Chapter 16
Cardiopulmonary Bypass in Children and Infants

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Introduction

Cardiac surgery can be considered one of most important medical advances of the twentieth century. 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 were not only related to the equipment but also to a better understanding of the normal and pathological physiology.

The better design and improved conduct of pediatric cardiopulmonary bypass (CPB) are responsible for the fact that complex cardiac anomalies can nowadays be corrected earlier in life 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.

In this chapter some of the improvements as well as some of the remaining problems will be discussed.

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.

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Vascular Access

Since the start of CPB in the early 1950s of the last century, nonoptimal vascular access was known 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. As a consequence, problems encountered in obtaining optimal arterial or venous access will be different.

Problems with arterial cannulation are mostly related to inappropriate sizing of the arterial cannula or to bleeding of the cannulation site. Undersizing of the 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, oversizing of the cannula will cause partial obstruction of the vessel lumen and increases the work load for the heart during weaning, when the heart has to eject against a high resistance. High resistance inside the cannula or arterial line is less of a problem as the cannula is located downstream of the arterial blood pump. In most centers sizing is done empirically based upon historical experience as most manufacturers only provide pressure-flow curves for their cannulas using water instead of with a blood analogue or blood. As water has a lower viscosity, this can lead to major bias. In order to overcome this problem, a simple technique has been proposed which is represented in Fig. 16.1 (De Wachter et al. 2002).

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

$$r_{water} = 997 \frac{kg}{m^3} \quad \text{water density}$$

$$h_{water} = 0.001 \frac{kg}{m \cdot s} \quad \text{water viscosity at } 20^{\circ}C$$

Blood characteristics during cardiopulmonary bypass

$$Hct := 25\% \quad \text{Hematocrit}[\%]$$

$$T_{blood} := 32 \quad \text{Arterial blood temperature}[^{\circ}C]$$

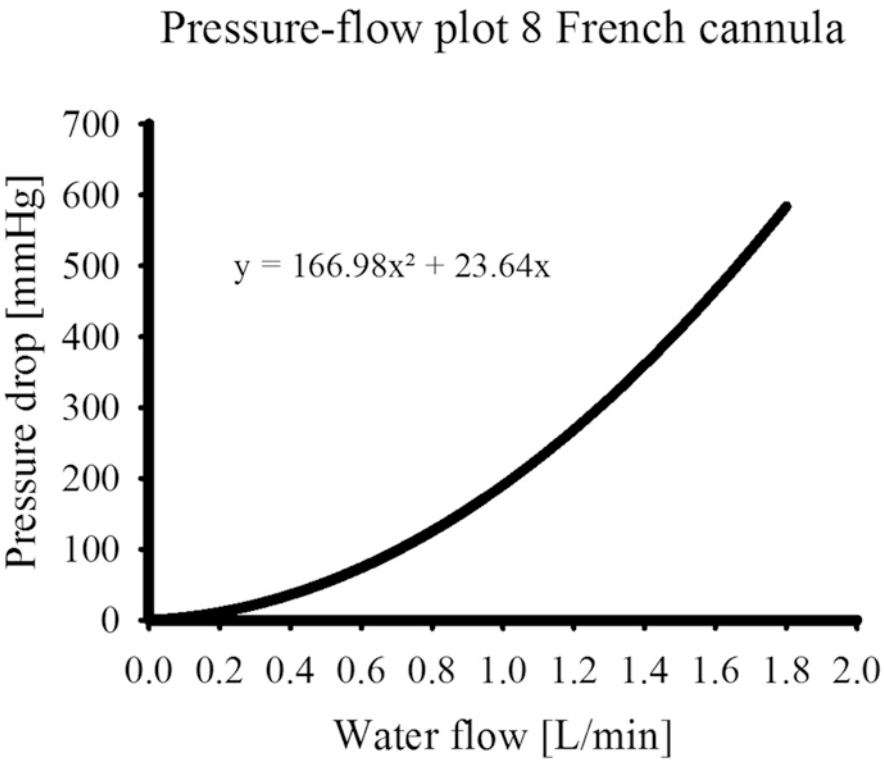

Fig. 16.1 Pressure flow curve (water) Medtronic DLP 77108 (Provided by the manufacturer)

