Hemodynamic Support

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I. Introduction
   A. Neonatal cardiovascular physiology differs in many ways from the physiology of the more mature human.
      1. Cardiac function
         a. Neonatal myocardium is structurally, metabolically, and functionally limited.
         b. Basal contractility is near to maximal levels, and therefore, any further demands on cardiac function, such as those resulting from increases of afterload, may not be met.
         c. Increases in afterload as a result of vasoconstriction often lead to decreases in ventricular output.
         d. Drug responses are often also quite different in the newborn; metabolic immaturity of the myocyte may lead to responses which are in a different direction in the newborn. For example, phosphodiesterase-3 inhibitors (e.g., milrinone) may lead to negative inotropic responses in the newborn, in contrast to the positive inotropic responses seen in the older subject.
         e. Only studies restricting the investigation to the newborn or the preterm newborn give adequate information.
      2. Vascular responses

         The development of vascular receptors is poorly studied. Alpha-mediated vasoconstriction is seen with the administration of catecholamine agents, even in very immature babies, but the gestational age at which other vascular responses may occur (those mediated by other catechol receptors, or other categories of responses, such as those mediated by endothelin or acetylcholine) are unknown.
      3. Shunts
         a. Because of the presence of shunts, newborn infants with normal hearts do not have a single variable called "cardiac output."
         b. Total perfusion of the body is the sum of SVC flow and IVC flow.
         c. In contrast, left ventricular output (LVO) only reflects systemic perfusion when the ductus arteriosus is closed.

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d. When the ductus is open, LVO is the sum of pulmonary venous return and any net shunting across the foramen ovale.
e. Right ventricular output (RVO) is the sum of systemic venous return and any net left-to-right shunting across the foramen ovale; as this shunt is often small, RVO can often be used as an indicator of total systemic perfusion.

B. Normal transition
1. The fetal circulation
a. In utero the pulmonary vascular resistance is very high, which keeps pulmonary blood flow low (less than 15 % of the combined ventricular output).
b. The majority of blood ejected by the right ventricle crosses the ductus and perfuses the low resistance placental circulation; thus, right ventricular afterload in utero is low.
c. Most upper body flow in utero is derived from the LVO.
2. At the time of birth the ductus arteriosus constricts and the RVO perfuses the lungs, after which pulmonary vascular resistance starts to fall; thus, right ventricular afterload transiently increases at birth, and then falls as the PVR decreases.

II. Hemodynamic problems
A. PPHN (Chap. 72)
1. Pathophysiology
a. This condition results from the failure of pulmonary vascular resistance to fall, or a recurrence of high resistance after the initial transition.
b. This may occur as a complication of meconium aspiration, pneumonia, pulmonary hypoplasia, other respiratory disorders, such as respiratory distress syndrome, or occasionally as an isolated phenomenon in babies with clear chest radiographs.
c. Right-to-left ductal shunting, although pathognomonic, is seen only in those with severe disease and an open ductus.
d. Many other infants have intracardiac shunting across the foramen ovale; such shunting depends on an inter-atrial pressure gradient. Right atrial pressures will be elevated in the presence of right ventricular failure, which may result from the high right ventricular afterload. Thus, right ventricular function is an important determinant of a good outcome in infants with PPHN.
e. Finally, hypoxemia may result from intrapulmonary shunting (that is, V/Q mismatch).
2. Clinical evaluation
a. PPHN may accompany respiratory distress, or occur in babies with little distress; such infants often need a high FiO_2 to achieve adequate saturation.
b. Pre-ductal saturation (right hand) and post-ductal saturation (a foot) may show a gradient, but its absence does not rule out the disease.
c. In most infants with severe respiratory failure there is some elevation of the pulmonary vascular resistance, which may contribute to the severity of their illness.
3. Supplementary testing
a. Echocardiography may show right-to-left or bi-directional shunts, at the ductus arteriosus or across the foramen ovale. In the presence of tricuspid regurgitation, right ventricular pressure can be estimated. Abnormal curvature of the inter-ventricular septum may give an indirect estimate of increased pulmonary arterial pressure.
b. If congenital heart disease is suspected, a hyperoxia test may be helpful, but can also be misleading.
4. Therapy
a. Supportive therapy, assisted ventilation, warmth, oxygen, and fluids are used.
b. Sedation may help in certain cases.

