Review Article

Recent innovations in perfusion and cardiopulmonary bypass for neonatal and infant cardiac surgery

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Abstract: The development and refinement of cardiopulmonary bypass (CPB) has made the repair of complex congenital heart defects possible in neonates and infants. In the past, the primary goal for these procedures was patient survival. Now that substantial survival rates have been achieved for even the most complex of repairs in these patients, focus has been given to the reduction of morbidity. Although a necessity for these complex neonatal and infant heart defect repairs, CPB can also be an important source of perioperative complications. Recent innovations have been developed to mitigate these risks and is the topic of this review. Specifically, we will discuss improvements in minimizing blood transfusions, CPB circuit design, monitoring, perfusion techniques, temperature management, and myocardial protection, and then conclude with a brief discussion of how further systematic improvements can be made in these areas.

Keywords: Neonatal cardiac surgery; cardiopulmonary bypass (CPB); perfusion; transfusion; hypothermia; cardioplegia; monitoring; biomarker

Submitted Feb 22, 2018. Accepted for publication Mar 21, 2018.
doi: 10.21037/tp.2018.03.05
View this article at: http://dx.doi.org/10.21037/tp.2018.03.05

Introduction

In nearly all instances, the ability of the pediatric heart surgeon to repair complex intracardiac and extracardiac congenital heart defects requires the use of cardiopulmonary bypass (CPB) and myocardial, cerebral, and somatic perfusion or protection. Improvements in technology and perfusion techniques have evolved to permit the survival of neonates after complex cardiac surgery. Clinical outcomes are now focused beyond survival, with increasing attention given to the status of diverse organ systems after neonatal cardiac surgery. The purpose of this article is to review the recent innovations in CPB technology, perfusion techniques, patient management and monitoring that have been developed to improve the outcomes of neonatal and infant cardiac surgery. Our discussion of these various facets revolves around several themes: minimization of red blood cell (RBC) and other blood product transfusion, regional perfusion or protection, and biomarkers to assess occult organ injury associated with CPB.

Techniques and technologies to minimize blood transfusion

RBC transfusions are an integral part of care for pediatric patients undergoing cardiac surgery. Although integral, there are risks associated with RBC transfusions that can translate into increased patient morbidity and mortality (1).

In years past, the major concerns with transfusions were with infectious disease transmission. Transfusion medicine has improved vastly and the focus has shifted to adverse transfusion reactions such as acute lung injury, immunomodulation, and thrombotic complications (1-3). With focus increasing on these risks, centers have reevaluated RBC administration algorithms, especially for neonate and infant populations due to having a higher incidence of adverse reactions compared to older pediatric and adult patient populations (1,4). To reduce the potential exposure and risks associated with RBC transfusions, there are practices that can be put in place in the intraoperative period.

RBC transfusion practice varies greatly within the pediatric population with no clear transfusion guidelines due to the wide patient variability. Karimi and colleagues illustrated that variability exists within RBC transfusion practice even when matched for diagnosis and procedure for a given age and complexity level (4). It was found that more RBC units were utilized in the year 2010 than 2005 and 2014 across all Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery (STAT) complexity categories. Differences in utilization between 2005 and 2014 could not be demonstrated, suggesting there have been no changes in RBC transfusion practice for that decade of time for the index diagnoses and procedures (4). Neonates and STAT five (most complex) patients received the greatest number of RBC transfusions compared to other ages and STAT categories but no difference was evident among STAT two, three, and four patients (4). The most variability in RBC transfusion practice occurs in the younger patient populations and those with higher STAT categories across all centers, and this has not changed for at least the 10 years included in the sited study.