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

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

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

$$\eta_{\text{blood}} = \eta_{\text{plasma}}\cdot\exp\left(2.31\cdot\text{Hct}\right) \quad \eta_{\text{blood}} = 2.314\cdot\text{cpoise}$$

Calculate ratios

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

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

$$Q := 0.8 \quad \text{Flow in L/min}$$
$$\Delta P_{\text{water}} := 166.98 \cdot Q^2 + 23.64 \cdot Q = 126$$
$$\Delta P_{\text{blood}} := 166.98 \cdot \rho_{\text{ratio}} \cdot Q^2 + 23.64 \cdot \eta_{\text{ratio}} \cdot Q = 156$$

Assessing access of the venous side is more complex due to more stringent boundary conditions. In the normal circulation, venous return toward the heart is governed by the pressure difference between the mean circulatory filling pressure and the pressure in the right atrium.

This pressure difference is approximately 7 mmHg (Guyton et al. 1954, 1957, 1962). When venous access is established, the wide, low-resistance, collapsible blood vessels are connected with smaller-diameter, stiff, artificial conduits of known physical characteristics. Because of the smaller diameters of both the venous line and the venous cannula, higher pressure differences are needed to obtain optimal venous drainage (Galletti and Brecher 1962). The necessary pressure difference to achieve optimal drainage will depend on tubing diameter, tubing length, and blood viscosity (Ni et al. 2001). The latter in its turn will be dependent on both hematocrit and temperature. In order to overcome the combined pressure drop of both venous cannula and venous line, a negative pressure is applied by using gravity (siphon) or assisted venous drainage. When applying negative pressure, venous drainage will first increase linearly with the increase in negative pressure, while the resistance will remain more or less constant. However, at a certain point, a further increase in pressure will partially collapse 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 will represent the smallest diameter and, thus, the highest resistance. Reducing the diameter by 50 % will reduce flow to 1/16th of the original flow. Also, the length of this smallest diameter is important, as doubling the length of the cannula will decrease flow by 50 %. Another point of interest is the ratio between the diameter of the vein and the cannula. According to Galetti, this ratio should be around 0.5 in order to avoid collapse of the vein around the side holes of the cannula (Galletti and Brecher 1962). Although the diameter ratio is important, also the design of the cannula and cannula tip (De Somer et al. 2002) will influence the 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 and Hulin 2006; Durandy 2009a, b). However, it should not be used as a solution for correcting improper cannula position. If VAVD is used under such conditions, one mainly will increase resistance in the cannula. At the same time, a higher blood velocity will be generated over those openings of the cannula which are not blocked by the improper position. Finally, this will increase shear stress and lead 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).

Table 16.1 Impact of tubing diameter on venous line pressure drop

Tubing diameter [inch]	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

The reported vacuum that should be applied for optimal drainage lies between −30 and −80 mmHg. The absolute value will depend upon where this negative pressure is measured in the circuit. The purpose of measuring the pressure is to estimate the pressure at the cannula tip as this will give us information with respect to risk for 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. This is illustrated in Table 16.1, which shows the impact on blood velocity and required pressure difference when 3/16 in. tubing or 1/4 in. tubing is used for obtaining a 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 and 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 will determine the maximum blood flow that can be obtained and thus oxygen delivery to the organs. Malposition of a 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 caval cannula may decrease cerebral venous drainage and potentially lead to brain dysfunction. Nowadays, many of these problems can be detected early in time by routine use of cerebral oxygenation by near-infrared spectroscopy (NIRS) (Gottlieb et al. 2006; Ginther et al. 2011; Redlin et al. 2011).

