THE INCIDENCE OF congenital heart defects is approximately 7 to 10 per 1,000 live births. With advancing technology and improved diagnostic, surgical, anesthetic, and postoperative management protocols, the tendency today is to perform the complete repair of defects early in infancy.

Infancy is defined as the period from birth until age 1. The management of cardiopulmonary bypass (CPB) in infancy has many challenges and increased risk of morbidity and mortality compared with that of the adult population. Infants are more prone to complications because of the immaturity of their organ systems. There is a need for a more complete understanding of the anatomic, metabolic, and physiologic differences between infants and adults, and patient care must be individualized considering the degree of hemodilution and hypothermia, acid-base strategies, flow rates, circuit designs, priming the pump, and choice of cannulae.

This review article outlines the differences between infants and adults regarding their responses to CPB and reviews the main subjects like hypothermia, hemodilution, acid-base strategies, inflammatory response, extracorporeal circuit, and CPB protocols for infants.

Since the first successful application of extracorporeal circulation in the 1950s, CPB has evolved and still is evolving, but basic concepts have remained the same: Oxygenation and carbon dioxide elimination, perfusion, systemic cooling and rewarming, and removal of blood from the heart to provide a blood-free surgical field. On the other hand, despite clear understanding of the basic concepts and many improvements, CPB management in infants still remains challenging and unique.

DIFFERENCES BETWEEN INFANTS AND ADULTS

There are major differences between infants and adults affecting their response to CPB (Table 1). Procedures performed on infants and children may require the extreme measures that are not necessary for adults, including deep hypothermia, hemodilution, different acid-base strategies, low perfusion pressures, and wide variation of perfusion flow rates. These measures notably vary from those of normal physiology and affect protection of normal organ function during CPB. In addition, their smaller circulating blood volume, higher oxygen consumption rate, reactive pulmonary vascular bed, immature organ systems, and altered thermoregulation may cause vulnerability to deleterious effects of CPB in infants.

The presence of large aorta-pulmonary collateral vessels or an interrupted aortic arch also necessitate changes in CPB strategies and cannulation techniques. The cardiac pathology with large intra- and extracardiac shunts may result in a greater redistribution of flow away from the vital organs during CPB and jeopardize systemic perfusion. In addition, development of collateral vessels secondary to cyanosis and vascular obstruction may result in significant blood loss and impair surgical field exposure.

Infants are characterized by a high metabolic rate and, thus, oxygen demand requiring higher flow rates per body surface area. Because they have limited cardiac and respiratory reserves, in physiologically stressful circumstances rapid changes of pH, lactic acid, glucose levels, and temperature may occur because of a compromised response to meet these demands.

Infants are prone to hypothermia because of their larger ratio of body surface area to weight and limited fat stores and have limited ability to deal with cold stress, which result in increased oxygen consumption and may cause metabolic acidosis.

Neonatal myocardium is known for its immaturity compared with the adult myocardium but is considerably more resistant to ischemia. In the newborn, only 30% of the myocardial mass acts as contractile tissue, compared with 60% of mature myocardium. In addition, pediatric myocardium has fewer mitochondria, less oxidative capacity, and incomplete autonomic innervations. Because the sympathetic innervations are also immature, the control of vascular tone and myocardial contractility depends on adrenal function via catecholamines rather than direct autonomic influences.

As is well documented, the infant myocardium relies heavily on glucose as its major substrate and also has a greater reliance on extracellular calcium for calcium-mediated excitation coupling.

The immature myocardium uses glucose as the main substrate and also has an increased ability to utilize anaerobic metabolism as well as an ability to metabolize fatty acids, ketones, and amino acids. Interestingly, 90% of ATP production in the mature heart is by the oxidation of the long chain fatty acids and not by utilization of glucose.

The immature myocardium is a great deal more sensitive to extracellular calcium levels than the mature myocardium. In
mature hearts, most of the calcium required for myocardial contraction is provided by the sarcoplasmic reticulum, whereas the sarcoplasmic reticulum is underdeveloped in the immature heart and has reduced storage capacity for calcium. The activity of the sarcoplasmic calcium ATPase, the enzyme responsible for calcium reuptake into the sarcoplasmic reticulum, also is reduced relative to mature myocardium. Therefore, the immature heart has lower intracellular calcium concentration with a greater dependence on extracellular calcium levels and is much more sensitive to calcium channel blockers than the mature heart. Use of cardioplegic solutions containing normal or high calcium concentrations may have detrimental effects, and use of solutions containing subphysiologic levels of calcium is recommended.

Boston Children’s Hospital’s experience shows that it is an advantage to have very low levels of ionized calcium during the cooling phase before aortic cross-clamping. There may be advantages in having a lower ionized calcium level during hypothermic bypass as well. Therefore, calcium is not recommended to be corrected until the later phase of rewarming.

Immaturity also affects a number of enzymatic processes, some examples of which are decreased antioxidant enzymatic activity, causing the immature myocardium to be more susceptible to anaerobic metabolism, and decreased 5'-nucleotidase activity, causing conversion of ATP to adenosine to decrease. In fact, the latter may explain why immature myocardium is more tolerant to ischemia.

