NORMAL CARDIO-RESPIRATORY PHYSIOLOGY IN NEONATES AND INFANTS

The neonate has a limited respiratory reserve and is prone to ventilatory failure and hypoxemia. They are mechanically disadvantaged by increased chest wall compliance, reliance on the diaphragm as the main muscle of respiration and a reduction in functional residual capacity (FRC) with an increase in closing capacity. Because of an increased metabolic rate, oxygen consumption is two to three times the adult level, yet their oxygen reserve is diminished due to a reduction in FRC. An increased proportion of total oxygen consumption is directed at the work of breathing and they have a relative fixed tidal volume and rate-dependent minute ventilation.

The immature myocardium has a diminished contractile mass (30% compared to 60% in mature myocardium), has a lower velocity of shortening, a diminished length tension relationship and a reduced ability to respond to afterload stress. The stroke volume is relatively “fixed” and an increase in cardiac output is heart rate dependent. The cytoplasmic reticulum and t-tubular system are underdeveloped and the neonatal heart is dependent on transsarcolemmal flux of extracellular calcium to both initiate and sustain contraction.

The large surface area to body mass ratio of infants and neonates predisposes them to hypothermia. This is a particular concern prior to induction of anesthesia. Hypoglycemia is also a risk during preparation for surgery and induction because of limited metabolic reserve and immaturity of the liver.

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Pathophysiology of Congenital Heart Defects

Pulmonary Blood Flow

1 – Increased flow

Increased pulmonary blood flow from an unrestricted or excessive left-to-right shunt may result in pulmonary hypertension and cardiac failure. Pulmonary artery pressures (PAP) are initially labile, but become fixed as pulmonary vascular obstructive disease (PVOD) develops due to structural changes in the pulmonary vasculature. The time course for developing PVOD depends on the amount of shunting and age at surgery. The progression to PVOD is more rapid when both the volume and pressure load to the pulmonary circulation is increased, such as with a large ventricular septal defect (VSD). When pulmonary flow is increased in the absence of elevated PA pressures, as with an atrial septal defect (ASD), pulmonary hypertension develops more slowly.

Respiratory work is increased in patients with excessive pulmonary blood flow. Interstitial edema and increased lung water from the elevated LV end-diastolic volume (LVEDV) and left atrial pressure (LAP) reduce lung compliance. Small airways resistance is increased by compression from distended pulmonary vessels and lung hyperinflation is often evident on chest X-ray. Patients may be tachypneic and have limited functional reserve and exercise tolerance. Large airways may also be extrinsically compressed by dilated pulmonary arteries and the left atrium.

During anesthesia, pulmonary vascular resistance and pressure may alter significantly secondary to the pattern of ventilation, airway obstruction, FiO₂, pH and PaCO₂.

2. Decreased flow

Pulmonary flow may be diminished secondary to pulmonary outflow obstruction or increased right-to-left intracardiac shunting. Patients are cyanosed and desaturated readily, and anesthetic management is directed at avoiding further reductions in pulmonary flow. It may be difficult to distinguish between the relative contributions of intracardiac and intrapulmonary shunts to hypoxemia, and the PaO₂ will be determined by the amount of intracardiac right-to-left shunt, pulmonary venous O₂ content and mixed venous O₂ content.

The consequences of chronic hypoxemia also need consideration. Polycythemia increases oxygen carrying capacity, but when the hematocrit rises above 60% the increased blood viscosity causes stasis, potential thrombosis and exacerbates tissue hypoxia. Dehydration must be avoided and intravenous maintenance fluids commenced while fasting preoperatively. Ventricular function may be compromised secondary to the elevated pulmonary and systemic vascular resistances and from myocardial ischemia. Bleeding disturbances are common in cyanotic patients and may be due to thrombocytopenia, defective platelet aggregation or clotting factor abnormalities.

Single Ventricle/Parallel Circulation

The balance between pulmonary and systemic blood flow is critical for patients with a “parallel circulation” whereby a single ventricle supplies both systemic and pulmonary flow. This balance is primarily influenced by vascular resistance and the size of the anatomic or surgically created shunt. Assuming normal mixed venous and pulmonary venous saturations, a systemic arterial saturation between 80-85% is appropriate.

