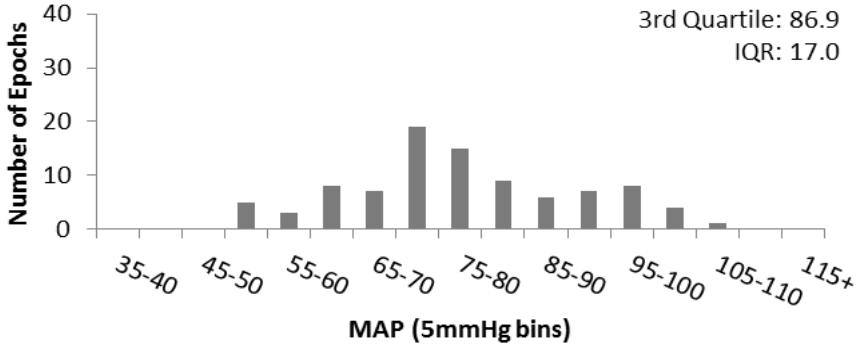
5-6 Mths QS-P

Median: 73.1
1st Quartile: 64.7
3rd Quartile: 82.9
IQR: 18.3



5-6 Mths AS-P

Median: 76.7
1st Quartile: 69.9
3rd Quartile: 86.9
IQR: 17.0



Appendix H

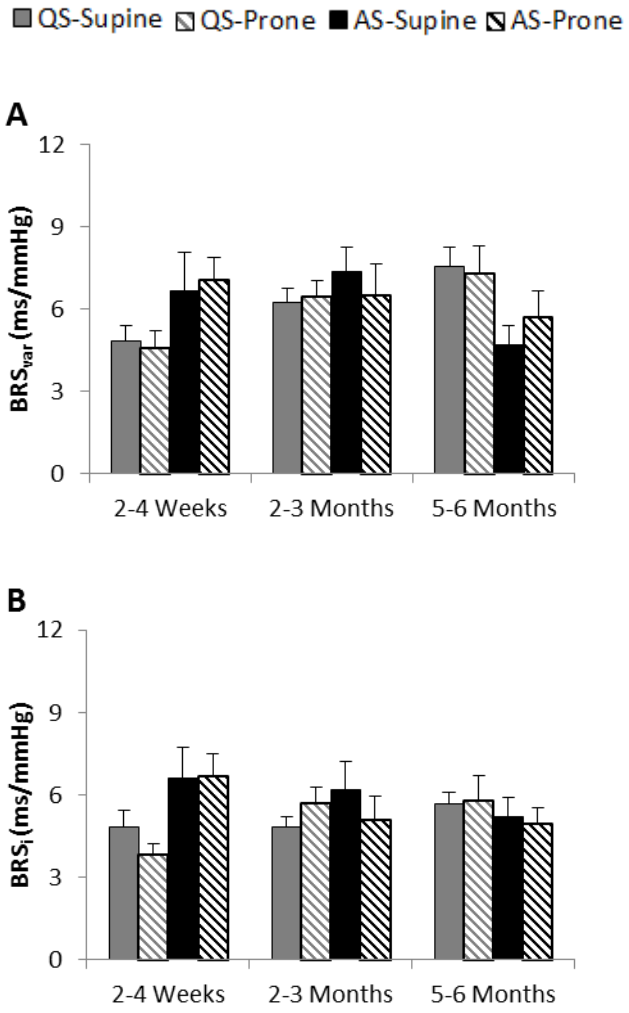


Figure 1: Effect of sleep state and position on time-domain measures of BRS A)BRS_{var} and B) BRS_i. Values are mean ± SEM.

Effect of Sleep Position in Preterm Infants

There was no effect of prone sleeping on BRS_{var} or BRS_i in either sleep state at any post-term age.