Pulmonary dysfunction is common after CPB because lungs are still immature at birth and continue to grow and mature up to 8 years of age. Lungs have 2 components, parenchymal and vascular, and both of them serve as a source and target of the inflammatory response during CPB. Both systemic inflammatory response and ischemia/reperfusion injury during CPB stimulate endothelial injury, resulting in capillary leak and extravasation of the fluid and the inflammatory cells to the parenchymal space and pulmonary edema, ending with poor oxygenation, reduced compliance, and reduced lung volumes. Patients with increased pulmonary blood flow may need intense medical therapy preoperatively to reduce pulmonary congestion. Another group of patients who briefly have unrestricted pulmonary blood flow preoperatively may end up with arterial media hypertrophy, which might result in pulmonary hypertension. This clinical picture can complicate the termination of bypass and may result in failure to wean from CPB and acute right-sided heart failure and may require extracorporeal support. Liquid ventilation, steroid use, and modified ultrafiltration (MUF) seem to improve pulmonary function. MUF is highly effective in reducing lung water and pulmonary morbidity. There are studies reporting that both the degree of hemodilution and increased flow rates during CPB may cause worsening of lung injury.

Renal dysfunction after CPB is another important cause of morbidity and mortality. The incidence of acute renal failure (ARF) varies between 0.7% to 59% depending on the complexity of the surgical procedure. In the pediatric population, kidney function does not reach to adult level until the age of 2. Glomerular filtration rate is lower in neonates and infants because of lower mean arterial pressure and high renovascular resistance. This results in impaired concentrating and diluting mechanisms, sodium reabsorption and excretion, and acid-base regulation. Use of CPB in infants is associated with higher fluid accumulation than adults, resulting in an increase in body water. The combined effects of hypothermia, nonpulsatile perfusion, and lower mean arterial pressures may cause release of hormones like vasopressin, renin, angiotensin, and catecholamines, which leads to renal vasoconstriction and reduced renal blood flow resulting in oliguria and elevated serum creatinine levels.

Blinder et al retrospectively studied 430 infants (<90 days old) who underwent congenital heart surgery. They used a modified pediatric version of the Acute Kidney Injury Network classification and found that postoperative acute kidney injury occurred in 52% of the infants: 31%, 14%, and 7% of infants reached acute kidney injury stage I, II, and III, respectively. Single-ventricle status, CPB, and higher reference serum creatinine levels were associated with postoperative acute kidney injury.

Recently, significant interest has arisen regarding prevention of fluid accumulation and its possible positive influence on mortality. The management of infants undergoing CPB is focused on a negative total body water balance and, therefore, loop diuretics commonly are used to increase urine output. Furosemide (1-2 mg/kg) or ethacrynic acid (1 mg/kg) every 4 to 6 hours, or both, induces diuresis and may reverse acute renal failure associated with CPB. Some centers recommend placement of peritoneal dialysis catheters at the end of surgery in high-risk infants for a better outcome. Furthermore, the use of MUF is effective in reducing total body water and limiting the undesired effects of CPB.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Adult</th>
<th>Pediatric</th>
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<tr>
<td>Minimum CPB temperature</td>
<td>Rare 15–25°C</td>
<td>Frequently</td>
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<tr>
<td>Use of total circulatory arrest</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Pump prime</td>
<td></td>
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<tr>
<td>Dilution of blood volume</td>
<td>25%–33%</td>
<td>150%–300%</td>
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<tr>
<td>Whole blood or RBC added</td>
<td>Rare</td>
<td>Frequent</td>
</tr>
<tr>
<td>Perfusion pressure</td>
<td>50–80 mmHg</td>
<td>20–50 mmHg</td>
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<tr>
<td>Acid-base management strategy</td>
<td>Alpha-stat</td>
<td>pH-stat at temperature &lt;28–30°C</td>
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<tr>
<td>Glucose management</td>
<td></td>
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<tr>
<td>Hypoglycemia</td>
<td>Frequent, requires insulin</td>
<td>Less common</td>
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<tr>
<td>Hypoglycemia</td>
<td></td>
<td>Common, reduced hepatic glycogen stores</td>
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NOTE. Modified from DiNardo and Zvara. Abbreviations: CPB, cardiopulmonary bypass; RBC, red blood cells.
The livers of small infants lead to diminished production of vitamin K–dependent clotting factors, and overall protein synthesis. This immaturity not only increases the risk of bleeding but also alters drug metabolism and may cause capillary leaks.

The coagulation system at birth continues its maturation during the first year of life. Besides, the pathophysiologic disorders that accompany congenital heart disease also have an impact. Coagulation disorders in neonates and infants either related to the patient or induced by CPB are more common than in adults. These abnormalities have been reported in 58% and 71% of children with noncyanotic and cyanotic defects, respectively.9 It has been demonstrated that cyanotic patients with hematocrit greater than 50% have prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT) and decreased levels of fibrinogen, platelets, and factors V and VIII.4 In addition, neonates and infants with congenital heart defects have low circulating levels of procoagulants and inhibitors.9 Immature coagulation system, impaired hepatosynthesis, disproportionate contact to nonphysiologic surface of the CPB circuit, extensive surgery, and more profound hypothermia levels also impair hemostasis in neonates and infants.10 Kern et al29 demonstrated that coagulation factor levels and platelet counts in neonates decrease by 50% and 70%, respectively, during CPB. As a result, administration of fresh whole blood (although not available in many hospitals), platelets, cryoprecipitate, and fresh frozen plasma may be beneficial to replace the numerically and functionally depleted blood cells and coagulation factors of pediatric patients after termination of CPB. Other approaches to reduce bleeding are using antifibrinolytics such as aminocaproic acid and tranexamic acid. In pediatric patients undergoing cardiac surgery, both aminocaproic acid and tranexamic acid reduce the number of patients transfused, total blood product transfusion, and blood loss within a wide age range.1,5,30 Although the use of DDAVP has been found to be successful in adult cardiac surgery patients, the same results have not been shown in pediatric patients. Studies have found no improvements in coagulation systems of patients who received the medication prophylactically.31,32

Glycemic control is poor, with a tendency to hypo- or hyperglycemia in infants. Hypoglycemia is quite common with congenital heart defects. The major causes are reduced synthetic function, decreased glycogen stores, and systemic hypoperfusion, which results in compromised hepatic function further impairing glucose production. On the other hand, infants often come to the operating room with glucose-containing infusions and they receive steroids during CPB that lead to hyperglycemia.

