Cardiopulmonary bypass

Scott D. Markowitz
William J. Greeley

Introduction

In order to facilitate the repair of congenital heart lesions, cardiopulmonary bypass (CPB) was developed. The earliest reported successes were in the 1950s with Gibbon and Lillehei performing intracardiac surgery using a variety of systems to oxygenate and pump the circulating blood in a surgical patient. These systems posed significant risk of death not only to the patient, but also to the patient’s parent who was being used as oxygenator and pump, using the technique of cross circulation. Many improvements have been made upon the original artificial systems, but the fundamental principles of extracorporeal circulation have remained the same. The extracorporeal circuit takes venous blood from the patient, pumps it through an oxygenator and filter, and returns it to the arterial system of the patient, thus bypassing the heart and lungs. Variation exists between types of pumps, oxygenators, venous reservoirs, and the size and coating of tubing and cannulae. New technologies and current research continues to improve outcome from congenital heart disease (CHD) surgery, and the effects of CPB on the patient continue to be elucidated. To better understand the physiology of CPB in the infant and child, it is helpful to first understand the differences between pediatric and adult bypass.

Differences between pediatric and adult cardiopulmonary bypass

The physiologic effects of CPB on neonates, infants, and children are significantly different than in adults (Table 5.1). During CPB, pediatric patients are exposed to different biologic extremes not seen in adults, including deep hypothermia (15–20°C), hemodilution (three to 15-fold greater dilution of circulating blood volume), low perfusion pressures

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Adult</th>
<th>Pediatric</th>
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<tbody>
<tr>
<td>Hypothermic temperature</td>
<td>Rarely below 25–32°C</td>
<td>Commonly 15–20°C</td>
</tr>
<tr>
<td>Use of total circulatory arrest</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Dilution effects on blood volume</td>
<td>25–33%</td>
<td>100–200%</td>
</tr>
<tr>
<td>Perfusion pressures</td>
<td>50–80 mmHg</td>
<td>20–50 mmHg</td>
</tr>
<tr>
<td>Influence of α- vs. pH-stat</td>
<td>Minimal at moderate hypothermia</td>
<td>Marked at deep hypothermia</td>
</tr>
<tr>
<td>Glucose regulation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Rare—requires significant hepatic injury</td>
<td>Common—reduced hepatic glycogen stores</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>Frequent—generally easily controlled with insulin</td>
<td>Less common—rebound hypoglycemia may occur</td>
</tr>
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Table 5.1 Cardiopulmonary bypass differences between adult and pediatric patients.

(20–30 mmHg), wide variation in pump flow rates (ranging from highs of 200 mL/kg/minute to total circulatory arrest), and differing blood pH management techniques (α-stat or pH-stat, or both sequentially). These parameters significantly differ from normal physiology and affect preservation of normal organ function during and after CPB. In addition to these prominent changes, subtle variations in glucose supplementation, cannula placement, presence of aortopulmonary collaterals, and patient age may also be important factors affecting organ function during CPB. Adult patients are infrequently exposed to these biologic extremes. In adult cardiac patients, temperature is rarely lowered below 25°C, hemodilution is more moderate, perfusion pressure is generally maintained at 50–80 mmHg, flow rates are maintained at 50–65 mL/kg/minute, and pH management strategy is less influential because of moderate hypothermic temperatures and rare use of circulatory arrest. Variables such as glucose supplementation rarely pose a problem in adult patients due to large hepatic glycogen stores. Venous and arterial cannulae are larger and less deforming of the atria and aorta, and their placement more predictable. Although superficially similar, the conduct of CPB in children is considerably different from that in adults. One would therefore expect marked physiologic differences in the response to CPB in the child.

Temperature
Hypothermic CPB is used to preserve organ function during cardiac surgery. Four distinct methods of CPB are used: normothermic CPB, moderate hypothermic CPB (25–32°C), deep hypothermia with low-flow CPB (15–20°C), or deep hypothermic circulatory arrest (DHCA). The choice of method of bypass to use is based on the required surgical conditions, patient size, the type of operation, surgeon preference, and the potential physiologic impact on the patient.

Moderate hypothermic CPB is the principal method of bypass employed for older children and adolescents. In these patients, venous cannulae are less obtrusive, and the heart can easily accommodate superior and IVC cannulation. Bicaval cannulation reduces right atrial blood return, and improves the surgeon’s ability to visualize intracardiac anatomy. Moderate hypothermia may also be chosen for less demanding cardiac repairs in infants, such as an atrial septal defect or an uncomplicated ventricular septal defect. Most surgeons are willing to cannulate the inferior and superior vena cavae in neonates and infants. However, in these patients this approach is technically more difficult and likely to induce brief periods of hemodynamic instability. Additionally, the pliability of the cava and the rigidity of the cannulae may result in caval obstruction, impaired venous drainage, and elevated venous pressure in the mesenteric and cerebral circulation.

Deep hypothermic CPB is generally reserved for neonates and infants requiring complex cardiac repair. However, certain older children with complex cardiac disease or severe aortic arch disease benefit from deep hypothermic temperatures. For the most part, deep hypothermia is selected to allow the surgeon to operate under conditions of low-flow CPB or total circulatory arrest. Low pump flows (25–50 mL/kg/minute) improve the operating conditions for the surgeon by providing a near bloodless field. Deep hypothermic circulatory arrest allows the surgeon to remove the atrial and/or aortic cannula. Utilizing this technique, surgical repair is more precise because of the bloodless and cannula-free operative field. Arresting the circulation, even at deep hypothermic temperatures, introduces the concern of how well deep hypothermia preserves organ function, with the brain being at greatest risk.

Recent reports have reconsidered the use of normothermic CPB in pediatric patients. In a study comparing hypothermic with normothermic CPB, no difference was detected in two biochemical markers for brain injury. Normothermic CPB requires higher pump flow rates and hematocrit to meet the metabolic demand of normothermic tissues. These adjustments may lead to more blood in the surgical field, and may reduce the margin of safety for preventing ischemic injury should mechanical failure occur with the CPB system.

