Cardiopulmonary Bypass in Children and Infants

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Abstract

Surgical correction of congenital heart disease with cardiopulmonary bypass remains a challenge. Conduct and components of the cardiopulmonary bypass are important as they can attenuate peri- and postoperative morbidity. This chapter will discuss the different components of cardiopulmonary bypass as well as the impact of cardiopulmonary bypass on systemic inflammation and coagulation.

Keywords

Cardiopulmonary bypass · Pump · Cannulas · Host response · Systemic inflammation

Introduction

One of most important medical advances of the twentieth century was cardiac surgery. John Gibbon performed the first successful cardiac operation with cardiopulmonary bypass (CPB) (Edmunds 2003). Initially, the technology was complex and unreliable and was, therefore, slow to develop. The introduction of better and more hemocompatible polymers in combination with better pumps and monitoring has led to extraordinary improvements over the years. These improvements relate not only to equipment but also to a better understanding of the normal and pathological physiology.

Better design and improved conduct of pediatric cardiopulmonary bypass (CPB) are responsible for the fact that complex cardiac anomalies can nowadays corrected earlier in live with low mortality and morbidity. Nevertheless, initiating CPB in a neonate remains a challenge because of child's low blood volume, its often immature organs, and abnormal anatomical structures.

This chapter discusses some of the improvements as well as some of the remaining problems.

Components of CPB

Due to the heterogeneity of the pediatric population and the often abnormal anatomy, there is no such thing as a standard CPB circuit for neonatal and pediatric cardiac surgery. The most challenging components are vascular access, tubing, pump, and oxygenator choice.

Vascular Access

Since the start of CPB in the early 1950s of last century, nonoptimal vascular access was known

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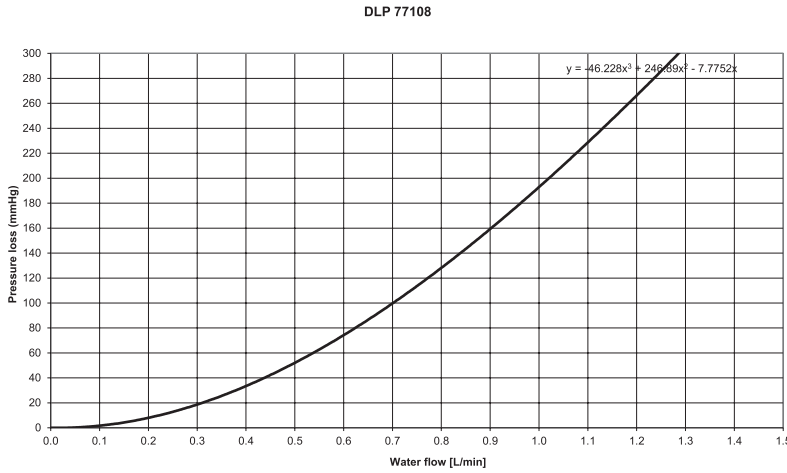
to have a direct impact on the hemodynamic support of a patient. From a physiological and anatomical point of view, the venous and arterial circulations are quite different. The arterial circulation is mainly a high pressure, low compliance system, whereas the venous system is a low pressure, high compliance system. Therefore, problems encountered in obtaining optimal arterial or venous access are different.

Inappropriate sizing of the arterial cannula, bleeding of the cannulation site, and rarer malposition of the cannula are potential problems with arterial cannulation. A too small cannula diameter leads to high shear stress and pressure drop over the cannula tip, which creates hemolysis and activates leukocytes and blood platelets. In addition, the high blood velocity inside the arterial cannula creates a jet inside the aorta causing selective perfusion, while the Venturi effect might steal blood from the brain vessels. On the other hand, a too large cannula will cause partial obstruction of the vessel lumen and increases afterload for the heart during weaning of CPB. High resistance inside the cannula or arterial line is less of a problem as the cannula is located downstream of the arterial blood pump. Many centers determine arterial cannula diameter empirical based upon historical experience. This is because manufacturers in general provide pressure–flow curves using water instead of blood or a blood analog. As water has a lower viscosity than blood, this can lead to major bias, especially in patients with an abnormal hematocrit or patients undergoing hypothermic cardiac surgery. In order to overcome this problem and to have a better estimate of the pressure–flow characteristics of a given cannula, a simple technique has been proposed, which is represented in (Fig. 1) (De Wachter et al. 2002).

Assessing access of the venous side is more complex due to boundary conditions that are more stringent. Venous return toward the heart depends upon the pressure difference between the mean circulatory filling pressure and the pressure in the right atrium. This pressure difference is relatively small, 7 mmHg (Guyton et al. 1954, 1957, 1962), and decreases with increases in right atrial pressure. The smaller the pressure difference, the more it jeopardizes venous drainage.

Venous vascular access connects wide, low-resistance, collapsible blood vessels with smaller diameter, stiff, artificial conduits of known physical characteristics. The smaller diameter of both venous line and venous cannula, compared to the native veins, requires a higher pressure difference than the physiological pressure difference to obtain optimal venous drainage (Galletti and Brecher 1962). The magnitude of that increase in pressure difference for obtaining optimal drainage depends on tubing diameter, tubing length, and blood viscosity (Ni et al. 2001). The latter depends on both hematocrit and temperature. Several methods are available to increase this pressure difference. Creating an additional negative pressure between cannula tip and venous reservoir increases the pressure difference. Placing the venous reservoir lower than the patient thus creating a siphon, due to the hydrostatic column between patient and reservoir, or applying a vacuum source to the venous reservoir are both used to achieve this. The latter has the additional advantages that the venous reservoir can be positioned at the level of the patient what significantly reduces the length of the tubing and that the amount of negative pressure is adaptable. Increasing negative pressure augments venous drainage in a linear manner while resistance remains more or less constant. However, excessive negative pressure is avoided as at a certain point a further increase in negative pressure leads to partial or full collapse of the vein, with no further increase in blood flow and, therefore, resistance will start to increase (Galletti and Brecher 1962). Correct choice of a venous cannula is critical, as it represents the smallest diameter and, thus, the highest resistance. Reducing its diameter by 50% reduces flow to 1/16th of the original flow. In addition, the length of the smallest part of the cannula diameter is important, doubling the length decreases flow by 50%. The high velocity inside the cannula in opposition to the lower velocity in the blood vessel creates a Venturi effect at the cannula tip and its side holes. As such, the ratio between the diameter of the vein and the diameter of the cannula is a point of attention. According to Galetti, this ratio should be around 0.5 in order to

Pressure flow curve (water) Medtronic DLP 77108 (provided by the manufacturer)



We can represent these data by a parabolic fit: $\Delta P_{water} = a \cdot Q_{water}^{2} + b \cdot Q_{water}$ In the example above we obtain: $\Delta P_{water} = 166.98 \cdot Q_{water}^{2} + 23.64 \cdot Q_{water}$

In order to obtain the values for blood with a given hematocrit and temperature we need to rescale the coefficients with ratios of density and dynamic viscosity:

$$a_{blood} = a_{water} \cdot \frac{\rho_{blood}}{\rho_{water}} \qquad b_{blood} = b_{water} \cdot \frac{\mu_{blood}}{\mu_{water}}$$

Calculate density and viscosity for water and blood

$\rho_{water} = 997 \frac{kg}{m^3}$ water density

$\eta_{water} = 0.001 \frac{kg}{m \cdot s}$ water viscosity at 20°C

Blood characteristics during cardiopulmonary bypass

$Hct := 25\%$ Hematocrit [%]

$T_{blood} := 32$ Arterial blood temperature [°C]

$$\rho_{blood} = 1.09 \frac{gm}{cm^3} \cdot Hct + 1.035 \frac{gm}{cm^3} \cdot (1 - Hct)$$

$\rho_{blood} = 1.049 \times 10^3 \frac{kg}{m^3}$ Blood density during CPB

$$\eta_{plasma} = \frac{\exp\left[-5.64 + \frac{1800}{(T_{blood} + 273)}\right]}{100} \cdot poise$$

Fig. 1 Method for conversion of water pressure flow curve into blood pressure flow curve

$$\eta_{blood} = \eta_{plasma} \cdot \exp(2.31 \cdot Hct) \qquad \eta_{blood} = 2.314 \cdot cpoise$$

Calculate ratios

$$\rho_{ratio} = \frac{\rho_{blood}}{\rho_{water}} = 1.052 \qquad \eta_{ratio} = \frac{\eta_{blood}}{\eta_{water}} = 2.314$$

What is the pressure drop over a 77108 DLP cannula during CPB at a blood flow of 0.8 L/min?