The need and problems of RBC transfusion during neonatal cardiac surgery

The ratio of a neonate's or infant's blood volume to extracorporeal circuit prime volume frequently approaches 1:1, and the amount of prime volume has been shown to be associated with the need for perioperative RBC transfusion (5). Consequently, the inclusion of leukocyte depleted packed red blood cells (LDPRBCs) as a prime constituent is necessary in order to maintain an adequate hematocrit during CPB. Fresh LDPRBCs are not physiologic and are characterized by low pH, sodium, bicarbonate, and base excess and by high potassium, glucose, and lactic acid (6). Irradiation of LDPRBCs, which is often necessary for athymic patients, increases potassium concentration (7-11). Shimpo and colleagues reported the presence of ammonia (NH_3) and bradykinin (12). Additionally, neutrophils in the residual plasma of packed RBCs have been reported to activate and release interleukin-8 and secretory phospholipase A_2 following transfusion (13). Leukocyte depletion does not completely remove leukocytes from packed RBCs. These residual leukocytes may become activated by contact with the foreign surface of the extracorporeal circuit during LDRBCs priming resulting in cytokine generation. Frequent patient instability during the transition to CPB has been observed manifestly in dysrhythmia and vasodilatation, followed later by increased pulmonary capillary permeability. These phenomena may be in part secondary to the transfusion of the extracorporeal circuit prime which contains these LDPRBCs and their proinflammatory, non-physiologic byproducts. Accordingly, receiving these blood products intraoperatively is associated with prolonged mechanical ventilation (14). Interestingly, Bishnoi and colleagues recently demonstrated that the age of packed RBCs used for circuit prime was not associated with morbidity and mortality after cardiac surgery in 400 children, however the average age of these patients was over 1 year, and thus these results cannot be extended to neonates and infants (15).

Addressing the transfusion problem: improving the quality of the blood prime, minimizing blood prime, and salvaging blood

For the past 25 years, methods have been developed to attenuate the effects of non-autologous blood extracorporeal circuit prime on neonatal and infant congenital heart surgery patients. Most commonly, these methods comprise centrifugal cell washing and blood prime ultrafiltration. While centrifugal cell washing as of 2004 was used in 60% of congenital heart surgery centers (16) and has been shown to be effective in correcting pH and lowering potassium, lactate and glucose (17-19), several studies have reported that the process increases cell wall fragility and leads to increased hemolysis (20-22). Blood prime ultrafiltration has also been reported to make the prime physiologic, but without the attendant hemolysis or additional disposables cost (23-26).

Another approach to minimize the effects of excessive hemodilution which then leads for RBC transfusion is to decrease the prime volume of the CPB circuit. In reality, these techniques do not physically decrease the volume of the extracorporeal circuit, but rely on controlled hemodilution and ultrafiltration. Techniques such as acute normovolemic hemodilution, retrograde autologous priming, venous autologous priming, and zero balance ultrafiltration (ZBUF) or dilution ultrafiltration (DUF) have been shown to decrease the utilization of RBC transfusion (27,28). While these techniques are useful for the larger patient, they have limited utility in neonates and infants since the volume in standard extracorporeal circuits are still sizeable relative to the blood volume of these small patients. However, ultrafiltration during CPB and post-CPB can be performed in smaller patients in the form of modified ultrafiltration, and it has been shown to decrease total body water accumulation, increase mean arterial blood pressure, improve left ventricular systolic function, and improve pulmonary compliance, in addition to other benefits (29-31).

Salvaging and administration of shed blood from the cell saver can significantly reduce the number of blood and blood product transfusions in the immediate post-operative period (32). Adopting a conservative RBC transfusion approach (transfusing a hemoglobin less than 7.0 g/dL for biventricular repairs or less than 9.0 g/dL for palliative procedures plus clinical indication) has been shown to be effective in reducing RBC transfusion while showing no significant differences in lactate, avO_2diff, or clinical outcomes (33).

Addressing the transfusion problem: miniaturization of the extracorporeal circuit

The most important area for improvement in terms of reduction of RBC transfusion requirements is the physical reduction of the extracorporeal circuit volume. For most programs, the largest circuit component contributing to the dilution of the patient is the overall length and internal diameter of the tubing used in the CPB circuit. However, a limited number of institutions have reduced tubing length and size to the point, that the components of the circuit (oxygenator, filter, hemoconcentrator, and heat exchanger) have become the largest contributor to the overall circuit volume (34,35). While there is no current standard for tubing size in extracorporeal circuits, it is a common practice to use the smallest internal diameter tubing that does not create excessive line pressure resulting in hemolysis, arterial cannula cavitation gaseous microemboli or aortic dissection caused by the high-pressure jet from an arterial cannula during the conduct of bypass (36).