Hemodilution
Although hemoconcentrated blood has an improved oxygen-carrying capacity, its viscosity reduces efficient flow through the microcirculation. With hypothermic temperatures, blood viscosity increases significantly and flow decreases. Hypothermia, coupled with the non-pulsatile flow of CPB, impairs blood flow through the microcirculation. Blood sludging, small vessel occlusion, and multiple areas of tissue hypoperfusion may result. Therefore, hemodilution is an important consideration during hypothermic CPB. The appropriate level of hemodilution for a given hypothermic temperature, however, is not well defined. Experimental evidence suggests that reducing hematocrits to as low as 15% provides a sufficient quantity of oxygen delivery to the myocardium at normothermia, provided intravascular volume, colloid osmotic pressure, and normotension are maintained. At hypothermic temperatures, hematocrits reduced to as low as 10% provide adequate oxygen delivery during CPB, as long as flow rates and perfusion pressure are maintained. Since red blood cells serve as the major reservoir of oxygen during circulatory arrest, hematocrit values closer to 20% are generally preferred for deep hypothermia when this technique is contemplated. Most centers maintain hematocrit levels at 20 ± 2% during deep hypothermia (15–20°C) and will allow the hematocrit to drift as low as 18% before transfusing additional red blood cells. Although this is an arbitrary limit, lower hematocrit values have not been systematically evaluated to ensure adequate oxygen delivery to tissue. Cerebral oxygen delivery is an especially important consideration,
since cerebral autoregulation is impaired at deep hypothermic temperatures and after DHCA.

In order to achieve a hematocrit of 20–25% in neonates and infants, banked blood should be added to the priming solution. The mixed hematocrit on CPB (Hct CPB = the hematocrit of the patient’s blood volume plus the total priming volume of the circuit) can be calculated by the formula:

\[
\text{Hct CPB} = \frac{\text{Hct preop} \times \text{BV}}{\text{TPV} + \text{BV}}
\]

Where Hct CPB is mixed Hct \((TPV + BV)\), BV is patient’s blood volume (estimated blood volume based upon the patient’s weight), TPV is total priming volume of the CPB circuit, and Hct preop is the starting hematocrit of the patient. This calculation allows an estimate of the hematocrit of the patient using an asanguinous prime and is therefore useful for older children and adolescents. In neonates and infants, the perfusionist must add blood to the pump prime in order to achieve a desired hematocrit during hypothermic CPB.

Currently, no evidence exists for defining the optimal hematocrit after weaning from CPB. Decisions concerning post-CPB hematocrits are made based on the patient’s post-repair function and anatomy. Patients with residual hypoxemia or those with moderate to severe myocardial dysfunction benefit from the improved oxygen carrying capacity of hematocrit levels of 40% or higher. Patients with a physiologic correction and excellent myocardial function may tolerate hematocrit levels of 20–25%. In children with mild to moderate myocardial dysfunction, accepting hematocrit levels between these extremes seems prudent. Therefore, in patients with physiologic correction, moderately good ventricular function, and hemodynamic stability, the risks associated with blood and blood product transfusion should be strongly considered during the immediate post-bypass period.

Prime composition and volume

The priming solutions used in pediatric CPB take on great importance because of the disproportionately large prime volume to blood volume ratio in children and the resulting effects on procoagulants (see Chapter 10). In adults the priming volume is equivalent to 25–33% of the patient’s blood volume, whereas in neonates and infants the priming volume may exceed the patient’s blood volume by 200%. Even contemporary low-volume bypass circuits rarely reduce this figure much below 150% in the smallest neonates. Therefore, care must be taken to achieve a physiologically balanced prime and limit the volume as much as possible. Most pediatric priming solutions, however, have quite variable levels of electrolytes, calcium, glucose, and lactate. Electrolytes, glucose, and lactate levels may be quite high if the prime includes large amounts of banked blood, or quite low if a minimal amount of banked blood is added. Calcium levels are generally very low in pediatric prime solutions; this may contribute to the rapid slowing of the heart with the initiation of bypass. The main constituents of the priming solution include: crystalloid, banked blood (to maintain a temperature-appropriate hematocrit), and colloid. Other supplements that may be added to the prime are mannitol, a buffer (sodium bicarbonate or tromethamine), and steroids. Many institutions add colloid or fresh frozen plasma to the pump prime in neonates and small infants or use whole blood in the priming solution. Low concentrations of plasma proteins have been shown experimentally to impair lymphatic flow and alter pulmonary function by increasing capillary leak. Although adding albumin to pump prime has not been shown to alter outcome in adults during CPB, one study has suggested that maintaining normal colloid osmotic pressure may improve survival in infants undergoing CPB. The addition of fresh frozen plasma or whole blood is an attempt to restore the level of procoagulants which are severely diluted with CPB in infants. Priming with fresh frozen plasma instead of 5% albumin significantly reduces chest tube drainage in infants undergoing complex surgery. For neonates and infants, blood must be added to the priming solution. Most institutions use packed red blood cells in their prime solution; however, some use whole blood. The use of whole blood supplements both red blood cells and the coagulation factors with a single donor exposure. In fact, low-volume bypass circuits may enable perfusionists and anesthesiologists to share a single unit of whole blood thereby limiting the donor exposure to one throughout the entire perioperative course. The addition of any blood products will cause a much higher glucose load in the prime. Hyperglycemia may increase the risk of neurologic injury if brain ischemia occurs. Mannitol is added to promote an osmotic diuresis and to scavenge oxygen-free radicals from the circulation. Steroids are added to stabilize membranes to produce the theoretical advantage of reducing ion shifts during periods of ischemia. Steroids, however, may raise glucose levels and this may be detrimental if there is a period of cerebral ischemia. Steroids remain one of the more controversial additives in priming solutions.

Centrifugal vs. roller pumps

A roller pump consists of a semicircular raceway with a central axis from which extends at least two arms that are 180° from one another, and rotate at an adjustable speed as measured in revolutions per minute (RPM). At the end of the arm is a roller which compresses the tubing against the raceway wall, creating a pressure difference between the inflow and outflow limbs as the roller rotates. The speed of rotation and the diameter of the tubing determine the pump flow. Roller pumps are commonly used for cardiotomy suction, and in pediatric bypass are the more common pump used for systemic perfusion. An advantage of roller pumps is the
Miniaturization of the cardiopulmonary bypass circuit

Minimizing the volume of pump prime for neonates and infants has been a priority due to the difficult balance between severe hemodilution and immunological and infectious risks associated with transfusion. A schematic of the CPB circuit is shown in Fig. 5.1. The ultimate goal of miniaturization of the circuit volume should be to provide a range of pump prime that would allow for adequate hemodilution and eliminate the need for supplemental banked blood for the smallest patients. Thus far efforts to reduce circuit size and volume have met limitations, which include increasing resistance to flow in narrower tubing, length of tubing limitations due to physical proximity of the CPB machine to the

Table 5.2 Cardiopulmonary bypass flow rates.