$Q := 0.8$ Flow in L/min

$$\Delta P_{water} := 166.98 \cdot Q^2 + 23.64 \cdot Q = 126$$

$$\Delta P_{blood} := 166.98 \cdot \rho_{ratio} \cdot Q^2 + 23.64 \cdot \eta_{ratio} \cdot Q = 156$$

Fig. 1 (continued)

avoid collapse of the vein around the side holes of the cannula (Galletti and Brecher 1962). Finally, also cannula and tip design (De Somer et al. 2002) influence drainage efficiency.

In children, vacuum-assisted venous drainage (VAVD) is becoming more and more the standard. This technique applies vacuum on the venous reservoir in order to increase the pressure differential (Durandy 2009a, b; Durandy and Hulin 2006). Using VAVD to augment venous drainage in case of malposition of one or more venous cannula(s) is avoided. Under such conditions, VAVD increases resistance in the cannula with marginal or no increase in drainage. Subsequently, it generates higher blood velocities over the nonblocked openings of the cannula. Finally, it increases shear stress and leads to an increase in hemolysis. Before applying any form of assisted venous drainage, one should check proper cannula placement. After this check, one can use assisted venous drainage in cases where one wants to reduce priming volume by placing the oxygenator at the same height as the patient or by using a smaller diameter venous line or by combining both strategies (Pappalardo et al. 2007).

Optimal negative venous drainage pressure for VAVD varies between −30 and −80 mmHg depending at which location pressure is measured. It is good practice to measure the negative pressure as it gives an estimate of the pressure at the cannula tip and helps in preventing vein collapse. Vein collapse will occur once the negative pressure at the cannula tip exceeds −4 mmHg. Unfortunately, the pressure at the cannula tip is difficult to obtain in clinical practice so most perfusionists measure the pressure somewhere between the cannula and the reservoir top. As a result, the obtained pressure value is the sum of the resistance in the cannula and the venous line between the measurement point and the cannula tip. The latter might explain the large differences in reported values. Table 1 is an illustration that shows for 3/16 in. tubing and 1/4 in. tubing, the differences in blood velocity and required pressure drop for a required venous drainage of 1 L/min.

In general, assisted venous drainage is helpful in all cases where siphon drainage alone is insufficient due to high resistances in the venous cannula and venous line, in cases where venous pressure remains high despite proper cannula position and in those cases where the operative field is not dry (Murai et al. 2005).

Optimizing arterial and venous vascular access is mandatory, as it determines maximum

Table 1 Fluid dynamical characteristics of venous tubing

Tubing diameter (7.in.)	3/16	1/4
Blood flow (L/min)	1	1
Pressure difference (mmHg)	51	11
Velocity (cm/s)	94	53
Reynolds number	2019	1514
Wall shear stress (dynes/cm^2)	54	15

Data generated with: Hematocrit: 25%; Temperature: 32°C; Tubing length: 150 cm

Table 2 Impact of tubing diameter on fluid dynamics

Tubing diameter (in.)	1/8	3/16	¼	3/8
Volume (mL/m)	8	18	32	71
Pressure difference (mmHg/L)	234	54	15	5
Velocity (cm/s)	210	94	53	23
Reynolds number	3028	2019	1514	1009
Wall shear stress (dynes/cm^2)	247	54	15	6

Data generated with: Hematocrit: 25%; Temperature: 32°C; Tubing length: 150 cm; Blood flow: 1 LPM

blood flow and thus oxygen delivery to the organs. Malposition of an arterial cannula can obstruct cerebral blood supply or cause a preferential flow into the descending aorta leading to an inappropriate oxygen supply to the brain. Alternatively, obstruction of the superior vena cava cannula may decrease cerebral venous drainage and potentially lead to brain dysfunction. Routine monitoring of cerebral oxygenation by near-infrared spectroscopy (NIRS) is a valuable help for early detection of such problems (Gottlieb et al. 2006; Ginther et al. 2011; Redlin et al. 2011).

Tubing

Tubing in the CPB circuit interconnects all main components of the circuit. The most common used polymer is PolyVinyl Chloride (PVC) with exception of the tubing used in the pump boot, which is often silicone. In opposition to PVC, silicone is not temperature sensitive and maintains its diameter and hardness during cooling. Original PVC contained di-(2-ethylhexyl)-phthalate (DEHP) as plasticizer in order to make PVC flexible. Recent concerns with respect to the potential toxicity of DEHP (Greiner et al. 2012) result in the demand of many centers for DEHP-free PVC tubing for their pediatric circuits.

Length and size of the tubing will have a major impact on volume, shear stress, and pressure drop (Table 2), and the clinician will have to make choice based upon the clinical conditions.

Blood Pumps

Pumps classify into two main categories: displacement pumps and rotary pumps. Periodic volumetric changes of a working space characterize energy in displacement pumps. A classic example of a displacement pump is the roller pump. The working principle is that two rollers, placed opposite to another, "roll" the blood through a piece of tubing. In case of completely occlusion of the tubing by the rollers, the pump can generate both positive and negative pressures. Therefore, a roller pump is multifunctional as it is able to pump blood as well as aspirate blood. A roller pump is relatively independent of factors such as resistance and hydrostatic pressure head, encountered in the average CPB circuit. The output of an occlusive roller pump depends upon two main variables: the number of revolutions per min of the pump head and the internal diameter and length of the tubing in the pump head:

$$Q = \pi \cdot \text{radius}^2 \cdot \text{length} \cdot \text{RPM}$$

where RPM is the revolutions per minute.

A disadvantage of roller pumps is spallation (Briceno and Runge 1992; Peek et al. 2000). Due to the continuous compression of the tubing by the roller, the polymer of the tubing starts to weaken and to erode, resulting in generation of small particles (Briceno and Runge 1992; Peek et al. 2000; Kim and Yoon 1998). In order to control spallation, it is advocated to use a

dynamic occlusion setting of the pump rollers (Tamari et al. 1997). As neonatal and pediatric CPB circuits have high resistances due to the small diameter tubing, roller pumps remain the first choice. In larger children or young adults, one might prefer a rotary pump and more specific a centrifugal pump. Centrifugal pumps operate on the principle of moving fluid by creating a pressure gradient between inlet and outlet of the pump. The rotation of the pump rotor creates a vortex responsible for the pressure gradient. The vortex creates an area of low pressure in the center and an area of high pressure on the sides. The resulting rate of blood flow will depend upon the pressure gradient and the resistance at the outlet of the pump. The latter is a function of two variables: the CPB circuit (oxygenator, filter, tubing, and arterial cannula) and the systemic vascular resistance of the patient. A centrifugal pump is a pressure pump because the flow produced by a centrifugal pump directly depends on the pressure that the centrifugal pump rotor generates, which depends on the number of revolutions per minute (RPM) and the rotor design. In contrast to a roller pump, a centrifugal pump is afterload dependent and, thus, susceptible to changes in resistance in both circuit and patient. This affects forward flow and makes it necessary to use a centrifugal pump in conjunction with a flow sensor. Although a centrifugal pump, due to its nonocclusive working principle, has no spallation, high resistances after the pump may lead to high shear stresses and hot spots inside the pump head (Araki et al. 1995a, b; Ganushchak et al. 2006). As a centrifugal pump is nonocclusive, which can lead to back flow when the RPM are set too low. This is in particular important during the start and weaning of the CPB.