Tubing

The tubing in the CPB circuit interconnects all of the main components of the circuit. A variety of polymers can be used for the manufacture of tubing, but most are made of PVC with exception of the tubing used in the pump boot which is often silicone. The length and size of the tubing will have a major impact on volume, shear

Table 16.2 Characteristics of different pediatric tubings

Tubing diameter [inch]	1/8	3/16	1/4	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

stress, and pressure drop (Table 16.2), and the clinician will have to make a choice based upon the clinical conditions.

Blood Pumps

From an engineering perspective, pumps can be classified into two main categories: displacement pumps and rotary pumps. The energy in displacement pumps is characterized by periodic volumetric changes of a working space. A typical displacement pump is the roller pump. The principle of operation of this pump is that two rollers, placed opposite to each other, "roll" the blood through a piece of tubing. When the pump completely occludes the tubing, the pump is capable of generating both positive and negative pressures, and therefore it can be also used as blood aspirating pump. Because of its working principle, a roller pump is relatively independent of factors such as resistance and hydrostatic pressure head, which are encountered in the average CPB circuit. The output of an occlusive roller pump depends upon two main variables: the number of revolutions per minute of the pump head and the internal diameter and length of the tubing held in the pump head:

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

where RPM = 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 the generation of small particles (Briceno and Runge 1992; Kim and Yoon 1998; Peek et al. 2000). In order to control spallation, it is advocated to use a dynamic occlusion setting of the pump rollers (Tamari et al. 1997). Due to the high resistances encountered in neonatal and pediatric CPB circuits, 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 the inlet and the outlet of the pump. The pressure gradient results from the creation of a vortex by the rotation of the pump

head. The rotating motion 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, arterial cannula) and the systemic vascular resistance of the patient. Because the flow produced by a centrifugal pump directly depends on the pressure that the centrifugal pump generates, a centrifugal pump is called a pressure pump. In contrast to a roller pump, a centrifugal pump is afterload dependent and thus influenced by changes in resistance in both the circuit and the patient. For this reason a centrifugal pump should always be used in conjunction with a flow meter. Although a centrifugal pump, due to its non-occlusive 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).

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 also 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 indispensible as some extensive repairs may require hypothermia and/or deep hypothermic circulatory arrest (DHCA). Most recent oxygenators are now available with an integrated filter thus avoiding the need for a separate arterial line filter (Lin et al. 2012; Ginther et al. 2013). 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, exclusively extraluminal hollow fiber membrane oxygenators are used. 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 connections all in relation to the size of the patient and the type of surgical repair. Table 16.3 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 % will increase its oxygen content by 45 mL oxygen per liter blood. This proposed value offered sufficient safety in acyanotic children but could pose a problem in cyanotic children that are often presented with much lower venous saturation. For this reason, contemporary pediatric oxygenators easily can have 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 16.3) 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 16.3 Characteristics of contemporary neonatal and 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]
Terumo FX05	0.5	PP	1.5	2.5	0.035
LivaNova D100[a]	0.22	PP	0.7	1	0.03
LivaNova D101[a]	0.61	PP	2.5	3.5	0.06
Maquet Neonatal Quadrox-i	0.38	PP	1.5	N/A	0.07
Maquet Pediatric Quadrox-i	0.8	PP	2.8	N/A	0.15
Medtronic Pixie[a]	0.67	PP	2	N/A	N/A
Medos Hilite 1000[a]	0.39	PP	1	N/A	0.074
Medos Hilite 2800[a]	0.8	PP	2.8	N/A	0.16