Hyperglycemia impairs neurologic outcome during focal and global cerebral ischemia. The role of glucose in potential cerebral injury appears to be due to 2 factors: ATP utilization and lactic acidosis.21,33,34 Despite studies showing detrimental effects of hyperglycemia on neurologic outcome in adult humans and animals, specific data are lacking in children.8,35 De Ferranti et al36 database review of 171 infants undergoing arterial switch operation demonstrated that high glucose level was not related with worse neurodevelopmental outcome. In addition, they suggested avoiding hypoglycemia, instead of glucose restriction, in infants undergoing cardiac surgery.36 The Boston Circulatory Arrest Study also suggested that normal blood glucose levels during reperfusion were associated with worse neurologic outcome compared with hyperglycemic levels.35,37 It is speculated that substrate deficiency may be an issue in the immature brain, and normal blood glucose levels during the reperfusion period after cerebral ischemia in infants may be insufficient for complete cerebral recovery. In spite of these studies, there is still no consensus in the pediatric cardiac literature regarding the use of optimal glucose management or tight glucose control.

Despite all advances in CPB techniques and management protocols, infants are still vulnerable to short- and long-term adverse neurologic outcomes. Although all organs are at risk for ischemia and reperfusion injury, the brain is the most susceptible and the least tolerant of these effects. The pediatric brain is subjected to ischemia and reperfusion injury with its rapid neuronal proliferation and development, heavy axonal growth, fragile vasculature, and high metabolic rate. The incidence of neurologic injury after infant cardiac repair is estimated to be 2% to 30%.38–41 Pre-existing risks for congenital heart disease and an associated tendency toward neurologic injury, CPB-induced (cerebral) injury, injury as a result of various surgical and perfusion strategies, and, finally, the injury observed during the vulnerable period after CPB exposure increase the risk for neurologic impairment in neonates and infants undergoing cardiac surgery.

Unlike in adults, in whom neurologic injury mostly involves thromboembolic stroke, in infants neurologic morbidity includes seizures, strokes, cognitive dysfunction, delayed chorioamnionitis syndrome, and visual-motor integration as well as changes in tone and mental status. Although the incidence of obvious injury has declined with the help of improved neuroprotective strategies, neurologic injuries sustained during surgery are still a problem causing long-term functional morbidities, especially neurodevelopmental outcomes, with their profound consequences to the patients and society. Many neurodevelopmental outcome studies in infants have focused the perioperative period as the origin of adverse outcomes. On the other hand, there is increasing evidence that patient-specific factors such as genetic abnormalities, socioeconomic status, and maternal education are more important determinants of neurodevelopmental outcome than perioperative management strategies.42

Hypothermia and deep hypothermic circulatory arrest (DHCA) commonly are used during pediatric CPB, based on the principle of lowering metabolic demands of the brain. However, despite the benefits of DHCA, prolonged DHCA durations result in increased incidence of neurologic injury.43 Deep hypothermia (<18°C) either with low-flow CPB or circulatory arrest has been used widely to offer optimal surgical conditions and to provide maximal organ protection for infants and children for years. However, the maximum duration of safe DHCA remains unknown. Cerebral autoregulation is lost and cerebral vascular responses to PaCO2 are weakened when deep hypothermia (18°–20°C) is used in infants. This effect might be due to cold-induced vasoparesis. On the other hand, pediatric-specific autoregulatory ranges have not been defined.44 Auto-regulatory limits may vary according to gestational and chronologic age, type of the structural heart disease, and the timing of surgical repair. Low-flow CPB, an alternative to DHCA,
maintains continuous cerebral circulation. On the other hand, there are no standards for low-flow CPB technique. De Ferranti et al. compared low-flow CPB and DHCA in 171 infants and found worse clinical neurologic outcome with the perioperative effects of DHCA than the low-flow group. Similarly, Bellinger et al.'s study involving 155 infants with surgically corrected transposition indicated that children undergoing low-flow bypass had better motor and speech performance but worse attention and behavior than children undergoing circulatory arrest.

Neuroprotection is not a single strategy but instead is a multifactorial approach. Strategies to optimize neurologic outcome still are being refined. Alternative perfusion techniques to DHCA such as regional antegrade cerebral perfusion, low-flow CPB, and intermittent cerebral perfusion have been developed. Other neuroprotective strategies during CPB include temperature regulation, acid-base management, less hemodilution, and blood glucose control. In addition, maintaining adequate perfusion pressure and O2 delivery; limiting inflammatory response by steroids, leukocyte-depleting filters, MUF, and heparin-coated circuits; and avoiding air embolism are recommended strategies for brain protection during CPB. Hirsch et al performed a systematic review of neuromonitoring and neuroprotection strategies and their effects on neurologic outcomes during and after CPB in infants; they compared the effects of blood gas management; hematocrit; electroencephalogram (EEG); cooling; glycemic control; S100β; transcranial Doppler (TCD); near-infrared spectroscopy (NIRS); and use of DHCA, low-flow cardiopulmonary bypass (LFCPB), and regional cerebral perfusion (RCP) and concluded that data supporting the use of current neuroprotective techniques are uncertain, except avoidance of extreme hemodilution.