Oxygenator

The oxygenator is without doubt the most important component in the CPB circuit. It is not only responsible for exchanging oxygen and carbon dioxide but for the administration of volatile anesthetics. The oxygenator comprises an integrated heat exchanger that allows cooling and warming of the patient. A heat exchanger is indispensable as some extensive repairs may require hypothermia and or deep hypothermic circulatory arrest (DHCA). Most recent oxygenators are available with an integrated filter, thus, avoiding the need for a separate arterial line filter (Ginther et al. 2013; Lin et al. 2012). In pediatric surgery, most centers use an open venous reservoir with integrated cardiotomy. The latter filters and defoams blood aspirated from the surgical field. The main reason for choosing open systems lays in the fact that open systems allow assisted venous drainage, which is helpful in optimizing venous drainage and in reducing priming volume (Durandy 2013, 2015).

Nowadays, extra luminal hollow fiber membrane oxygenators are standard. For neonatal and pediatric usage, several sizes are available. The final decision which to use is usually made based upon priming volume, surface area, rated blood flow, and available connector sizes, all in relation with the size of the patient and the type of surgical repair. Table 3 shows the characteristics of some neonatal and pediatric oxygenators. Originally, the reference flow of a given oxygenator was defined by the Association for the Advancement of Medical Instrumentation (AAMI) as the flow rate at which normothermic whole blood having a hemoglobin content of 120 g/L, a base excess of 0, and a venous saturation of 65% increases its oxygen content by 45 mL oxygen/L blood. This proposed value offers sufficient safety in acyanotic children but could be insufficient in cyanotic children that often have a low venous saturation requiring a higher oxygen transfer. For this reason, design of contemporary pediatric oxygenators allows oxygen transfers up to 75 mL/L at the nominal maximum flow given by the manufacturer. As a result, the reference flow (AAMI conditions) can be much higher (Table 3) than the recommended flow. Based upon this characteristic, one could use a smaller oxygenator, with the resulting lower hemodilution and contact activation, in selected cases (Durandy 2010a).

Table 3 Characteristics of pediatric oxygenators

Oxygenator	Membrane surface area (m^2)	Membrane material	Maximum blood flow (L/min)	Reference blood flow (L/min)	Heat exchanger surface area (m^2)	Connections (in.)	Priming volume (mL)	Maximum reservoir volume (mL)
Terumo FX05	0.5	PP	1.5	2.5	0.035			
Liva nova D100[a]	0.22	PP	0.7	1	0.03	3/16–1/4	31	500
Liva nova D101[a]	0.61	PP	2.5	3.5	0.06	1/4	87	1500
Maquet neonatal quadrox-i	0.38	PP	1.5	N/A	0.07	3/16–1/4	40	800
Maquet pediatric quadrox-i	0.8	PP	2.8	N/A	0.15	3/16–1/4	99	1700
Medtronic pixie[a]	0.67	PP	2	N/A	N/A	1/4	48	1200
Medos hilite 1000[a]	0.39	PP	1	N/A	0.074	1/4	57	700
Medos hilite 2800[a]	0.8	PP	2.8	N/A	0.16	3/16–1/4	98	1600

PP microporous polypropylene, *PET* polyethylene terephthalate, *N/A* not available
[a] No integrated filter

Priming and Hemodilution

Total priming volume of a CPB circuit depends upon the selected components (De Somer et al. 1996a). It is sometimes more beneficial to select a smaller oxygenator that will function close to its maximal capacity for flow than selecting a large oxygenator that will function toward its lower level. However, independent of the choice of oxygenator size its priming volume is predefined. Priming volume taken by the tubing, on the other hand, is determined by its length and diameter and mainly controlled by the surgical team (Ni et al. 2001). The total amount of priming volume is important, as it determines the dilution of the blood components. Composition of the priming fluid is an important point of consideration as it determines the final blood composition after mixing with the child's blood. Excessive dilution of blood coagulation factors below 45% should be prevented by using fresh frozen plasma in the priming solution (Brauer et al. 2013). This is especially important in cyanotic children as they have in general a lower plasma volume or in children with complex repairs (Pouard and Bojan 2013). As many institutions do not routinely screen coagulation factors before cardiac surgery, some centers use preoperative fibrinogen concentration as a surrogate reference. Ideally, postdilution fibrinogen concentration should be above 1 g/L.

A large variation between centers exists for target hemoglobin values during CPB. Literature reports values as low as 50 g/L up to 100 g/L (Nicolas et al. 1994; Gruber et al. 1999). Due to a lack of sufficient randomized prospective studies (Wilkinson et al. 2014), it is still unclear what is the optimal hemoglobin concentration during CPB. In practice, one should not focus solely on hemoglobin concentration, as the final oxygen delivery (DO_2) toward the organs depends on both hemoglobin concentration and pump flow. Consequently, one can tolerate lower hemoglobin concentrations as long as vascular access allows for high pump flows, but when anatomical or technical limitations limit the maximum blood flow, a higher hemoglobin concentration might be desirable. Following case gives an example of

the above for a child with a body surface area of 0.22 m^2. If target minimum DO_2 at normothermia for the child is 340 mL/min/m^2, required blood flow is 564 mL/min at a hemoglobin of 100 g/L, but this blood flow needs to double to 1130 mL/min in order to achieve the same target DO_2 at a hemoglobin of 50 g/L. It is obvious that the latter is less evident.

There is no proven benefit for the prophylactic use of a combination of fresh frozen plasma and packed red cells without solid clinical arguments (Wilkinson et al. 2014; Desborough et al. 2015).

Apart from the impact of the priming solution on blood coagulation and oxygen transport, its composition will also affect colloid oncotic pressure and electrolyte balance. There is evidence that maintaining a higher colloid oncotic pressure in neonates, by adding albumin, results in less fluid overload at the end of CPB in comparison to a pure crystalloid priming solution (Pouard and Bojan 2013).

Reflection on the composition of priming volume becomes even more important as more and more centers prefer normothermic conditions even for complex repairs such as transposition of the great arteries (Durandy 2010b).

In the early days of cardiac surgery, clinicians believed hemodilution was beneficial for the cardiac surgical population as it helped to reduce or avoid blood prime. Despite this advantage, it became obvious over the years, due to better monitoring techniques and extensive research, that hemodilution has its limits. Hemodilution will have a linear impact, when blood flow is constant, on total oxygen content. Diluting a patient with a hematocrit of 40% to a hematocrit of 20% decreases oxygen content per liter blood by 50%. In healthy patients, not on CPB, an increase in cardiac output compensates for this loss in oxygen-carrying capacity, facilitated by the reduced viscosity caused by the hemodilution. However, on CPB many centers use a fixed blood flow per square meter of body surface, typically between 2.2 and 3.0 L/min/m^2. Maintaining a fixed flow during excessive hemodilution may jeopardize oxygen delivery to the tissue, as the physiological compensatory increase in flow is absent.