c. The only proven directly acting therapy is inhaled nitric oxide (Chap. 63), which can be commenced at between 2 and 20 ppm.
d. Hyperoxia should be avoided, as it may impair nitric oxide-mediated pulmonary vasodilation, and increase pulmonary vascular reactivity.
e. Hyperventilation should be avoided, as progressive systemic hypotension may occur.
f. Infusions of sodium bicarbonate should be avoided, as their use has been associated with increased need for ECMO and poorer outcomes.
g. Cardiac supportive therapy may be required, but it is unclear which agent has the best effect. Epinephrine use at low to moderate doses (0.05–0.2 mcg/kg/min) improves systemic oxygen delivery in animal models. Norepinephrine leads to pulmonary vasodilation in some animal models.

B. Septic shock
1. Pathophysiology
a. There are little data regarding the usual hemodynamic features of septic shock in the newborn.
b. Older patients with gram-negative septic shock commonly have excessive vasodilation accompanied by a normal or increased cardiac output and hypotension, so-called warm shock.
c. It is not clear if this is true in newborn infants, who often have different organisms (e.g., group B streptococcus) and have a different cardiovascular physiology. Neonatal *animals* with group B streptococcus demonstrate vasoconstrictive "cold shock," with hypotension being a pre-terminal event.
2. Clinical evaluation
a. In cold shock, signs of peripheral vasoconstriction are common: prolonged capillary filling, oliguria, and inactivity.
b. In warm shock, pulses may be bounding, but signs of inadequate tissue oxygen delivery may be seen (e.g., lactic acidosis and poor urine output).
3. Supplementary testing
a. Echocardiography may be helpful for estimating cardiac filling, contractility, and systemic blood flow, and in determining therapeutic interventions.
b. There is no clear evidence that this improves outcomes, but it does allow more rational therapy.
4. Therapy
a. There is little good evidence regarding therapeutic options in infants with septic shock.
b. A physiology-based approach would suggest that infants with clinical shock but with adequate blood pressure may benefit from dobutamine (which increases systemic perfusion without having much effect on blood pressure).
c. Infants with shock and hypotension may preferably be treated with epinephrine, which appears to increase both blood pressure and systemic perfusion. Norepinephrine may be a useful alternative.
d. Combinations of drugs have unpredictable effects. Pharmacokinetics and receptor status of babies vary considerably; therefore, dose responses are extremely variable and doses need to be individualized.
e. In adults with septic shock, there is little evidence that clinical outcomes vary according to the drug chosen; randomized trials comparing different agents show differences in short term clinical responses, but generally not in survival.
f. Fluid boluses are often administered, based on the assumption that sepsis leads to a functional hypovolemia.

(1) Although this may be true in certain cases, a recent trial in older infants and children showed an increase in mortality in children with early septic shock who received a fluid bolus.
(2) If fluid boluses are administered, crystalloids and colloids have different hemodynamic responses, with a greater and more prolonged increase in perfusion with colloids than with saline, but with little or no evidence of differential clinical outcomes, the agent of choice in the newborn is uncertain.