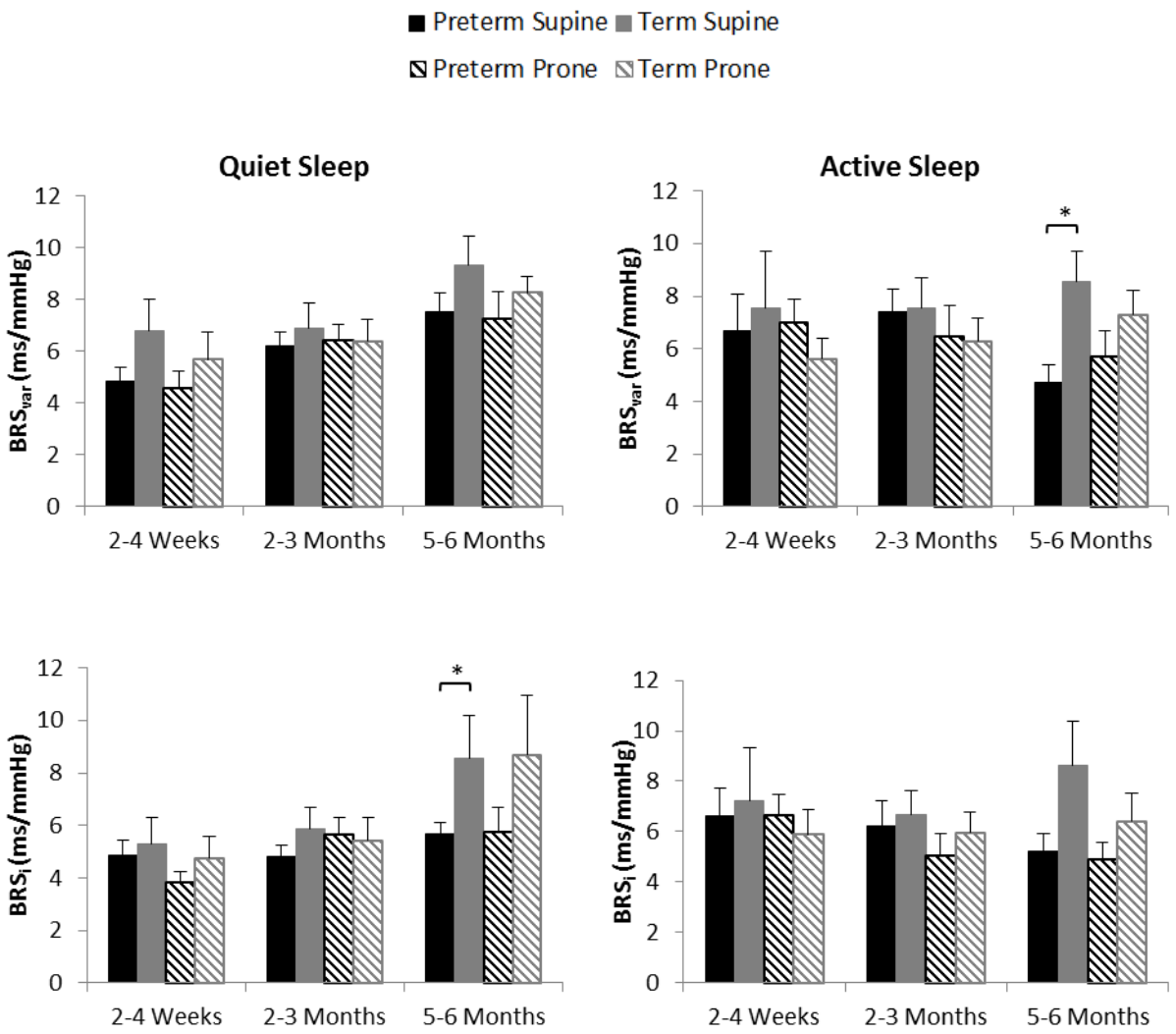


Figure 2: Effect of preterm birth on time-domain measures of BRS. BRS_{var} (top) and BRS_i (bottom) in quiet sleep (left) and active sleep (right). Values are mean ± SEM.* $p < 0.05$ preterm vs term

Effect of Preterm Birth

In the supine position, BRS_{var} was higher in the term compared to preterm infants in AS at 5-6 months ($p<0.05$) and BRS_i was higher in term compared to preterm infants in QS ($p<0.05$) with a trend seen in AS ($p=0.068$) at 5-6 months. In the prone position there was no significant effect of preterm birth on BRS_{var} or BRS_i in either sleep state at any post-term age.