Another disadvantage of hemodilution is the decrease in viscosity and plasma proteins. The decrease in viscosity leads to a loss in capillary density in the microcirculation (Tsai et al. 1998). Recent research showed that using fluids with a higher viscosity attenuates this negative effect. Increasing plasma viscosity correlates directly with increased perivascular nitric oxide concentration. Higher concentrations of local nitric oxide dilate and increase vascular density of the microcirculation in the organs (Tsai et al. 2005). Although the fluids used in this study had a viscosity higher than those commercially available, it seems favorable to use priming solutions with a higher viscosity (Manduz et al. 2008). A decrease in plasma proteins results in decreased plasma colloid oncotic pressure. Such a reduction may play an important role in the fluid accumulation observed after CPB. Tissue edema is secondary to increased capillary permeability caused by the systemic inflammatory response induced by CPB. In neonates, the combination of increased capillary permeability and the decrease of the colloid oncotic pressure seems to worsen the situation (Jonas 2004). Maintaining colloid oncotic pressure during bypass has been linked to decreased myocardial edema (Foglia et al. 1986) and reduced fluid accumulation. Lower fluid accumulation was associated with a shorter stay in intensive care and a lower mortality (Haneda et al. 1985).

Metabolism During CPB

The primary function of CPB is to maintain circulation in order to prevent organ dysfunction during and after surgical repair. Adequate oxygen delivery (DO_2) is one of the most important variables in achieving this goal. Oxygen delivery depends upon hemoglobin concentration and pump flow. In adults, it has been demonstrated that there exists a close correlation between the lowest hematocrit on bypass and morbidity (Habib et al. 2003). However, it is questioned whether this is due to the low hematocrit or due to a low DO_2 (Ranucci et al. 2005), which is the

combination of both hematocrit and blood flow. Recent research during normothermic (>32 °C) adult cardiac surgery showed that maintaining DO_2 above 280 mL/min/m^2 reduces the incidence of acute kidney injury from 29.8% to 12.1%. Transferring this value to the more heterogeneous pediatric population is not evident due to:

- Higher metabolism in neonates
- Presence of both cyanotic and noncyanotic children
- A broader range of hypothermia used during congenital heart surgery
- Different acid–base strategies (pH-stat versus α-stat)
- Existence of large intra- or extracardiac shunts

Despite those difficulties, recent research has established a cutoff value for DO_2 of 340 mL/min/m^2 at normothermia in neonates undergoing congenital cardiac surgery (Bojan et al. 2020; Reagor et al. 2020; Zhang et al. 2021). This value is reduced by 22 mL for each degree Celsius the patient is cooled. Maintaining DO_2 above this critical value attenuates the occurrence of hyperlactatemia and reduces the risk for AKI by 2.5 times. This underlines that when a center prefers a lower hematocrit during CPB, it must be compensated for by a higher blood flow. On the other hand, when anatomical limitations limit the size of the vascular access cannulas one should keep hematocrit higher during CPB.

The microcirculation is the ultimate destination of red blood cells to transport oxygen to the tissue cells. Its success defines the primary function of the cardiovascular system. Inside the microcirculation, there are two main determinants of oxygen transport to the tissue: convective transport of red blood cells to the capillaries and the passive diffusion of oxygen leaving the RBC to the mitochondria in the cells (Ince 2014). The formula for convective transport is:

$$DO_2 = \left[\left(\text{cte} \cdot \text{Hb} \cdot \text{S}\right) + \left(PO_2 \cdot k\right)\right] \cdot Q$$

where$Q$ is the blood flow [mL/min];
Hb is the hemoglobin concentration [g/mL];
cte = [1.34 mL/g];
S is the amount of oxygen bound to hemoglobin [%];
PO_2 is the partial oxygen tension [mmHg]; and
k is the oxygen solubility [mL/mL].

For a long time, the convective part of oxygen transport, being blood flow, was considered the sole factor to supply the microcirculation with oxygen. Today, one recognizes that the diffusion component of oxygen transport is at least as important as the convective component. The further away a tissue cell is from the oxygen-carrying red blood cell, for example, by excessive hemodilution (Atasever et al. 2011) or edema, the less time, even in the presence of sufficient flow within the capillaries, the oxygen has in reaching these cells. Diffusive capacity of the microcirculation depends upon the functional capillary density (FCD), which represents the number of capillaries in a given volume of tissue. Fick's law describes it as the product of the difference between the partial pressure of oxygen at the red blood cell minus that at the mitochondria, times the diffusion constant divided by the distance between the red blood cell and the mitochondria (Ince 2014; Boerma and Ince 2010). Immediately after and during CPB, there is a loss of FCD. The percentage loss depends upon the degree of hemodilution, viscosity, and the filling status of the microcirculation. In case of a decreased FCD, more cells become dependent from the oxygen supply delivered by a single capillary (Krogh 1919). Increasing cardiac output alone may be insufficient to correct the resulting tissue hypoxemia, and often there is need for microcirculatory recruitment procedures. Potential treatment options besides increasing flow are increasing partial CO_2 tension, increasing mean arterial pressure, and maintaining a normal viscosity. In order to validate the efficiency of the different options, NIRS is extremely helpful as it helps to define the pressure range in which the autologous regulation is maintained (Moerman et al. 2013).

A special group within the neonatal and pediatric CPB population is children with cyanotic heart disease. There is vivid debate on what is the best oxygenation strategy in this group, espe-

cially in the period before ischemia and during reperfusion of the myocardium after surgical repair. Maintaining high partial oxygen tensions in cyanotic patients at the beginning of CPB leads to reoxygenation injury with significant organ damage, including the myocardium, and triggers the systemic inflammatory response (Modi et al. 2002; del Nido et al. 1987, 1988; Caputo et al. 2014; Kagawa et al. 2014). One of the strategies proposed to avoid reoxygenation injury is the use of controlled reoxygenation. This technique targets an arterial partial oxygen tension (PaO_2) similar to the patient's preoperative oxygen saturation when starting CPB. Experimental models (Ihnken et al. 1995, 1998a) using this strategy showed less reoxygenation injury in adult patients (Ihnken et al. 1998b) and, more recently, in cyanotic pediatric patients with mixed pathologic features that are undergoing cardiac surgery (Caputo et al. 2009).

Another challenge is defining the best oxygenation strategy for children requiring deep hypothermia with circulatory arrest (DHCA) or hypothermia with low flow. Hypothermia slows down the metabolism. The relationship between cerebral metabolic rate for oxygen ($CMRO_2$) and temperature (McCullough et al. 1999) follows a log-linear model. However, even at a temperature of 20 °C, $CMRO_2$ is still 24% of baseline. Therefore, it is extremely important to ensure uniform cerebral hypothermia as it is critical for a successful outcome after DHCA. Cooling changes in oxygen binding to hemoglobin and in plasma solubility require special attention. Hypothermia shifts the oxygen dissociation curve (ODC) to the left. The P50 value, partial oxygen tension at which the hemoglobin is 50% saturated, is around 26.6 mmHg at 37 °C but will decrease to approximately 13 mmHg at 20 °C, making it more difficult to release hemoglobin-bound oxygen at tissue level. This has an important impact. At normothermia venous, oxygen saturation needs to decrease to 30% before $CMRO_2$ decreases to less than 90% of normal. However, in infants cooled to 17 °C venous oxygen saturation must be maintained at values greater than 95% to maintain $CMRO_2$ higher than 90% (Dexter and Hindman 1995). Due to this increase in hemoglobin's affinity for oxygen at 19 °C, 80% of the $CMRO_2$ will be no longer primarily provided by hemoglobin-bound oxygen but by dissolved oxygen (Dexter et al. 1997). In order to improve oxygen availability during DHCA, many centers use a pH-stat acid–base strategy. This approach targets a pH of 7.4 at the real blood temperature, e.g., 20 °C. The higher carbon dioxide content will shift the ODC more to the right, and P50 will increase from 13 mmHg to 15.3 mmHg. But pH-stat by itself is insufficient as the shift to the right is limited and needs companionship of measures to improve the amount of dissolved oxygen. Using hyperoxia is most effective. It is important to notice that the definition of hyperoxia in this context means a venous partial oxygen tension of >400 mmHg (Pearl et al. 2000). Increasing oxygen tension from 125 mmHg to 525 mmHg will increase the amount of soluble oxygen from 4 mL/L to 18 mL/L and increase safe DHCA time by 20 min in a child at 16 °C.

