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Title: Supporting Preterm Cardiovascular Function

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Abstract

Preterm infants are at higher risk of adverse neurodevelopmental outcomes. Inadequate cerebral oxygen delivery resulting from poor cardiovascular function is likely to be a significant contributor to preterm brain injury. In this context, improved support of cardiovascular function is integral to improving preterm outcomes. Many of the treatments used to support preterm cardiovascular function are based on adult physiology and may not be appropriate for the unique physiology of the preterm infant. The preterm heart is structurally immature with reduced contractility and low cardiac output. However, there is limited evidence that inotropic support with dopamine and/or dobutamine is effective in preterm babies. Hypovolemia may also contribute to poor preterm cardiovascular function: there is evidence that capillary leakage results in considerable loss of plasma from the circulation of newborn preterm babies. In addition, the vasoconstrictor response to acute stimuli does not develop until quite late in gestation and is limited in the preterm infant. This may lead to inappropriate vasodilatation adding to functional hypovolemia. The first line treatment for hypotension in preterm infants is volume expansion with crystalloid solutions but this has limited efficacy in the preterm infant. More effective methods of volume expansion are required. Effective support of preterm cardiovascular function requires better understanding of preterm cardiovascular physiology so that treatments can target mechanisms that are sufficiently mature to respond.

Key words

Infant, Extremely Premature

Hypotension

Hypovolemia

Vasodilatation

Among survivors of extreme preterm birth (before 28 weeks) or extremely low birthweight (<1000g), 10-15% develop cerebral palsy and 40-60% have some form of motor disability, a third of which is severe (1, 2). Cognitive impairments and learning disabilities are present in 50% of extremely preterm infants, and there is an increased risk of attention deficit/hyperactivity disorder and autism (3). There is an association between low systemic blood flow and adverse neurodevelopmental outcome (4) suggesting that low cerebral blood flow and inadequate cerebral oxygen delivery contribute to high preterm disability rates.

Very low birthweight infants have a resting cerebral blood flow (corrected for body weight) that is approximately half that at term and one-quarter of adult values (5, 6). This may reflect a lower cerebral oxygen requirement, but observations of increased cerebral oxygen extraction, and lower cerebral venous oxygen saturation suggest that, in some preterm infants, cerebral blood flow is near a critical lower limit and may even be lower than that required for normal oxygen delivery (5, 7, 8). In many very preterm infants cerebral tissue oxygenation is below the normal range for stable very preterm infants during the first days of life (9) supporting the hypothesis that poor cerebral tissue oxygenation contributes to disability.

In neonatal intensive care, treatments are focussed on increasing blood pressure and/or cardiac output to maintain cerebral oxygen delivery. This approach is based on the assumption that cerebral autoregulation is not fully developed in the preterm infant (10) and so increasing blood pressure and/or cardiac output will improve cerebral blood flow and oxygen delivery. Standard treatments are volume expansion with saline and inotropic support, usually with dopamine or dobutamine. Although some interventions produce increases in blood pressure and/or cardiac output in very preterm infants, almost half of the infants treated fail to respond (11-13). No treatments have improved long term neurodevelopmental outcome (11, 14, 15). The use of these treatments is based on the assumption that they will act in the preterm cardiovascular system in the same way that they do in the adult. However, there are some unique aspects of the preterm circulation that need to be considered.

The preterm heart

Studies in preterm animals indicate that the myocytes of the preterm heart are smaller than those in the term heart (16, 17). In addition, there are low numbers of binucleated myocytes, high numbers of proliferating cells and low numbers undergoing apoptosis compared to the term heart, indicating that preterm myocytes have not yet reached maturity (16, 17). Myocyte maturation is accelerated by glucocorticoid exposure and by stress including anaemia (16-18). Transverse tubules are absent in early gestation and the sarcoplasmic reticulum is poorly developed (19). The preterm heart also has a lower the rate of calcium uptake by the sarcoplasmic reticulum (20). Preterm myocytes contain less contractile material and the contractile filaments are less well organised (19). The expression of troponin C and troponin I are lower in the preterm heart and this is associated with a lower maximum Ca^{2+}-activated

force (21). Mitochondria are scattered throughout the cytoplasm rather than aligned in rows between the myofibrils (19). The extracellular matrix is also less developed in younger fetuses (17). Trying to make this immature heart work harder by administering inotropes may not be helpful.