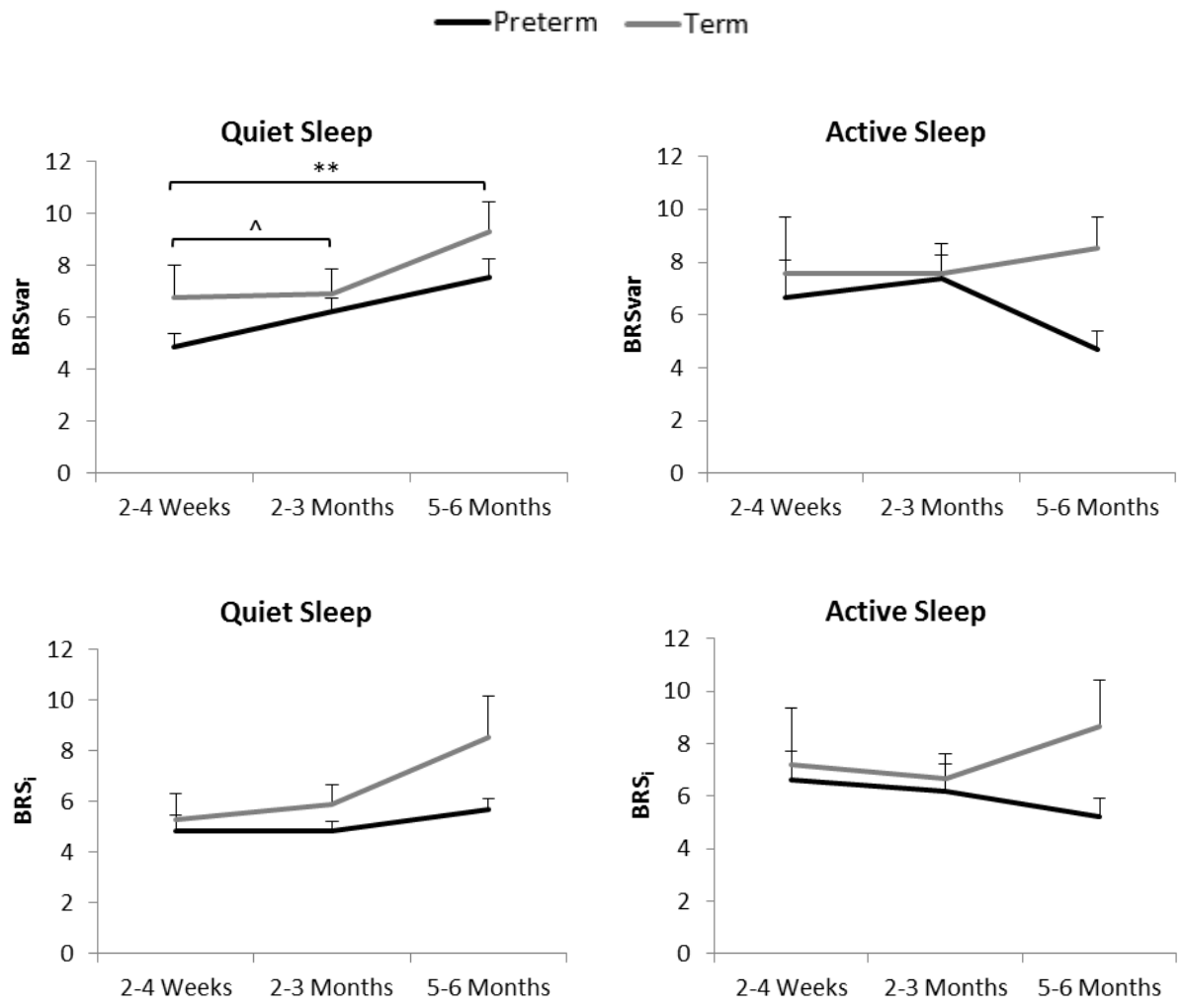


Figure 3: Effect of post-term age on BRS_{var} (top) and BRS_i (bottom) in quiet sleep (left) and active sleep (right) in preterm and term infants in the supine position. Values are mean ± SEM. **p < 0.01 2-4 weeks vs 5-6 months. ^p<0.05 2-4 weeks vs 2-3 months. Black indicates preterm; grey indicates term.