Because of the many variables involved, it remains a challenge to predict neurological outcome after DHCA or hypothermia with low flow. Children's Hospital Boston did an impressive amount of research in this domain looking at the impact of all variables discussed above. Based upon their research, the best approach for DHCA is the combination of hyperoxia with a higher hematocrit and pH-stat strategy. The hypothermia will decrease metabolic rate and, thus, increase the safe duration of DHCA, while the use of a higher hemoglobin and hyperoxia will allow for better hyperoxygenation of the brain before onset of DHCA. NIRS is a valuable tool for monitoring efficiency of hyperoxygenation and for monitoring remaining metabolism and oxygen consumption during DHCA. Depending on the degree of hyperoxygenation, the lower the metabolic rate, the longer it takes CMRO2 to reach a plateau with minimal oxygen extraction. The time between the onset of DHCA and the onset and duration of this plateau period are predictors of behavioral and histological evidence of injury after DHCA (Sakamoto et al. 2001).

Systemic Inflammation During CPB

Inflammation is the humoral and cellular protective response to injury (Davies and Hagen 1997). During cardiac surgery, a multifactorial systemic inflammatory reaction (SIRS) occurs. This reaction is triggered by almost every part of the procedure, starting with anesthesia (Gu et al. 2002), skin incision, and sternotomy, followed by the contact activation between blood and foreign surface of the CPB and later by the ischemia and reperfusion of the myocardium (Durandy 2014). Additional triggers are hypothermia and blood transfusions, which all affect the magnitude of the inflammatory response (Laffey et al. 2002). Activation of complement, coagulation, fibrinolysis, inflammatory cytokines, and cytodestructive mediators generated by white cells (Butler et al. 1993) are all part of SIRS. Initially, research to attenuate SIRS targeted systemic cytokines but it failed to link other host response systems to adverse clinical events (Landis 2009). Up to today, the clinical advances to attenuate SIRS have been disappointing.

Controlling Host Response

Despite systemic anticoagulation, Factor XII, fibrinogen, and globulins are absorbed onto the foreign surface of the CPB within seconds after initiation and generate thrombin in direct relation to CPB time (Brister et al. 1993; Boisclair et al. 1993). Activation of the coagulation cascade starts with tissue factor bearing white blood cells, such as monocytes. These will generate in response to injury small amounts of thrombin. This thrombin is sufficient to initiate hemostasis but not enough to cause thrombus formation (Monroe et al. 2002) as it can be rapidly scavenged by circulating antithrombin. However, in case of circulating activated platelets, thrombin will bind to them via the high-affinity thrombin receptor, protease-activated receptor-1 (PAR1), initiating several positive feedback loops. The latter is called the "amplification phase" and allows massive formation of thrombin generation that is essential for stable clot formation. When thrombin generation is not controlled during CPB, it may create both a prothrombotic risk to the grafted vessel as risk for systemic bleeding. The latter is due to the consumption of coagulation factors in combination with the unwanted activation of the platelet PAR1 receptor by thrombin (Landis 2009; Ferraris et al. 1998). The impact on platelet function by thrombin is an important cause of the clinical platelet deficit during and after CPB surgery and is witnessed by a drop in platelet count as a diminished capability to aggregate.

Proinflammatory activation of leukocytes and endothelial cells via bradykinin and PAR1 receptors expressed throughout the vasculature. (Kaplanski et al. 1997, 1998; Kamiya et al. 1993) is linked to kallikrein and thrombin and may explain some of the febrile and capillary leak symptoms seen after CPB (Landis 2009; Wachtfogel et al. 1995; Lidington et al. 2000). Inhibition of the proteolytic activation of PAR1 attenuates the proinflammatory activation of platelets and endothelial cells. (Day et al. 2006; Poullis et al. 2000). The beneficial effect of this approach was demonstrated in neonates with hypoplastic left heart syndrome, were the use of aprotinin improved survival after stage 1 repair (Tweddell et al. 2002).

Cardiopulmonary bypass activates the complement system via the classical pathway of C3, generated by IgM and IgG antibody adsorption by the CPB circuit (Landis et al. 2008). Several measures can help to control complement activation. Introduction of closed systems, smaller circuits, and coating of all foreign surface with a bioactive or biopassive coating all showed a small attenuation in complement and cytokine generation, but none of these measures could demonstrate major clinical improvements (De Somer et al. 2000; Eisses et al. 2007).

During the early phase of CPB, the direct contact between blood and foreign material leads to the generation of proinflammatory cytokines such as TNF-α, IL6 and IL8. This proinflammatory phase is followed by an anti-inflammatory phase, which occurs 2–24 h after initiation of CPB. It is characterized releasing anti-

inflammatory markers such as IL1 and IL10. The anti-inflammatory phase is mainly governed by the body (McBride et al. 1995).

The systemic host response depends also on leukocytes. Expression of the complement receptor CR3 on neutrophils and monocytes mediates leukocyte adhesion to polymers. Although phagocytosis of the polymers of the CPB circuit by these adhering cells is not possible, it will trigger the same cytodestructive inflammatory cytokine, protease, and reactive oxygen pathways that occur during genuine phagocytosis (Rothlein et al. 1994; Shappell et al. 1990). Another important source of oxidative stress is intravascular hemolysis, due to local areas of high shear stress in the CPB circuit (De Somer et al. 1996b). This shear stress will lead to the formation of free plasma hemoglobin. Another important source of free plasma hemoglobin generation is the aspiration of wound blood. The first defense mechanism against free plasma hemoglobin is haptoglobin, an inhibitor of free plasma hemoglobin. Once exhausted, free plasma hemoglobin can abrogate vasoprotective responses due to the scavenging of endothelial nitric oxide and may accumulate in the proximal tubules, causing direct renal injury, especially in patients with diabetes (Minneci et al. 2005). Peak oxidative stress due to hemolysis is mostly observed after the release of the cross-clamp as this is the moment when most wound blood is aspirated from the mediastinal and pleural cavities and precedes inflammatory cytokine generation (Christen et al. 2005). A significant contribution to the "systemic inflammatory response" may therefore be due to oxidative stress and loss of vascular nitric oxide responses secondary to hemolysis. Avoiding or controlling aspiration of blood from the surgical field will attenuate free plasma hemoglobin generation and activate blood platelets. Separating this blood from the systemic blood has shown to improve outcome (Aldea et al. 2002).

From the above, it is clear that we should replace the terminology systemic inflammatory response by a definition that is emphasizing the multisystemic etiology of this disorder such as systemic "host" response to surgery. Interventions should focus to target multiple effector pathways simultaneously. In order to increase knowledge, studies should better report the observed systemic host response. A consensus paper looking at the published research pointed out that better reporting should comprise (1) minimal CPB and perfusion criteria that may affect outcomes, (2) causal inflammatory markers that link exposures to outcomes, and (3) markers of organ injury that are practical to measure yet clinically meaningful (Landis et al. 2008).