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

Priming and Hemodilution

The total priming volume of a CPB circuit is determined by the components selected (De Somer et al. 1996b). It is important to select a smaller oxygenator that will function close to its maximal capacity for flow rather than selecting a large oxygenator that will function toward its lower level. However, independent of the choice of oxygenator, its priming volume will be fixed. The 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 will determine the dilution of the blood components. However, also the composition of the priming fluid is a point of consideration. 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, often fibrinogen concentration is used as a reference, keeping its concentration above 1 g/L. Huge differences in target hemoglobin during CPB are reported going from 50 to 100 g/dL (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. But one should not focus alone on hemoglobin concentration as

final oxygen delivery (DO_2) will be dependent on both hemoglobin concentration and pump flow. As a consequence one can tolerate lower hemoglobin concentrations as long as vascular access allows for high pump flows, but when anatomical limitations restrict vascular access, a higher hemoglobin concentration might be desirable. This can be easily demonstrated by the following example: if we consider a minimum DO_2 of 300 mL/min/m^2 in a child with a body surface of 0.22 m^2, then the required blood flow would be 490 mL/min at a hemoglobin of 100 g/L, but we would need a blood flow of 1970 mL/min at a hemoglobin of 50 g/L to achieve the target DO_2. It is quite obvious that the latter is hardly obtainable.

Prophylactic use of both fresh frozen plasma and packed red cells without arguments is not recommended (Wilkinson et al. 2014; Desborough et al. 2015).

Beside the impact of the priming solution on blood coagulation and oxygen transport, its composition will also affect colloid oncotic pressure. There is evidence that priming with a high-colloid oncotic pressure, by adding albumin, results in less fluid overload by the end of CPB and is advantageous in neonates compared to a priming solution only containing crystalloids (Pouard and Bojan 2013).

Reflection on the composition of the priming volume and composition becomes even more important; now 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, hemodilution was seen as a huge benefit for the cardiac surgical population of that time as it could 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. Hemodiluting a patient with a normal hematocrit of 40 % to a hematocrit of 20 % will thus decrease the oxygen content per liter blood by 50 %. When this happens in healthy patients, not on CPB bypass, this loss will be compensated by a compensatory increase in cardiac output which is facilitated by the reduced viscosity caused by the hemodilution. During CPB a fixed blood flow per square meter of body surface is used, typically between 2.2 and 3.0 L/min/m^2. Maintaining this fixed flow during excessive hemodilution might 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 density of capillaries in the microcirculation (Tsai et al. 1998). Research has shown that this negative effect can be in part attenuated by using fluids with a higher viscosity for hemodilution as increasing the viscosity of plasma is directly associated with increased perivascular nitric oxide concentration, an effect related to vasodilatation, and increased perfusion and capillary density compared with the same procedure using fluids with a lower viscosity (Tsai et al. 2005). Although the fluids used in this study had a viscosity much higher than those commercially available, it seems favorable to use priming solutions with a higher viscosity (Manduz et al. 2008). The decrease in plasma proteins will result in a decrease in plasma colloid oncotic pressure which may play an important role in the fluid accumulation often seen after CPB. Tissue edema is secondary to increased capillary permeability caused by the

systemic inflammatory response induced by CPB. In neonates the combination of this 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. The lower fluid accumulation was then 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 the circulation in order to prevent organ dysfunction during and after the surgical repair. Oxygen delivery is one of the most important variables in achieving this goal. Oxygen delivery will depend upon the hemoglobin concentration and the pump flow. In adults it has been demonstrated that there exist 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 by itself or due to a low DO_2 (Ranucci et al. 2005). Recent research showed that maintaining DO_2 above 280 mL/min/m^2 could reduce the incidence of acute kidney injury from 29.8 to 12.1 %. As this research was done in an adult population at temperatures above 32°C, one could question whether these findings could be extrapolated to a pediatric population. But it clearly demonstrates that when a low hematocrit is targeted during CPB, one will need to maintain higher blood flows. On the other hand, when anatomical limitations limit the size of the vascular access, one should keep the hematocrit higher during CPB.