C. Hypovolemic shock
   1. Pathophysiology
      a. Hypovolemia can result from blood loss (e.g., ruptured vasa praevia), or occasionally in infants following placental abruption (in this situation the blood lost is usually mostly maternal).
      b. Partial umbilical cord occlusion, as may occur with a tight nuchal cord, or cord prolapse, will initially occlude the umbilical vein, prior to the arteries, reducing circulating blood volume.
      c. Large volume feto-maternal hemorrhage will also lead to hypovolemia, but is rare before 28 weeks' gestation, mostly occurring in late preterm and term infants.
      d. Neonatal animal models suggest that blood pressure and perfusion can be maintained up to the loss of about 20 mL/kg by vasoconstriction; after that, further blood loss leads to shock and hypotension.
   2. Clinical evaluation: Infants are usually pale, tachycardic, and poorly perfused with prolonged capillary refill.
   3. Supplementary testing:
      a. Echocardiographic assessment of cardiac filling may be helpful but clear indices of circulating blood volume do not exist.
      b. Central venous pressure (CVP) measurements are of limited usefulness, as they are often low in the newborn, and remain low despite volume administration. CVP may provide useful trend data.
   4. Therapy
      a. Administration of volume.
      b. Saline will temporarily restore perfusion in emergency resuscitation; blood, as soon as available, is required to restore oxygen carrying capacity.

D. Cardiogenic shock
   1. Pathophysiology
      a. Cardiomyopathy
      b. Congenital heart disease (e.g., HLHS)
      c. Asphyxial injury
   2. Clinical evaluation
      a. Poor perfusion and tachycardia are the hallmarks of primary cardiac dysfunction.
      b. Metabolic acidosis with increasing serum lactate, and oligo- or anuria are danger signs.
   3. Supplemental testing
      a. Echocardiography is essential; identification of the coronary artery origins should be considered important unless another diagnosis is likely.
      b. Structural heart disease and cardiomyopathy should be ruled out.
   4. Therapy
      a. Avoiding excessive preload and those therapies which increase afterload makes physiologic sense.
      b. Dobutamine and low dose epinephrine are reasonable first choices.

E. Extreme prematurity: Hypotension or shock?
   1. Pathophysiology
      a. Many extremely preterm infants receive cardiovascular intervention, very often for a *numerically* low blood pressure.
      b. Numerous studies show that there is no correlation between mean arterial pressure and systemic perfusion; most preterm hypotensive infants have low blood pressure for reasons of low vascular resistance and are supplying adequate oxygen to their vital tissues.
      c. Hypotensive babies with good clinical perfusion can have good outcomes without intervention.
      d. There is no clear answer regarding the appropriateness of treatment for hypotension in infants with either clinical signs of good perfusion, or those with documented normal systemic blood flow.
      e. Many centers do not intervene medically for such infants, and institute close surveillance; usually blood pressure will spontaneously rise over the subsequent few hours.
      f. Hypotension in association with poor perfusion is a very hazardous situation with poor outcomes; some babies in this situation will be found to be septic, and others may have primary cardiac dysfunction.
   2. Clinical evaluation
      a. An overall evaluation including clinical signs of poor perfusion and supplementary tests is required to determine whether an extremely preterm infant with a numerically low blood pressure has inadequate perfusion.
      b. The clinical evaluation includes capillary filling time, warmth of peripheries, urine output, and the level of spontaneous activity.
   3. Supplementary testing
      a. Echocardiography, for measurement of systemic flow (SVC flow less than 40 mL/kg/min is associated with increased risk of intraventricular hemorrhage and poor long-term outcome).
      b. An elevated or rising serum lactate is a sign of inadequate tissue oxygen delivery, as long as it is correctly sampled and processed, and a combination of an elevated lactate and a prolonged capillary refill is associated with low systemic perfusion.
      c. Near infra-red spectroscopy to measure cerebral oxygen tension has promise, but more work is required. It may also prove useful for determining intestinal perfusion.
   4. Therapy
      a. If there is no evidence of peripheral under-perfusion, then hypotension may not need to be treated.
      b. For infants with hypotension and signs of poor perfusion or poor systemic flow, therapeutic approaches are uncertain. Low to moderate dose epinephrine, (or perhaps a combination of dopamine and dobutamine) is physiologically reasonable as a way of improving cardiac function, and elevating blood pressure as well.
      c. Fluid boluses are over-used, and hypotensive extremely preterm infants are rarely hypovolemic; in the presence of a history compatible with volume loss, 10 mL/kg of normal saline can be tried empirically.