Conclusions

Instituting CPB in a neonate or child for correction of congenital heart disease remains a challenge. Future research should focus on:

- Further miniaturization of the CPB circuit
- Improved vascular access
- Better strategies to control inflammation
- Better understanding of fluid homeostasis during and after CPB.

References

Aldea GS, Soltow LO, Chandler WL, Triggs CM, Vocelka CR, Crockett GI, et al. Limitation of thrombin generation, platelet activation, and inflammation by elimination of cardiotomy suction in patients undergoing coronary artery bypass grafting treated with heparin-bonded circuits. J Thorac Cardiovasc Surg. 2002;123(4):742–55.

Araki K, Taenaka Y, Masuzawa T, Tatsumi E, Wakisaka Y, Watari M, et al. Hemolysis and heat generation in six different types of centrifugal blood pumps. Artif Organs. 1995a;19(9):928–32.

Araki K, Taenaka Y, Wakisaka Y, Masuzawa T, Tatsumi E, Nakatani T, et al. Heat generation and hemolysis at the shaft seal in centrifugal blood pumps. ASAIO J. 1995b;41(3):M284–7.

Atasever B, Boer C, Goedhart P, Biervliet J, Seyffert J, Speekenbrink R, et al. Distinct alterations in sublingual microcirculatory blood flow and hemoglobin oxygenation in on-pump and off-pump coronary artery bypass graft surgery. J Cardiothorac Vasc Anesth. 2011;25(5):784–90.

Boerma EC, Ince C. The role of vasoactive agents in the resuscitation of microvascular perfusion and tissue oxygenation in critically ill patients. Intensive Care Med. 2010;36(12):2004–18.

Boisclair MD, Lane DA, Philippou H, Sheikh S, Hunt B. Thrombin production, inactivation and expression during open heart surgery measured by assays for activation fragments including a new ELISA for prothrombin fragment F1 + 2. Thromb Haemost. 1993;70(2):253–8.

Bojan M, Gioia E, Di Corte F, Berkia I, Tourneur T, Tourneur L, et al. Lower limit of adequate oxygen delivery for the maintenance of aerobic metabolism during cardiopulmonary bypass in neonates. Br J Anaesth. 2020;31024-4(19):S0007–912.

Brauer SD, Applegate RL 2nd, Jameson JJ, Hay KL, Lauer RE, Herrmann PC, et al. Association of plasma dilution with cardiopulmonary bypass-associated bleeding and morbidity. J Cardiothorac Vasc Anesth. 2013;27(5):845–52.

Briceno JC, Runge TM. Tubing spallation in extracorporeal circuits. An in vitro study using an electronic particle counter. Int J Artif Organs. 1992;15(4):222–8.

Brister SJ, Ofosu FA, Buchanan MR. Thrombin generation during cardiac surgery: is heparin the ideal anticoagulant? Thromb Haemost. 1993;70(2):259–62.

Butler J, Rocker GM, Westaby S. Inflammatory response to cardiopulmonary bypass. Ann Thorac Surg. 1993;55(2):552–9.

Caputo M, Mokhtari A, Rogers CA, Panayiotou N, Chen Q, Ghorbel MT, et al. The effects of normoxic versus hyperoxic cardiopulmonary bypass on oxidative stress and inflammatory response in cyanotic pediatric patients undergoing open cardiac surgery: a randomized controlled trial. J Thorac Cardiovasc Surg. 2009;138(1):206–14.

Caputo M, Mokhtari A, Miceli A, Ghorbel MT, Angelini GD, Parry AJ, et al. Controlled reoxygenation during cardiopulmonary bypass decreases markers of organ damage, inflammation, and oxidative stress in single-ventricle patients undergoing pediatric heart surgery. J Thorac Cardiovasc Surg. 2014;148(3):792–801 e8; discussion 0-1.

Christen S, Finckh B, Lykkesfeldt J, Gessler P, Frese-Schaper M, Nielsen P, et al. Oxidative stress precedes peak systemic inflammatory response in pediatric patients undergoing cardiopulmonary bypass operation. Free Radic Biol Med. 2005;38(10):1323–32.

Davies MG, Hagen PO. Systemic inflammatory response syndrome. Br J Surg. 1997;84(7):920–35.

Day JR, Taylor KM, Lidington EA, Mason JC, Haskard DO, Randi AM, et al. Aprotinin inhibits proinflammatory activation of endothelial cells by thrombin through the protease-activated receptor 1. J Thorac Cardiovasc Surg. 2006;131(1):21–7.

De Somer F, Foubert L, Poelaert J, Dujardin D, Van Nooten G, Francois K. Low extracorporeal priming volumes for infants: a benefit? Perfusion. 1996a;11(6):455–60.

De Somer D, Foubert L, Vanackere M, Dujardin D, Delanghe J, Van Nooten G. Impact of oxygenator design on hemolysis, shear stress, and white blood cell and platelet counts. J Cardiothorac Vasc Anesth. 1996b;10(7):884–9.

De Somer F, Francois K, van Oeveren W, Poelaert J, De Wolf D, Ebels T, et al. Phosphorylcholine coating of extracorporeal circuits provides natural protection against blood activation by the material surface. Eur J Cardiothorac Surg. 2000;18(5):602–6.

De Somer F, De Wachter D, Verdonck P, Van Nooten G, Ebels T. Evaluation of different paediatric venous cannulae using gravity drainage and VAVD: an in vitro study. Perfusion. 2002;17(5):321–6.

De Wachter D, De Somer F, Verdonck P. Hemodynamic comparison of two different pediatric aortic cannulas. Int J Artif Organs. 2002;25(9):867–74.

del Nido PJ, Benson LN, Mickle DA, Kielmanowicz S, Coles JG, Wilson GJ. Impaired left ventricular post-ischemic function and metabolism in chronic right ventricular hypertrophy. Circulation. 1987;76(5 Pt 2):V168–73.

del Nido PJ, Mickle DA, Wilson GJ, Benson LN, Weisel RD, Coles JG, et al. Inadequate myocardial protection with cold cardioplegic arrest during repair of tetralogy of fallot. J Thorac Cardiovasc Surg. 1988;95(2):223–9.

Desborough M, Sandu R, Brunskill SJ, Doree C, Trivella M, Montedori A, et al. Fresh frozen plasma for cardiovascular surgery. Cochrane Database Syst Rev. 2015;7:CD007614.

Dexter F, Hindman BJ. Theoretical analysis of cerebral venous blood hemoglobin oxygen saturation as an index of cerebral oxygenation during hypothermic cardiopulmonary bypass. A counterproposal to the "luxury perfusion" hypothesis. Anesthesiology. 1995;83(2):405–12.

Dexter F, Kern FH, Hindman BJ, Greeley WJ. The brain uses mostly dissolved oxygen during profoundly hypothermic cardiopulmonary bypass. Ann Thorac Surg. 1997;63(6):1725–9.

Durandy Y. The impact of vacuum-assisted venous drainage and miniaturized bypass circuits on blood transfusion in pediatric cardiac surgery. ASAIO J. 2009a;55(1):117–20.

Durandy YD. Pediatric cardiac surgery: effect of a miniaturized bypass circuit in reducing homologous blood transfusion. J Thorac Cardiovasc Surg. 2009b;138(6):1454; author reply -5.

Durandy Y. Perfusionist strategies for blood conservation in pediatric cardiac surgery. World J Cardiol. 2010a;2(2):27–33.