CHALLENGES FOR CPB IN INFANTS

Hypothermia

In infants, CPB commonly is conducted with systemic hypothermia. The main clinical effect of systemic hypothermia is to preserve global organ function by reducing systemic oxygen consumption. Basically, the degree of hypothermia defines the amount of flow required to perform the surgical repair. The patient size, the type and expected duration of surgery, and the potential physiologic effects on the patient also contribute to the decision-making process. Although there is not a well-defined hypothermia classification, it may be classified as mild (30°-34°C), moderate (25°-30°C), and deep hypothermia (15°-22°C) with low-flow CPB or DHCA. Q10 shows the degree of chemical reaction decrease rate for every 1°C. Greely et al. suggest a higher Q10 for infants (3.65 v 2.6) compared with adults, indicating greater metabolic suppression associated with hypothermia. They remind that this may be the reason why infants tolerate longer periods of "imperfect" perfusion or ischemia.

When a prolonged period of circulatory arrest is necessary, a primary indication for using hypothermia is cerebral protection. However, it should be kept in mind that at deep hypothermia (18°-22 C), because of loss of cerebral autoregulation, cerebral blood flow is correlated with mean systemic arterial pressure.

The rate of cooling and rewarming of body temperature is proportional to the blood flow per unit of tissue mass. Thus, small organs with large proportionate blood flows cool and rewarm rapidly (eg, kidney, adrenal, heart); large tissue masses, such as skeletal muscle or fat, cool and rewarm slowly. Rapid cooling and rewarming have been demonstrated to be suboptimal for deep hypothermic circulatory arrest, and even if small infants can sometimes decrease to 18°C within 10 minutes, it is not homogenous. The cooling period should last at least for 20 minutes and may at times approach 30 minutes, and patient-perfusate temperature difference should be less than 8° to 10°C because the rate and efficacy of cooling and rewarming appear to be important in the occurrence of brain injury. Bellinger et al. reported better cognitive developmental scores with longer cooling periods in infants undergoing CPB.

A sudden decrease in perfusion temperature results in a sudden release of intracellular calcium stores within the sarcoplasmic reticulum and may play an important part in the development of the entity described as rapid cooling contracture, which is thought to play a role in postbypass myocardial dysfunction. However, rapid cooling, when performed in an appropriate setting, may not impair myocardial function. It has been demonstrated that with the hypocaloric primes commonly used in neonatal and infant surgery today, rapid cooling and cold induction of ischemia do not seem to be deleterious.

Rewarming may be enhanced by increasing pump flow, which in this setting may result in unacceptable systemic hypertension because the calculated systemic vascular resistance (SVR) is relatively high after exposure to hypothermia. The 2 approaches are to wait for the vasodilation to resolve or pharmacologically induce patient vasodilation (eg, with nitroprusside, hydralazine). The trend is again to follow an 8° to 10°C temperature gradient during rewarming, because rapid rewarming may result in cerebral ischemia as a result of cold-triggered vasoparesis and hypothermia-induced increased vascular resistance, which uncouples cerebral blood flow and metabolism rates. Time required for rewarming varies with arterial perfusate temperature, patient temperature, and systemic flow. Excessive perfusate heating also is not advisable because of possible denaturation of plasma proteins and to prevent the gaseous bubble formation.

Hemodilution

Hypothermia significantly increases blood viscosity, which results in impaired blood flow through the microcirculation. High hematocrit levels and nonpulsatil flow also may impair microcirculatory perfusion. Thus, hemodilution is an important asset during hypothermic CPB. However, the disadvantages of hemodilution may offset the benefits of improved viscosity at hypothermia, causing anemia with decreased oxygen-carrying capacity and reduced levels of plasma proteins and clotting factors, leading to tissue edema and coagulopathy.

Estimated blood volume of an infant <10 kg is 85 mL/kg; therefore, a 5-kg child has a blood volume of approximately 425 mL. Bypass circuit volumes are very large relative to blood volumes in infants, leading to significant hemodilution. The priming volume should be kept minimal to reduce hemodilution. This goal may be achieved by using proper size tubing and miniaturization of the CPB circuits. Positioning the CPB machine as close as possible to the patient also will help to reduce the priming volume.
Hematocrit levels as low as 10% supply adequate oxygen to the tissues during hypothermia. However, during the rewarming period when oxygen demand increases, these levels may be inadequate.\(^5\,6\) The required hematocrit level varies depending on the degree of hypothermia. The Boston group demonstrated improved outcome in infants undergoing hypothermic bypass with higher hematocrit levels during CPB.\(^7\) It has been reported that extreme hemodilution to a hematocrit level of 20% impairs oxygenation, and according to Hirsch et al, no single intervention other than avoidance of hemodilution has been found to be protective.\(^57\) Currently, most centers maintain hematocrit levels around 25% to 30%, with moderate hypothermia for increasing O₂ delivery to the vital organs.\(^9\)

Strategies for CO₂ Management: Alpha- or pH-stat Mode

Optimal acid-base management during CPB has been the focus of much debate and related research. Two different blood gas management strategies are used for the effect of CO₂ on arterial and intracellular pH during hypothermia. These strategies directly influence blood flow to the brain and other organs. In the alpha-stat method, no CO₂ is added to the circuit; pH is adjusted to be 7.4 and not corrected to temperature. Theoretically, this method maintains normal cerebral blood flow autoregulation and improves metabolic recovery during rewarming by decreasing the microemboli incidence. In the pH-stat strategy, CO₂ is added to the circuit to achieve a pH of 7.4, which is corrected to the patient’s actual temperature. pH-Stat management results in a greater cerebral blood flow than needed to meet the brain’s metabolic demands; autoregulation is lost. Overperfusion improves brain cooling and cerebral tissue oxygenation but at the same time carries a risk of microemboli to the brain, especially in atherosclerotic patients.\(^55\)