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Flow range (patient warm)</th>
<th>Flow range (patient cold)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–5</td>
<td>125–175</td>
<td>75–100</td>
</tr>
<tr>
<td>5–10</td>
<td>100–150</td>
<td>75–100</td>
</tr>
<tr>
<td>10–20</td>
<td>$BSA \times [2.6–3.0]$</td>
<td>$BSA \times [2.0–2.2]$</td>
</tr>
<tr>
<td>20–40</td>
<td>$BSA \times [2.4–3.0]$</td>
<td>$BSA \times [2.0–2.2]$</td>
</tr>
<tr>
<td>&gt; 40</td>
<td>$BSA \times [2.2–2.6]$</td>
<td>$BSA \times [2.0–2.2]$</td>
</tr>
</tbody>
</table>

$BSA$, body surface area (in m$^2$).

Fig. 5.1 Schematic diagram of cardiopulmonary bypass circuit. This scheme depicts a membrane oxygenator with integral hard-shell venous reservoir and external cardiotomy reservoir. Many circuits have the cardiotomy reservoir, venous reservoir, and oxygenator integrated into one single unit. The systemic blood pump may be either a roller or centrifugal pump. Most pediatric venous cannulations are bicaval with two separate venous cannulae instead of the single venous cannula depicted here. Carbon dioxide can also be added to the inspired gas to facilitate pH-stat blood gas management. Arrows indicate direction of flow; P, pressure sensor; T, temperature sensors; X, placement of tubing clamps. Reproduced with permission from Hessel EA, Hill AG. Circuitry and cannulation techniques. In: Gravlee GP, Davis RF, Kurusz M, Utley JR, eds. Cardiopulmonary Bypass: Principles and Practice, 2nd edn. Philadelphia, PA: Lippincott, Williams & Wilkins, 2000: 69–97.
operative field, and minimum oxygenator membrane surface area. Additionally, the venous reservoir represents a safety net for periods of reduced venous drainage. While progress has allowed pump primes of as little as 150–180 mL, this volume does not permit an asanguinous prime to be used safely for most neonates. In order to reduce the volume necessarily remaining in the venous reservoir, centers have successfully employed actively assisted venous drainage.

Vacuum assisted bypass

Considerations regarding the disadvantages of severe hemodilution and therefore the need for sanguinous pump prime have led to many changes in circuit design including integration of circuit components to limit prime volume, and efforts to limit circuit volume by actively assisted venous drainage. This technique permits a decrease in the height difference between the patient and the venous reservoir as compared to passive (standard) venous drainage, thus shortening the length of venous and arterial tubing, limiting circuit volume. The use of active drainage also permits venous tubing and cannulae of smaller diameter to be utilized, again limiting circuit volume. However, active venous drainage involves risks that must be weighed against potential advantages.

There are two general ways in which suction may be applied to the venous system for augmented drainage. A sealed, hard-shelled venous reservoir may be connected to a controlled suction device. This exposes the patient to the considerations of a hard reservoir such as a blood–air interface which is procoagulant/proinflammatory, and it permits the possibility of massive air entrainment into the arterial limb of the circuit should the reservoir fall below a critical level. The second method of active venous drainage involves the placement of a pump on the venous limb. Although this would permit the use of a soft-reservoir, limiting the blood gas interface, the problems inherent in both systems would still apply. The concerns for augmented venous drainage are twofold: first, the vacuum created may lyse red blood cells, increasing free hemoglobin in the circuit and increasing the risk of renal injury; and second, the flow of venous blood must be carefully regulated or there is a risk of inadequate drainage leading to increased superior vena cava (SVC) or inferior vena cava (IVC) pressures and the ascites or tissue edema that can follow, or too much suction which could lead to entrainment of air into the CPB circuit.

Pulsatile cardiopulmonary bypass

Pulsatile perfusion has been used successfully for pediatric congenital heart surgery. Although the use of non-pulsatile bypass is much more common, there exists evidence that indicates areas of potential advantage of using pulsatile perfusion during phases of CPB. In a comparison of conventional vs. pulsatile perfusion around a period of DHCA for congenital heart surgery, the pulsatile group showed more rapid cooling and rewarming, and increased urine production during bypass. One study also showed a decreased total pump time in the pulsatile perfusion group. There also seems to be decreased systemic vascular resistance during pulsatile perfusion. In animal studies, pulsatile perfusion enhances cerebral and renal blood flow during bypass in a piglet model of perfusion and DHCA. In a randomized crossover study there was no difference in cerebral perfusion by near-infrared spectroscopy comparing pulsatile and non-pulsatile bypass, and in another comparison, no difference in plasma cortisol and adrenocorticotropic hormone (ACTH) was detected during and after perfusion of children using moderate hypothermia. Controversy remains over the advantages for application in humans as various pump/oxygenator and filter combinations yield inconsistent results and a universal standard for comparison between pumps and techniques has not yet been achieved.

Management of cardiopulmonary bypass

Initiation of cardiopulmonary bypass

Arterial and venous cannulation of the heart prior to initiating CPB may result in significant problems in the peri-bypass period. A malpositioned venous cannula has the potential for vena caval obstruction. The problems of venous obstruction are magnified during CPB in the neonate because arterial pressures are normally low (20–40 mmHg), and large relatively stiff cannulae easily distort these very pliable venous vessels. A cannula in the IVC may obstruct venous return from the splanchnic bed, resulting in ascites from increased hydrostatic pressure and/or directly reduced perfusion pressure across the mesenteric, renal, and hepatic vascular beds. Significant renal, hepatic, and gastrointestinal dysfunction may ensue and should be anticipated in the young infant with unexplained ascites. Similar cannulation problems may result in SVC obstruction. This condition may be more ominous during bypass. Under these circumstances, three problems may ensue: (i) cerebral edema; (ii) a reduction in regional or global cerebral blood flow (CBF); and (iii) a reduced proportion of pump flow reaching the cerebral circulation causing inefficient brain cooling. In the operating room it is advisable either to monitor SVC pressures via an internal jugular catheter or by looking at the patient’s head for signs of puffiness or venous distension after initiating bypass. Neurological monitoring, such as near-infrared cerebral oximetry or transcranial Doppler ultrasound, can rapidly detect decreases in CBF due to SVC obstruction. Discussions with the perfusionist regarding adequacy of venous return and/or large cooling gradients between the upper and lower
body should alert the anesthesiologist and the surgeon to potential venous cannula problems. Patients with anomalies of the large systemic veins (persistent left SVC or azygous continuation of an interrupted IVC) are at particular risk for problems with venous cannulation and drainage.

