Cardiopulmonary bypass in infants and children: what’s new?

Introduction

In the early 1950s the pioneers of congenital cardiac surgery, among them Bigelow, Lewis and Gibbon, realised that hypothermia and inflow occlusion alone would not allow further advances in the field. In 1954, Lillehei introduced the technique of controlled cross circulation, where the patient’s parent functioned as the extracorporeal oxygenator. Only the development of mechanical cardiopulmonary bypass circuits in the late 1950s made advanced congenital cardiac surgery possible. Since then, extracorporeal perfusion circuits have come a long way: from monkey lungs, film and bubble oxygenators, to modern miniature membrane oxygenators with centrifugal pumps, vacuum-assisted venous drainage and in-line gas monitoring.1

The following is a short review of the important differences between adult and paediatric cardiopulmonary bypass (CPB), and a discussion of recent trends and developments.

Cardiopulmonary bypass in infants and children: what’s different?

For congenital cardiac surgery, the extracorporeal circuit must be adjusted to a wide range of age groups and size variations, from 1.5 kg premature infants to 100 kg adolescents or adults. Infants and children have smaller circulating blood volumes, higher oxygen consumption rates and, often, highly reactive pulmonary vascular beds. In addition, neonates and infants have labile thermoregulation and immature organ systems with multiple implications for ischaemic tolerance and inflammatory response. Many complex repairs require a bloodless operative field which can be difficult to achieve in the presence of intracardiac or extracardiac shunts, aortopulmonary collaterals, or otherwise increased pulmonary venous return.

Challenging problems for paediatric cardiopulmonary bypass

1. Haemodilution

The relatively large bypass prime volumes, compared with the circulating blood volumes, in infants and children lead to significant haemodilution (see Table I). Even with the newest technology, the minimum prime volume for circuits allowing full support in neonates at normothermia is 220 ml, 180 ml if the arterial filter is excluded. The disadvantages of haemodilution clearly outweigh the benefits of improved viscosity at low temperatures: anaemia with decreased oxygen-carrying capacity, reduced levels of plasma proteins and clotting factors leading to tissue oedema and coagulopathy, electrolyte imbalances and exaggerated release of stress hormones and complement activation.1,4

2. Optimal haematocrit on CPB and the role of blood products

The optimal haematocrit (Hct) on bypass remains controversial, particularly for neonates. In the past, a Hct of 20% (or even less) was considered acceptable, given the theoretical advantage of improved microcirculation and the reduced need for transfusion. Some recent studies in infants have demonstrated negative effects on peri-operative outcomes and neurological development when lower Hct (20% vs. 30%) was used. On the other hand, proponents of haemodilution and asanguinous primes argue that these studies mainly focused on certain subgroups, and that surgical technique, temperature and flow rates are major confounding factors. The use of allogenic blood can alter immunologic responses and contribute to the systemic inflammatory response. Controversy also exists regarding the type of blood product used during bypass. Packed red blood cells (leukocyte reduced and washed), reconstituted whole blood, or fresh whole blood? The potential advantage of adding clotting factors and AT III to the prime must be weighed up against the negative effects associated with blood storage and activation of inflammatory pathways. At least in one study, the outcome was actually worse with the use of fresh whole blood compared with component therapy.1-6

3. pH management

During hypothermia, the dissociation constant of water increases, resulting in decreased levels of hydrogen and hydroxyl ions. To preserve neutrality, cold blooded, ectothermic animals increase their blood pH by relative hyperventilation, i.e. they maintain normoventilation despite reduced CO2 production. This form of pH management is called alpha stat, named after the alpha imidazole rings of histidine, one of the major blood buffers. Using alpha stat management, the pH is adjusted to be 7.4 and not corrected to the respective temperature. This strategy seems to preserve intracellular electrochemical neutrality as well as enzymatic function, and improve metabolic recovery during rewarming. In contrast with the pH stat strategy used by hibernating animals, CO2 is added to achieve a pH of 7.4 corrected to the patient’s actual temperature. Despite increased intracellular acidosis and enzyme dysfunction, experimental studies...
Table I: Differences between adult and paediatric CPB