Acid-base management strategy probably is not as vital during moderate hypothermia, but it may be critical in deep hypothermia.\(^8\) Differences in mechanisms of brain injury in adults and children affect the variety of outcomes related to the acid-base management strategy. In adults, embolus plays an important role in adverse neurologic outcome, whereas hypoperfusion is the key element in children.\(^56\) Thus, decrease in cerebral blood flow during alpha-stat management may be protective by limiting cerebral microemboli in adults. On the other hand, in the pediatric population, despite controversial data, pH-stat management strategy seems advantageous because it improves cerebral cooling homogeneity and oxygen delivery before, during, and after deep hypothermia.\(^8\) A recent study\(^37\) has demonstrated that the use of pH-stat strategy in infants younger than 9 months undergoing deep hypothermic CPB was associated with lower morbidity. However, in another study, no significant difference in neurologic outcome was found between alpha- and pH-stat managements.\(^38\) There are also conflicting results in some neurodevelopmental studies.\(^39\,62\) Jonas et al\(^61\) found that alpha-stat strategy before DHCA was associated with poorer developmental scores, although Bellinger et al\(^62\) from Boston Children’s Hospital reported no difference between the alpha- and pH-stat strategies.\(^42\) The heterogeneity of reported results has led some authors to recommend a combined strategy, such as using pH-stat during the cooling phase of deep hypothermic CPB and alpha-stat during the rewarming period.\(^42\,56,59,60\)

The effects of pH-stat management on the other organ systems also have been studied. It has been reported that pH-stat management provides improved myocardial performance, less inotropic use, less hypotension, and less metabolic acidosis after CPB in patients with pulmonary hypertension and cyanotic heart defect as a result of better cooling with hypercapnia-induced vasodilatation.\(^42\)

Systemic Inflammatory Response

Cardiopulmonary bypass triggers a series of systemic inflammatory and immunologic responses through the injury of specific blood elements, embolic events, and activation of complex inflammatory and stress response systems, which protect the body against bleeding, thrombosis, and invasion by foreign organisms.\(^63\) Because their immune system is immature, these more profound responses in neonates and infants result in increased morbidity and mortality rates. These unexpected responses in infants result in postbypass acute respiratory distress syndrome, pulmonary hypertension, total body edema, coagulation abnormalities, myocardial dysfunction, and hemodynamic instability.\(^64\)

Several therapeutic interventions have been used to reduce CPB-induced inflammatory response. Potential areas of therapeutic intervention include pharmacologic strategies such as use of corticosteroids,\(^65\,66\) serine protease inhibitors, phosphodiesterase inhibitors, nitric oxide (NO) donors, antioxidants, and complement inhibitors\(^67\) and mechanical techniques such as heparin-bonded circuits, circuit miniaturization, hemofiltration, leukocyte filters, and the use of DHCA versus low-flow bypass.\(^6,21,44,55\) Mechanical techniques generally have been considered more effective in the pediatric population.\(^6,56\)

Systemic Blood Flow

Optimal blood flow rates for infants are based on infants’ body mass and effective organ perfusion. Recommended full flow rates for CPB in children are summarized in (Table 2).\(^5\) Another important question is about the application of pulsatile versus nonpulsatile flow during the cardiopulmonary bypass. Even if the pulsatile flow has been reported to improve blood flow through the organs during CPB and function of systems in the post-CBP period, this technique is not in broad use yet. Alkan et al\(^68\) described in their studies that the pulsatile flow has improved myocardial function and preserved pulmonary and renal functions as well. In another series of studies, Undar et al\(^69\) stated that cerebral flows were better maintained with the pulsatile group, and with the lower levels of interleukin-8 (IL-8) postbypass; they speculated that improved organ function and better microvasculature preservation would result.\(^70,71\)

The adequacy of the systemic and cerebral perfusion also should be monitored closely with direct measures, such as

<table>
<thead>
<tr>
<th>Table 2. Full Cardiopulmonary Bypass Flow Rates in Infants</th>
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<tr>
<td>Patient Weight (kg)</td>
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<tr>
<td>---------------------</td>
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<tr>
<td>&lt; 3</td>
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<tr>
<td>3-10</td>
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<td>10-20</td>
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Abbreviation: CPB, cardiopulmonary bypass.
cardiac index and mean arterial pressure generated by the pump, cerebral oximetry, TCD, NIRS, jugular bulb saturation, and systemic venous oxygen saturation (SvO₂), and with indirect measures like acid-base status, plasma lactate, and urine output. The data concerning NIRS and neurodevelopmental outcomes are limited in quality. There is no consistent evidence that the use of NIRS is associated with improved neurodevelopmental outcomes. NIRS may be considered as a monitoring methodology and looks promising for the future.47

CANNULAE AND CIRCUIT

Arterial and Venous Cannulation

The arterial limb is the pressurized side of the extracorporeal circuit and the arterial cannula is the narrowing point at the site of entry back to the ascending aorta and the circulation, but some cases may require different positions for the cannula. Size of the cannula is quite critical for providing adequate flow to vital organs. A small cannula may cause blood cell damage as a result of exposure to the turbulence caused by the narrow lumen, or a large cannula may cause obstruction of the retrograde flow or may traumatize the aorta.