The overall resistance created by the extracorporeal circuit is based on the Hagen-Poiseuille equation (37): $\Delta P=(8\ \mu LQ)/\pi R^4$, where ΔP is the pressure difference between the two ends, "L" is the length of tubing, "μ" is the dynamic viscosity of the circulating blood, "Q" is the volumetric flow rate, and "R" is the tubing radius. The internal diameter (R^4) contributes significantly to the overall resistance, however the contribution of length and flow rate cannot be neglected. These factors serve as potential limitations to the miniaturization of the extracorporeal circuit. Additionally, when determining circuit length and configuration, consideration must be given to include the ability to remove GME and to access the circuit during emergency procedures (36,38).

Oxygenators

An ideal oxygenator is defined as having the ability to achieve balanced oxygen and carbon dioxide exchange with minimal blood damage or activation. In addition, there needs to be high permeability of gas exchange at the alveolar-capillary interface (ACI) (39). Currently, gas exchange occurs at the ACI by passive diffusion and is governed by Fick's Law.

Oxygenators designed for neonatal and pediatric CPB have improved significantly over the last decade. The use of oxygenator fiber bundles wrapped with an arterial line filter (ALF) has proven safe and are routinely used (36). While this is an effective method for larger patient populations, the ability to uniquely size these oxygenators to individual patients does not exist. This requires each oxygenator to be used within targeted patient weight range or calculated blood flow range. The range these oxygenators operate within results in patient mismatch at the lower end of the operating range. Currently, commercially-available oxygenators have prime volumes approaching 10 mL (35).

ALFs

The purpose of ALFs is to prevent the infusion of particles and gas into the patient. Separate ALFs are still in use, but with the current generation of integrated oxygenator-ALFs, they should be used sparingly, if at all. Separate ALFs expose patients to extra static prime volume and surface area (40). Integrated oxygenator-ALFs are composed of an additional media placed around the outside of the gas exchange media to capture gaseous emboli and prevent it from reaching the patient. This reduces prime volume by alleviating the need for a stand-alone ALF and the associated prime volume. The use of integrated oxygenator-ALFs have been associated with improved clinical outcomes in pediatric cardiac surgery patients (41).

Pumps

The characteristics of the ideal blood pump are summarized as (42,43):

(I) Low priming volume;
(II) Durable/no mechanical failures;
(III) Easy to set up and operate;
(IV) No hemolysis or damage to formed elements of the blood;
(V) Antithrombogenic;
(VI) No anticoagulation required;
(VII) Electrical control;
(VIII) Reproducible stroke volume;
(IX) Battery backup.

For pediatric CPB, occlusive roller pumps are the propulsion method of choice. The stroke volume is consistent, and able to be varied by changing the tubing diameter within the pump head/raceway configuration. This provides the ability to properly size the pump boot to the patient with consideration for achieving the desired cardiac output and minimizing prime volume. Recent research has indicated that even more pulsatile flow may be beneficial in preventing cellular edema associated with non- or minimally-pulsatile flow (44).

The prime volume of the pump is primarily dictated by the length and size of tubing used. Therefore, reductions in prime volume can be accomplished by decreasing length and diameter of the tubing. Decreasing the length of the tubing provides the additional advantage of decreasing circuit resistance, while decreasing the diameter of the tubing results in an increase in circuit resistance. Thus, it is more advantageous to decrease the distance (tubing length) between the pump and the patient. This can be accomplished by mounting pumps on masts of the CPB machine that can then be positioned more closely to the patient (35). However, there are also practical limitations to the proximity of the pump to the patient as it increases the chance of sterile field compromise and limits space for the scrubbed surgical team.

Monitoring of CPB

Physical parameter measurements and data capture

Monitoring of patients undergoing CPB is antiquated and needs modernization. Historically, patient hemodynamics are displayed as heart rate, systolic, diastolic and mean arterial pressures, central venous pressure, oxygen saturations, and temperature. During CPB the perfusionist monitors hemodynamic variables and their relationship with line pressures, pump outputs, pump head speed, temperatures, arterial and venous oxygen saturations, oxygen content, hemoglobin and hematocrit, and in-line blood gas trends. There are a number of derived parameters that can then be calculated from these variables: cardiac output, oxygen delivery, oxygen consumption, oxygen extraction ratio, venous-to-arterial carbon dioxide difference (45-47). These measurements and derived parameters are therefore obtained relatively infrequently, and thus identifying and responding to important changes may be delayed.

