Limitations and vulnerabilities of the neonatal cardiovascular system: considerations for anesthetic management

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Summary
Development of the cardiovascular system through the last trimester of pregnancy and the subsequent neonatal period is profound. Morphological changes within the myocardium make the heart vulnerable to challenges such as fluid shifts and anesthetic drugs. The sensitivity of the myocardium to metabolic challenges and potential harm of drugs needed to maintain adequate blood pressure and cardiac output are highlighted. Traditional monitoring under anesthesia has focussed on maintaining oxygenation and heart rate in the neonate with less attention paid to blood pressure, cardiac output, and more importantly organ well-being. There is now a better understanding of the limitations of blood pressure homeostasis in the neonate and the potential consequences of marginal hypoperfusion. This article highlights some of these vulnerabilities particularly as they relate to anesthesia and surgery in the very young.

Introduction
The neonatal cardiovascular system does not represent a small-scale model of the mature organism. The fetal heart is morphologically immature and is functionally adapted to a low-pressure, hypoxic environment where there is minimal pulmonary blood flow (<8%) and low systemic vascular resistance. Quite apart from the radical adjustment to an extra-uterine circulation at birth, the neonatal heart has to rapidly adapt to a dual circulation with significantly greater systemic vascular resistance and increased metabolic requirements.

Traditionally, the neonatal heart and circulation has been seen as a robust system in that it appears to stand the traumas associated with birth and quite substantial periods of hypoxia. Much of the focus of anesthesia of the neonate has been centred on the prevention of hypoxia and the maintenance of heart rate with less attention to blood pressure and adequacy organ flow. The challenge of optimizing cardiovascular support under anesthesia is now more recognized and requires understanding of the limitations of myocardial function, response to inotropes, and immaturity of cardiovascular control. This article sets out to highlight some of these key issues that need consideration when anesthetizing the neonate.

The neonatal myocardium
The structure and function of the myocardium changes markedly in the neonatal period, and during this time, it is vulnerable and poorly adapted to the challenges of anesthesia and surgery. Histologically, the myocardial cells are disorganized compared with the mature myocardium, less compacted and with increased noncontractile tissue and water between contractile units (1,2). This is reflected of the higher proportion of extracellular fluid and total body water compared with the older infant. As a result, the neonatal myocardium is inefficient as a filling and contracting unit: ventricular compliance is considerably reduced and wall tension/intraventricular pressure rises rapidly with increased end diastolic volume (3). There is also poor responsiveness to preload (a flat Starling curve) and a vulnerability to overfilling, with wall tension rising rapidly, coronary perfusion falling, overdistention, and heart failure. However, within the first month of life, diastolic relaxation improves
significantly, and with it the ability to respond to intravascular fluid shifts (4).

Cellular energy is derived primarily from glucose and glycolysis in the hypoxic fetal environment, where oxygen availability is limited (5). After birth, the neonate progresses to a combination of carbohydrate and short-chain fatty acids with a decrease in glycogen and lactate concentrations and finally to all energy sources with the primary source obtained from long-chain fatty acids in the adult (6). Despite the ability of the neonatal myocardium to use glycolysis as an oxygen-independent source of high-energy phosphates, myocardial energy requirements come at their greatest in the neonate compared with both fetus and adult, reflecting the age-related requirements of cardiac index (7,8). Given the limitation of external glycogen and other energy stores in the neonate maintenance of energy input and avoiding hypoglycemia or excessive cardiac work load is essential to avoid fatigue and substrate failure, which can occur abruptly and catastrophically in this age group.

The excitation contraction coupling and later relaxation (diastolic phase) are points of particular vulnerability in the neonatal heart. In the adult, ionized calcium enters the cell with depolarization through L-type channels and passes rapidly through the t-tubular system. The calcium influx triggers calcium release from within the sarcoplasmic reticulum (SR) in response to interaction with the ryanodine receptor, and this in turn activates the myosin/actin contractile process. During diastole, calcium is rapidly sequestered within the SR to allow relaxation of the contractile elements. The neonatal heart has reduced L-type channels on the myocardial cell surface, and entry of calcium into the cell is primarily by T-type channels, calcium-handling proteins, and the reverse sodium/calcium exchange mechanism that is more usually associated with calcium removal from the cell (9,10). Propagation of the calcium flux into the cell is poor due to the immaturity of the t-tubular system, and at the SR, the paucity of ryanodine receptors is associated with a limited release of calcium to activate contraction (11). Finally, the reuptake into the SR is limited at the end of systole, preventing effective relaxation during diastole. Cardiac contraction in the neonate is therefore much more dependent extracellular, and nuclear calcium for the initiation of contraction and maintenance of adequate plasma calcium concentrations may be a factor in cardiac performance (12,13). Development of the SR, t-tubular system, and calcium-handling proteins appears to be rapid, and it has been suggested that they are relatively mature by 3 weeks in the human neonatal heart (14).