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Adult patient</th>
<th>Paediatric patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated blood volume</td>
<td>65 ml/kg (4-5 litres for 70 kg)</td>
<td>&lt; 10 kg; 85 ml/kg (285 ml for 3 kg)</td>
</tr>
<tr>
<td>Dilution effects on blood volume</td>
<td>25 - 33%</td>
<td>100 - 200%</td>
</tr>
<tr>
<td>Addition of whole blood or packed red blood cells to prime</td>
<td>Rarely</td>
<td>Usually</td>
</tr>
<tr>
<td>Oxygen consumption</td>
<td>2 – 3 ml/kg/min</td>
<td>6 – 8 ml/kg/min</td>
</tr>
<tr>
<td>Full CPB flow at 37°C</td>
<td>50 – 75 ml/kg/min</td>
<td>150 – 200 ml/kg/min for &lt; 3 kg</td>
</tr>
<tr>
<td>Minimum CPB temperature</td>
<td>Rarely &lt; 25 - 32°C</td>
<td>Commonly 15 - 20°C</td>
</tr>
<tr>
<td>Use of total circulatory arrest or regional low flow perfusion</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Perfusion pressures</td>
<td>50 – 80 mmHg</td>
<td>20 – 50 mmHg</td>
</tr>
<tr>
<td>Acid-base management</td>
<td>Mainly Alpha-stat</td>
<td>Alpha-stat and/or pH-stat</td>
</tr>
<tr>
<td>Measured PaCO₂ differences</td>
<td>30 – 45 mmHg</td>
<td>20 – 80 mmHg</td>
</tr>
<tr>
<td>Glucose regulation</td>
<td>Rare (major hepatic injury)</td>
<td>Common; reduced stores</td>
</tr>
<tr>
<td>hypoglycaemia</td>
<td>Common; treated with Insulin</td>
<td>Less common; risk for rebound hypoglycaemia</td>
</tr>
</tbody>
</table>

Modified from references 2 and 3

have shown some advantages of pH stat, including improved cerebral perfusion, more homogenous cooling and better oxygen delivery. The clinical relevance is widely debated. Studies in neonates undergoing cardiac surgery with deep hypothermic arrest demonstrated initially improved outcomes, but no difference at follow-ups several years later. Nevertheless, convinced of the theoretical benefits, many centres use pH stat for neonatal surgery involving deep hypothermia, or combined strategies with cross over during the cooling phase.1,3,5

4. Systemic inflammatory response

Extracorporeal circulation is well known to trigger an extensive inflammatory reaction, especially in neonates and infants where the relatively large circuit size, the blood prime and the need for increased flow rates result in greater exposure of blood to the foreign surface. Immature and developing organ systems are particularly vulnerable to these inflammatory injuries. Complement and neutrophil activation, kinin production, arachidonic acid activation, cytokines, thrombin, platelet-activating factors and endothelins are all components of the global inflammatory response to CPB. Current anti-inflammatory strategies include the use of steroids, serine protease inhibitors, modified ultrafiltration and heparin-bonded circuits.1,6

5. Deep hypothermic arrest versus regional low flow perfusion

In the past, deep hypothermic arrest (DHCA), with rapid cooling to 18°C and removal of all cannulae for 45 to 60 minutes, was considered to be the standard technique for complex neonatal repairs. Over the years, numerous studies demonstrated the potential hazards and negative effects on the neurological development. It is only lately that, after advances in myocardial protection, circuit technology and cannula and vent design, new surgical techniques with continuous low flow regional perfusion emerged into clinical practice. Initial discussions focused on the optimal flow rates and best strategies to monitor cerebral blood flow. A wide range of patient populations, surgical approaches and perfusion strategies make direct comparisons of these techniques very difficult, and the few published studies are flawed by small numbers and other limitations in study design.7 The most recent publications suggest worse outcomes with increased cerebral oedema, pulmonary dysfunction and neurological injury after prolonged exposure to low flow perfusion.8 It seems that short periods of DHCA are better tolerated than continuous perfusion. This observation has led to new recommendations for “safe” DHCA:

“…prebypass treatment with steroids and anti-inflammatory agents, hyperoxygenation before the initiation of DHCA, adequate duration of cooling (minimum of 20 minutes), maintenance of higher hematocrits during cooling, using pH stat blood gas management strategy during the cooling phase especially for high-risk patients (aortopulmonary collaterals, preexisting cyanosis), limiting the duration of DHCA exposure by providing intermittent cerebral perfusion for 1 - 2 minutes at 15 - 20 minutes intervals, modified ultrafiltration after CPB and attention to postoperative cerebral “energetics”…”1,5
6. **Ultrafiltration**

Neonates and infants tend to accumulate large amounts of fluid during bypass, resulting in whole body oedema with pulmonary and myocardial dysfunction. Often, the sternum has to be left open for a few days. Several different ultrafiltration techniques have been developed to address this problem:

- **Conventional ultrafiltration (CUF)** occurs throughout the bypass run, or whenever the venous reservoir volume is sufficient to allow filtration. Particularly with the newer miniaturised circuits, the effective fluid removal is limited and difficult to predict.

- **Dilutional ultrafiltration (DUF)** and zero-balance ultrafiltration (Z-BUF) are more effective for the removal of inflammatory mediators than for haemocoagulation. Both techniques involve replacing a high volume ultrafiltrate with equal amounts of crystalloid solutions.

- **Modified ultrafiltration (MUF)** is used after weaning from bypass and before protamine administration, either arteriovenous directly from the aortic cannula or venovenous via a roller pump. To maintain an adequate blood volume in the patient, the ultrafiltrate is replaced by blood from the circuit, resulting in better haemocoagulation. To minimise the negative effects of MUF (prolonged bypass exposure and bleeding, hypothermia, iatrogenic air embolism, increased plasma heparin concentration, decreased levels of anaesthetic and antifibrinolytic agents, etc), specific endpoints are usually set: time (15 - 20 minutes), haematocrit (40%) or extracted volume (750 ml/m²). Sometimes different ultrafiltration techniques are combined to achieve better results.1,3,4

7. **Neurologic outcomes**

Over 85% of infants born with congenital heart disease (CHD) are expected to reach adulthood and, for most lesions, the focus has shifted from simple mortality to neurologic outcome and quality of life. A wide range of mechanisms can contribute to the neurologic injury and determine the outcome:

- **Fixed factors: genetic syndromes, structural central nervous system malformations, low birth weight and prematurity;**
- **Pre-operative factors: ischaemia and cyanosis;**
- **Intra-operative events;**
- **Circuit induced events: emboli and reperfusion injury; and**
- **Postoperative factors: low cardiac output and hyperthermia.**

Neuroimaging studies showed that newborns with CHD already have a higher incidence of pre-existing cerebral anomalies (20 - 40%), especially periventricular leucomalacia (PVL). PVL is caused by injury to immature oligodendroglial cells and was initially described in preterm babies. After CPB, over 50% of neonates have evidence of PVL on magnetic resonance imaging. In order to minimise additional neurologic injury to the immature brain of infants with CHD, all contributing factors have to be considered. These include optimising the care in the pre- and postoperative period; improving the current techniques for deep hypothermic arrest or regional low flow perfusion; aggressive treatment of collateral steal, either pre- or intraoperatively; developing new strategies for the prevention of microemboli; improving neuromonitoring with the use of cerebral oximetry and transcranial Doppler; and, finally, further research on hyperoxia, reperfusion injury and modulation of the inflammatory response.9

**Future trends and developments**

**Miniaturisation of extracorporeal circuits**

Hopefully, within the next few years, further advances in perfusion technology will help to minimise the prime volume of oxygenators, filters, centrifugal pumps, tubing and raceways. This will reduce haemodilution, the inflammatory response and blood exposure.6

**“Coated” circuits**

Heparin-bonded circuits and circuits coated with poly-2-methoxyethylacrylate have been shown to reduce the inflammatory response to bypass and preserve platelet function. But, unless large multicentre studies can demonstrate significant impacts on outcome, cost containment will most likely prevent their widespread paediatric use.10

**Anti-inflammatory strategies**

In addition to pre-operative steroids, coated circuits, modified ultrafiltration and, until recently, aprotinin, new pharmacologic anti-inflammatory agents are being developed, mainly focusing on the inhibition of complement activation and modulation of inflammatory gene expression.

Unfortunately, it may take many years before these new drugs will be clinically available for infants and children.10

**Selected References**