Durandy Y. Warm pediatric cardiac surgery: European experience. Asian Cardiovasc Thorac Ann. 2010b;18(4):386–95.

Durandy Y. Vacuum-assisted venous drainage, angel or demon: PRO? J Extra Corpor Technol. 2013;45(2):122–7.

Durandy Y. Minimizing systemic inflammation during cardiopulmonary bypass in the pediatric population. Artif Organs. 2014;38(1):11–8.

Durandy Y. Use of blood products in pediatric cardiac surgery. Artif Organs. 2015;39(1):21–7.

Durandy YD, Hulin SH. Normothermic bypass in pediatric surgery: technical aspect and clinical experience with 1400 cases. ASAIO J. 2006;52(5):539–42.

Edmunds LH Jr. Advances in the heart-lung machine after John and Mary gibbon. Ann Thorac Surg. 2003;76(6):S2220–3.

Eisses MJ, Geiduschek JM, Jonmarker C, Cohen GA, Chandler WL. Effect of polymer coating (poly 2-methoxyethylacrylate) of the oxygenator on hemostatic markers during cardiopulmonary bypass in children. J Cardiothorac Vasc Anesth. 2007;21(1):28–34.

Ferraris VA, Ferraris SP, Singh A, Fuhr W, Koppel D, McKenna D, et al. The platelet thrombin receptor and postoperative bleeding. Ann Thorac Surg. 1998;65(2):352–8.

Foglia RP, Partington MT, Buckberg GD, Leaf J. Iatrogenic myocardial edema with crystalloid primes. Effects on left ventricular compliance, performance, and perfusion. Curr Stud Hematol Blood Transfus. 1986;53:53–63.

Galletti PM, Brecher GA. Heart-lung bypass principles and techniques of extracorporeal circulation. New York: Grune & Stratton; 1962. p. 171–93.

Ganushchak Y, van Marken LW, van der Nagel T, de Jong DS. Hydrodynamic performance and heat generation by centrifugal pumps. Perfusion. 2006;21(6):373–9.

Ginther RM Jr, Gorney R, Cruz R. A clinical evaluation of the Maquet Quadrox-i neonatal oxygenator with integrated arterial filter. Perfusion. 2013;28(3):194–9.

Ginther R, Sebastian VA, Huang R, Leonard SR, Gorney R, Guleserian KJ, et al. Cerebral near-infrared spectroscopy during cardiopulmonary bypass predicts superior vena cava oxygen saturation. J Thorac Cardiovasc Surg. 2011;142(2):359–65.

Gottlieb EA, Fraser CD Jr, Andropoulos DB, Diaz LK. Bilateral monitoring of cerebral oxygen saturation results in recognition of aortic cannula malposition during pediatric congenital heart surgery. Paediatr Anaesth. 2006;16(7):787–9.

Greiner TO, Volkmann AS, Hildenbrand S, Wodarz R, Perle N, Ziemer G, et al. DEHP and its active metabolites: leaching from different tubing types, impact on proinflammatory cytokines and adhesion molecule expression. Is there a subsumable context? Perfusion. 2012;27(1):21–9.

Gruber EM, Jonas RA, Newburger JW, Zurakowski D, Hansen DD, Laussen PC. The effect of hematocrit on cerebral blood flow velocity in neonates and infants undergoing deep hypothermic cardiopulmonary bypass. Anesth Analg. 1999;89(2):322–7.

Gu YJ, Schoen P, Tigchelaar I, Loef BG, Ebels T, Rankin AJ, et al. Increased neutrophil priming and sensitization before commencing cardiopulmonary bypass in cardiac surgical patients. Ann Thorac Surg. 2002;74(4):1173–9.

Guyton AC, Polizo D, Armstrong GG. Mean circulatory filling pressure measured immediately after cessation of heart pumping. Am J Physiol. 1954;179(2):261–7.

Guyton AC, Lindsey AW, Abernathy B, Richardson T. Venous return at various right atrial pressures and the normal venous return curve. Am J Physiol. 1957;189(3):609–15.

Guyton AC, Langston JB, Carrier O Jr. Decrease of venous return caused by right atrial pulsation. Circ Res. 1962;10:188–96.

Habib RH, Zacharias A, Schwann TA, Riordan CJ, Durham SJ, Shah A. Adverse effects of low hematocrit during cardiopulmonary bypass in the adult: should current practice be changed? J Thorac Cardiovasc Surg. 2003;125(6):1438–50.

Haneda K, Sato S, Ishizawa E, Horiuchi T. The importance of colloid osmotic pressure during open heart surgery in infants. Tohoku J Exp Med. 1985;147(1):65–71.

Ihnken K, Morita K, Buckberg GD, Ignarro LJ, Beyersdorf F. Reduction of reoxygenation injury and nitric oxide production in the cyanotic immature heart by controlling pO2. Eur J Cardiothorac Surg. 1995;9(8):410–8.

Ihnken K, Morita K, Buckberg GD. Delayed cardioplegic reoxygenation reduces reoxygenation injury in cyanotic immature hearts. Ann Thorac Surg. 1998a;66(1):177–82.

Ihnken K, Winkler A, Schlensak C, Sarai K, Neidhart G, Unkelbach U, et al. Normoxic cardiopulmonary bypass reduces oxidative myocardial damage and nitric oxide during cardiac operations in the adult. J Thorac Cardiovasc Surg. 1998b;116(2):327–34.

Ince C. The rationale for microcirculatory guided fluid therapy. Curr Opin Crit Care. 2014;20(3):301–8.

Jonas RA, editor. Comprehensive surgical management of congenital heart disease. London: Arnold; 2004.

Kagawa H, Morita K, Uno Y, Ko Y, Matsumura Y, Kinouchi K, et al. Inflammatory response to hyperoxemic and normoxemic cardiopulmonary bypass in acyanotic pediatric patients. World J Pediatr Congenit Heart Surg. 2014;5(4):541–5.

Kamiya T, Katayama Y, Kashiwagi F, Terashi A. The role of bradykinin in mediating ischemic brain edema in rats. Stroke. 1993;24(4):571–5; discussion 5-6.

Kaplanski G, Fabrigoule M, Boulay V, Dinarello CA, Bongrand P, Kaplanski S, et al. Thrombin induces endothelial type II activation in vitro: IL-1 and TNF-alpha-independent IL-8 secretion and E-selectin expression. J Immunol. 1997;158(11):5435–41.

Kaplanski G, Marin V, Fabrigoule M, Boulay V, Benoliel AM, Bongrand P, et al. Thrombin-activated human endothelial cells support monocyte adhesion in vitro following expression of intercellular adhesion molecule-1 (ICAM-1; CD54) and vascular cell adhesion molecule-1 (VCAM-1; CD106). Blood. 1998;92(4):1259–67.

Kim WG, Yoon CJ. Roller pump induced tubing wear of polyvinylchloride and silicone rubber tubing: phase contrast and scanning electron microscopic studies. Artif Organs. 1998;22(10):892–7.

Krogh A. The number and distribution of capillaries in muscles with calculations of the oxygen pressure head necessary for supplying the tissue. J Physiol. 1919;52(6):409–15.

Laffey JG, Boylan JF, Cheng DC. The systemic inflammatory response to cardiac surgery: implications for the anesthesiologist. Anesthesiology. 2002;97(1):215–52.

Landis RC. Redefining the systemic inflammatory response. Semin Cardiothorac Vasc Anesth. 2009;13(2):87–94.

Landis RC, Arrowsmith JE, Baker RA, de Somer F, Dobkowski WB, Fisher G, et al. Consensus statement: defining minimal criteria for reporting the systemic inflammatory response to cardiopulmonary bypass. Heart Surg Forum. 2008;11(5):E316–22.