In recent years, there has been considerable interest in the potential ability of the myocardium to remodel its structure after cardiac repair and even to regenerate myocardial tissue through stem cells. Recent data would support the hypothesis that the human neonatal heart has a greater regenerative ability than adult hearts that may be due to greater numbers of stem cells and their ability to differentiate (15). This bodes well for future research in that this capacity may allow triggers for cell regeneration to be enhanced in the infant heart that has been affected by congenital, acquired, or even iatrogenic derived injury.

Heart and vascular responses to inotropes

Given that the neonatal heart has a much reduced capacity to increase its stroke volume in response to increasing preload (16), beta-agonist catecholamines are commonly used to increase cardiac output by increasing myocardial contractility and heart rate, in conjunction with drugs that optimize pulmonary or systemic vascular resistances. However, there is an increasing understanding that while catecholamines have a place in management of the neonate both in terms of myocardial performance and manipulation of the systemic vascular resistance, the immature heart is very vulnerable to the intrinsic effects of these drugs on the myocardium. Irrespective of age, cardiac tissue requires adequate myocardial perfusion via the coronary arteries to deliver oxygen and substrates. Published values for blood pressure are significantly higher than that usually accepted in the anesthetized neonate (17,18), but within the pediatric anesthetic community, there is considerable uncertainty of what constitutes hypotension requiring intervention (18). There are limited modalities available to increase blood pressure in the normal heart: intravenous fluid administration to maintain vascular volume, inotropes and chronotropes, which can improve stroke volume/heart rate, and vasoconstriction, which will raise blood pressure but at the expense of increased heart work unless the systemic vascular resistance is reduced (for example in conditions such as sepsis). While catecholamines may achieve the initial goal of raising blood pressure to levels that will perfuse the coronary arteries and increase flow to other vital organs, the neonatal heart appears to be vulnerable to the effects of catecholamines in terms of myocardial damage and depletion of energy substrates. In an intact neonatal piglet model (2–4 Kg), heart rate was increased for a period of 2 h either with pacing or with epinephrine infusion (19). While there was limited change in the paced group, there was increased ventricular wall stiffness in the catecholamine group, and within the myocardial cell, evidence of areas of damage with sarcolemmal rupture and mitochondrial damage.
with swelling and calcium deposition. The pathological changes appear to be age related with the neonatal heart being the most vulnerable (20). Suggested causes are reduced sequestration of calcium within the SR, failure of the ATP calcium relaxation mechanism, and free radical generation from catecholamine oxidation. It may also be related to the exhaustion of energy supply with falling levels of ATP after catecholamine treatment (19). This observation was also seen in a comparative study of neonatal and mature sheep where heart work was increased to similar levels of oxygen consumption using an epinephrine infusion (20). In the mature sheep, increased heart work was associated with stable myocardial ATP/ADP concentrations, while increasing calcium reuptake by the SR in diastole and promoting release of calcium at the SR, increases the availability of calcium within the sarcoplasmic reticulum by enhancing calcium entry into the cell and promoting release of calcium at the SR, while increasing calcium reuptake by the SR in diastole (21). Given the poor diastolic relaxation associated with the neonatal heart and limitations of calcium flux as described above, PDE blockade would be expected to have beneficial effects throughout the cardiac cycle. Previous data have also shown that milrinone can restore the efficiency of beta-agonists in the isolated myocyte after a period of reperfusion, making it a drug that has value in combination with a catecholine not only for its intrinsic effect but as a catecholamine sparing drug (22). In the peripheral vascular smooth muscle, PDE3 blockade causes relaxation via both cAMP and cGMP mechanisms.

An early study with milrinone in 10 neonates after cardiac surgery demonstrated an increased cardiac index with falls in systemic and pulmonary vascular resistance (23). This was followed by what has to date been the definitive trial of milrinone in the prevention of low cardiac output syndrome (LCOS) after cardiac bypass surgery in neonates (24). The trial has been criticized for not having an active comparator with a vasodilator, but it has transformed management of the neonate having bypass surgery away from the extensive use of potent dilators at the outset to a more consistent use of milrinone with minimal use of catecholamines. Nevertheless, there are some highly successful units who have continued to publish excellent results using radical alpha-blocking drugs such as phenoxybenzamine in the most complex patients (25).