The microcirculation is the ultimate destination of red blood cells (RBC) 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 convective transport is represented by:

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

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

For a long time, it was considered sufficient to maintain blood flow in order to provide the tissue in the microcirculation with oxygen. However, an equal contribution to oxygen transport to tissue is governed by the ability of oxygen to reach the cells from the red blood cell by passive diffusion. The further away the tissue cell is from the oxygen-carrying RBC, for example, by excessive hemodilution (Atasever et al. 2011), or the less oxygen solubility of tissue cells (e.g., by edema), the more difficulty, even in the presence of sufficient flow in the filled capillaries, the oxygen

will have in reaching these cells. The diffusive capacity of the microcirculation depends upon the functional capillary density (FCD), or the density of capillaries in a given volume of tissue, and is described by Fick's law as the product of the difference between the partial pressure of oxygen at the RBC minus that at the mitochondria times the diffusion constant divided by the distance between the RBC and the mitochondria (Boerma and Ince 2010; Ince 2014). Immediately after and during CPB, there will be a loss of FCD. The percentage loss will depend upon the degree of hemodilution, the viscosity, and the filling status of the microcirculation. As a consequence more cells will depend upon the oxygen supply by a single capillary (Krogh 1919). Just increasing cardiac output maybe insufficient to correct the resulting tissue hypoxemia, and microcirculatory recruitment procedures are needed. 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).

Special groups within the neonatal and pediatric CPB population are cyanotic children. There is quite a debate on what is the best oxygenation strategy in this group especially 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 (del Nido et al. 1987; del Nido et al. 1988; Modi et al. 2002; 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. It has been shown to ameliorate reoxygenation injury in experimental models (Ihnken et al. 1995; Ihnken et al. 1998a), 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 to define the best oxygenation strategy for children requiring deep hypothermia with circulatory arrest (DHCA) or hypothermia with low flow. Hypothermia will slow down the metabolism. The relationship between the cerebral metabolic rate for oxygen ($CMRO_2$) and temperature is best represented by a log-linear model (McCullough et al. 1999). However it should be noted that at a temperature of 20°C, the $CMRO_2$ is still 24 % of baseline. For this reason it is extremely important to ensure uniform cerebral hypothermia as it is critical to the successful use of DHCA. At the same time, efforts should be made to increase oxygen availability to the cells. Hypothermia will shift 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 the hemoglobin-bound oxygen at the tissue level. During normothermia venous saturation can decrease to 30 % before $CMRO_2$ will decrease to less than 90 % of normal, but in infants at 17°C, venous saturation must be maintained at greater than 95 % to maintain $CMRO_2$ at

greater than 90 % of its temperature appropriate value (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 to 15.3 mmHg. However, pH-stat by itself is insufficient as the shift to the right is limited and thus has to be accompanied with measures to improve the amount of dissolved oxygen. This can be done by using hyperoxia. 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 to 525 mmHg will increase the amount of soluble oxygen from 4 to 18 mL/L and 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. An impressive amount of research in this domain has been done at Children's Hospital in Boston 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. The efficiency of the hyperoxygenation and monitoring of remaining metabolism and oxygen consumption during DHCA can be done with NIRS. The better the hyperoxygenation and the lower the metabolic rate, the longer the period of declining saturation. Finally, a plateau will be reached with minimal oxygen extraction. The duration of this plateau period is a useful predictor of behavioral and histological evidence of injury after DHCA (Sakamoto et al. 2001).

Systemic Inflammation During CPB

Inflammation is the body's humoral and cellular protective response to injury (Davies and Hagen 1997). The systemic inflammatory reaction during cardiac surgery is multifactorial and triggered by almost every part of the procedure, starting with anesthesia (Gu et al. 2002), skin incision, and sternotomy. Subsequently, systemic inflammatory reaction syndrome (SIRS) is further triggered during CPB by contact activation between blood and foreign surface and later by the ischemia and reperfusion of the myocardium (Durandy 2014). Also hypothermia and blood transfusions are known to activate the inflammatory response (Laffey et al. 2002). The first descriptions of the systemic inflammatory response to CPB correctly identified multiple causal factors, including the activation of complement, coagulation, fibrinolysis, inflammatory cytokines, and cytodestructive mediators generated by white cells (Butler et al. 1993). Initially research mainly focused on systemic cytokines

and failed to link other host response systems to adverse clinical events (Landis 2009). Despite decades of research, the clinical advances to attenuate SIRS have been disappointing.