Strategies to limit pulmonary blood flow/Increasing pulmonary vascular resistance

A fall in pulmonary vascular resistance (PVR) will increase pulmonary blood flow and the volume load to the ventricle in patients with a large left to right shunt, e.g. VSD, complete atrio-ventricular canal (CAVC), and patients with “parallel” circulation physiology, e.g. hypoplastic left heart syndrome (HLHS), systemic to pulmonary artery shunts and truncus arteriosus. Myocardial work is increased and, if pulmonary blood flow is excessive, systemic perfusion may fall resulting in hypotension and progressive acidemia. During anesthesia PVR can be maintained or increased by using a low FiO₂ and altering ventilation to achieve a normal pH and PaCO₂. The addition of CO₂ to the fresh gas flow to promote a respiratory acidosis, or addition of nitrogen to reduce the FiO₂ are useful techniques for raising PVR.

Care must be taken on induction as patients may be relatively hypovolemic from diuretic therapy and
preoperative fasting. Preload, contractility and heart rate must be maintained; afterload reduction is well tolerated and will reduce both pulmonary flow and myocardial work.

**Strategies to increase pulmonary blood flow/ Decrease PVR**

Following repair of defects with large left-to-right shunts, the PAP and PVR may initially remain labile. Pulmonary vascular endothelial dysfunction following bypass and ischemia/reperfusion has been demonstrated by diminished response to acetylcholine, an endothelial dependent vasodilator. Numerous factors, however, contribute to increased PVR after bypass. They include loss of lung volume and FRC from atelectasis, pneumothorax and pleural effusion, and increased lung water secondary to the inflammatory response to bypass, excess pulmonary venous return during bypass and inadequate venting. Maneuvers to help control. PVR include:

a. **Attenuation** of the stress response with deep anesthesia and paralysis.

b. **Manipulation** of gas exchange using a high inspired oxygen concentration, hyperventilation to induce a respiratory alkalosis, and bicarbonate to maintain a metabolic alkalosis. Ideally the pH should be around 7.50 and the arterial CO₂ 30 mmHg. As a cautionary note, vigorously inducing a respiratory alkalosis after bypass may be detrimental because cerebral blood flow is reduced and the oxygen-hemoglobin curve shifts to the left.

c. **The pattern of ventilation** and maintenance of lung volumes is important; atelectasis and a decrease in lung compliance may cause a significant rise in PVR. Conversely, hyperinflation with excessive lung volumes and PEEP will also increase PVR. Changes in ventilation must be made cautiously and frequently reassessed.

d. **Pharmacologic manipulation.** PA smooth muscle relaxation either via c-GMP (Nitric Oxide, Sodium Nitroprusside) or c-AMP (Isuprel, prostacyclin, prostaglandin).

**Ventricular Failure**

Congestive heart failure (CHF) may develop from a volume or pressure load imposed on the ventricles. Considerable remodeling of the ventricles, and recovery of function, is possible after reconstructive surgery, but the time course over which irreversible ventricular dysfunction develops is variable. Generally, if surgical intervention to correct the volume overload is undertaken within the first 1 to 2 years of life, residual dysfunction is uncommon. As the time course to develop significant ventricular dysfunction is longer in patients with a chronic pressure load compared to a chronic volume load, symptoms may not be apparent unless the obstruction is severe and prolonged.

A volume load may result from an excessive left to right shunt and valve regurgitation. For patients with a left to right shunt, as PVR decreases in the first 2 months after birth, and the hematocrit falls to its lowest physiologic value, pulmonary blood flow and ventricular volume load, will increase. These patients often present with failure to thrive and signs of CHF, requiring initial stabilization with digoxin, diuretics and vasodilators. Corrective or palliative surgery is performed early to limit pulmonary flow and its sequelae.

**Mechanical ventilation**

The importance of ventilation management during anesthesia, before and after cardiopulmonary bypass (CPB) cannot be over-emphasized. Besides influencing gas exchange, the pattern of ventilation, effect on lung volumes and changes in intrathoracic pressure are critical for optimal cardio-respiratory interaction.

The increase in mean intrathoracic pressure during mechanical ventilation is beneficial for patients with CHF because ventricular wall stress is reduced by a fall in ΔP across the myocardium (LaPlace’s law). On the other hand, output from the pulmonary ventricle may be reduced during positive pressure ventilation secondary to a reduction in preload and increase in afterload in patients with poor RV compliance and outflow obstruction.