Problems with aortic cannula placement also occur. When the cannula is placed, pressure in the arterial side of the circuit should be measured. The pressure should be between the mean and the systolic pressure of the patient. Transfusion of 10–50 mL of bypass prime should be given slowly, while pressure in the arterial circuit is measured. Pressure should remain low, signifying a cannula placement in the center of the lumen of the aorta. The aortic cannula may slip beyond the takeoff of the innominate artery and, therefore, selectively flow to the right side of the cerebral circulation. Also, the position of the tip of the cannula may promote preferential flow down the aorta or induce a Venturi effect to steal flow from the cerebral circulation. This problem has been confirmed during CBF monitoring by the appearance of large discrepancies in flow between the right and left hemisphere after initiating CPB. Other clues to cannula misplacement include better cooling in the lower body than in the upper body. The presence of large aortic to pulmonary collaterals, such as a large patent ductus arteriosus (PDA), may also divert blood to the pulmonary circulation from the systemic circulation thereby reducing CBF and the efficiency of brain cooling during CPB. The surgeon should gain control of the ductus either prior to or immediately after instituting CPB to eliminate this problem and, if possible, large aortopulmonary collaterals should be embolized in the cardiac catheterization laboratory prior to the operative procedure. Neonates with significant aortic arch abnormalities (e.g. aortic atresia, interrupted aortic arch) may require radical modifications of cannulation techniques, such as placing the arterial cannula in the main pulmonary artery and temporarily occluding the branch pulmonary arteries to perfuse the body via the PDA, or even dual arterial cannulation of both the ascending aorta and main pulmonary artery. Some centers utilize two arterial catheters, one in a radial artery, and one in the femoral or umbilical artery, to demonstrate adequate pressure in the lower body during bypass for interrupted or hypoplastic aortic arch. Such adaptations require careful vigilance to ensure effective, thorough cooling of vital organs.

Once the aortic and venous cannulae are positioned and connected to the arterial and venous limb of the extracorporeal circuit, bypass is initiated. The arterial pump is slowly started and once forward flow is assured, venous blood is drained into the oxygenator. Pump flow rate is gradually increased until full circulatory support is achieved. If venous return is diminished, arterial line pressure is high, or mean arterial pressure is excessive, pump flow rates must be reduced. High line pressure and inadequate venous return are usually due to malposition or kinking of the arterial and venous cannulae, respectively. The rate at which venous blood is drained from the patient is determined by the height difference between the patient and the oxygenator inlet and the diameter of the venous cannula and line tubing. Venous drainage can be enhanced by increasing the height difference between the oxygenator and the patient or by using a larger venous cannula. Venous drainage can be reduced by either decreasing the height difference between the oxygenator and the patient or by partially clamping the venous line.

In neonates and infants, deep hypothermia is commonly used. For this reason, in some institutions the pump prime is kept cold (18–22°C). When the cold perfusate contacts the myocardium during the institution of CPB, heart rate slows immediately and contraction is impaired. Other centers prefer to avoid this perceived stress on the myocardium and keep the prime temperature very close to the patient’s temperature. The contribution of total blood flow pumped by the infant’s heart rapidly diminishes. Therefore, to sustain adequate systemic perfusion at or near normothermic temperatures, the arterial pump must reach full flows quickly. Cardiopulmonary bypass is initiated in neonates and infants by beginning the arterial pump flow first. Once aortic flow is ensured, the venous line is unclamped and blood is siphoned out of the right atrium into the inlet of the oxygenator. Flowing before unclamping the venous line prevents the potential problem of exsanguination if aortic dissection or misplacement of the aortic cannula occurs. Neonates and infants have a low blood volume to prime volume ratio, and intravascular volume falls precipitously if the venous drainage precedes aortic inflow. Once aortic cannula position is verified, pump flow rates are rapidly increased to maintain effective systemic perfusion. Since coronary artery disease is rarely a consideration, the myocardium should cool evenly unless distortion caused by the cannulae compromises the coronary arteries. When a cold prime is used, caution must be exercised in using the pump to infuse volume prior to initiating CPB. Infusion of cold perfusate may result in bradycardia and impaired cardiac contractility before the surgeon is prepared to initiate CPB. This again is a reason why many centers do not utilize cold prime.

Once CPB begins, careful observation should be focused to ensure appropriate circuit connections, myocardial perfusion and optimal cardiac decompression. Ineffective venous drainage can rapidly result in ventricular distension. This is especially true in infants and neonates where ventricular compliance is low and the heart is relatively intolerant of excessive preload augmentation. If ventricular distension occurs, pump flow must be reduced and the venous cannula repositioned. Alternatively, the heart may be decompressed by placing a cardiotomy suction or small vent in the appropriate chamber.

**Pump flow rates**

Recommendations for optimal pump flow rates for children
have historically been based both on the patient’s body mass and evidence of efficient organ perfusion as determined by arterial blood gases, acid-base balance, and whole body oxygen consumption during CPB. At hypothermic temperatures metabolism is reduced. Pump flow rates can therefore be reduced and still meet or exceed the tissues’ metabolic needs (see the discussion of low-flow CPB in the Deep hypothermic circulatory arrest section below). Some centers utilize higher flows of 150–200 mL/kg/minute at all temperatures, combined with vasodilation produced by α-receptor blockade, with the goal of preservation of organ function and capillary integrity. Outcome data proving one approach superior to the other are lacking.