The development and commercialization of near infrared spectroscopy (NIRS) technology has permitted the estimation of regional oxygen saturation (rSO_2). Several studies have validated the use of intraoperative cerebral rSO_2 monitoring by demonstrating a correlation with brain perfusion during CPB in infants (48). Additionally, the application of somatic rSO_2 provides an indicator for renal or lower body perfusion. A cerebral NIRS value below 45% and a renal NIRS value below 40% has a strong correlation with the incidence of ECMO or hospital death and a renal NIRS below 30% correlated with prolonged ICU stay (49,50). This information coupled with standard blood gas and lactate analysis provides a basic picture of perfusion adequacy.

More advanced indicators of perfusion such as oxygen deliver (DO_2) and carbon dioxide production (VCO_2) and the associated ratio can provide more insight into tissue oxygenation than indicators such as mixed venous oxygen saturation (SvO_2) alone. It has been suggested that DO_2 values <260 mL/min/m^2 during bypass are associated with increased lactate formation (51,52). Hyperlactemia is associated with decreased DO_2 and an increased VCO_2 during CPB with critical values being a VCO_2 >60 mL/min/m^2 and a DO_2/VCO_2 ratio <5 (52). These data suggest organ dysoxia may be induced when critical values for DO_2 are reached, leading to tissue acidosis and consequent increase in VCO_2. Therefore, monitoring these parameters in real time provide great value to the perfusionist, especially when attempting to conserve blood utilization (i.e., operating under low hematocrit conditions) in neonates and infants. The possibility of measuring these important parameters in real time coupled with an electronic medical record (EMR) with quality indicator alerts raises awareness to a perfusion inadequacy and improves quality while reducing clinical variability (53). Altogether, a more informed decision can be made on blood utilization throughout an individual CPB case in the neonate and infant setting. However, despite the evidence, routine measurement of DO_2 and VCO_2 is not the standard of care during CPB.

The use of institutional and multi institutional databases should be leveraged to evaluate the safety and efficacy of standard and novel CPB techniques during neonatal and infant cardiac surgery. However, this requires CPB records construction with electronic capture of data elements during the procedure for variables such as hemodynamics (systemic arterial and central venous pressure) pump flow (output), line pressures, temperatures, hematocrit, PO_2, venous line saturation, arterial line saturation, and cerebral monitoring devices (such as INVOS or Fore-sight). Ideally, these data points would be captured at least every minute and entered into national and international datasets. Even today, many centers still utilize hand-written records with data recorded every 10 and 15 minutes. These data records are currently considered to be an accurate representation of the bypass period; however, upon investigation, they appear to represent a blending of data points towards accepted norms and a minimization of outlier data points (54,55). Once these patient specific and frequent data points are available, they can to be used in conjunction with other clinical databases such as the Society of Thoracic Surgeons Congenital Heart Surgery (STS) (56), Pediatric Cardiac Critical Care Consortium (PC4) (57,58), and Pediatric Acute Care Cardiology Collaborative (PAC3) (59-61), and Extracorporeal Life Support Organization Registry (ELSO) (62,63) to examine the relationships between patient parameters and practices utilized during CPB with short and long term patient outcomes (64). With the development of these analytic tools, the impact on circuit construction and patient monitoring will enable the better targeting of RBC transfusion to individual patients or patient populations.