Venous cannulation and strategies carry great importance for congenital heart disease repair because adequate venous return to the bypass circuit is mandatory for successful CPB in an infant. The myocardium easily can be affected with the increased ventricular wall tension if the venous return is not adequate. When an intracardiac repair is necessary via opening the right atrium, bicaval cannulation is performed using 2 separate straight, right-angled, or different kinds of cannulae to provide better exposure and to prevent risk of venous flow obstruction. Special considerations may be needed when there is a persistent left superior vena cava or if there is a left atrial isomerism with an interrupted inferior vena cava. If deep hypothermic circulatory arrest is the choice of perfusion technique, then single venous cannulation to the right atrium may provide the desired venous return while the patient is cooling down.

In case of emergency or redo cases, when there is a need for central venous or arterial cannulation, the small size of the vessels and lack of appropriate cannulae for femoral arterial and venous cannulation might make the peripheral access difficult for small infants and can complicate the course of surgery.72

Vacuum-assisted venous drainage is also a useful tool in which small venous cannulae are used, during lower half mini-sternotomy cases, in which the right atrium is cannulated via internal jugular vein and for prime reduction by using smaller venous lines or initiating bypass with an unprimed venous line, but needs an experienced technician and carries the risk of gaseous microemboli.

The types of vacuum-assisted venous drainage applications are placing a nonocclusive pump in the venous line, vacuum applied to a cardiotomy, and use of a roller head to provide controlled occlusion and limited negative pressure. Some centers are also using dual venous lines for certain types of applications.

Bypass Circuit and Circuit Miniaturization and Tubing

Miniaturization of the bypass circuits and reduction of the volume that are needed to prime the circuits have been the most important advancements that technology had to offer pediatric CPB for the past 20 years. The new design of the CPB circuits has helped to reduce the use of perioperative blood products, which led to decreased postoperative edema and fewer mechanical ventilation days.73 Especially for neonates smaller than 5 kg, prime reduction is achieved by using ½-inch arterial line tubing, which has a prime volume of 0.2 mL/inch, and 1-inch venous line tubing, which primes with 0.45 mL/inch. When this low-prime tubing is used in conjunction with a low-prime oxygenator, like RX-5 Terumo Cardiovascular or a Lilliput 1 oxygenator with an open reservoir, a low prime volume (<180 mL) can be achieved easily. Techniques that investigators have used to create these smaller circuits have included low prime volume oxygenators, reservoirs, and arterial filters; shorter extracorporeal circuitry; remote pump heads; use of venous vacuum (which can end up with use of smaller venous tubing); and removal of the certain parts of the classic circuit, most commonly the arterial line filter; all seem to be helpful to decrease postoperative morbidity after cardiac surgery in neonates and infants. Investigators have demonstrated that priming volumes as low as 110 mL can be achieved and used safely even in the neonatal population.42,72,74–80

Minimal tubing size should be preferred to reduce the prime volume and inflammation, but tubes must be large enough to maintain adequate flow rates and ensure low line pressures. The tube length should be shortened by positioning the pump as close as possible to the surgical field; the bypass circuit is placed at the operating room table with the surgeon and assisting and almost straddling the circuitry.77,81

One of the ideal ways of reducing inflammatory response is the surface modification of the circuit. This can be achieved by techniques like coating, chemical modification, and attachment of macromolecules and by blending of polymers.42,82 Use of heparin-bonded circuits reduces inflammatory mediators during and after CPB, drops tissue plasminogen activator release, and preserves platelet numbers via decreased platelet activation.77,82

Pumps

There are basically 2 types of pumps available for use in pediatric cardiac surgery. Roller pumps remain the most widely used system for pediatric perfusion. They provide continuous nonpulsatile flow; the blood moves in a forward direction by partially occluding the tubing between the roller and the pump casing, as “milking” a constrained piece of tubing. Roller pumps are capable of delivering flows <0.5 L/min and are capable of generating both positive and negative pressure. They can generate positive pressure to pump blood through the perfusion circuit and to the patient. Roller pumps also generate negative pressure, which can be used to pull volume from the venous reservoir and for cardiotomy suction.72

In contrast to hemolysis at the arterial pump head, there can be considerable hemolysis with high-flow suction where blood and air are mixed in the suction line at high velocity. The air-blood interface appears to be the source of hemolysis rather than direct injury to red cells by the roller pump. Minimizing suction head RPM will reduce air entrainment and thereby limit hemolysis.
Centrifugal pumps are newer devices. Their principle of mechanism is that the blood enters the pump while the high-speed rotating impellers are creating a vortex using a centrifugal cone. Less priming volume and fewer traumatized blood cells are 2 advantages of centrifugal pumps.6

Oxygenators

Oxygenators are responsible for the gas exchange through the CPB system. They must provide efficient gas exchange over a wide range of temperatures (10°C to 40°C), pump flow rates (0 to 200 mL/kg/min), hematocrit levels (15%–30%), line pressures, and gas flow rates. There are basically 2 types: Bubble oxygenators and membrane oxygenators. Bubble oxygenators were used during the early history of CPB; direct contact of the circulating blood with the fresh gas in the form of microbubbles caused increased hemolysis and produced significant numbers of inflammatory mediators. Currently, membrane oxygenators are more popular. There are 2 types of membranes in use, true and microporous, and there are 2 types of microporous membrane oxygenators, hollow fiber and folded membrane. Gas transfer is maintained through the microporous hollow fibers, which allows higher flow rates with higher gas transfer rates. Smaller total membrane area that needs less priming volume with better gas exchange capacity is an advantage, but there is increased risk of air embolism if negative pressure develops in the blood side of the membrane. The heat exchanger generally is integrated into the oxygenator and allows the cooling and rewarming of the blood during gas exchange. The volatile anesthetics also may be delivered through this system.

Venous Reservoir

The venous reservoir is one of the basic components of the CPB, which collects the blood from the circulation through venous cannulae and suction systems that aspirate blood from the surgical field.