**Deep hypothermic circulatory arrest**

Neonates and infants who require extensive repair of complex congenital heart defects may have these procedures performed using DHCA. This technique facilitates precise surgical repair under optimal conditions, free of blood or cannulae in the operative field, providing maximal organ protection, and often resulting in shortened total CPB time. The scientific rationale for the use of deep hypothermic temperatures rests primarily upon a temperature-mediated reduction of metabolism. Induced hypothermia decreases the metabolic rate, as well as whole body and cerebral oxygen consumption by a factor of 2–4 for every 10°C reduction in temperature in neonates and infants. These results are consistent with in vitro models, which relate temperature reduction to a decrease in the rate constant of chemical reactions. The reduction in oxygen supply during deep hypothermic low-flow CPB (DHCPB) is associated with preferential increases in vital organ perfusion (e.g. to the brain) and by increased extraction of oxygen.

Therefore, to some extent Duchess exerts a protective effect by reducing the metabolic rate for oxygen, promoting preferential organ perfusion and increasing tissue oxygen extraction.

Extensive clinical experience using DHCA has shown the duration of the safe circulatory arrest period may last up to 45 minutes. Beyond this duration, the incidence of permanent and transient neurologic sequelae may increase. Both the duration of the arrest period and variations in perfusion technique during cooling and rewarming influence the development of these problems. However, the effect of deep hypothermia on tissue metabolism and oxygen consumption and extraction clearly does not explain the entire protective effect of “safe” DHCA. Cortical PO2 and PCO2 levels indicate basal cerebral metabolic activity continues during DHCA (i.e. anaerobic metabolism develops after local tissue oxygen stores are consumed). During brain ischemia, excitatory amino acids (EAAs) such as glutamate and aspartate are released and are putative mediators of ischemic damage. Hypothermia has been shown to significantly decrease the release of EAAs, potentially contributing to the central nervous system protective effect. In addition, hypothermia transforms a normal semiliquid cellular membrane to a semisolid, which may act to prevent calcium influx during reperfusion and thereby account for additional protection noted in some experimental models.

Although all organ systems are at risk for the development of ischemic and reperfusion injury, as manifested by lactate and pyruvate production during DHCA, the brain appears to be the most sensitive and the least tolerant of these effects. Brain stem and cortical evoked potentials as well as processed electroencephalographs (EEGs) are altered after DHCA. The abnormalities in the evoked potentials appear to be related to the duration of DHCA and are attributed to altered metabolism. During reperfusion after the arrest period CBF and metabolism remain depressed in neonates and small infants. Importantly, during the use of these extremes of temperature, it appears that autoregulation is lost and cerebral perfusion becomes highly dependent on the conduct of extracorporeal perfusion and presumably post-bypass hemodynamic performance (Fig. 5.5).

Current controversy exists regarding the immediate-term and long-term neuropsychologic effects of DHCA. Early reports regarding the long-term consequences of DHCA on brain development and intelligence were conflicting. Transient neurologic dysfunction and other reversible cerebral injuries have been reported. These transient, subtle neuropsychologic disturbances have led investigators to examine more systematically the long-term outcome after DHCA.

More recently a number of more sophisticated studies examining the outcome after DHCA have been performed. In a recent randomized clinical trial comparing the incidence of brain injury following DHCA or low-flow CPB, DHCA was demonstrated to have longer EEG recovery times and a higher incidence of clinical seizures in the early postoperative period. The DHCA group also had a higher incidence of electroencephalographs (EEGs) are altered after DHCA.44–46 Brain stem and cortical evoked potentials as well as processed electroencephalographs (EEGs) are altered after DHCA.44–46 The abnormalities in the evoked potentials appear to be related to the duration of DHCA and are attributed to altered metabolism. During reperfusion after the arrest period CBF and metabolism remain depressed in neonates and small infants (Figs 5.2–5.4). Importantly, during the use of these extremes of temperature, it appears that autoregulation is lost and cerebral perfusion becomes highly dependent on the conduct of extracorporeal perfusion and presumably post-bypass hemodynamic performance (Fig. 5.5).

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Adenosine triphosphate (ATP) and intracellular pH after arrest and reperfusion, which suggests that pH-stat blood gas management may have protective mechanisms due to an increased rate of brain cooling. In a study comparing the effects of pH-stat and α-stat management on cerebral oxygenation and blood flow, the cerebral protective effect of pH-stat management was demonstrated and indicated that the kinetics of cerebral deoxygenation might contribute to the mechanism of protection. Because of the potential for neurologic dysfunction after DHCA, some institutions use low-flow deep hypothermic CPB as an alternative technique. Since low-flow bypass can produce ischemia if flow is too low and because it lengthens the CPB time, compared

Great arteries. The authors found a strong positive correlation between arterial $P_{CO_2}$ during cooling before circulatory rest and developmental score. This suggested that children undergoing α-stat blood gas management strategy had a worse developmental outcome than where a pH-stat strategy was employed. In a recent randomized clinical trial of neonates undergoing cardiac surgery using DHCA, pH-stat management was noted to have faster EEG recovery times and fewer postoperative seizures compared to an α-stat bypass group. Therefore pH-stat management may be beneficial.

Experimental studies have also suggested the superiority of pH-stat strategy. Using pH-stat strategy, animals had greater CBF during cooling and better recovery of cerebral
DTCA. A higher hematocrit of 30, lower temperature of 18°C, and pH-stat blood gas management all significantly delayed the decay in cerebral oxygenation and the onset of the nadir, lengthening the period of “safe” DTCA. This suggests a clinical strategy for DTCA monitoring and management using NIRS.