Furthermore, the expression of β_1-adrenoceptors in the preterm heart is half of that in the term heart, so there are fewer β_1-adrenoceptors for adrenergic inotropes to act upon (22). In the preterm piglet, both dopamine and dobutamine treatment resulted in smaller increases in contractility and arterial blood pressure compared with the term piglet (23). Cardiac output and cerebral blood flow in preterm piglets was approximately half that in term piglets and was not increased by either dopamine or dobutamine infusion (23, 24). Thus, it is not surprising that in preterm infants there is no clear benefit from any of the commonly used inotropic medications, as discussed in a recent review (25).

This structural immaturity limits the pressure range over which the preterm heart is capable of optimal function. The preterm piglet heart lacks the ability to maintain cardiac output when afterload rises above 45mmHg (26), supporting the view that large increases in mean arterial pressure are not beneficial, and may indeed be harmful. The preterm piglet heart also functions poorly at low preloads, but does have significant preload reserve. This means that significant increases in cardiac output may be gained by increasing preload (26). These observations suggest that treatments to improve preterm cardiac function should ideally target increases in preload without excessive increases in afterload.

The preterm vascular system

The preterm vascular system may also play a role in the aetiology of preterm cardiovascular compromise. The preterm infant is adapted for the *in utero* environment and not *ex utero* life. *In utero* it is protected from low temperatures by the mother, so there is little need for thermoregulatory vasoconstriction. The fetus is also protected from external threats and there is minimal requirement for acute redistribution of cardiac output for 'fight-or-flight' reactions. On the other hand, a predisposition to vasodilatation in the fetus would provide for maximal nutrient delivery to all tissues to sustain a rapid proportional growth rate that will not be matched at any subsequent time in life. For the fetus therefore, it is beneficial to be predisposed toward vasodilatation.

In preterm fetal sheep there is a reduced vasoconstrictor response to cord occlusion and reduced ability to maintain peripheral vasoconstriction compared with the near term fetus (27). In the fetal sheep there is also reduced vascular responsiveness to adrenergic and peptidergic vasoconstrictors, and increased responsiveness to cholinergic vasodilator stimulation (28), although it is possible that these reduced responses may reflect the lower oxygen requirements of the fetus (29). However, these effects are also apparent postnatally when preterm piglets are exposed to a mild hypoxic stimulus. Endogenous catecholamine levels are similar in preterm and term piglets, and increase more than 20-fold following hypoxia in both groups (30). Term piglets respond with reductions in skin blood flow indicating an effective vasoconstrictor response, but peripheral blood flow is not reduced in preterm piglets, suggesting an inability to respond to these high levels of endogenous catecholamines (30). Preterm human infants also have high levels of endogenous catecholamines on the first day of life, equivalent to or higher than term infants (31, 32), but these high levels of catecholamines do not lead to higher blood pressure or systemic blood flow.

Clinical studies have confirmed that this relatively vasodilated state persists for several days after birth in preterm infants. There is a significant inverse relationship between skin microvascular flow at 24h after birth and gestational age in infants born at 24-36 weeks gestation; that is, the more premature the infant, the higher their microvascular flow (33). Similarly Wu et al (1980) observed that skin and muscle blood flow on the first 7 days after birth is much higher in preterm infants than in term infants (34). That study also noted that flow decreased with postnatal age, but most dramatically in the most premature infants. There was a direct correlation between gestational age and peripheral vascular resistance in both skin and muscle. Vascular resistance in preterm infants was less than half of that in term infants. Lower vascular resistance in preterm infants (27-34w) compared with term infants was also observed by Kidd et al (35). In very low birthweight infants an increase in skin and subcutaneous blood flow is thought to be due to vasodilatation in the transitional period (36). Vasodilatory capacity in response to local warming is significantly greater in infants born at 24-28 weeks gestation than those born at 29-36 weeks (33). This is strong evidence that the preterm infant is thus predisposed toward vasodilatation.