Cardioplegia Delivery System

Cardioplegia is the cold crystalloid or blood-based solution that is used to preserve myocardial function during surgical repair. Cardioplegia arrests the heart in diastole by its high potassium concentration and helps to cool the heart, thus reducing myocardial oxygen and energy demand by decreasing the metabolic rate. Cardioplegia may be delivered either by anesthesiologist or by perfusionists. The cardioplegia delivery pressure and the temperature of the cardioplegia solution should be monitored closely to provide satisfactory myocardial protection.

Filters and Bubble Traps

The microporous filters are in general use for trapping air and debris to decrease the risk of embolization. They are located at various sites to minimize the risk. Leukocyte filters are used to decrease the entry of leukocytes to the systemic circulation and used as a strategy to reduce free-radical generation, which may improve the myocardial protection and early postoperative lung function recovery.

Hemoconcentration and Ultrafiltration

In infants, total body water tends to increase significantly after open cardiac surgery, resulting more commonly in edema in the peripheral system but also in the vital organs such as brain, heart, gut, and lungs. This excess water either may be decreased by reducing the amount of crystalloid in the pump prime or removed by diuresis and dialysis or by filtration methods used during or after CPB.

There are 3 types of ultrafiltration (UF) methods: Conventional, modified, and zero balance. In most centers conventional UF is applied during CPB and used mainly for hemoconcentration. Modified UF, which was popularized by Elliot et al,83 is used after weaning from CPB to remove not only the fluids but the inflammatory materials that are smaller than albumin, such as IL-6, C3a, and C5a. Zero-balance UF is performed using a circuit identical to that of conventional UF right after the rewarming phase by administering a replacement fluid into the venous reservoir to compensate for the ultrafiltrate volume. Hemoconcentration and removal of the inflammatory material are demonstrated to be beneficial but are not in general use, probably because of the complexity of the circuit and the risk of air embolism.84 Use of modern circuits to obtain less hemodilution with less prime volume, and routine application of conventional UF to achieve hematocrit levels of >30%, are other reasons for not favoring the use of modified UF. Even though there is still no consensus on type of modified UF to be used (arteriovenous or venovenous) or duration or ultrafiltrate amount, studies have shown benefits of modified UF, including improved postoperative hemodynamics and left ventricular function and decreased pulmonary vascular resistance and myocardial edema.85

Priming the Pump

The amount and components of the prime solution in the CPB circuit change depending on the length and diameter of the tubing used and center’s protocol for the desired hematocrit levels. The main concern in neonates and infants is that the priming volume dilutes the patient’s blood content 2 to 3 times, whereas it only equals 1/4 to 1/3 of the total blood volume in adult population. Hematocrit levels may need quite a workup to maintain the desired values. There is an ongoing effort to miniaturize the circuits further to target less hemodilution, in which the priming volumes are decreased as low as 115 mL.86

Another consideration is to determine whether colloid or crystalloid fluids will be used as the priming volume. To avoid excessive hemodilution, packed red blood cells are preferred over whole blood because the latter may promote neurologic injury during cerebral ischemia with its high glucose content.6 Blood used for priming the pump may be at least 1 week old because the fresher units should be reserved for postbypass transfusion. It should be kept in mind that because of the anaerobic metabolism of the red blood cells, bank blood older than 48 to 72 hours contains higher potassium, lactate, and pyruvate levels. In addition, the citrate in the bank blood causes hypocalcaemia by binding to the serum calcium.

In neonates and infants undergoing deep hypothermic CPB (15–20°C), a hematocrit of 20% ± 2% generally is safe; whereas for normothermia or mild hypothermia, hematocrit
levels around 30% should be targeted. When the decision on desired hematocrit has been made, the amount of bank blood to be added to the prime can be calculated from a simple formula that has been applied for many years:

Prime RBC VOL = \[ \text{[on - by pass HCT]} \times \frac{\text{[Pt BV + Prime BV]}}{\text{[Pt RBC VOL]}} \]

where prime RBC VOL is volume of blood required in prime, on-bypass HCT is desired hematocrit on bypass, Pt BV is patient’s calculated blood volume (weight in kg multiplied by 80), prime BV is total priming volume, and Pt RBC VOL is Pt BV multiplied by the patient’s hematocrit.72

Colloid osmotic pressure (COP) is maintained with addition of albumin to the priming solution, targeting a COP pressure of 18 mmHg, and prebypass crystalloid dilution during induction should be avoided as well as return of the crystalloid cardioplegic solution into the circulation because lower patient COP before bypass remained the only significant predictor for low COP at the end of bypass, which worsens clinical outcomes.88

Mannitol is an osmotic diuretic that is used to enhance diuresis and to prevent adhesion of platelets to the circuit surfaces. Mannitol is also a free radical scavenger, which may play a role in the reduction of reperfusion injury and has also been shown to be beneficial for ischemic myocardium by improving resting coronary blood flow and subendocardial flow and reducing cell size to normal.72

Steroids are used as the main anti-inflammatory agents to prevent capillary leak and to maintain the acid-base equilibrium; and, as Clarizia et al suggested, intraoperative steroid use is associated with improved postoperative outcomes for children undergoing high-risk cardiac surgery, with further benefits associated with a preoperative dose. Magnesium, calcium, and sodium bicarbonate are also added to the prime solution.72,73,87,89

Myocardial Protection

The inadequate metabolic capacity of the infant myocardium will cause the pediatric heart to suffer even more during the more complex intracardiac procedures of the congenital heart disease portfolio and temperature fluctuations compared with adult heart surgery.