Other factors such as surface cooling, anesthetic agents, and cerebral protective agents may influence and modify the central nervous system protective effects of DHCPB.
and DHCA. However, the potential added protection from anesthetic drugs, barbiturates, lidocaine, or calcium channel blockers is unknown. There are no clinical studies in children systematically examining the influence of these pharmacologic agents on cerebrovascular physiology or neurologic outcome. Therefore, the use of these agents remains entirely speculative and unformed. Clearly, further controlled study of the long-term effects of DHCA with added pharmacologic agents on neuropsychologic outcome in children is necessary. Equally important, the manner in which the patient is cooled and rewarmed may affect outcome,65,66 and merits further investigation, even before the testing of pharmacologic drugs. It has been demonstrated that rapid cooling to deep hypothermic temperatures in less than 20 minutes is associated with higher incidence of acute and long-term neurologic morbidity.67,68

**Selective cerebral perfusion**

Because of the concern that prolonged DHCA may lead to neurologic morbidity, alternative techniques have been developed that limit or eliminate DHCA for some types of surgery, particularly neonatal aortic arch reconstructive surgery such as the Norwood stage I palliation for hypoplastic left heart syndrome, or aortic arch reconstruction for hypoplastic or interrupted aortic arch. Selective cerebral perfusion provides blood flow to the brain, while the remainder of the body is not perfused, providing a bloodless operating field similar to DHCA.69 One such technique is called regional low-flow cerebral perfusion (RLFP), and utilizes a 3.0 or 3.5 mm polytetrafluoroethylene (PTFE) graft sutured to the right innominate artery before bypass.70 This graft serves as the arterial inflow during bypass, and as a modified Blalock-Taussig shunt if needed after bypass. A standard arterial cannula is placed in the distal end of the PTFE graft, and a single venous cannula in the atrium. Full-flow bypass is instituted in this manner, the patient is cooled, usually to deep hypothermic temperatures, and during the period of aortic reconstruction, snare is placed around the base of the right innominate, left carotid, and left subclavian arteries, as well as the descending thoracic aorta. The brain is perfused via the right innominate artery and right vertebral artery (via the right subclavian artery), and the circle of Willis to the left cerebral hemisphere. Bypass flow rates during this technique are less than full flow, and have ranged from 20 to 90 mL/kg/minute. Neurologic monitoring in the form of near-infrared cerebral oximetry and transcranial Doppler ultrasound have been utilized to determine adequate flow during RLFP (see Chapter 8).71 Regional low-flow cerebral perfusion delivers oxygenated blood to both cerebral hemispheres,72 and also has the potential advantage of providing some limited blood flow to subdiaphragmatic visera in the neonate, through an extensive arterial collateral system.73 Using RLFP, the period of DHCA during the Norwood stage I palliation is limited to that needed for atrial septectomy and moving the cannula to the neoaorta after its reconstruction, a total of less than 10 minutes. Despite the theoretical advantages of selective cerebral perfusion, to date there are no published outcome studies comparing it to DHCA.

**Discontinuation of cardiopulmonary bypass**

When weaning from CPB, blood volume is assessed by direct visualization of the heart and monitoring right atrial or left atrial filling pressures. When filling pressures are adequate, the patient fully warmed, acid-base status normalized, hematocrit optimized, heart rate adequate and sinus rhythm achieved, the venous drainage is gradually occluded and the patient can be weaned from bypass. The arterial cannula is left in place so that a slow infusion of residual pump blood can be used to optimize filling pressures. Myocardial function is assessed by direct cardiac visualization and either a transthoracic left or right atrial catheter, a percutaneous internal jugular catheter, or by the use of intraoperative echocardiography. Pulse oximetry can also be used to assess the adequacy of cardiac output,74 systemic arterial saturation, or the inability of the oximeter probe to register a pulse may be a sign of very low output and high systemic resistance.75 After the repair of complex congenital heart defects, the anesthesiologist and surgeon may have difficulty separating patients from CPB. Under these circumstances, a diagnosis must be made and includes: (i) an inadequate surgical result with a residual defect requiring repair; (ii) pulmonary artery hypertension; and (iii) right or left ventricular dysfunction. Two general approaches are customarily used, either independently or in conjunction with one another. An intraoperative “cardiac catheterization” can be performed to assess isolated pressure measurements from the various great vessels and chambers of the heart (i.e. catheter pullback measurements or direct needle puncture to evaluate residual pressure gradients across repaired valves, sites of stenosis and conduits, and oxygen saturation data to examine for residual shunts).76 Alternatively, echo-Doppler may be used to provide an intraoperative image of structural or functional abnormalities to assist in the evaluation of the postoperative cardiac repair.77,78 If structural abnormalities are found, CPB can be reinstituted and residual defects repaired prior to leaving the operating room. Leaving the operating room with a significant residual structural defect adversely affects survival and increases morbidity.77,78 The echo-Doppler can rapidly identify right and left ventricular dysfunction and suggest the presence of pulmonary artery hypertension. In addition, echo-Doppler can identify regional wall motion abnormalities due to ischemia or intramyocardial air that will direct specific pharmacological therapy and provide a means of assessing the results of these interventions (see Chapter 7).79
The inflammatory process and the effects of cardiopulmonary bypass

Cardiopulmonary bypass leads to the release of inflammatory and anti-inflammatory mediators. Exposure of blood elements to the extracorporeal circuit, hypothermia, tissue injury, reperfusion, and non-pulsatile flow all may contribute to mediator release. Patients with severe cyanosis may also have elevated levels of proinflammatory cytokines preoperatively. Studies have shown that some reduction in the inflammatory reaction may be possible by pre-treating the patient with dexamethasone, and the use of modified ultrafiltration (MUF) has shown reduction of inflammatory mediators as well as other benefits. Interleukin 6 (IL-6), IL-8 and tumor necrosis factor (TNF) have all been shown to increase in the bypass and post-bypass period; their levels are reduced by hemofiltration on bypass.80

Glucose regulation

In recent years, a substantial amount of clinical and experimental data has shown conclusive evidence of the detrimental effect of hyperglycemia during complete, incomplete, and focal cerebral ischemia.81–83 The role of glucose in potentiating cerebral injury appears to be due to two factors: ATP utilization and lactic acidosis.84,85 The anaerobic metabolism of glucose requires phosphorylation and the expenditure of two molecules of ATP before ATP production can occur. This initial ATP expenditure may result in a rapid depletion of ATP and may explain why hyperglycemia worsens neurologic injury. Lactic acidosis is also important in glucose-augmented cerebral injury. An important role, however, may be as a glycolytic enzyme inhibitor. Lactate slows anaerobic ATP production, by inhibiting glycolysis immediately after ATP is consumed in the phosphorylation of glucose.86

Hyperglycemia

Although a strong scientific argument can be made for the detrimental effects of hyperglycemia during ischemia, there is very little evidence supporting worsening neurologic outcome from hyperglycemia during CPB and/or DHCA in children. A retrospective review of 34 children undergoing DHCA suggested a worse neurologic outcome in the hyperglycemic children; however, the results were reported as a non-significant statistical trend.87 A pathologic review of acquired neurologic lesions in patients undergoing the stage I repair of hypoplastic left heart syndrome suggested hyperglycemia as a significant associated finding in patients with extensive cerebral necrosis or intraventricular hemorrhage. Although associated, a host of other potentially damaging factors (e.g. periods of hypoxia, low diastolic and systolic pressure, and thrombocytopenia) were statistically associated with the observed neuropathology.88 Since hyperglycemia accompanies a generalized stress response, the literature has failed to distinguish whether glucose directly contributes to neurologic injury or merely serves as a marker for a high-risk population who ultimately suffer neurologic insult as a result of other factors.

