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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

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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: rosemary.horne@monash.edu (R.S.C. Horne).

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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