Biomarkers of cerebral injury

Children with congenital heart disease are at an increased risk of experiencing developmental delay or other neurocognitive disabilities such as mild cognitive impairment, impaired social skills, impulsive behavior, or impaired executive function (65,66). It is suggested this may be related to abnormal neurogenesis from a decrease in cerebral oxygen delivery during gestation and is positively associated with decreased brain volume and decreased gyrification (67). Thus, monitoring and assessment of neurologic function in the pediatric patient is paramount. Careful clinical examination remains the mainstay approach to assess for the possibility of neurological complications after cardiac surgery, however this method has obvious limitations in the neonate and infant. Therefore, more sensitive strategies are needed to assess for neurological injury in these small patients. Currently, several serum biomarkers are under investigation for their potential in providing information regarding brain injury (68). Three potential biomarkers for clinical application in pediatric cardiac surgery patients are s100β, neuron-specific enolase (NSE), and glial fibrillary acidic protein (GFAP).

s100β is an acidic calcium-binding protein and is detectable in biologic fluids including cerebral spinal fluid (CSF), blood, urine, amniotic fluid, saliva, and milk. It is primarily concentrated in the glial cells and neurons of the central nervous system (CNS), but is also found in extra-CNS sources including adipose tissue as well. Measurement is possible in biologic fluids via commercially available assays. It has been shown to increase in patients undergoing CPB (69) and not correlated with extra-source adipose tissue release (70). However, there is a lack of studies describing normal s100β levels in the broader pediatric population. In addition, s100β needs to be correlated with a standard of care diagnostic tool used for detecting brain damage, such as magnetic resonance imaging (MRI) (71).

NSE is 78 kDa dimeric glycolytic enzyme in neuronal cytoplasm and is detectable in CSF and blood following injury to neurons. During cardiac surgery involving hypothermic circulatory arrest, normothermic CPB or off pump cardiac surgery, CSF and serum levels of NSE have been reported to increase (69). An association between neurocognitive deficiency and NSE levels following cardiac surgery has also been reported (72). However, like s100β, there are currently no reports of assay levels in larger populations or studies associated with standard of care diagnostic tools.

GFAP is a glial specific protein that has been shown to elevate rapidly in the presence of neuron damage or astroliosis. Serum levels of GFAP are reported to be increased in neonates with hypoxic-ischemic encephalopathy (HIE) when compared against neonates without HIE (73). However other investigators have found no correlation between GFAP levels and neurocognitive outcomes at 36 months (74). Further research is needed to determine clinical significance of elevated GFAP and appropriate treatments associated with these findings.

Perfusion techniques

Aortic arch reconstruction for complex congenital abnormalities is routinely performed in neonates and children with deep hypothermic circulatory arrest (DHCA). This strategy provides neurological and splanchnic protection by decreasing the metabolic demands of the body through hypothermia, resulting in many years of successful outcomes (75). However, DHCA is not without risks, both neurologic and systemic (76-82).

In an effort to decrease the neurologic risks associated with isolated DHCA alone, many have chosen to provide cerebral blood flow with selective antegrade cerebral perfusion (SACP). This adjunct to standard perfusion is employed to improve cerebral blood flow and minimize cerebral injury during DHCA. In addition to supplying the brain during the period of arch reconstruction, SACP also achieves partial systemic flow via collateral vessels and thus potentially reducing splanchnic ischemia (83,84). Because of the theoretical improvement in neuroprotection with SACP, many surgeons have also begun experimenting with moderate hypothermia to reduce the risks associated with deep hypothermia (post-operative inflammation and renal injury) (85) and rewarming (86,87). However, appropriate temperature goals are still debated.

Several studies have been performed comparing DHCA to SACP in children, including randomized controlled trials and retrospective reviews. In a randomized trial by Algra and colleagues looking at new neurologic injury after DHCA or SACP, no statistically significant difference was noted in immediate post-operative MRI findings or motor and cognitive outcomes at 24 months between the two groups (88). Likewise, in another randomized trial by Ohye *et al.* examining the effects of SACP *vs.* DHCA on psychomotor and mental development, no statistically significant differences were seen between the primary endpoints of the two groups (89,90). Retrospective reviews have given similar results.

These studies have provided mixed results, but have in general suggested that SACP is not inferior to DHCA alone and likely provides adequate neurologic protection. Unfortunately, the heterogeneity of the study methods regarding patient selection (single ventricle *vs.* two ventricles *vs.* both), optimal SACP flows, optimal pH monitoring (alpha-stat *vs.* pH-stat) and optimal SACP-associated temperatures (mild, moderate or deep hypothermia) makes drawing broad conclusions regarding this technique very difficult and thus further study is needed to clarify these points.