Following a modified Fontan procedure, where pulmonary flow is dependent on the pressure gradient from the RA to LA, a significant increase in intrathoracic pressure from excessive peak inspiratory pressure or positive end expiratory pressure (PEEP) may severely reduce pulmonary flow; early resumption of spontaneous ventilation is recommended.
ANESTHESIA

The induction of anesthesia is a critical time and must proceed as efficiently as possible to reduce stress in patients with limited cardio-respiratory reserve. For most cases, invasive monitoring lines are not in place prior to induction, and noninvasive monitoring with pulse oxymetry, blood pressure, and electrocardiography (ECG) is necessary.

A number of induction techniques can be used depending on myocardial function and pulmonary reserve. Inhalational induction with volatile anesthetics such as halothane and sevoflurane are commonly used for general pediatric anesthesia, and are suitable for most patients with congenital heart disease (cyanotic and non-cyanotic) provided myocardial function is preserved. However, the myocardial depressant effect of these agents on the immature myocardium means these techniques should be used with caution in infants and neonates with complex congenital heart diseases (CHD). Further, loss of airway patency, obstruction and hypoventilation can lead, to early onset of desaturation and bradycardia. Intravenous (IV) induction is preferable although IV access may be difficult, particularly in patients who have had multiple surgical procedures. Considerable stress and hypothermia, may result in the neonate and infant if excessive time is taken trying to establish intravenous access. In these situations, an intramuscular induction can be used.

Following induction and securing of the airway, arterial and central venous lines are placed. Once again it is important not to waste time trying to establish percutaneous access and an arterial cut-down should be considered if there are any difficulties. Central venous access is rarely required pre-bypass unless inotropic support is necessary or there are concerns about potential bleeding. Transthoracic lines can be placed prior to discontinuing bypass and used for monitoring, drug infusions, and volume replacement.

Factors influencing anesthesia management include patient age, preoperative clinical condition, surgical procedure, bypass duration, degree of hypothermia and the anticipated postoperative management. Most patients having complex repairs, particularly neonates and infants, are anesthetized with a high dose opioid combined with pancuronium and an air/oxygen gas mixture. Neonates and infants generate a significant humoral and metabolic response to stress. Lactic acidemia, hyperglycemia, high levels of catabolic hormones, and a negative nitrogen balance, greater incidence of sepsis, DIC and even death during the postoperative period, have been demonstrated in neonates who have undergone cardiac surgical procedures with anesthetic techniques that failed to suppress the stress response. High doses of the synthetic opioids fentanyl (75-100 mcg/kg) and sufentanil (5-10 mcg/kg) provide reliable hemodynamic stability and suppression of the stress response. Additional doses are required during cardiopulmonary bypass because opioid levels decrease significantly in children secondary to hemodilution, drug binding to the circuit and increased volume of distribution. Benzodiazepines provide additional suppression of the stress response and amnesia.

Patients undergoing less complex surgery and who have been stable preoperatively can be managed with a combination of opioids and inhalational agent, thereby allowing an earlier wean and extubation in the cardiac intensive care unit.

Fast Track management with early extubation is also applicable to children. Provided patients are hemodynamically stable, have satisfactory gas exchange and have no surgical complications such as bleeding, most children undergoing elective repair should be suitable for early extubation.

CARDIOPULMONARY BYPASS

Inflammatory response

There may be significant morbidity associated with bypass in neonates and infants that compromises subsequent recovery from surgery. First, the large pump surface area and priming volume relative to blood volume increases the exposure of blood to non-endothelialized surfaces and increases inflammatory mediator release. Second, deep hypothermic circulatory arrest or low flow bypass is more commonly used which increases the risk of ischemia / reperfusion injury. The humoral responses include activation of complement, kallikrein, eicosinoid and fibrinolytic cascades; cellular responses include platelet activation and an inflammatory response that stimulates neutrophil activation and release of proteolytic and vasoactive substances.
Over recent years the intimate relationship between the systemic inflammatory response and endothelial injury to bypass has been investigated and strategies to attenuate the response evaluated.