Hypoglycemia

Hypoglycemia is a frequent concern in neonates during the perioperative period. Reduced hepatic gluconeogenesis coupled with decreased glycogen stores place the newborn at increased risk of hypoglycemic events. In newborns with CHD, reduced systemic perfusion (e.g. critical coarctation, hypoplastic left heart syndrome, critical aortic stenosis) may result in worsening hepatic biosynthesis, further impairing glucose production. These patients may be fully dependent on exogenous glucose; therefore, it is not uncommon for them to require 20–30% dextrose infusions to maintain euglycemia in the pre-bypass period. Older children are not immune to hypoglycemic events and are therefore susceptible to hypoglycemic-induced neurologic injury. Patients with low cardiac output states (cardiomyopathies, pre-transplant patients, critically ill postoperative patients) requiring reoperation and substantial inotropic support are at risk of reduced glycogen stores and intraoperative hypoglycemia.89

The impact of hypoglycemia during bypass is further complicated by the consequences of hypothermia, carbon dioxide management, and other factors that may modify normal cerebrovascular responses during bypass. In a dog model, insulin-induced hypoglycemia to 30 mg/dL did not alter the EEG findings; however, after 10 minutes of hypocapnic hypoglycemia, the EEG became flat.90 When regional blood flow was examined in these animals, cortical and hippocampal blood flow remained normal, whereas other regions of the brain had reduced flow. The loss of EEG activity from hypoglycemia alone does not normally occur above glucose levels of 8 mg/dL.90

During deep hypothermic CPB and DHCA, CBF and metabolism are altered. The additive effect of hypoglycemia, even if mild, may cause alterations in cerebral autoregulation and culminate in increased cortical injury.88,91 The common practice of using hyperventilation to reduce pulmonary vascular resistance in neonates and infants during weaning from CPB and in the early post-bypass period could further exacerbate hypoglycemic injury. Glucose monitoring and rigid maintenance of euglycemia are an important part of CPB management in the congenital heart patient.

Renal effects

After CPB, the combined effects of hypothermia, non-pulsatile
perfusion, and reduced mean arterial pressure causes release of angiotensin, renin, catecholamines, and antidiuretic hormone. These circulating hormones promote renal vasoconstriction and reduce renal blood flow. Yet despite the negative impact of CPB on renal function, studies have been unable to link low-flow, low-pressure, non-pulsatile perfusion with postoperative renal dysfunction. The factors that best correlate with postoperative renal dysfunction are preoperative renal dysfunction and profound reductions in post-CPB cardiac output. Preoperative factors include primary renal disease, low cardiac output, and dye-related renal injury after cardiac catheterization.

The incidence of acute renal insufficiency after pediatric cardiac surgery is 3–8%. Multiple causative factors are involved whose final common pathway is oliguria and an elevated serum creatinine. Diuretics have been the mainstay of promoting urine flow after pediatric CPB. Furosemide in a dose of 1–2 mg/kg and/or ethacrynic acid 1 mg/kg every 4–6 h induces a diuresis and may reverse renal cortical ischemia associated with CPB. After DHCA, it is not unusual to observe a 24-h period of oliguria or anuria that resolves over the next 12–24-h period. The use of diuretics is effective only after these patients have initiated spontaneous urine output.

Glomerular filtration rate, creatinine clearance, and medullary concentrating ability are substantially reduced in neonates and young infants. Therefore, the use of CPB in these patients is associated with greater fluid retention than is typically seen in older children and adult patients. The net result may be increased total body water, increased organ weight (e.g. lungs, heart), and greater difficulty with postoperative weaning from ventilatory support. The use of ultrafiltration during rewarming or after CPB is effective in reducing total body water, limiting the damaging effects of CPB, and decreasing the postoperative ventilation period.

Pulmonary effects

While cardioplegia protects the heart, there is no parallel protection afforded the lung during bypass. Pulmonary dysfunction is common after CPB and its pathogenesis is poorly understood. In broadest terms, lung injury is mediated in one of two ways: first, an inflammatory response due to leukocyte and complement activation, and, secondly, a mechanical effect culminating in surfactant loss, atelectasis with resultant ventilation-to-perfusion mismatch, loss of lung volumes, and altered mechanics of breathing.

Pulmonary function after CPB is characterized by reduced static and dynamic compliance, reduced functional residual capacity, surfactant deficiency and an increased A–a gradient. Atelectasis and increased capillary leak due to hemodilution, and hypothermic CPB are the most likely etiologies. Hemodilution reduces circulating plasma proteins, reducing intravascular oncotic pressure, and favors water extravasation into the extravascular space. Hypothermic CPB causes complement activation and leukocyte degranulation. Leukocytes and complement are important in causing capillary–alveolar membrane injury and microvascular dysfunction through platelet plugging and release of mediators which increase pulmonary vascular resistance. The technique of MUF may reduce lung water and pulmonary morbidity during the postoperative period.