In addition to exploring techniques to improve neurologic protection/perfusion during DHCA, some surgeons are now experimenting with splanchnic perfusion as well. As previously described, systemic complications of DHCA are common as deep hypothermia promotes oxidative stress and capillary leak (91,92). Moreover, the collateral flow provided by SACP alone may not be sufficient to sustain the somatic circulation (93). Therefore, direct splanchnic flow could improve renal and gut perfusion and minimize the need for deep hypothermia, thus potentially alleviating the ill effects of hypothermia without minimizing its benefits.

The feasibility of splanchnic perfusion was detailed in a paper by Imoto and colleagues in which they described combined descending aorta and innominate artery perfusion during the Norwood procedure under moderate hypothermia (29–31 ℃). According to this account, no evidence of seizures, focal neurologic defects, coagulopathy or acute renal injury were noted in any of the 10 neonates on which this technique was utilized (94).

As with SACP, there is a paucity of high level studies and randomized controlled trials. In a retrospective review by Raees and colleagues, a statistically significant difference was seen in glomerular filtration rates between the group that underwent splanchnic perfusion at 30–32 ℃ and the group that underwent SACP with DHCA at 18–20 ℃, with the splanchnic perfusion group showing a higher GFR. Additionally, serum creatinine on post-operative day three was also significantly higher in the SACP group. However, no significant differences were seen in postoperative length of stay, postoperative lactate levels or time on a ventilator. Moreover, the ratio of increase of post-operative serum creatinine *vs.* preoperative serum creatinine was also the same between treatment groups (95). While this data may suggest that splanchnic perfusion at mild hypothermia provides comparable protection, it in no way suggests superiority and further studies will need to be performed in order to better illustrate this principle.

Widespread adoption of these strategies during aortic arch surgery is hampered by the multiple additional steps during that are required to implement these creative perfusion techniques and the interference caused by extra cannulas during aortic arch reconstruction. Nonetheless, continued refinement and increased use of these innovative techniques and may one day provide enough impetus to perform a rigorous comparison to DHCA in a prospective randomized clinical trial.

Temperature management

The goal of CPB is to provide adequate oxygen delivery to the body, via appropriate circuit flow, to meet the goals of oxygen demand throughout the operation. The adequacy of this delivery can be measured via multiple parameters including blood pressure, cerebral oximetry and lactic acid levels. Often, body temperature is modified to affect oxygen demand during an operation. By reducing systemic temperatures, metabolic demand can be greatly diminished allowing for reduced pump flow, decreased coronary and pulmonary venous return and an improvement in surgical field visibility. However, hypothermia can also cause challenges in this population including negatively affecting cellular membrane stability and ATP production and utilization and increasing coagulopathy (96). Hypothermia can also interfere with oxygen and glucose uptake in the brain, as well as distort the pH of blood (97,98). As such, the ideal temperature for congenital cardiac surgery is controversial and dependent upon the surgeon and the surgical procedure being performed (96).

In an effort to better elucidate practice patterns in North America, including operative temperature management, the Congenital Heart Surgeons Society submitted a survey to 122 members regarding operative management of a complex congenital abnormality (99). Four disease scenarios were given (truncus arteriosus, tetralogy of Fallot, mitral valve repair and mitral valve replacement), one for each age group (neonates, infants, children and adolescents) of the scenario. As expected, there were wide ranges of surgeon directed temperature goals across age groups and scenarios (99). However, even significant variability in systemic temperature management existed within the same age/scenario group, demonstrating that no uniform temperature goal has been universally accepted for even common procedures (99). Likewise, international data suggests variability even in the determination of a target temperature of DHCA (100).

Xiong and colleagues performed a systematic review and meta-analysis of the benefits of normothermia versus hypothermia for pediatric patients undergoing CPB and found that seven randomized controlled trials met their inclusion criteria (96). In looking at the outcomes cumulatively across the trials, there was no significant differences in post-operative lactate levels, creatinine levels, CPB duration or cross clamp duration between groups in various case types (96). As such, no substantial evidence exists to dictate temperature management in many common congenital procedures.