While there is little doubt as to the effectiveness of the drug, the multiple actions of the drug on a variety of target sites leave the question of why it works and leave the way open for more effective drugs in the treatment for neonatal LCOS in the future. Experimentally, it appears to have a preservative action on energy stores within the mitochondria by blockade of specific ion channels (26), and in adult cardiac surgery, the delivery of adequate doses of milrinone prebypass is associated with the maintenance of cAMP stores within the myocardium after removal of the aortic cross-clamp (27). These data would suggest a role for instituting milrinone not just as a loading dose on bypass once the cross-clamp has been applied, but well before.

One of the problems with the drug in intensive care is that while it prevents vasoconstriction immediately after bypass surgery (28), it cannot alone reliably modulate vasodilation and neonates may then still require additional vasodilators. However, if high-dose infusions are maintained over several days in the treatment for LCOS, the drug accumulates, resulting in vasodilation and hypotension that can be confused with pump failure or sepsis. Understanding the pharmacokinetics of milrinone in terms of adequate loading but reducing maintenance infusion rates over time in the neonate with limited renal function and low cardiac output has helped to recognize and avoid this problem (29,30).

Down-regulation of beta-receptors in the sick neonatal heart results in catecholamine resistance and escalation of dosage with less effect. Adult data from atrial tissue suggest that this may be due to uncoupling of the beta-receptors with reduced levels of cAMP in response to beta-stimulation (31). There is current interest in the use of low-dose vasopressin (AVP) in pediatric intensive care to overcome the effects of catecholamine resistance following Cardiopulmonary bypass in the neonate. This seems counterintuitive as one of its major actions is to
increase peripheral resistance. However, AVP does have some intrinsic inotropic effect, increases myocardial sensitivity to catecholamines, and causes both coronary and pulmonary vasodilatation (32). A small retrospective study showed that, during the first postoperative day, patients who had been started on AVP immediately after surgery required less fluid resuscitation and catecholamines (33). There were also trends toward shorter periods of mechanical ventilation and intensive care stay.

**Cardiovascular control in the neonate**

Autonomic control of the cardiovascular system is significantly reduced in the neonate leaving it prone to blood pressure variations. From comparative anatomic studies, the autonomic innervation of the heart appears to be present from birth (34), but immature. Studies of the autonomic function using frequency analysis of heart-rate variability indicate that at birth all autonomic responses are limited but that the sympathetic component is the more dominant (35). In infancy, this reverses and parasympathetic component becomes more dominant until later childhood. Additionally, the preterm and ex-preterm infant have enhanced vulnerability from lack of cardiovascular autoregulation, which fails to catch up with the responsiveness of the term infant for up to 2 years (36,37). One of the consequences of the reduced autonomic responses is the flattening of baroreceptor sensitivity (38). The result is that the responsive changes in heart rate and vascular resistance from reduced blood pressure are more limited. These limitations in cardiovascular homeostasis make the neonate vulnerable to maintaining blood pressure within tight limits, particularly under anesthesia when autonomic reflexes are further suppressed (39). Data are now beginning to emerge that the consequences of hypotension from drug administration may be significant in terms of both short- and long-term neurological outcomes (40). This issue is dealt with in more detail elsewhere in this neonatal edition of Pediatric Anesthesia.

In addition to global cardiovascular control, individual-organ-specific autoregulation helps to maintain blood flow independently of blood pressure within the normal operating range of blood pressure. Cerebral blood flow is also greatly affected by changes in arterial CO2 tension and hypoxia. Hypocarbia causes vasoconstriction and has been implicated in the development of periventricular leukomalacia in premature infants (41). Hypoxia has a vasodilatory effect. Healthy neonates do show autoregulation in respect of cerebral blood flow (CBF), and this may be present from an early gestational age (42). However, evidence is increasing that in sick neonates, cerebral autoregulation is lost. In the newborn lamb, 20 min of hypoxia results in the loss of autoregulation for several hours (43). Healthy term neonates are able to normalize CBF after a rise in blood pressure, but not sick term infants and all preterms; there is correlation between the elevation of blood pressure and CBF, indicating some failure of cerebral autoregulation (44). Given that anesthetic agents impair cerebral autoregulation even at low concentrations, the necessity to control blood pressure, oxygenation, and carbon dioxide tensions during anesthesia in the vulnerable neonate that has very limited compensations is of key importance. Interest is now growing in monitors such as tissue and cerebral oximetry that can measure organ perfusion as well as the simpler cardiovascular parameters.

**Conflict of interest**

No conflicts of interest declared.

References

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The neonatal cardiovascular system