

Cardiovascular Consequences of Preterm Birth in the First Year of Life

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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 Pflanzner, 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 (SD Δ R-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 ($\Delta HR\%$) 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 ($\Delta HR\%$) 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 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% CO₂ 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 whilst 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 SpO₂ 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 Belgium 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 \leq 44 weeks PMA. "Extreme events" were defined as apnoeas persisting <30s duration or bradycardia <60 bpm for at least 10s in infants \leq 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

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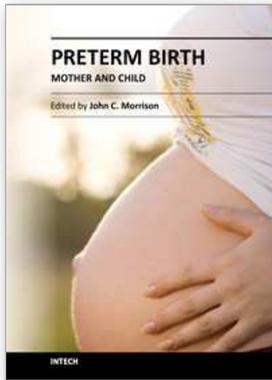
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While there are many studies and books regarding preterm birth, both the obstetric and in the neonatal/pediatric literature, what is missing is the integration of data from obstetrics through neonatal course and into pediatrics as the neonate transverse childhood. A continued dialogue between specialties is essential in the battle against preterm birth in an attempt to relieve the effects or after-effects of preterm birth. For all of our medical advances to date, preterm birth is still all too common, and its ramifications are significant for hospitals, families and society in general.

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