1. **Treating the consequences of endothelial injury**
   a. **Stress response attenuation.**
   b. **Modification of pump prime:** Maintaining a higher hematocrit and colloid oncotic pressure in the bypass perfusate may reduce edema and has also been demonstrated to improve cerebral recovery after deep hypothermic circulatory arrest.
   c. **Delayed sternal closure:** The inflammatory response with capillary leak and edema following cardiopulmonary bypass continues into the postoperative period and may compromise myocardial and pulmonary function. Sternal closure may cause a constrictive or tamponade effect, and delayed closure be necessary once mediastinal edema has diminished.

d. **Hemofiltration:** Besides hemoconcentration, inflammatory mediators including complement and the cytokines, IL-6, IL-8, IL-1β and TNF are also removed by a process of convection and adsorption. Improved systolic and diastolic pressures are observed during filtration and improved pulmonary function has also been noted with reduction in pulmonary vascular resistance and total lung water. The duration of ventilation postoperatively, pediatric ICU and hospital stay has also been reduced.

   Hemofiltration techniques include:
   i. Modified ultrafiltration (MUF): of the patient blood volume after completion of bypass.
   ii. Conventional hemofiltration: both the patient and circuit are filtered during bypass.
   iii. Zero-balance ultrafiltration: recently described, high volume ultrafiltration essentially washes the patient and circuit blood volumes during the rewarming process.

2. **Modifying inflammatory mediator release**
   a. Hypothermia.
   b. Steroids: Commonly used, but inconclusive benefit. A dose of 30 mg/kg of Solumedrol is given the night of surgery, followed by a dose of 10 mg/kg upon induction of anesthesia.
   c. Aprotinin: Non-specific serine protease inhibitor. Besides antifibrinolytic properties, aprotinin also attenuates the inflammatory response by inhibiting thrombin and kallikrein release, and elastase release following the neutrophil respiratory burst. There has been recent literature demonstrating a high incidence of kidney dysfunction from aprotinin in adults following cardiac surgery. This was inconclusive, however, and was not demonstrated in the pediatric age group.

3. **Adhesion molecule modification**

   Significant advances are being made in the development of drugs that will prevent the adhesion molecule/endothelial interaction which is pivotal in the inflammatory response.

**Hypothermia**

Because of the large body surface area to mass ratio in neonates and infants, a 2-3°C reduction in core temperature is common following induction of anesthesia and prior to bypass. The use of cooling/warming blankets, low ambient temperature and reduced overhead operating light intensity helps maintain a low temperature during bypass and minimizes radiant heating of the myocardium. Surface cooling is aided by placement of ice bags on and around the head and will assist with brain cooling.

Despite full rewarming, mild hypothermia after discontinuing bypass often develops in neonates and infants. Active measures to decrease radiant and evaporative losses are necessary because of the increased metabolic stress, pulmonary vaso-reactivity, coagulopathy and potential for dysrhythmias associated with hypothermia. However, hyperthermia must be also avoided because of the associated increased metabolic demand, particularly when myocardial function may be depressed and cerebral autoregulation impaired.

There are two broad bypass management strategies:

1. **Deep hypothermia (<18°C) with low/intermittent flow or circulatory arrest**

   Deep hypothermic circulatory arrest (DHCA) provides optimal operating conditions for intracardiac repairs with an empty relaxed heart, and reduces the
duration on bypass and exposure of circulating blood to foreign surfaces. Prolonged ischemia to the brain is a major disadvantage and is both time and temperature dependent.

Low flow deep hypothermic bypass is preferable with improved neurologic protection. Flow rates between 30-50 ml/kg/min are often referred to as “low flow”, but the optimal flow rates during low flow bypass are not firmly established. Flows as low as 10 cc/kg have been used in animal studies evaluating low flow bypass, with maintenance cerebral phosphocreatine, ATP and intracellular pH at or above baseline both during bypass and reperfusion.

2. Moderate hypothermia with normal or increased pump flow

Bi-caval cannulation is generally used. The risk of cerebral ischemia is reduced, but CPB is prolonged and operative conditions may not be ideal.

Pump flow rates are generally higher in neonates and infants, reflecting the increased metabolic rate. During bypass, there is no one measure of index that assures adequate perfusion. Generally, flow rates of 100-150 ml/kg/min, or indexed flows to 2.2-2.5 L/min/m², should provide adequate flow at normothermia. Venous oxygen saturation greater than 75% suggests adequate perfusion. However, these values may be misleading in patients with poor venous drainage, severe hemodilution, malposition of the aortic cannula or in the presence of a large left to right shunt. On-line continuous monitoring of blood gas and saturation of oxygen is important to identify trends in oxygen extraction.

References