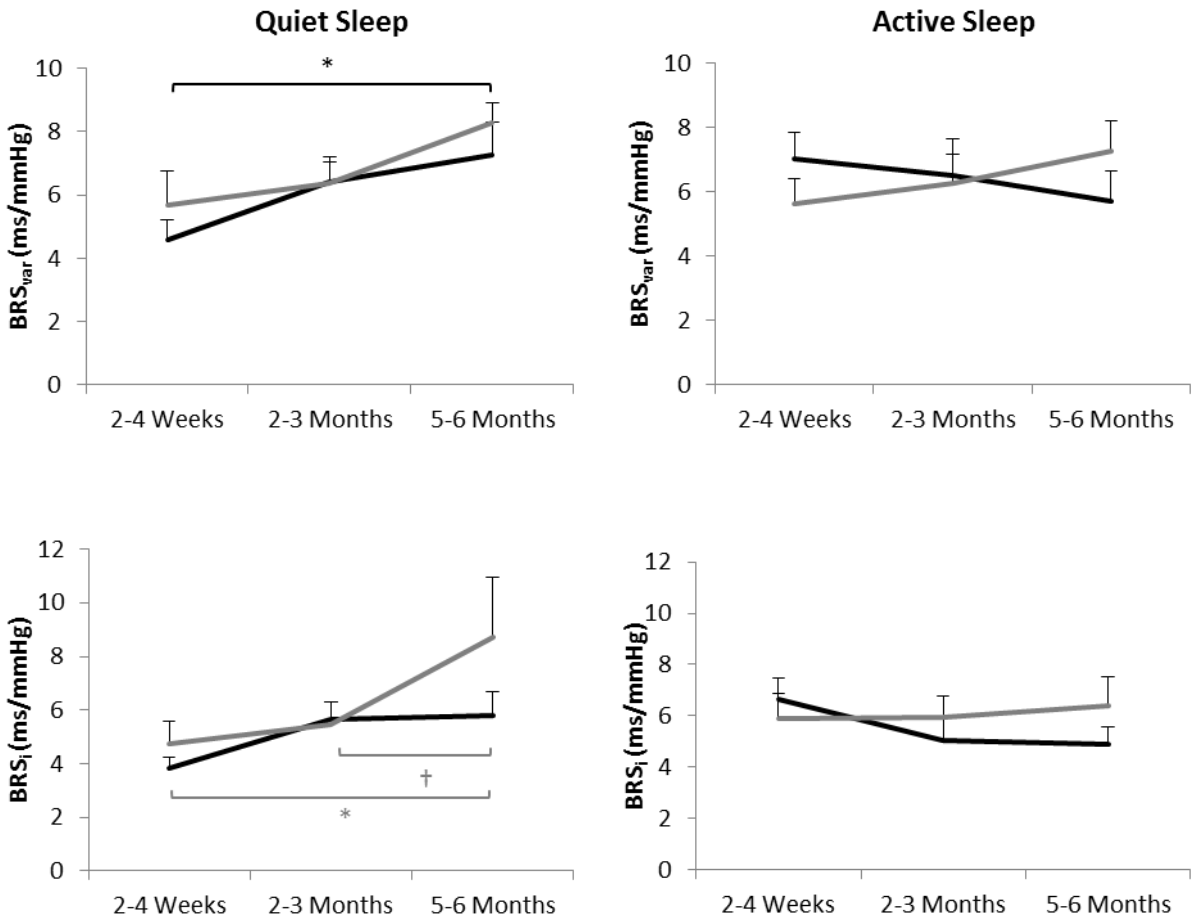


Figure 4: Effect of post-term age on BRS_{var} (top) and BRS_i (bottom) in quiet sleep (left) and active sleep (right) in preterm and term infants in the prone position. Values are mean ± SEM. *$p < 0.05$ 2-4 weeks vs 5-6 months. † $p< 0.05$ 2-3 months vs 5-6 months. Black indicates preterm; grey indicates term.

Effect of Post-Term Age

In preterm infants in QS, BRS_{var} was higher at 5-6 months compared to 2-4 weeks in the prone positions. There was no effect of post-term age on BRS_{var} in QS or AS in the supine position or in AS in the prone position. There was no effect of increasing post-term age on BRS_i in either sleep position or sleep state.