Neurologic effects

The true incidence and severity of neurologic injury related to CPB is difficult to determine, as injury may have occurred due to the lesions or an event in the perinatal period that can be difficult to recognize preoperatively. Furthermore, neurodevelopmental abnormalities in children with CHD may be due to one or all of the following: genetic or metabolic factors, the cardiac lesions themselves, the stresses of the perinatal period with a greatly reduced cardiac reserve, or direct injury from the CPB/perioperative interventions. Injuries related to CPB may include intracranial hemorrhage, embolic injury, inadequate preservation during periods of low flow or total circulatory arrest, and reperfusion-related injuries. Injury may include stroke, developmental delay, and seizure activity. Attempts to reduce injury caused by CPB have included filters, membrane oxygenators, pulsatile perfusion, and pharmacologic additives. Filters may be used to reduce bubbles, thrombi, emboli, or leukocytes. Only a few years ago, bubble oxygenators were standard practice in major institutions, without the use of arterial line filters. However, this practice has been abandoned because a significant reduction in the number of cerebral emboli can be demonstrated using membrane oxygenators and arterial filters. Leukocyte depletion has been advocated as an adjunct in order to reduce morbidity related to the inflammatory response. In a piglet study, no benefit to CBF was noted with the use of a leukocyte depleting filter. For infants, there was no significant benefit noted when undergoing bypass with the aid of a leukocyte filter.

Use of modified ultrafiltration

The overall morbidity and mortality after cardiac surgery in children is influenced by the effects of CPB. During the initiation of CPB considerable hemodilution occurs.

This hemodilution is the result of the priming volume required for the CPB circuit. Under many circumstances this hemodilutional effect is intentional, decreasing blood viscosity and thereby preventing sludging when the patient is cooled to temperatures below 20°C. After CPB, hemodilution is associated with tissue edema and organ dysfunction. Because blood elements are exposed to the non-endothelialized
In addition, the hematocrit is raised after CPB enhancing oxygen delivery to the tissues. Secondly, MUF has been shown to remove some of the deleterious vasoactive substances associated with the inflammatory response to CPB. This effect is mediated by reducing circulating cytokines, which are associated with capillary leak syndrome. Examination of the ultrafiltrate shows that it contains low molecular weight, inflammatory mediators including C3A, C5A, IL-6A, IL-8A, TNF, myocardial depressant factor, and various other cytokines. Several studies have shown that compared to control patients, patients that have MUF after CPB have substantially less total body water, less complement, and IL release, require less blood transfusions, and show a faster recovery of systolic blood pressure. Other studies have shown direct clinical benefit after ultrafiltration; MUF has been shown to increase left ventricular systolic function, decreasing end-diastolic pressure, thereby improving left ventricular compliance. Modified ultrafiltration improves cerebral metabolism, which may reduce and reverse the known deleterious effects of DHCA. Modified ultrafiltration reduces postoperative blood use, chest tube drainage, plural effusions, and hospital stay in patients after cavopulmonary operations.

An alternative to MUF is conventional filtration during the rewarming period of CPB. In an experimental model examining MUF vs. conventional ultrafiltration, MUF alone was effective in reducing weight gain and myocardial edema, and was associated with improving left ventricular function. Outcomes with MUF vs. conventional ultrafiltration are not different with regard to fluid balance, hematocrit, mean arterial pressure, left ventricular function, duration of ventilation, intensive care or hospital stay, or mortality. Possible
complications of MUF include air embolus, patient cooling during ultrafiltration, and bleeding.\textsuperscript{113} These theoretical and technical potential complications appear not to be of substantial concern. It is the view of most groups that the benefits of MUF far exceed the risk.\textsuperscript{114}

**Stress response and cardiopulmonary bypass**

The release of a large number of metabolic and hormonal substances including catecholamines, cortisol, growth hormone, prostaglandins, complement, glucose, insulin, β-endorphins, and other substances characterizes the stress response during hypothermic CPB.\textsuperscript{123–125} The likely causes for the elaboration of these substances include contact of blood with the non-endothelialized surface of the pump tubing and oxygenator, non-pulsatile flow, low perfusion pressure, hemodilution, hypothermia, and response to surgical stress. Other factors that may contribute to elevations of stress hormones include delayed renal and hepatic clearance of proinflammatory mediators during hypothermic CPB, myocardial injury, and exclusion of the pulmonary circulation from bypass. The lung is responsible for metabolizing and clearing many of these stress hormones. The stress response generally peaks during rewarming from CPB. There is strong evidence that the stress response to surgical trauma can be blunted through the use of high dose opioid anesthesia.\textsuperscript{123–125}

It is unclear at what level elevated circulating stress hormones become detrimental, since this is a normal neonatal adaptive response. There is little question that these substances could mediate undesirable effects such as myocardial damage (catecholamines), systemic and pulmonary hypertension (catecholamines, prostaglandins), pulmonary endothelial damage (complement, prostaglandins), and pulmonary vascular reactivity (thromboxane). The benefits of controlling the stress response with fentanyl in premature infants undergoing PDA ligation and with sufentanil in neonates with complex CHD has been demonstrated.\textsuperscript{126,127} Although blunting the stress response seems warranted, there is additional evidence suggesting that the newborn stress response, especially the endogenous release of catecholamines, may be an adaptive metabolic response necessary for survival at birth.\textsuperscript{128} Thus the complete elimination of an adaptive stress response may not be desirable. To what extent acutely ill neonates with CHD are dependent on their stress response for maintaining hemodynamic stability is currently unknown.

It is therefore prudent to maintain a depth of anesthesia adequate to attenuate the stress response, but to attempt to block the response all together may not be necessary. Acceptable anesthesia during CPB may be best accomplished by either the continuous administration of an inhalation anesthetic via a vaporizer connected to the pump oxygenator, careful titration of incremental doses of opioids, or the precise administration of an opioid or opioid and benzodiazepine by a continuous infusion technique. Primary opioid anesthetic techniques result in reduced stress hormone release and decreased postoperative metabolic acidosis and lactate production when compared with primary halothane anesthesia, and are therefore a preferred technique in complex CHD.\textsuperscript{126} If depth of anesthesia is accomplished by the administration of large doses of opioids (e.g. fentanyl or sufentanil), postoperative mechanical ventilation will be necessary. By contrast, residual levels of inhalation anesthetic drugs (e.g. halothane or isoflurane) can produce transient myocardial depression at the termination of CPB, complicating separation from CPB.
In conclusion, there have been dramatic improvements in the morbidity and mortality for congenital heart surgery in neonates, infants and children. While much of this success has been due to improved surgical techniques, preoperative assessment, and postoperative care, nonetheless our understanding of the pathophysiologic effects of CPB and their reduction have also contributed to this success. Continued improvements in perfusion techniques and strategies are expected to further improve outcomes during and after pediatric cardiac surgery.

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CHAPTER 5 Cardiopulmonary bypass


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