As the fetus approaches term and in the immediate postnatal period, there is maturation of both cardiac and vascular receptors, and sympathetic pathways, in preparation for the different cardiovascular and thermoregulatory needs of life after birth. Over the first month of life the sympathetic nervous system of the pig becomes more functional with a decreasing threshold and increasing magnitude of response to electrical stimulation of renal and lumbar nerves (37). The expression of β_1-adrenoceptors in the heart increases two-fold between 91d gestation and term (115d) in the piglet (22). The density of vasoconstrictor α_1-adrenoceptors in aortic smooth muscle is much lower in fetal sheep (125-140d) than in the ewe (38). In both the heart and the peripheral vascular system there are changes in the gasotransmitters responsible for vasodilatation, with evidence of interactions between nitric oxide, carbon

monoxide and hydrogen sulphide production in the preterm infant (39). These changes act to shift the vasoconstriction/vasodilatation balance away from vessel relaxation as term approaches (40). In the renin-angiotensin system the number of vasoconstrictor AT_1 receptors in the major blood vessels increases while the number of vasodilator AT_2 receptors decreases (41). However, premature delivery before this maturation occurs leaves the preterm neonate at risk of inappropriate vasodilatation. If the well-adapted preterm fetus suddenly becomes a preterm neonate, then the dominant state of vasodilatation is disadvantageous. Excessive vasodilatation will lead to reduced preload and a significant reduction in cardiac output (26). Higher microvascular flows in preterm infants are associated with lower mean arterial pressures, and there is a significant inverse correlation between microvascular flow and mean arterial blood pressure (42). There is also a positive relationship between microvascular flow and illness severity. Infants who died soon after birth were more likely to have had higher microvascular flow suggesting that inappropriate peripheral vasodilatation contributes to cardiovascular compromise (42). There are also sex differences in this vasodilatory state. More severe vasodilatation is seen in male infants, those who also have greater risk of adverse outcomes (33, 43, 44).

Blood volume in the preterm infant

Lack of an adequate blood volume may contribute to compromised preterm cardiovascular function. It is sometimes assumed that hypovolemia does not occur in the preterm neonate. This assumption is based on the observation that volume expansion with saline is ineffective for improving outcomes (13). There is also evidence that preterm infants have a higher % total body water than term infants (45). However, several factors may contribute to early hypovolemia in preterm infants.

As the pulmonary circulation opens with expansion of the lungs, the capacity of the vascular compartment is increased. High levels of circulating catecholamines at birth (31, 32) may assist the term neonate to successfully adapt to this increased capacity by increasing systemic vasculature resistance. However, as discussed above, the preterm neonate is less responsive to catecholamines (23, 30). As a result, the preterm infant may not compensate for this increased vascular capacity leading to a functional hypovolemia. In addition to these vascular factors, early loss of fluid from the vascular compartment due to excessive leakage from capillaries results in a significant loss of intravascular volume. The rapid loss of labelled albumin from the circulation coupled with early increases in haemoglobin concentration suggest whole plasma is lost from the circulation of the preterm infant (46, 47). Loss of protein from the circulation will exacerbate leakage and hypovolemia.

Hypovolemia in preterm neonates may be very detrimental. In the preterm piglet, cerebral blood flow in preterm animals is about half of that in term piglets (23, 48). When blood volume is reduced, the term piglet adapts by increasing cerebral vascular conductance and maintaining cerebral blood flow. This adaptation is not seen in preterm piglets leading to extremely low cerebral blood flow that is likely below that required to meet oxygen delivery requirements (48).