Induction, maintenance and reperfusion are the 3 main phases of myocardial protection and cardioplegia delivery strategies. After the initiation of CPB and cross-clamp application, induction cardioplegia is delivered to establish the electrical silence of the myocardium. Intermittent doses of cardioplegia are needed every 10 to 30 minutes to maintain myocardial hypothermia and to stay at the arrest phase, to buffer the acidosis and replenish the high-energy phosphates. Also, adequate distribution of the coronary blood flow and optimized cardioplegia delivery pressures are important.17

In another study, no significant differences in the clinical outcomes were demonstrated between the crystalloid and blood cardioplegia methods; however, in cyanotic patients, cold blood cardioplegia followed by terminal warm cardioplegia “hot shot” significantly reduced the decrease in adenosine triphosphate, indicating better myocardial protection.90

Anticoagulation and Heparin Reversal

An anticoagulation regimen ideally would suppress the activation of the coagulation cascade during exposure of patient’s blood to the external surfaces of the CPB circuit and be completely reversible at the termination of the bypass. Heparin is the most common drug in use and contains a mixture of polysulfated glycosaminoglycans, acts mainly by inactivating the thrombin and factor Xa, and potentiates the activity of the naturally circulating enzyme inhibitor antithrombin factor III (ATIII). Anticoagulation attempts for the newborns and infants with deficient ATIII levels may present as heparin resistance, in whom standard doses of heparin used for anticoagulation (4 mg/kg [1 mg = 100 IU]) may not be efficient and adding fresh frozen plasma or recombinant AT III may resolve the problem.91,92

Activated coagulation time (ACT) traditionally is used to monitor the activity of heparin and before heparin administration is usually around 130 seconds. Most centers believe that ACT should be maintained at > 350 to 450 seconds during CPB in order to minimize the risk of disseminated intravascular coagulation. The use of the HEPCON device (Heparin Management System, Medtronic, Minneapolis, MN) and monitoring the heparin concentration during CPB are the alternative approaches.73 Guzzetta et al92 found that with the heparin concentration on CPB technique, there was decreased thrombin generation as well as preserved factor VIII levels; however, this technique requires increased blood product requirements.

Heparin-induced trombocytopenia/thrombosis (HIT/HITT) is a rare complication that is common after previous heparin exposure. There are 2 types of HIT. HIT-1 presents with a transient nonimmune-mediated decrease in the platelet count and does not necessitate the discontinuation of heparin. HIT-2 shows an immune-mediated decrease in the platelet count by >50%, in which the antibodies are formed against platelet factor 4 (PF4), which may require the use of direct thrombin inhibitors such as tinzaparin, lepirudin, bivalirudin, and argatroban or glycoprotein IIb/IIIa inhibitors like abciximab, eptifibatide, and tirofiban to replace the heparin.94,95 However, doses for such alternative anticoagulants are not well established for the pediatric patient population.95

Heparin is easily reversible at the end of CPB with Protamine. Protamine is the agent being used to reverse the effects of heparin. Severe reactions to protamine may be less common in infants than in adults.84,85 Determining the dose of protamine is difficult without knowing the circulating concentrations of heparin. The protamine dose on automated heparin/protamine titration will result in a smaller dose than predicted based on the initial heparin bolus and the last ACT.58 It is important to avoid overdosing protamine because unbound protamine has anticoagulant properties.86,87 A further complicating factor in heparin reversal is ultrafiltration, which is used in 75% of centers performing congenital heart surgery.86 Because heparin molecules are too large to pass through the filter, heparin levels increase during ultrafiltration87 and patients who have undergone high-volume ultrafiltration may require correspondingly higher doses of protamine.86

Limited clinical evidence suggests that administration of recombinant activated factor VII (rFVIIa) is often effective in reducing coagulopathic bleeding resistant to conventional
therapy after congenital heart surgery but carries significant risk of thrombosis in this group of patients who are already at high risk of thrombotic complications. rFVIIa cannot produce hemostasis alone and should only be administered after trans-fusion of sufficient platelets, plasma, and fibrinogen to form the substrate for hemostasis.96

In conclusion, congenital heart diseases are a unique field of anomalies and the overall care requires extraordinary teamwork and high standards of care. A better understanding of the physiology and pathophysiology of small infants has decreased the mortality of pediatric heart surgery patients, even for most of the complex cases, by carefully individualizing their management. Since its introduction to the field, there has been so much progress in the application and techniques of CPB, and it is still progressing. Understanding the differences in the maturity of the organ systems between adults and infants significantly affected the management of the cardiopulmonary bypass system. The advancements of hardware, like miniaturizing the circuit by shortening tubing length, decreasing tubing diameter, and using low-prime devices, have helped to reduce the inflammatory response, which is the main cause of CPB side effects. Myocardial protection techniques better preserved the heart muscle functions, and the routine application of modified ultrafiltration prevented fluid overload and excess inflammation. The optimization of DHCA use by restricting DHCA time, extreme hemodilution, and the combined acid-base management strategies, such as pH-stat during cooling and alpha-stat at rewarming, were some of the measures that helped to reduce the neurologic complications. Neuromonitoring and blood glucose control by avoiding hypoglycemia and hyperglycemia were just some of the other neuroprotective strategies. CPB optimization and minimizing the inflammatory response by using pharmaceutical and mechanical methods are the mainstays of the thought process. The future looks promising for this challenging group of patients in light of recent advancements. However, despite the large amount of information available regarding infant CPB, there is still much room for improvement. CPB in infancy is a broad subject to write a review on and there are many detailed reviews for most of the subtopics in the subject, but the authors hope this article will help the reader to have a general understanding and overview of the subject and a key for detailed further reading.

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