Controlling the Host Response

Despite heparinization, factor XII is absorbed onto the foreign surface of the CPB within seconds after initiation, and thrombin will be generated in direct relation to CPB time (Boisclair et al. 1993; Brister et al. 1993). Under normal conditions the intrinsic coagulation will generate in response to injury and small amounts of thrombin. This thrombin is sufficient to initiate hemostasis but not enough to cause thrombus formation (Monroe et al. 2002). The signal becomes amplified when thrombin binds to platelets through its high-affinity thrombin receptor and protease-activated receptor-1 (PAR1) and initiates several positive feedback loops. At the end of this so-called amplification phase, the stage is set for the large burst of thrombin generation that is essential to stable clot formation. Uncontrolled thrombin generation in the bypass circuit may create a prothrombotic risk to the grafted vessel but as well a risk for systemic bleeding. The systemic bleeding risk is caused by the consumption of clotting factors and the unwanted activation of the platelet PAR1 receptor by thrombin in the bypass circuit (Ferraris et al. 1998; Landis 2009). Desensitization of platelets by thrombin is the main cause of the clinical platelet deficit recognized in CPB surgery. Kallikrein and thrombin are also linked to proinflammatory activation of leukocytes and endothelial cells via bradykinin and PAR1 receptors expressed throughout the vasculature (Kamiya et al. 1993; Kaplanski et al. 1997, 1998). The proinflammatory pathways activated by kallikrein and thrombin may explain some of the febrile and capillary leak symptoms seen in CPB (Wachtfogel et al. 1995; Lidington et al. 2000; Landis 2009). Proinflammatory activation of platelets and endothelial cells can be inhibited by agents that antagonize proteolytic activation of PAR1 (Poullis et al. 2000; Day et al. 2006). The benefit of this approach was demonstrated in neonates with hypoplastic left heart syndrome, where the use of aprotinin improved survival after stage 1 repair (Tweddell et al. 2002).

The complement system is activated via classical pathway of C3, secondary to IgM and IgG antibody absorption by the CPB circuit. (Landis et al. 2008). Many attempts have been done to control complement activation. Introduction of closed systems and 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).

Proinflammatory cytokines such as TNF-α, IL6, and IL8 are activated early during CPB, typically after 5–120 min. This initial proinflammatory phase is triggered by direct contact with foreign material. About 2–24 h after initiation of CPB, this initial release is followed by second anti-inflammatory phase, releasing

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

Leukocytes may also contribute to the systemic host response through the elaboration of reactive oxidant species. Neutrophils and monocytes will express their complement receptor CR3 which will mediate leukocyte adhesion to polymers. The adhered cells will try to phagocytose the polymer which the will trigger the same cytodestructive inflammatory cytokine, protease, and reactive oxygen pathways as occurs during genuine phagocytosis (Shappell et al. 1990; Rothlein et al. 1994). 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. 1996a). This shear stress will lead to the formation of free plasma hemoglobin.

Free plasma hemoglobin in the bloodstream can abrogate vasoprotective responses due to 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 occurs at the time of cross clamp release, earlier than the first detectable 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. Especially aspiration of blood from the surgical field can contain high amounts of free plasma hemoglobin and activated 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 on the multisystemic etiology of this disorder such as systemic "host" response to surgery. Interventions should be focused to target on multiple effector pathways simultaneously. In order to increase knowledge, we should better report the observed systemic host response. A consensus paper looking at the published research pointed out that better reporting should comprise of (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

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