Myocardial protection

Cardioplegia solutions are used during pediatric cardiac surgery to arrest the heart in a relaxed diastolic phase to allow maximum myocardial protection. Immature myocytes provide a different challenge than mature myocytes to achieve maximum protection. Immature myocardial tissue is more resistant to ischemia, but more susceptible to myocardial edema associated with frequent cardioplegia administration (98). An international survey performed in 2011 revealed that del Nido cardioplegia was the most commonly used solution in North America with 32% of centers using it (100). Two years later a North American survey resulted in an increase to 40% of centers reporting it was used in their practice (99).

The accepted standard has historically been a high potassium depolarizing extracellular solution, such as the Buckberg and St. Thomas solutions. This solution is typically infused at 4–8 ℃ every 20 minutes for a total dose of 30 mL/kg in a blood: crystalloid manner utilizing various ratios (i.e., 4:1, 8:1, and 16:1) to provide adequate myocardial protection. Approximately 5% of centers will employ an adjustable-potassium microplegia technique using the high potassium depolarizing solution (99). Due to the minimal crystalloid concentration this type of cardioplegia has a relatively small impact on hemodilution and have been an asset to reduction of blood usage during pediatric cardiac surgery. Immediately before the removal of the cross clamp, 21% of centers surveyed used a warm intermediate-rich reperfusion solution in an effort to control the myocardial reperfusion (99).

There is a current shift away from using a high potassium depolarizing extracellular multidose solution and towards a single dose modified depolarizing intracellular solution like histidine-tryptophan-ketoglutarate (HTK) solution or del Nido solution (100). Although originally developed for cardioplegia (101), the HTK solution has been used for many years primarily as an organ preservation solution for transplantation (102). A small number of surgeons are still using it for myocardial protection during CPB (99). There are concerns of the resulting hyponatremia due to the large dose required (99). The del Nido solution, developed by Dr. Pedro del Nido, is a new agent and is gaining support as an effective and convenient cardioplegic agent as the dosing can be given at longer intervals (103). The del Nido solution was also specifically designed for the pediatric population. The immature myocardium is susceptible to edema and also has a higher sensitivity to intracellular calcium (104). The del Nido solution specifically addresses these issues with the addition of mannitol with dual functions of oxygen free radical scavenging and osmotic properties, and magnesium that acts as a calcium channel blocker (103). One benefit of using the del Nido solution has been a decrease in defibrillation rates after the removal of the aortic cross clamp in pediatric patients (104). In a prospective randomized clinical trial, use of a single dose of the del Nido solution was associated with an increase in cardiac index in patients with low cardiac output syndrome and a lower concentration of serum troponin-I, interleukin 6 (IL-6), and tumor necrosis factor (TNF), myocardial injury and inflammatory markers (105). Anecdotally, another benefit of the del Nido solution is a reduction of aortic cross clamp times, but a multicenter retrospective analysis would need to be performed to verify this.

Conclusions

In just five decades, development of CPB and perfusion techniques have catapulted neonatal and infant cardiac surgery into mainstream, standard of care. Now that these patients are surviving their complex repairs, success is now being measured in terms of the resultant morbidity after cardiac surgery requiring CPB. Continued development of CPB technology, perfusion techniques, and patient management will lead to reduced RBC utilization, decreased postoperative recovery time, and improved long term clinical outcomes. However, perfusion practice is widely variable and there are few high-quality studies being performed to systematically and rigorously assess the efficacy and impact of novel interventions, devices, and technologies related to perfusion management and CPB.

We propose that continuous perfusion monitoring and data recording as well as perioperative injury biomarkers should receive a high priority of development by health care research funding bodies worldwide. This would provide the infrastructure for subsequent multicenter studies on new CPB technologies and perfusion methods. It is through these large studies that definitive conclusions can be made on studies comparing perfusion related interventions. Thus, standardization of perfusion practice can be achieved, and, more importantly, neonates and infants undergoing cardiac surgery worldwide would receive the best possible outcomes.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Sturmer D, Beaty C, Clingan S, Jenkins E, Peters W, Si MS. Recent innovations in perfusion and cardiopulmonary bypass for neonatal and infant cardiac surgery. Transl Pediatr 2018;7(2):139-150. doi: 10.21037/tp.2018.03.05