The effect of post-term age on BRS was similar between term and preterm infants. In both the supine and prone positions in QS, BRS_{var} increased more from 2-4 weeks to 5-6 months in term infants than in preterm infants. In the prone position, BRS_i increased in preterm infants but not in term infants. In AS, there was no significant effect of post-term age on BRS_{var} or BRS_i in either term or preterm infants in either sleep position.

Appendix I

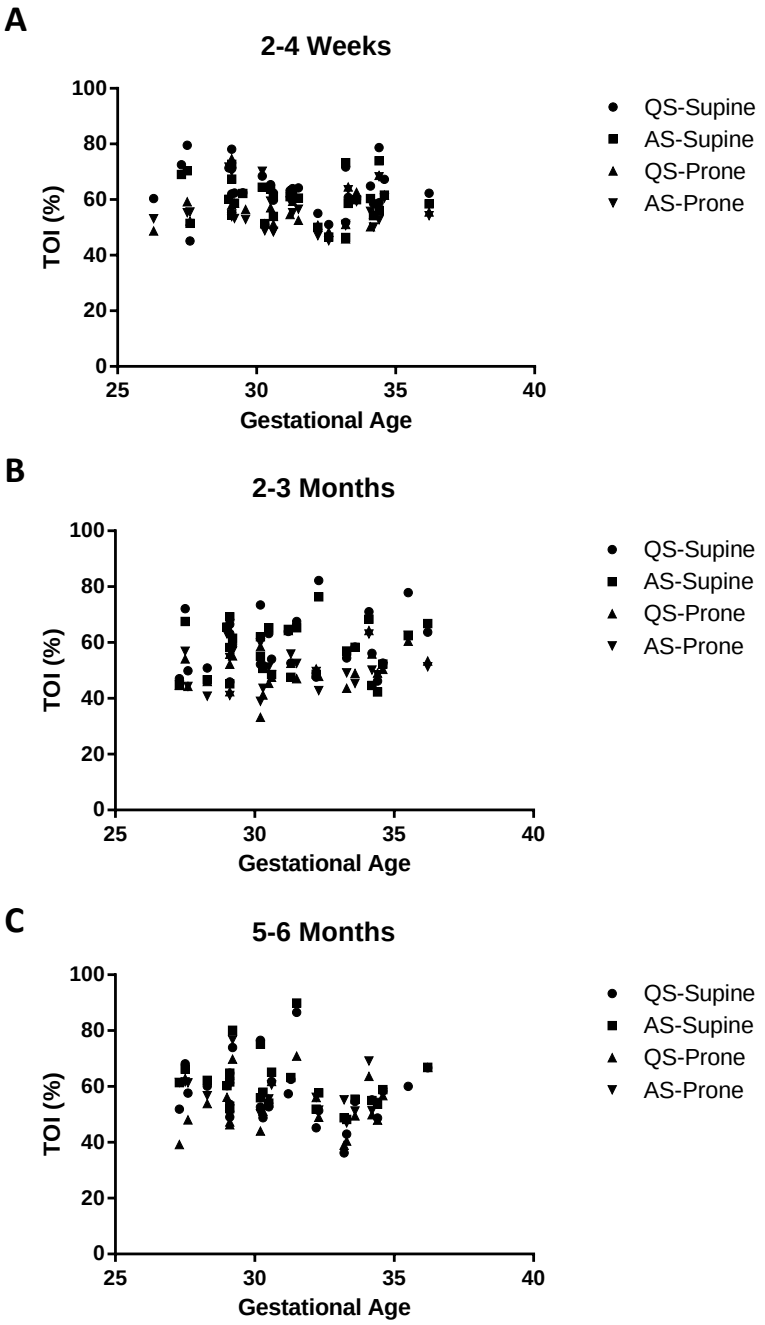


Figure 1. Correlation between gestational age and cerebral TOI at A) 2-4 weeks CA (QS-S $r^2 = 0.02$; AS-S $r^2 = 0.03$; QS-P $r^2 = 0.00$; AS-P $r^2 = 0.00$), B) 2-3 months CA (QS-S $r^2 = 0.03$; AS-S $r^2 = 0.00$; QS-P $r^2 = 0.05$; AS-P $r^2 = 0.01$ and C) 5-6 months CA (QS-S $r^2 = 0.03$; AS-S $r^2 = 0.07$; QS-P $r^2 = 0.00$; AS-P $r^2 = 0.08$)