There is insufficient evidence to support the use of saline for volume expansion in preterm infants and there is no improvement in outcome (13). In adults, saline rapidly leaves the vascular system and also causes vasodilatation (49, 50). It is not surprising then that there is little benefit in the preterm neonate where capillaries are leaky and excessive vasodilatation is already present. In addition, saline distributes throughout the extracellular space – plasma and interstitial fluid. In the fetus and neonate, the plasma:interstitial volume ratio is decreased, thus decreasing the proportion that would remain in the plasma (51, 52). There is in fact some

evidence that saline may be harmful. In the adult, in addition to vasodilatation, saline infusion leads to acidosis (53, 54). In preterm piglets, saline infusion of 10-30 ml/kg does not improve mean arterial pressure and is associated with increased acidosis and a more negative arterial base excess (Fig 1). It is critical to develop more effective methods of volume expansion in the preterm neonate. Volume expansion with whole blood or packed red cells may, in theory, be more effective than saline. Red blood cells will remain within the circulation and will have the added benefit of increasing the oxygen carrying capacity of the blood. Beneficial effects of delayed cord clamping and placental transfusion support the hypothesis that volume expansion with blood may be more effective than saline (55).

Developing New Treatments

The first step in the development of new treatments to support preterm cardiovascular function is a better understanding of the aetiology of preterm cardiovascular compromise. Is compromised function due to incomplete cardiac maturation, poor control of the peripheral circulation or hypovolemia? It is likely that a combination of these will be present and that factors may differ between individuals. This highlights the need for improved methods to monitor cardiac function, preload, peripheral vascular function and blood volume. Our data in preterm piglets illustrate the futility of using an inappropriate treatment. If the piglet is hypovolemic, treatment with inotropes does not address the real problem. Dopamine and dobutamine have limited effectiveness for increasing mean arterial pressure or cardiac contractility in preterm piglets, but are even less effective when blood volume is reduced (Fig 2). Thus, inotropes cannot restore function that is reduced due to hypovolemia. Perhaps many preterm babies have undetected hypovolemia and this is why their response to inotropes is so poor.

When the aetiology of compromised preterm cardiovascular function is understood, it is critical to apply treatments that target the specific issues. Treatments that promote improved control of the peripheral circulation are essential. Venoconstriction may reduce functional hypovolemia resulting from increased vascular capacity. Preventing hypovolemia will harness the significant preload reserve of the preterm heart and increase cardiac output without inducing excessive afterload. Effective volume expansion may also lead to improved cardiac function through increased preload, and improve outcomes. Treatments must target the unique preterm physiology and not simply assume that the preterm physiology and treatment response is the same as adults, or even older children.

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Figure Legends

Figure 1: Mean arterial pressure (MAP), arterial pH and base excess (ABE) in untreated (n=3) and saline infused (n=4) preterm piglets on the first day of life at 97d gestation (equivalent to approximately 27 human weeks, piglet term is 115d). All piglets had mean arterial pressure <27mmHg at baseline. Saline treated piglets received three infusions of 10 ml/kg of 0.9% saline over a total of 3h following baseline measurements. All measurements were repeated 4 hours after baseline. At 4 hours, MAP (Student's t test, P=0.024), pH and ABE (arterial base excess) (both Mann-Whitney U test, P=0.034) were significantly lower in saline treated preterm piglets than in untreated piglets. * indicates significant difference between untreated and saline treated piglets (P<0.05).

Figure 2: Mean arterial pressure and cardiac contractility in term (115d) and preterm (97d) piglets during baseline, low dose (10µg/kg/min) and high dose (20µg/kg/min) dopamine or dobutamine treatment and in the presence of normovolemia and hypovolemia. N = 6-10 piglets per group at each data point. Inotropes have minimal effects in normovolemic preterm piglets but are less effective when preterm piglets are hypovolemic. In the presence of hypovolemia, inotropic treatment is less likely to lead to normal function than inotropic treatment in the presence of normovolemia. * indicates a significant difference between normovolemia and hypovolemia conditions at a given dose ($P<0.05$).