Lidington EA, Haskard DO, Mason JC. Induction of decay-accelerating factor by thrombin through a protease-activated receptor 1 and protein kinase C-dependent pathway protects vascular endothelial cells from complement-mediated injury. Blood. 2000;96(8):2784–92.

Lin J, Dogal NM, Mathis RK, Qiu F, Kunselman A, Undar A. Evaluation of Quadrox-i and Capiox FX neonatal oxygenators with integrated arterial filters in eliminating gaseous microemboli and retaining hemodynamic properties during simulated cardiopulmonary bypass. Perfusion. 2012;27(3):235–43.

Manduz S, Sapmaz I, Sanri US, Karahan O, Bascil H, Dogan K. The influence of priming solutions used in cardiopulmonary bypass on blood viscosity in hypothermic conditions. ASAIO J. 2008;54(3):275–7.

McBride WT, Armstrong MA, Crockard AD, McMurray TJ, Rea JM. Cytokine balance and immunosuppressive changes at cardiac surgery: contrasting response between patients and isolated CPB circuits. Br J Anaesth. 1995;75(6):724–33.

McCullough JN, Zhang N, Reich DL, Juvonen TS, Klein JJ, Spielvogel D, et al. Cerebral metabolic suppression during hypothermic circulatory arrest in humans. Ann Thorac Surg. 1999;67(6):1895–9; discussion 919-21.

Minneci PC, Deans KJ, Zhi H, Yuen PS, Star RA, Banks SM, et al. Hemolysis-associated endothelial dysfunction mediated by accelerated NO inactivation by decompartmentalized oxyhemoglobin. J Clin Invest. 2005;115(12):3409–17.

Modi P, Imura H, Caputo M, Pawade A, Parry A, Angelini GD, et al. Cardiopulmonary bypass-induced myocardial reoxygenation injury in pediatric patients with cyanosis. J Thorac Cardiovasc Surg. 2002;124(5):1035–6.

Moerman A, Denys W, De Somer F, Wouters PF, De Hert SG. Influence of variations in systemic blood flow and pressure on cerebral and systemic oxygen saturation in cardiopulmonary bypass patients. Br J Anaesth. 2013;111(4):619–26.

Monroe DM, Hoffman M, Roberts HR. Platelets and thrombin generation. Arterioscler Thromb Vasc Biol. 2002;22(9):1381–9.

Murai N, Cho M, Okada S, Chiba T, Saito M, Shioguchi S, et al. Venous drainage method for cardiopulmonary bypass in single-access minimally invasive cardiac surgery: siphon and vacuum-assisted drainage. J Artif Organs. 2005;8(2):91–4.

Ni YM, Leskosek B, Shi LP, Chen YL, Qian LF, Li RY, et al. Optimization of venous return tubing diameter for cardiopulmonary bypass. Eur J Cardiothorac Surg. 2001;20(3):614–20.

Nicolas F, Daniel JP, Bruniaux J, Serraf A, Lacour-Gayet F, Planche C. Conventional cardiopulmonary bypass in neonates. A physiological approach—10 years of experience at Marie-lannelongue hospital. Perfusion. 1994;9(1):41–8.

Pappalardo F, Corno C, Franco A, Giardina G, Scandroglio AM, Landoni G, et al. Reduction of hemodilution in small adults undergoing open heart surgery: a prospective, randomized trial. Perfusion. 2007;22(5):317–22.

Pearl JM, Thomas DW, Grist G, Duffy JY, Manning PB. Hyperoxia for management of acid-base status during deep hypothermia with circulatory arrest. Ann Thorac Surg. 2000;70(3):751–5.

Peek GJ, Thompson A, Killer HM, Firmin RK. Spallation performance of extracorporeal membrane oxygenation tubing. Perfusion. 2000;15(5):457–66.

Pouard P, Bojan M. Neonatal cardiopulmonary bypass. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu. 2013;16(1):59–61.

Poullis M, Manning R, Laffan M, Haskard DO, Taylor KM, Landis RC. The antithrombotic effect of aprotinin: actions mediated via the proteaseactivated receptor 1. J Thorac Cardiovasc Surg. 2000;120(2):370–8.

Ranucci M, Romitti F, Isgro G, Cotza M, Brozzi S, Boncilli A, et al. Oxygen delivery during cardiopulmonary bypass and acute renal failure after coronary operations. Ann Thorac Surg. 2005;80(6):2213–20.

Reagor JA, Clingan S, Gao Z, Morales DLS, Tweddell JS, Bryant R, et al. Higher flow on cardiopulmonary bypass in pediatrics is associated with a lower incidence of acute kidney injury. Semin Thorac Cardiovasc Surg. 2020;32(4):1015–20.

Redlin M, Huebler M, Boettcher W, Kuppe H, Hetzer R, Habazettl H. How near-infrared spectroscopy differentiates between lower body ischemia due to arterial occlusion versus venous outflow obstruction. Ann Thorac Surg. 2011;91(4):1274–6.

Rothlein R, Kishimoto TK, Mainolfi E. Cross-linking of ICAM-1 induces co-signaling of an oxidative burst from mononuclear leukocytes. J Immunol. 1994;152(5):2488–95.

Sakamoto T, Hatsuoka S, Stock UA, Duebener LF, Lidov HG, Holmes GL, et al. Prediction of safe duration of hypothermic circulatory arrest by near-infrared spectroscopy. J Thorac Cardiovasc Surg. 2001;122(2):339–50.

Shappell SB, Toman C, Anderson DC, Taylor AA, Entman ML, Smith CW. Mac-1 (CD11b/CD18) mediates adherence-dependent hydrogen peroxide production by human and canine neutrophils. J Immunol. 1990;144(7):2702–11.

Tamari Y, Lee-Sensiba K, Leonard EF, Tortolani AJ. A dynamic method for setting roller pumps nonocclusively reduces hemolysis and predicts retrograde flow. ASAIO J. 1997;43(1):39–52.

Tsai AG, Friesenecker B, McCarthy M, Sakai H, Intaglietta M. Plasma viscosity regulates capillary perfusion during extreme hemodilution in hamster skinfold model. Am J Physiol. 1998;275(6 Pt 2):H2170–80.

Tsai AG, Acero C, Nance PR, Cabrales P, Frangos JA, Buerk DG, et al. Elevated plasma viscosity in extreme hemodilution increases perivascular nitric oxide concentration and microvascular perfusion. Am J Physiol. 2005;288(4):H1730–9.

Tweddell JS, Hoffman GM, Mussatto KA, Fedderly RT, Berger S, Jaquiss RD, et al. Improved survival of patients undergoing palliation of hypoplastic left heart syndrome: lessons learned from 115 consecutive patients. Circulation. 2002;106(12 Suppl 1):I82–9.

Wachtfogel YT, Hack CE, Nuijens JH, Kettner C, Reilly TM, Knabb RM, et al. Selective kallikrein inhibitors alter human neutrophil elastase release during extracorporeal circulation. Am J Physiol. 1995;268(3 Pt 2):H1352–7.

Wilkinson KL, Brunskill SJ, Doree C, Trivella M, Gill R, Murphy MF. Red cell transfusion management for patients undergoing cardiac surgery for congenital heart disease. Cochrane Database Syst Rev. 2014;2:CD009752.

Zhang Y, Wang B, Zhou XJ, Guo LJ, Zhou RH. Nadir oxygen delivery during pediatric bypass as a predictor of acute kidney injury. Ann Thorac Surg. 2021;113(2):647–53.