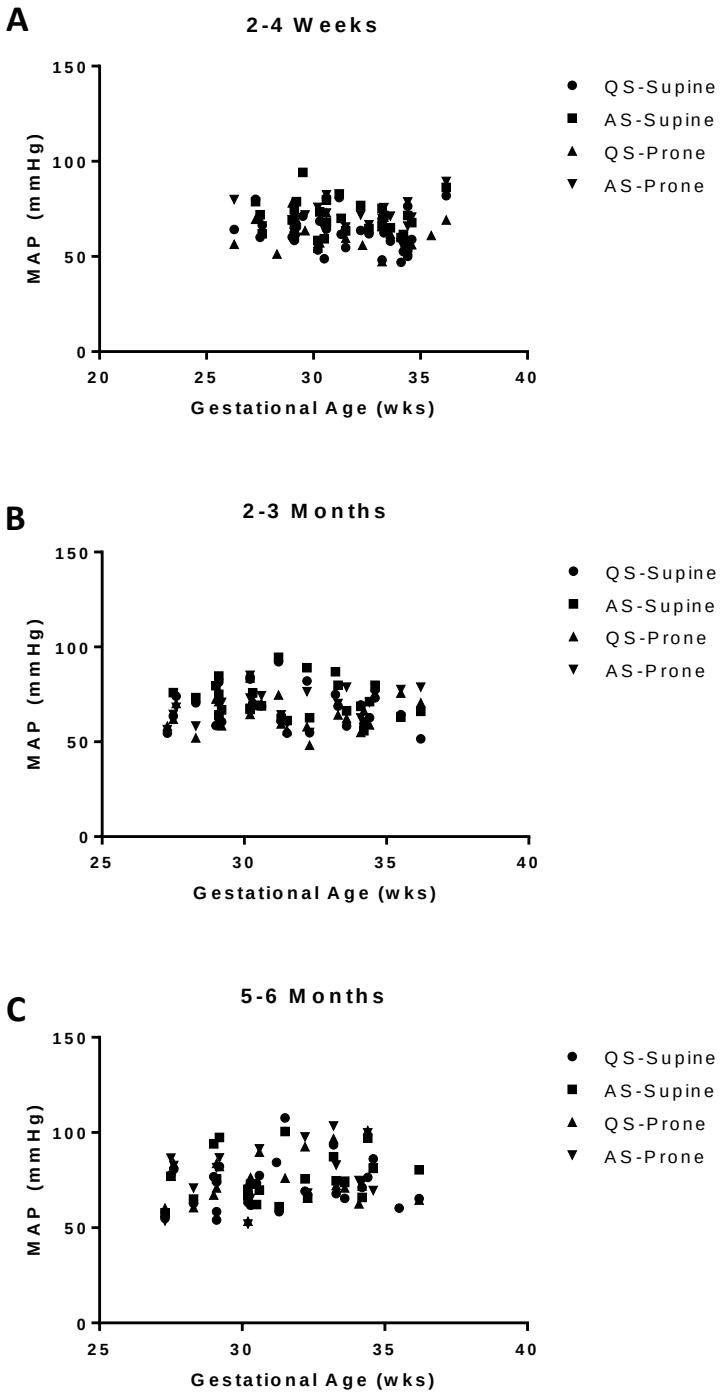


Figure 2. Correlation between gestational age and mean arterial pressure (MAP) at A) 2-4 weeks CA (QS-S $r^2 = 0.02$; AS-S $r^2 = 0.02$; QS-P $r^2 = 0.04$; AS-P $r^2 = 0.02$), B) 2-3 months CA (QS-S $r^2 = 0.02$; AS-S $r^2 = 0.03$; QS-P $r^2 = 0.02$; AS-P $r^2 = 0.07$ and C) 5-6 months CA (QS-S $r^2 = 0.01$; AS-S $r^2 = 0.04$; QS-P $r^2 = 0.02$; AS-P $r^2 = 0.06$)